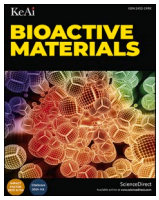
Bioactive Materials 49 (2025) 456–485

Contents lists available at ScienceDirect

Bioactive Materials

journal homepage: www.keaipublishing.com/en/journals/bioactive-materials



Review article

The revolutionary role of placental derivatives in biomedical research

Saeid Moghassemi [a], Saba Nikanfar [a], Arezoo Dadashzadeh [a], Maria João Sousa [a], Yuting Wan [a], Fengxuan Sun [a,b], Arthur Colson [a,b], Sven De Windt [a,c], Lena Kwaspen [a,c], Marc Kanbar [a,c], Keyvan Sobhani [a], Jie Yang [a], Hanne Vlieghe [a], Yongqian Li [a], Frédéric Debière [a,b], Christine Wyns [a,c], Christiani A. Amorim [a,*]

[a] Pôle de Recherche en Physiopathologie de la Reproduction, Institut de Recherche Expérimentale et Clinique, Université Catholique de Louvain, Brussels, Belgium
[b] Department of Obstetrics, Cliniques Universitaires Saint-Luc, Brussels, Belgium
[c] Department of Gynecology and Andrology, Cliniques Universitaires Saint-Luc, Brussels, Belgium

ARTICLE INFO

Keywords:
Placenta
Stem cells
Extracellular matrix
Extracellular vesicle
Decellularization
Biomedical research
Regenerative medicine

ABSTRACT

The human placenta is a transient yet crucial organ that plays a key role in sustaining the relationship between the maternal and fetal organisms. Despite its historical classification as "biowaste," placental tissues have garnered increasing attention since the early 1900s for their significant medical potential, particularly in wound repair and surgical application. As ethical considerations regarding human placental derivatives have largely been assuaged in many countries, they have gained significant attention due to their versatile applications in various biomedical fields, such as biomedical engineering, regenerative medicine, and pharmacology. Moreover, there is a substantial trend toward various animal product substitutions in laboratory research with human placental derivatives, reflecting a broader commitment to advancing ethical and sustainable research methodologies. This review provides a comprehensive examination of the current applications of human placental derivatives, explores the mechanisms behind their therapeutic effects, and outlines the future potential and directions of this rapidly advancing field.

1. Introduction

The human placenta plays a crucial role as an interface between the maternal and fetal systems. This organ supports fetal development by delivering nutrients and oxygen, eliminating waste, preventing immune rejection, and reducing the risk of infection, using the umbilical cord (UC) for exchanges between the mother and fetus [1,2]. In the 16th century, the medical use of the human placenta was described in China, and its application in modern medicine began in the early 20th century for skin grafting [3]. Subsequent decades saw numerous research investigations and clinical trials, leading to advancements in placental tissue derivatives application in wound healing, surgical procedures, cell therapy, bioengineering, and regenerative medicine [4]. This variety of applications is due to the diverse functions and forms of placental tissues, as well as their composition rich in bioactive macromolecules, growth factors, extracellular matrix (ECM) proteins, glycosaminoglycans (GAGs), and stem cells [5].

Despite its vital importance, this invaluable organ is designated as a natural post-childbirth biowaste and represents a significant untapped resource [2]. In 2023 alone, UNICEF reported 134,279,612 births worldwide, representing a vast repository of placenta. This easily accessible human tissue offers a cost-effective and xeno-free material for research and clinical applications. Furthermore, the lack of significant ethical barriers highlights a substantial opportunity for using placental derivatives to advance various areas in biomedical research, including tissue engineering, regenerative medicine, biotechnology, and therapeutic development [1,6].

Moreover, the potential of using placenta-derived materials as an alternative to animal-derived products is particularly promising, as it addresses many of the challenges related to immunogenicity, contamination, and ethical concerns, offering a xeno-free, cost-effective, and readily available resource for advancing both biomedical research and clinical applications. Animal-derived biomaterials, such as bovine serum albumin (BSA), fetal bovine serum (FBS), fetal calf serum (FCS), bovine pituitary extract (BPE), various types of antibodies, and ECM proteins are widely utilized as consumables in different biomedical research

Peer review under the responsibility of editorial board of Bioactive Materials.
* Corresponding author.
E-mail address: christiani.amorim@uclouvain.be (C.A. Amorim).

https://doi.org/10.1016/j.bioactmat.2025.03.011
Received 19 October 2024; Received in revised form 11 March 2025; Accepted 14 March 2025
Available online 19 March 2025

applications. Nonetheless, due to animal origin, these products' utilization poses potential immunogenicity, contamination, biological variability, and ethical considerations regarding animal welfare [7,8]. In addition, the utilization of these products presents a bottleneck in translating biomedical research to clinical applications [9,10]. Recognizing this impediment, numerous commercial xeno-free media have been specifically formulated, underscoring a concerted effort to overcome these limitations and enhance the feasibility of clinical applications [11–13]. Due to its accessibility, placenta tissue is a promising source of base materials for biomedical research applications. Despite their potential, these derivatives have not undergone comprehensive characterization. This review aims to thoroughly analyze the current applications of human placental derivatives and present the most relevant perspectives.

2. Overview of placental development, structure, and function

2.1. Placenta development and morphology

The development of the placenta commences with the implantation of the blastocyst in the uterus. During this stage, the trophoblast cells, the outer cell layer of the blastocyst, undergo differentiation, giving rise to mononucleated cytotrophoblast and multinucleated syncytiotrophoblast cells, which respectively form the inner and outer layers of the placenta (Fig. 1a and b). Meanwhile, the inner cell mass of the blastocyst develops into the embryo [14]. Upon implantation, syncytiotrophoblast cells initially invade the maternal endometrium. Afterward, chorionic villi emerge from the layer of syncytiotrophoblast cells in the uterine wall, later covered by a layer of cytotrophoblast cells (CTCs), which also compose the outermost layer of the placenta, serving as a protective barrier. Fetal blood vessels develop within the chorionic villi, while maternal blood vessels encircle these villi in the intervillous spaces, known as lacunae. This structure facilitates the exchange of nutrients and gases between the maternal and fetal circulatory systems [15,16].

Around 3–4 weeks after implantation, the placenta's overall organization is established, reaching full functionality and maturity around 10–12 weeks. This mature placenta features a maternal basal plate and a fetal chorionic plate, to which the UC is attached (Fig. 1c). A healthy and successful placental development is indispensable to prevent placenta-related diseases such as pre-eclampsia and recurrent miscarriage [17].

2.2. Anatomy and structural composition

The postpartum placenta is a disk-shaped organ with a diameter of 16–20 cm and a weight of approximately 500 g and contains several distinct layers, each varying in thickness and function [18]. The outermost layer, the amniotic epithelium, and basal lamina are 20–30 μm thick, followed by the amniotic mesoderm at 15–30 μm. The intermediate zone has a variable thickness and is loosely structured. Beneath this is the chorionic mesoderm, 15–20 μm thick, and the trophoblast layer, which ranges from 10 to 50 μm (Fig. 1b). The innermost decidua layer can be up to 50 μm thick, completing the primary structural organization [19]. Together, these layers facilitate the exchange of gases, nutrients, and waste between maternal and fetal blood, with the UC, consisting of one vein and two arteries, serving as the critical conduit for this exchange [20]. The chorionic villi, which extend from the chorionic plate, are essential for the exchange of nutrients, gases, and waste between the maternal and fetal circulatory systems (Fig. 1b). These villi are lined by syncytiotrophoblasts, a multinucleated epithelial layer in direct contact with maternal blood. Beneath this surface, cytotrophoblasts provide structural integrity and help regenerate the syncytiotrophoblast layer as needed. Maternal blood enters the intervillous space via remodeled spiral arteries, allowing for the efficient exchange of essential substances before it is drained through uterine veins. The basal plate contains extravillous trophoblasts and decidual cells that are crucial for maintaining the placenta's structure and function [21].

2.3. Immunological features and endocrine function

The immunological features of the placenta are essential to maintaining maternal-fetal tolerance and for successful pregnancy. The complex cross-communication of immune cells, trophoblast, and decidual stromal cells determines maternal-fetal immunotolerance and regulates fetal growth [22]. Placental derivatives, which carry immunomodulatory properties, may offer innovative solutions for controlling immune responses in tissue repair and regeneration [23]. Recognizing the immunological environment in **the** placenta could provide insight into how placental derivatives might be used to modulate immune

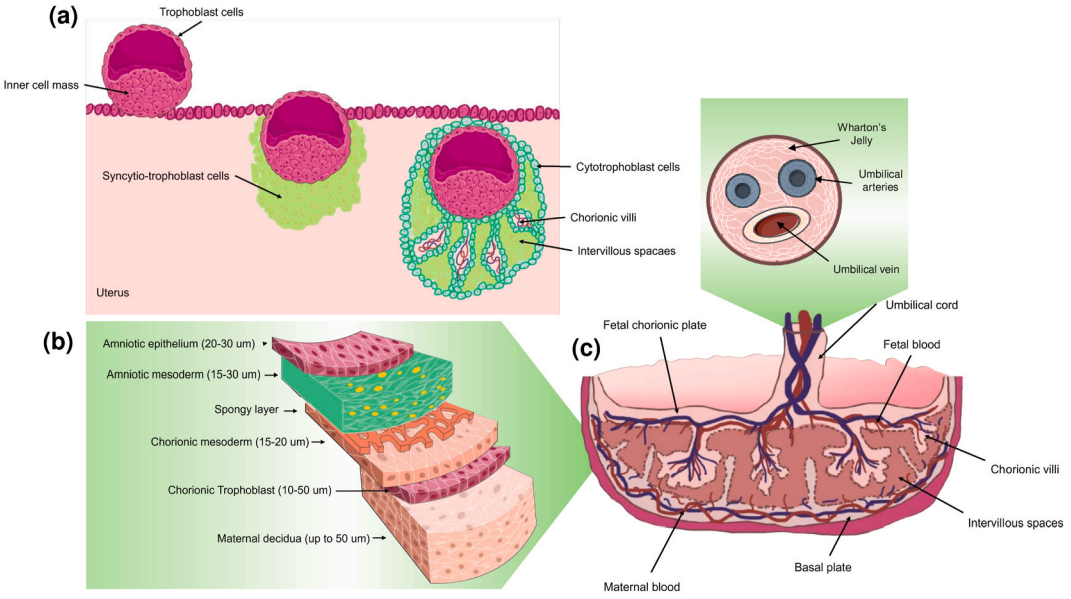


Fig. 1. The early development and structure of the placenta. Placenta early development (a), After the blastocyst implantation, the placental development starts with the invasion of syncytiotrophoblast cells into the maternal uterine tissue. This invasion leads to the formation of chorionic villi, which are subsequently covered by CTCs to create the protective outer shell of the placenta, (b) the illustration of the layers of the placental membrane, and (c) the mature placenta structure, which exhibits both fetal and maternal blood circulation.

responses in clinical applications, especially in the context of regenerative therapies.

During early pregnancy, uterine natural killer (NK) cells and macrophages play critical roles in establishing immune tolerance within the decidua, protecting the fetus from maternal immune rejection. Their influence seems to decrease as pregnancy progresses. These immune cells, along with trophoblasts, ensure a non-inflammatory environment during critical processes such as implantation and trophoblast invasion, where typical inflammatory responses, such as mast cell activation or granulation tissue formation, are notably absent [24,25]. This unique immunotolerant state is primarily due to the absence of MHC Ia antigens on trophoblasts, which would otherwise activate maternal immune cells [26]. Uterine NK cells also play a crucial role in balancing immune tolerance and responsiveness. By inhibiting dendritic cell maturation, these cells prevent the activation of cytotoxic immune responses that could harm the developing fetus [22]. The immunomodulatory capabilities of these immune cells suggest that placental derivatives could be harnessed to suppress unwanted immune reactions and support tissue integration in regenerative therapies.

Moreover, the endocrine activities of placenta, mediated by hormones such as progesterone, estradiol, and human chorionic gonadotropin (hCG), play a key role in modulating the immune system. Progesterone, in particular, regulates the differentiation of endometrial stromal cells into decidual cells. This process not only facilitates embryo implantation but also modulates the maternal immune response through the secretion of Glycodelin A, an immunomodulatory factor that inhibits T lymphocyte proliferation and NK cell activity [27–29]. hCG, secreted by the placenta, further enhances immune tolerance by promoting NK cell proliferation and regulating dendritic cell function at the maternal-fetal interface [30]. The interaction between hormonal fluctuations and immune system regulation during pregnancy reveals a complex and dynamic system. Estradiol and progesterone exert direct and indirect effects on immune cell activity, either promoting or inhibiting specific immune responses depending on the needs of the maternal-fetal interface [28–33]. The immunological and endocrine dynamics of the placenta create a specialized microenvironment that prevents immune rejection while supporting fetal development. These properties, particularly the placenta's ability to modulate immune responses, position placental derivatives as promising candidates for regenerative medicine.

3. Placenta-derived stem cells

3.1. Stem cells derived from placenta and fetal membranes

According to the "first international workshop on placenta-derived stem cells", various cells with a stemness potential can be derived from the different parts of the placenta. The most common cells include mesenchymal stem cells (MSCs) [34,35], amniotic epithelial cells (AECs), and trophoblastic cells (TCs) [35]. Fig. 2 provides an overview of the various sources of placenta-derived stem cells and their potential applications.

Placenta MSCs are multipotent cells that can be isolated from the amniotic membrane, the chorionic plate/villi, or the decidua basalis/parietalis of the placenta [36]. Placental MSCs isolated from the decidua parietalis/basalis are of maternal origin, while those from the remainder

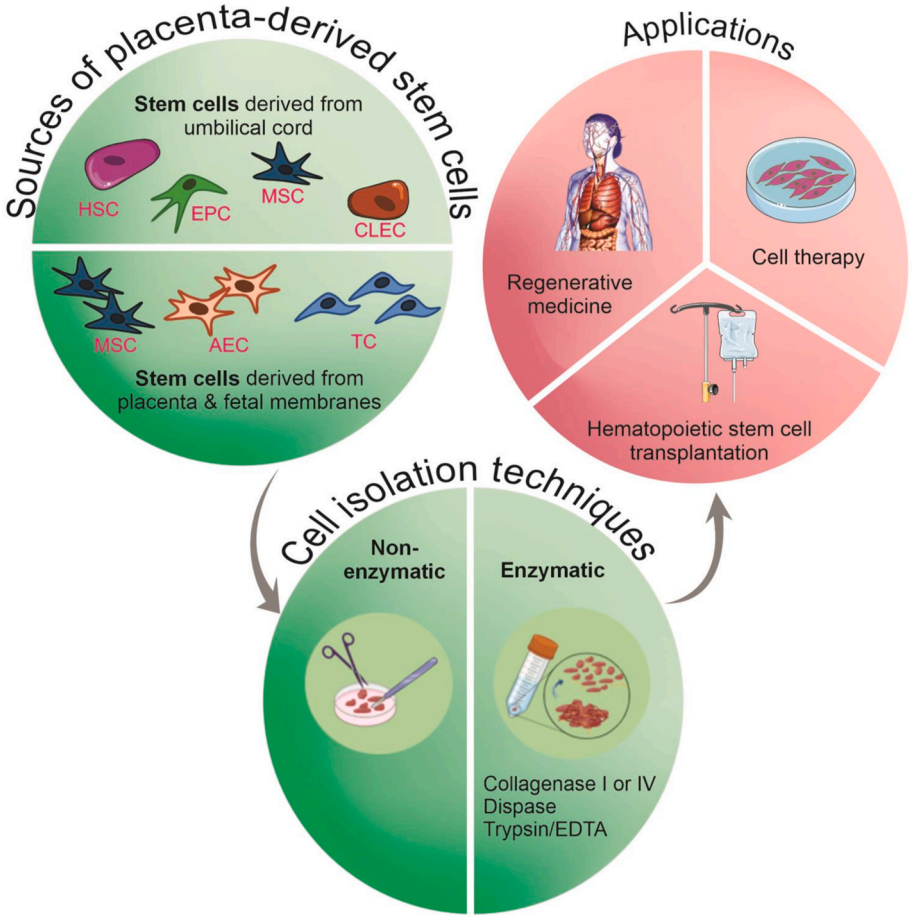


Fig. 2. Schematic representation of placenta-derived stem cells and potential applications. The sources of placenta-derived stem cells, various isolation techniques, and potential therapeutic applications. Abbreviations: Amniotic epithelial cells, AECs; Cord lining epithelial cell, CLEC; Endothelial progenitor cell, EPC; Mesenchymal stem cells, MSCs; Hematopoietic stem cell, HSC; Trophoblastic cells, TCs.

layers are of fetal origin [34,37]. Isolation of MSCs out of these tissues can be performed using enzymatic [34,38,39] or non-enzymatic techniques [40]. Enzymatic digestion protocols utilize various proteolytic enzymes, including Collagenase I or IV, dispase, Trypsin, ethylenediaminetetraacetic acid (EDTA), and these protocols may vary depending on the placental layer from which the cells are isolated [41]. Non-enzymatic techniques, such as the culture explant method, though more time-consuming, are known to improve the integrity preservation of the isolated MSCs. After isolation, placenta-derived MSCs must undergo characterization using flow cytometry, *in vitro* differentiation and must be plastic-adherent when maintained in standard culture conditions to ensure they meet standard MSC criteria as determined by the International Society of Cellular Therapy [42].

Placenta-derived MSCs offer several advantages over other sources, primarily due to their high cellular yield, making them particularly valuable in clinical practice [38]. A full-term placenta typically weighs 500–700g, from which a substantial yield of MSCs can be obtained, ranging between 5.19-6.60 x 10^9 cells per gram. Hence, placenta-derived MSCs are abundantly available and can be produced on a large scale [38].

Due to their ability to migrate, adhere, and engraft into target tissues, placenta-derived MSCs hold significant potential for treating various diseases. Their primary mechanism of action involves enhancing the body's endogenous repair processes [43]. Nowadays, clinical trials are exploring their use in treating pulmonary conditions, with results varying in efficacy and safety outcomes. A trial on idiopathic pulmonary fibrosis using allogeneic placenta-derived MSCs showed improved lung function and walking distance, while another on acute respiratory distress syndrome (ARDS) with bone marrow MSCs showed no benefits [44]. Studies also suggest that allogeneic MSCs can be just as effective as autologous MSCs in disease treatment [45].

AECs are multipotent cells that derive from the epithelial layer of the amnion of term placenta [46]. They express pluripotent stem cell markers but also have MSC-like phenotypes [47]. These cells can differentiate into different tissue types, such as pancreatic, hepatic, and neuronal tissues in both *in vitro* and *in vivo* conditions [35] as well as in vaginal epithelium for a vaginal reconstruction for the treatment of vaginal atresia [48,49] or Mayer-Rokitansky-Küster-Hauser syndrome. Besides their plasticity, these cells have low immunogenicity and non-tumorigenicity, which makes them also candidate starting material for tissue engineering or transplantation [50].

TCs derive from the trophectoderm layer of the blastocyst and can be isolated from placental villi [51]. Depending on the term of the pregnancy, the composition of the TC types is different. First of all, the trophectodermal cells are responsible for the implantation of the blastocyst in the uterine wall, whereafter the cells are named as cytotrophoblast cells or CTC [52]. These CTCs differentiate further in syncytiotrophoblast or extravillous trophoblasts [53,54]. Due to ethical challenges, our understanding of trophoblast differentiation is limited. To address this, researchers use trophoblast stem cells (TSCs) and trophoblast organoids, both derived from first-trimester placentas, as models to study placental development [55]. In 2018, Okae et al. were the first to derive and maintain proliferative human villous CTCs—later identified as TSCs —in long-term culture [56]. These TSCs [57], along with enriched CTC suspensions from placental villi [58–60], have been successfully used to create trophoblast organoids.

3.2. Stem cells derived from umbilical cord

The UC is a rich and accessible source of various stem and progenitor cells, holding significant promise for regenerative medicine and therapeutic applications [61]. Therefore, the potential to utilize UC as an alternative source of stem cells holds great value and could significantly contribute to advancements in biomedical research, particularly regenerative medicine and tissue engineering [62]. Following the biopsy, stem cells can be isolated using manual, semi-automated, or automated purification methods [63]. In addition, UC stem cells require less stringent antigen typing, exhibit greater tolerance to HLA mismatches [64], and pose a lower risk of infection transmission compared to bone marrow, underscoring their significance as valuable alternative sources. Moreover, the UC is readily available without adverse effects for donors, as it is essentially a medical waste product [65]. Among the diverse cellular populations retrievable from the UC are hematopoietic stem cells (HSCs), the endothelial progenitor cells (EPCs) [61], the cord lining epithelial cells (CLECs) [61,66], and the MSCs [61,67].

The inaugural successful transplantation with UC-derived HSCs was conducted on a child diagnosed with Fanconi's Anemia in 1988 [68]. Subsequently, UC cell banking facilities have been established worldwide to facilitate the efficient selection and transportation of UC-derived HSCs [69,70]. Furthermore, these cells exhibit a superior capacity for *in vitro* and *in vivo* proliferation and expansion, compared to bone marrow HSCs [71]. UC-derived HSCs offer a viable alternative for patients requiring human leukocyte antigen (HLA)-matched donors for HSC transplantation due to reduced HLA-similarity requirements [69,70,72]. Collecting UC blood at birth is advantageous as it poses no harm to the mother or child [69]. Optimal *ex vivo* expansion of UC-derived HSCs necessitates careful consideration of the cell density (1×10^4 up to 1×10^6 cells/ml) as well as the addition of several cytokines. For instance, interleukin-3, interleukin-6, stem cell factor, thrombopoietin, and fetal liver tyrosine kinase 3 ligand and granulocyte colony-stimulating factor are frequently used during the expansion of UC HSCs. The presence of feeder cells, such as MSC from mice, human bone marrow or human UC and placenta also appeared to be beneficial for **cell expansion**. Notably, MSC feeder cells generate low quantities of cytokines such as the ones **that** are used to expand the UC HSCs [73]. Currently, Omidubicel is an FDA-approved drug designed to shorten neutrophil recovery time in adult and pediatric patients undergoing myeloablative conditioning followed by umbilical cord blood transplantation for the treatment of hematological malignancies [74]. Furthermore, a clinical trial is underway in the United States and Europe to evaluate the safety and relapse-free survival of umbilical cord blood expanded with ECT-001-CB technology (UM171 molecule) for treating high-risk hematologic malignancies in adults and children.

In addition to the UC HSCs, EPCs can be derived from the UC blood as well as from peripheral blood and the bone marrow [75]. However, a study by Ingram et al. established a hierarchy of EPCs based on clonogenic and proliferative potential assays. Their analysis revealed that UC-derived EPCs formed more rapidly and abundantly colonies, exhibited higher telomerase activity, and retained this activity over culture time, compared to adult peripheral EPCs [76]. Moreover, UC-derived EPCs have been utilized for tissue engineering of microvessels [77]. Studies have shown that administering human UC-derived EPCs in rats can reduce intimal damage following the use of stent retrievers [78].

CLECs are multipotent epithelial stem cells found in the UC lining membrane, which is an extension of the placenta to the fetus [66]. Studies suggest that CLECs are likely to be immunoprivileged, as evidenced by their extended survival in immunocompetent BALB/c mice following transplantation compared to xenotransplanted keratinocytes [79]. Additionally, mucin-expressing CLECs, a specific subtype of epithelial stem cells, can express both epithelial and mesenchymal markers and exhibit efficient proliferation in a low serum-supplemented medium [80]. Not much is known about these cells; however, they can be used as feeder cells to culture human limbal epithelial cells instead of mouse 3T3 feeder cells, which carry the risk of transmitting zoonotic diseases [81]. Additionally, these cells were used to engineer a CLEC-derived corneal epithelium, which was successfully transplanted into a rabbit's eye [82]. Furthermore, CLECs accelerated wound healing in a porcine model, demonstrating their potential for tissue regeneration and therapeutic applications [83].

Notably, the UC lining membrane contains a 1:1 ratio of the multipotent UC lining MCSs and the CLECs [66]. Interestingly, MSCs from the

UC have the best proliferation rate *in vitro* compared to placental MSCs [36]. Furthermore, compared to the MSCs derived from the Wharton jelly, placental disk, and UC blood, the UC lining MSCs have superior proliferation, survival, and migration capabilities post-xenotransplantation in immunocompetent BALB/c mice, and overall low *in vitro* immunogenicity in xenogeneic and allogenic settings [84]. Additionally, another study showed the lower immunogenicity of UC lining MSCs compared to bone marrow-derived MSCs in both xenogeneic *in vitro* and *in vivo* environments, as well as in allogenic *in vitro* scenarios [85]. Up to now, the regenerative capabilities of UC-derived MSCs have sparked considerable interest and have shown potential in regenerating various tissues, such as retinal nerve cells and corneal tissue [86], in the treatment of knee osteoarthritis [87], rheumatoid arthritis [88], liver cirrhosis [89,90], premature ovarian failure [91] and diverse lung diseases [92]. In addition, allogenic human UC blood MSCs are an approved treatment (Medipost) in South Korea for treating acute osteoarthritis, offering a promising therapeutic option for patients seeking relief from joint pain and inflammation [44].

3.3. Cell therapy using umbilical cord/placenta-derived stem cells

HSC transplantation, commonly known as a bone marrow transplant, is a procedure used to treat cancers such as leukemia. It involves introducing healthy HSCs, either from the patient (autologous) or a donor (allogeneic), to restore or replace dysfunctional or depleted bone marrow [93].

The UC is an excellent alternative source of HSCs, notably for patients with hematologic diseases where there are no available donors who are HLA identical. UC-derived stem cells have demonstrated the ability to enhance bone marrow function, facilitating the eradication of malignant cells and replacing dysfunctional cells in immune-deficient patients, depending on the specific disease [94]. Since 1988, over 40, 000 UC blood transplantations have successfully been performed worldwide for more than 80 different diseases [95–97]. Additionally, an estimated 800,000 cord blood units are cryopreserved in public UC banks, with an additional 5 million units stored in private banks [95,96]. At the research level, UC blood has also been established as a preferable source material for the generation of induced pluripotent stem cells [98], especially with HLA homozygous units for allogeneic cell therapies [99,100]. An example of this is the successful derivation of iPSCs from human UC blood which were further differentiated into functional cardiomyocytes, though not being further characterized *in vivo* [101]. The ongoing progress of this research and the potential use of UC in this field present an intriguing area for future exploration.

UC blood contains valuable multipotent stem cells and has become a focal point in regenerative medicine research due to its therapeutic potential [102]. It is currently utilized in the treatment of various disorders, including cardiovascular [103], hepatic [104], ophthalmic [105], neurological [106], and endocrine disorders [96,107]. Recent studies have highlighted its promise in addressing hypoxic-ischemic encephalopathy [108,109], ischemic stroke in adults [110], and Parkinson's disease [111], attributing its efficacy to new blood vessel generation and nerve cell regrowth support [112]. In 2009, Moodley et al. demonstrated that the administration of UC-derived MSCs **leads** to reduced inflammation in patients with bleomycin-induced lung injury. This effect was attributed to the role of UC-derived MSCs in suppressing pro-inflammatory cytokines [113].

UC-derived stem cells exhibit self-renewal capabilities, effuse angiogenic factors, and immunomodulatory properties, rendering them well-suited for addressing wound healing [114,115]. Research has underscored the efficacy of UC-derived stem cells in attenuating scar tissue formation and mitigating the risk of infection, demonstrated both *in vivo* through inhibited collagen deposition and *in vitro* through enhanced re-epithelialization and collagen synthesis in hypoxic conditioned medium (CM) compared to conventional antibiotic treatment [116,117]. Moreover, after treatment with these cells, augmenting vascular density and substantially reducing wound size by over 80 % has been observed [118,119]. Notably, the therapeutic potential of UC blood has extended to addressing diabetic foot, exemplified in a 2022 clinical trial demonstrating favorable tolerance, accelerated healing within 1.5 months, and a noteworthy 3-year amputation-free survival rate compared to standard conservative treatments [120]. This compelling clinical evidence supports the viability and clinical efficacy of UC-derived stem cells in wound healing applications, indicating a promising avenue for further exploration and application in regenerative medicine.

Furthermore, UC-derived cells and the tissue itself have also been demonstrated to be valuable sources for bioengineering purposes. Recently, a protocol was published resulting in the efficient removal of the cellular and nuclear content while retaining the ECM components. This decellularized gel was further used to support the chondrogenic differentiation of umbilical MSCs [121]. Placental MSCs are superior to bone-marrow-derived MSCs in terms of proliferation and differentiation capacities [122,123]. They have demonstrated the ability to regulate macrophage polarization, thereby reducing lipopolysaccharide-induced macrophage inflammation [124]. These cells have also been widely studied as potential treatment options for diseases**, including** multiple myeloma, lymphoma, and leukemia. Notably, when injected into the bone marrow of a severe combined immunodeficiency rat model, placenta-derived MSCs were shown to promote bone formation and inhibit both myeloma bone disease and tumor growth in a dose-dependent manner [125].

In addition to their therapeutic potential, modified placenta-derived cells, such as human AEC primed with paclitaxel, have been explored as efficient drug delivery systems for cancer treatment. These human amniotic membrane-derived primed AECs showed no cytotoxicity *in vitro* to paclitaxel after 24h priming and their CMs could reduce proliferation, and viability and increase the proportion of apoptotic cells of cultured human HeLa and human MCF-7 cancer cells. Thus, these modified cells retain their inherent anticancer properties when primed, making them promising candidates for targeted therapies [126].

Placenta-derived MSCs are increasingly recognized for their potential to treat various diseases, including autoimmune and inflammatory disorders, cancer, cardiovascular and neurodegenerative diseases, and aging [127]. Their therapeutic benefits stem from key attributes such as the ability to differentiate into multiple cell types, low immunogenicity, strong immunomodulatory effects, and the secretion of growth factors, cytokines, and chemokines that support tissue repair, promote angiogenesis, and reduce cell death [36,128].

Placental MSCs have demonstrated multifaceted therapeutic effects in various models. In chronic skin wounds of diabetic rats, these cells improved wound closure by enhancing microvessel formation through the secretion of proangiogenic factors such as VEGF (vascular endothelial growth factor), HGF (hepatocyte growth factor), bFGF (basic fibroblast growth factor), TGF-β (transforming growth factor beta), and IGF-1 (insulin-like growth factor 1). Consistent with these findings, Li et al. combined placental MSCs with a bioengineered dermal scaffold and observed enhanced healing effects, particularly improved vascularization in tendon-exposed wounds in rabbits, compared to the scaffold alone [129]. In diabetic foot ulcer models, similar findings have been reported. A hydrogel matrix composed of polyethylene glycol (PEG) diacrylate and sodium alginate, combined with collagen I, has been shown to enhance the viability and function of MSCs, thereby creating a more favorable environment for their activity. The combination of a gel loaded with MSCs resulted in accelerated wound closure, enhanced re-epithelialization, increased collagen deposition, and improved *in vivo* vascularization [130]. Additionally, in a model of carbon tetrachloride-induced liver injury in rats, placental MSCs reduced leukocytic infiltration and increased secretion of anti-inflammatory cytokines, underscoring their diverse therapeutic potential across different physiopathological contexts [131]. In reproductive medicine, transplantation of placental MSCs has been utilized

for several applications, including rejuvenating the aging or damaged ovaries [132], alleviating endometrial fibrosis, and promoting endometrial cell proliferation after ethanol-induced damaged endometrium in rats [133,134]. Studies have demonstrated that transplanted placental MSCs spheroids can increase estrogen production and enhance folliculogenesis in ovariectomized rats [135]. In a mouse model of intrauterine adhesions, placental MSCs improved endometrial thickness, angiogenesis, and stromal cell activity, resulting in higher pregnancy rates and increased litter size [136]. Moreover, the transplantation of MSCs in damaged testes enhanced spermatogenesis and testosterone production by modulating markers related to proliferation, antioxidants, autophagy, apoptosis, and oxidative stress [137–139].

As another potential application, multiple injections of placenta-derived MSCs have been shown to retard the aging process in aged female mice, as evidenced by opposite trends in body weight evolution, increased serotonin levels, higher liver proliferation, and elevated mitochondrial biogenesis compared to naturally aging female mice [140]. Moreover, Yin et al. genetically modified human placenta-derived MSCs to express FGF2 and PDGF-BB genes to treat ischemic limbs in mice. A significantly increased collateral vessel formation and increased capillary and arteriole density were observed 4 weeks after cell therapy [141].

4. Umbilical cord blood serum

The umbilical cord blood serum (UCBS) is abundant in various bioactive substances that facilitate the healthy and rapid development of fetal tissues and organs. Research indicates that UCBS contains elevated levels of growth factors, including epidermal growth factor (EGF), fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF), platelet-derived growth factor-BB (PDGF-BB), granulocyte colony-stimulating factor (G-CSF), transforming growth factor (TGF), and nerve growth factor (NGF), along with stem cell factor (SCF), chemokines such as monocyte chemoattractant protein-1 (MCP-1) and stromal cell-derived factor (SDF-1), and cytokines such as interleukin-1B, interleukin-4, interleukin-5, interleukin-6, interleukin-7, interleukin-10, and interleukin-15, in comparison to adult serum [142–144]. The presence of these plentiful bioactive substances endows UCBS with outstanding biological functions, including immune modulation, promotion of cell proliferation, angiogenesis, and tissue repair. Due to its rich content of bioactive substances, ability to facilitate cell growth, and low immunogenicity, UCBS has applications in regenerative medicine and tissue engineering [145]. Table 1 shows the biological function of the key bioactive substances in UCBS.

Table 1
Key bioactive substances, including growth factors, cytokines, and chemokines, in UCBS and their biological functions.

Bioactive substance	Biological Function	Ref.
EGF	Regulating the proliferation, migration, and differentiation of various cells; Epidermal regeneration.	[146]
FGFs	Promoting cell proliferation, migration, differentiation, survival, and angiogenesis; Supporting tissue repair; Facilitating tissue regeneration.	[147, 148]
VEGF	Enhancing vascular permeability; Promoting angiogenesis; Supporting tissue repair; Regulating inflammatory responses.	[149]
IGF-I	Promoting cellular proliferation, differentiation, and the growth of bones, muscles, and other tissues	[150]
PDGF-A/B	Promoting cell proliferation and differentiation; Vascularization, cell migration, and embryonic development	[151]
NGF	Supporting the survival and development of neurons; Repair and regeneration of nerves; Playing roles in pain perception and inflammatory responses	[152]
HGF	Promoting cell regeneration and anti-fibrotic properties	[153]
TGF	Playing roles in tissue repair and immune regulation; Promoting tissue fibrosis	[154]
ILs	Regulating different cellular immune and inflammatory responses	[155]
TNF-α	Pro-inflammatory factor; Enhancing the bactericidal and tumoricidal functions of T cells and macrophages	[156]
SCF	Promoting the survival and migration of HSCs and progenitor cells; and facilitating their proliferation and differentiation.	[156]
Chemokines	Playing role in immune regulation by facilitating migration and localization to mediate immune responses; Antiviral mediation	[157]
Retinoic Acid	Crucial in cellular differentiation; Having functions in promoting cell proliferation and immune regulation	[158]
Fibrinogen	Supporting the migration of inflammatory cells within damaged tissues; Providing a matrix framework; Supporting tissue reconstruction	[159]
Prealbumin	Binding to and transporting thyroid hormones and vitamin A; Playing a regulatory role in metabolism	[160]

Abbreviations: Epidermal growth factor, EGF; Fibroblast growth factors, FGFs; Hepatocyte growth factor, HGF; Hematopoietic stem cells, HSCs; Interleukins, ILs; Insulin-like growth factors, IGF; Nerve growth factor, NGF; Platelet-derived growth factor, PDGF; Stem cell factor, SCF; Transforming growth factor, TGF; Tumor necrosis factor-α, TNF-α; Vascular endothelial growth factor, VEGF.

4.1. UCBS in ophthalmology

The UCBS application in ophthalmology represents a significant advancement in managing **various** pathological conditions affecting the ocular surface. These conditions include dry eye syndrome, recurrent corneal erosions, graft versus host disease, persistent epithelial defects, limbal stem cell deficiency, and neurotrophic keratopathy [161,162]. Research has shown that UCBS eye drops outperform peripheral blood serum (PBS) and artificial tears (AT) in promoting corneal healing and reducing haze in murine models of ocular chemical injury. Huang. et al. reported that UCBS and umbilical cord platelet-rich plasma (UCPRP) induce substantial axonal regeneration in benzalkonium chloride-induced corneal injury in mice through the regulation of the Il-17 signaling pathway and neuropeptide Y [163]. A multicenter trial also found improvements in dry eye disease (DED) with both CBS and PBS, with CBS offering greater relief of symptoms and corneal protection. The therapeutic efficacy of umbilical cord serum (UCS) eye drops in DED was supported by a meta-analysis, highlighting notable improvements in Schirmer I test, tear break-up time (TBUT), ocular surface disease index (OSDI), and corneal fluorescein staining scores. Nevertheless, larger randomized controlled trials (RCTs) with prolonged follow-up durations are necessary to comprehensively assess the long-term safety and efficacy of UCS in managing DED [164].

The UCBS application is a safe and effective adjunctive treatment for resistant corneal ulcers, helping to improve healing and visual outcomes [165]. UCBS exhibits a bacteriostatic effect due to the presence of components like lysozyme, immunoglobulin G (IgG), and complement. This formulation is safe and effective in treating corneal epithelial defects in diabetic patients after vitrectomy. Additionally, the use of preservative-free serum reduces the risk of toxic reactions on the ocular surface [86,166]. UCBS eye drops contain key neurotrophic and growth factors, including nerve growth factor (NGF) and insulin-like growth factor 1 (IGF-1), which support corneal nerve regeneration and promote epithelial healing. This formulation significantly aids in the recovery of patients with corneal epithelial defects [167]. Additionally, UCBS treatment has shown superior efficacy compared to artificial tears and autologous serum eye drops in restoring the ocular surface after acute chemical injuries [168,169].

4.2. UCBS as a replacement for animal-derived serum in cell culture

The use of FBS raises concerns about potential disease transmission

from animals to humans, necessitating the establishment of animal serum-free culture, particularly in cell therapy [170]. MSC exhibits significant potential for cell-based therapies. A major obstacle to their clinical application is the safety risk associated with FBS; an essential component of all media currently employed for MSC culture. Research indicates that UCBS has the potential to demonstrate comparable effectiveness to FBS in culturing human amnion-derived stem cells [171]. It has been reported that the CM generated by culturing human UC-MSCs with human cord blood serum improves stem cell stemness and secretome profiles [172]. Furthermore, Afzal et al. have demonstrated that human UCBS can effectively substitute FBS in routine MSC culture, making it well-suited for application in the manufacturing process of UC-derived MSCs within the cell therapy industry [170]. Dendritic cell therapy is an encouraging treatment strategy for cancer. However, while previous methods have relied on FBS for inducing and expanding monocytes, the resulting cells have limited clinical applicability. Viet et al. have demonstrated that human UCBS or UCPRP can serve as substitutes for FBS in generating dendritic cells for clinical applications, offering low immunogenicity [173]. Furthermore, Sandra et al. found that human UCBS exhibits a greater capacity to stimulate fibroblast proliferation than FBS [174]. Therefore, UCBS presents a promising alternative to FBS in biomedical research. However, further comprehensive studies are necessary to explore its potential applications.

4.3. UCBS in biomedical engineering

The utilization of cord serum in conjunction with synthetic bioscaffold materials has been instrumental in the regeneration of various tissue types, such as tympanic membrane, bone, and nerve [145].

The research by Jang et al. revealed that the UCBS application on a three-dimensional (3D) porous collagen scaffold significantly improved the regeneration of chronic tympanic membrane perforation and led to an early-stage acoustic-mechanical recovery, surpassing the outcomes of the paper patch method. The healed tympanic membrane exhibited comparable thickness to a normal tympanic membrane [175]. Moreover, data from Jang et al. [176] suggest the use of a 3D porous polycaprolactone (PCL) scaffold coated with human UCBS in mastoid obliteration enhances osteogenesis. Furthermore, a novel fibrous nerve conduit, incorporating PCL microfibers supported by collagen and human UCBS, provides an enhanced micro-environmental for the regeneration of facial nerves and demonstrates greater therapeutic potential for regenerating facial nerve transection damage compared to the autograft technique [177].

5. Placental conditioned medium

Placental CM contains a variety of bioactive molecules, including cytokines and growth factors, which are secreted from isolated placental cells. The specific composition and effects of the CM are closely tied to the type of placenta cell isolated, as well as the gestational age at which the isolation occurs. The CM from mesenchymal stem cells (MSCs-CM) is the predominant type currently in use, mediums from cytotrophoblasts, syncytiotrophoblasts, and decidual cells also show promise for various applications.

5.1. CM from human placenta-derived MSCs

The application of MSCs-based treatments has been extensively investigated for their functions in various diseases. However, the direct administration of MSC has been associated with a potential risk of a protumorigenic effect [178]. Alternatively, using MSCs-derived CM, enriched in extracellular vesicles (EVs) and immunomodulatory factors including cytokines, chemokines, and growth factors, has emerged as a cell-free bioengineering approach to modulate immune responses and regulate the cell cycle. Notably, the use of human placenta-derived MSCs-CM (hPMSCs-CM) has demonstrated favorable regenerative and therapeutic effects across a wide array of pathological conditions, particularly in the fields of oncology, gynecology, and obstetrics, cardiology, and fibrotic diseases, with outcomes comparable to direct MSC administration [179]. Studies revealed that hPMSCs-CM can induce cell cycle arrest and increase apoptosis in cervical cancer cells and that CM from hypoxic hPMSCs-CM exhibited enhanced anti-cancer effects [180]. Similarly, experiments conducted in hepatocellular carcinoma cell lines have shown that hPMSCs-CM can regulate the cell cycle, induce apoptosis, and reduce cancer cell migration [181]. These findings suggest the potential of hPMSCs-CM in treating cervical and liver cancers, although further *in vivo* research is warranted. Moreover, in rat models, hPMSCs-CM has demonstrated the ability to mitigate radiation-induced premature ovarian failure by attenuating reticulum stress-related apoptosis [182].

In cardiovascular bioengineering, the administration of hPMSCs-CM has shown promise in improving the repair of acute myocardial infarction in experimental rat models, presenting a potential advancement in treating this critical condition [183]. Furthermore, the detection of several enzymes involved in ECM-remodeling, along with cytokines, and miRNAs possessing anti-fibrogenic and anti-inflammatory properties in hPMSCs-CM, has prompted studies to evaluate its potential in mitigating conditions such as intestinal fibrosis and Duchenne muscular dystrophy [184,185]. Additionally, research has indicated that the hPMSCs-CM may offer a novel therapeutic approach to wound healing by protecting against scar formation [186]. The findings underscore the diverse therapeutic possibilities associated with hPMSCs-CM, offering a compelling area for further exploration and development in the medical field (Fig. 3).

5.2. CM from ***other*** human placenta-derived cells

Primary trophoblasts, including cytotrophoblasts and syncytiotrophoblasts, secrete a vast array of bioactive molecules. However, their potential applications remain largely unexplored, partly due to their limited availability. Recent studies have revealed that the CM from the choriocarcinoma cell line (BeWo, CCL-98) changes HSCs transcriptome *in vitro*, including the upregulation pathways associated with stem cell maintenance, proliferation, and immune responses [187]. Trophoblast-derived CM treatment has been found to promote the osteogenic differentiation of MSCs while inhibiting adipogenesis, thus showcasing potential clinical interventions for bone regeneration and related bioengineering therapies including bioprinting, biomaterial-based scaffolds, bioactive implants, and tissue-engineered bone grafts [188]. In addition, *in vitro* research has highlighted the protective effects of CM derived from human AECs against chemotherapy-induced ovarian damage by promoting angiogenesis and tube formation. This may lead to innovative approaches in fertility preservation and ovarian tissue engineering and bioengineered ovarian constructs [189]. However, the applications of these findings remain constrained, likely attributable to the inherent challenge of isolating primary trophoblasts from the human placenta.

The bioengineering potential of placental CM is extensive, presenting a cell-free and regenerative therapeutic platform applicable to a diverse range of areas, including oncology, cardiovascular repair, fibrosis treatment, and reproductive medicine. As advancements in biotechnology continue and *in vivo* validation is achieved, placental CM has the capacity to transform regenerative medicine and precision bioengineering, facilitating significant progress across various clinical applications.

6. Placental extracts

Placental extracts have been studied and used in clinical treatments for centuries, particularly in East Asia, with growing interest in recent decades due to their remarkable ability to regulate cell behavior,

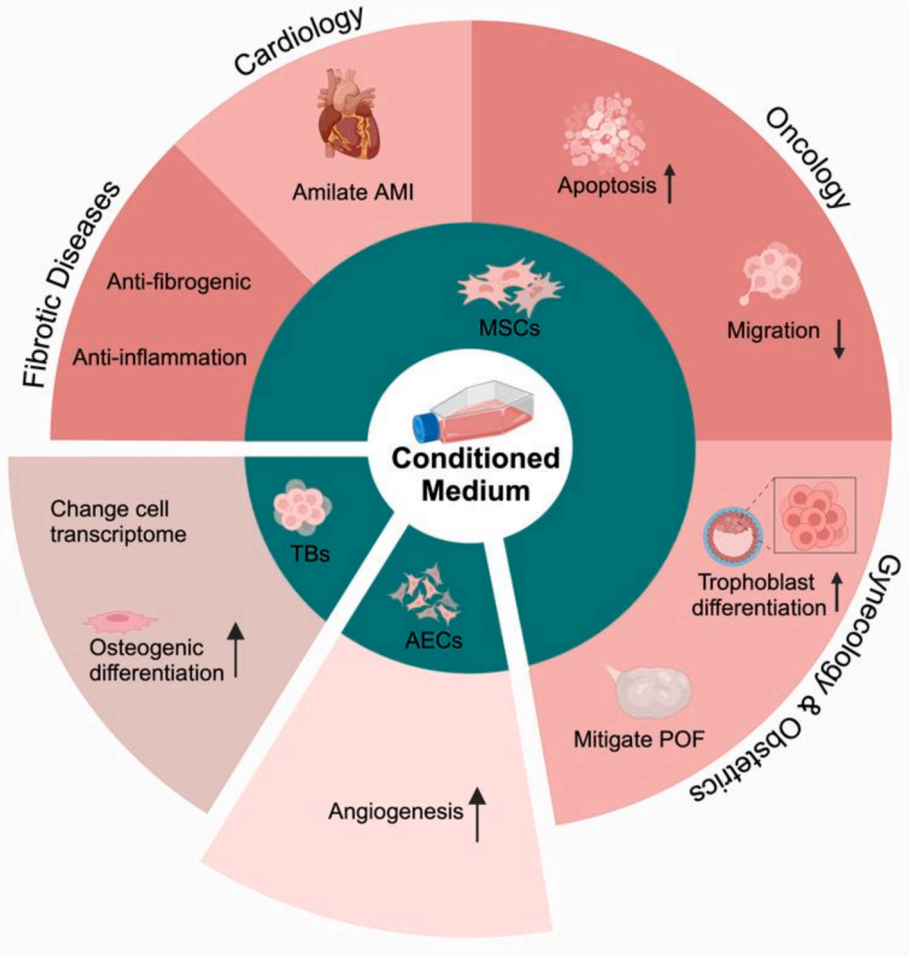


Fig. 3. Application of placental CM. CM derived from placental MSCs has shown significant therapeutic potential across diverse diseases, including fibrotic disorders, cardiovascular diseases, cancers, as well as conditions related to gynecology and obstetrics. Meanwhile, studies demonstrated that CM from TBs altered HSCs transcriptome and promoted osteogenic differentiation. Furthermore, CM from AECs induced angiogenesis and tube formation in the ovary. Abbreviations: acute myocardial infarction, AMI; amniotic epithelial cells, AECs; Conditioned medium, CM; hematopoietic stem cells, HSCs; mesenchymal stem cells, MSCs; trophoblasts, TBs; premature ovarian failure, POF.

promote tissue regeneration, and enhance bioengineering applications. The process of producing placental extracts involves collecting the placenta, cleaning, homogenizing, extracting, filtering, purifying, and sterilizing the product. The final efficacy and composition are significantly influenced by the gestational weeks of the placenta and the extraction method employed. Moreover, standardized bioengineering protocols for placental extract production are still lacking, resulting in data heterogeneity. Placental extract-based formulations, including biomedical-grade creams, injectables, and oral liquids, are widely used in regenerative medicine, tissue engineering, and therapeutic cosmetics.

6.1. Components

Tissue processing is designed to concentrate essential nutrients (such as vitamins, trace elements, and amino acids), nucleic acids, and bioactive proteins and peptides (including collagen, elastin, laminin, cytokines, and growth factors). This process plays a crucial role in regulating various cellular functions, including proliferation, adhesion, migration, and differentiation [1,190–192].

6.1.1. Nutrients

The placental extracts are rich in diverse types of vitamins, especially the vitamin B family. High concentrations of vitamins B1, B2, B5, B6, B7, B9, and B12 have been identified in human placental extracts, along with the presence of calcium, copper, iron, magnesium, manganese, phosphorus, potassium, silicon, sodium, and zinc [193,194]. Furthermore, essential and non-essential amino acids such as alanine, aspartic acid, histidine, arginine, phenylalanine, proline, tryptophan, lysine, tyrosine, leucine, and valine have been detected in the placental extracts, which are also associated with regulating the expression of collagen, elastin, and fibronectin [195–197].

6.1.2. Nucleic acids

One of the key bioactive components derived from the placenta is polydeoxyribonucleotide (PDRN), a mixture of deoxyribonucleotide polymers of varying lengths. It plays a crucial role in activating the salvage pathway, supporting the synthesis of nucleosides, nucleotides, and nucleic acids [198]. This gene-modulating ability shows promise for DNA repair, regenerative medicine, and strategies for neurological regeneration [199,200].

6.1.3. Proteins and peptides

The placenta has been reported to contain a high abundance of cytokines and growth factors [201,202]. Placental extracts have been shown to include key bioactive molecules such as ILs, tumor necrosis factor (TNF), granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), epidermal growth factor (EGF), fibroblast growth factor (FGF), HGF,

insulin growth factor (IGF), PDGF, transforming growth factor (TGF), and VEGF. These bioactive molecules in placental extract make it suitable for engineered tissue grafts, vascularized skin substitutes, and scaffold-based regenerative therapies.

6.2. Placental extract applications

The mammalian placental extracts have been extensively utilized in contemporary cosmetics and clinics due to their excellent antioxidant and anti-inflammatory properties, cell fate regulation, immunoregulation, and hormone-like expression (Fig. 4).

Extensive research has confirmed the antioxidant and anti-inflammatory properties of the placental extracts. Key antioxidants in human placental extracts are uracil, tyrosine, phenylalanine, tryptophan, collagen-derived peptides, and α-fetoprotein. These components are crucial in neutralizing free radicals and preventing cell membrane damage [203–205]. Studies conducted in murine models showed that the administration of mammalian placental extracts significantly mitigates oxidative damage, reduces the expression of pro-inflammatory cytokines such as TNF-α, IL-1β, IL-6, and IL-10, and decreases macrophage polarization, suggesting applications in anti-aging formulations, inflammatory disease treatments, and biocompatible wound dressings [206–209]. Furthermore, placental extracts play a crucial role in regulating cellular proliferation, differentiation, and renewal. Building on these insights, they have been explored for various clinical applications. For example, animal studies have demonstrated that placental extracts can alleviate rhinitis symptoms by modulating macrophage polarization [209]. Growing evidence highlights the protective effects of placental extracts on liver health, including their role in alleviating steatohepatitis by enhancing metabolic function, safeguarding endothelial cells, and modulating immune responses [210,211]. Placental extract treatment, with its anti-inflammatory properties, helps mitigate neuronal damage in the hippocampus of rat models [212]. Moreover, when combined with bioprinting technology, the human placenta extracts have demonstrated superior regenerative effects in rat models, positioning them as promising biomaterials for orthopedic tissue engineering and craniofacial reconstruction [213].

In dermatology, placental extracts have demonstrated significant potential for addressing various clinical and cosmetic skin concerns, including rejuvenation, anti-aging, and skin whitening. Studies have shown that placental extracts enhance the expression of genes associated with the ECM and antioxidants in human dermal fibroblast cells [188]. Notably, these extractions have demonstrated efficacy in treating wounds, chronic non-healing ulcers, and burns through the induction of epithelialization and reduction of infiltration and pain syndrome alleviation by increasing the expression of TGF-β in the early phase, VEGF in the late phase, and FGF [214–217]. Furthermore, the application of placental extract-containing hydrogel has shown promising effects in promoting full-thickness wound healing. The potential benefits also extend to bioengineered skin substitutes, scar reduction therapies, and the regulation of melanin synthesis in normal human melanocytes [218–221]. Finally, human placental extracts may offer a new therapeutic approach to mitigating hair loss by inducing root elongation in rat vibrissa hair follicles and delaying catagen progression, opening avenues for novel alopecia treatments and follicular bioengineering [222].

Lastly, it is hypothesized that human placental extracts can modulate hormone expression. Studies involving Korean women revealed that human and porcine placental extracts mitigated menopausal symptoms and fatigue by increasing their estradiol levels [223,224]. Importantly, no safety concerns were reported in these clinical trials. Therefore, placental extracts seem to have a promising potential therapeutic value in hormone-like therapy, and further research involving more patients

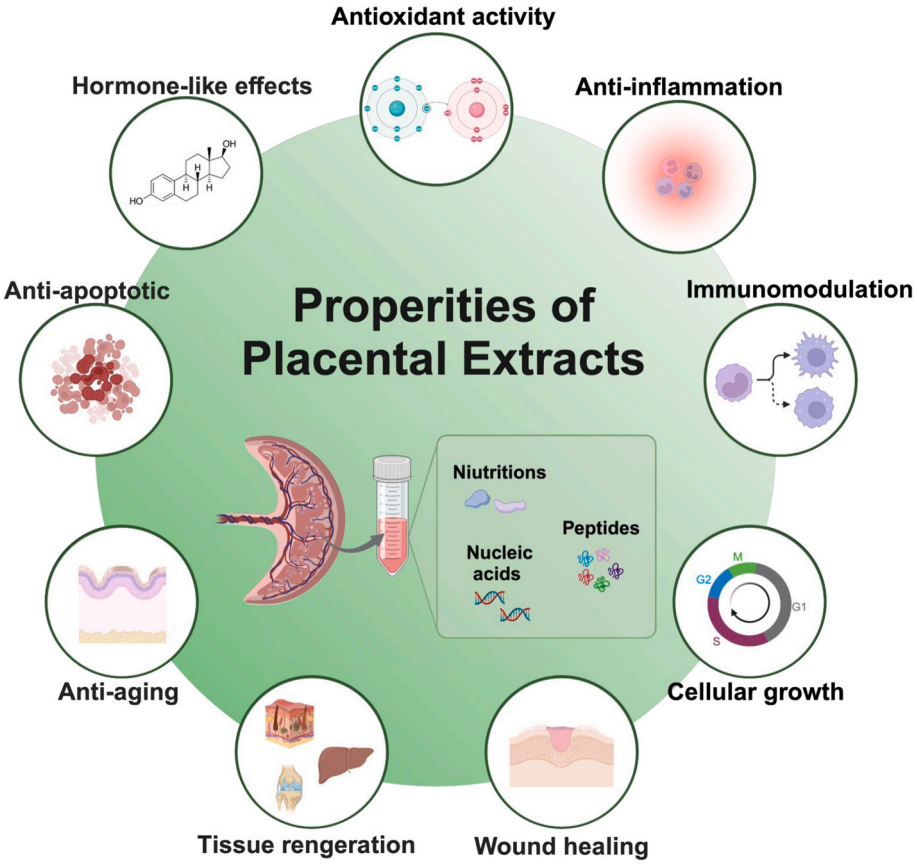


Fig. 4. Placental extract properties. The properties of placental extract encompass potent antioxidant and anti-inflammatory activities, regulation of cell fate, immunomodulation, tissue regeneration promotion, and hormone-like effects.

and races is needed to observe if other hormones are expressed in placental extracts.

Placental extracts are emerging as a revolutionary tool in bioengineering, regenerative medicine, and biomedical therapeutics. With their rich composition of growth factors, cytokines, nucleic acids, and bioactive peptides, placental extracts provide versatile applications in wound healing, tissue regeneration, dermatology, and reproductive health. Integrating bioprinting technology, hydrogel-based drug delivery systems, and scaffold-assisted regenerative medicine could further enhance their biomedical applications, paving the way for next-generation regenerative therapies, personalized medicine, and bioengineered tissue replacements.

7. Placental decellularized extracellular matrix

The development of bioengineered scaffolds has shown significant progress and widespread application. However, their ability to facilitate tissue regeneration is constrained by challenges related to immunogenicity and alignment with the mechanical and biochemical properties of native tissues and organs. Nevertheless, the emergence of decellularized ECM (dECM) scaffolds offers a promising solution. Decellularization is a meticulously controlled process aimed at all cellular components' removal, including cell nuclei and organelles, while retaining the structural and functional properties within the ECM [225,226]. The dECM authentically replicates the **3D** structures of native tissue and incorporates various bioactive components, providing an ideal non-immunogenic environment [227].

The placenta holds significant promise as a natural scaffold due to its abundant availability, robust vascular tissue architecture, and rich ECM [228]. A notable development occurred in 2003 with the first documented use of a decellularized human placenta as a vascular scaffold in tissue engineering [229]. This matrix comprises a range of collagen types, including I, III, IV, and VI, alongside non-collagenous glycoproteins and proteoglycans like fibronectin, fibrillin I, laminin, tenascin C, thrombospondin I, heparan sulfate proteoglycans, decorin, and elastin [230]. Moreover, the placenta tissue is rich in growth factors and cytokines that bind to the ECM [231]. This composition makes the ECM a valuable resource for various applications.

The main methodology for cellular extraction from tissue includes physical, chemical, and enzymatic techniques or a combination of these. Physical methods aim to enhance cell detachment by disrupting cell membranes. Commonly employed physical methods involve agitation, freeze/thaw cycles, and pressure application to facilitate detergent rinsing and cell removal. Chemical treatments represent another avenue for cell extraction, encompassing a diverse array of agents such as ionic and nonionic detergents, acid/base solutions, organic solvents, hypo- and hypertonic solutions, chelating agents, and non-denaturing detergents. These treatments are intended to disrupt chemical bonds and interactions among various macromolecules, thereby assisting in cell release. Enzymatic treatments offer a targeted approach by specifically addressing proteins and DNA within cells or cell-matrix interactions, thereby promoting cellular detachment [227]. Fig. 5 illustrates a variety of decellularization techniques used for decellularizing the placenta. While most of these methods can effectively remove cellular components and decellularize tissues, each can introduce specific disadvantages. For instance, mechanical forces and freeze-thaw cycles may rupture ECM structures, and SDS can disrupt collagen, fibronectin, and small bioactive molecules. Similarly, Triton X-100 might damage collagen and **GAGs,** whereas peracetic acid can denature ECM proteins, potentially compromising collagen integrity and reducing growth factor levels [232–236]. However, the concentration and duration of treatment with each of these components may significantly influence the extent of damage caused. Recognizing these potential impacts on the structure, components, and biomechanical properties of the ECM is crucial for optimizing decellularization protocols to preserve ECM integrity while effectively removing cells.

Following the decellularization, the resulting dECM can be transformed into different forms to provide the opportunity to re-engineer the desired microenvironment. These forms include whole organs, hydrogels, bioink for bioprinting, sheets, sponges, and electrospun nanofibers, either independently or in combination [237–242]. One of the most popular forms of dECM is hydrogel which is created by incorporating it into a polymer mixture, followed by crosslinking through the addition of an initiator. Alternatively, dECM can undergo self-assembly, a process dependent on temperature and composition [239,241,243]. Moreover, dECM can also be prepared as a printable ink to create various 3D

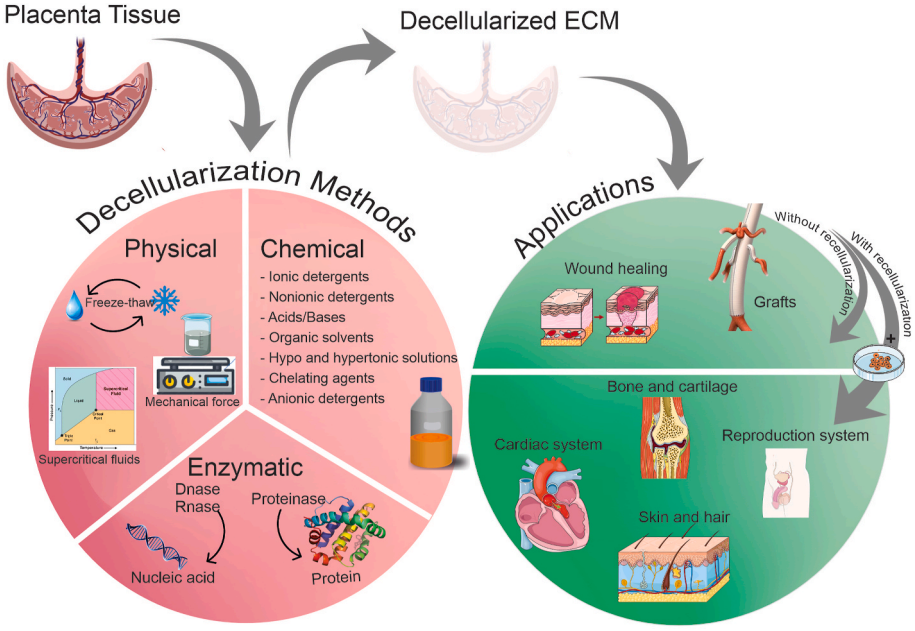


Fig. 5. Illustration of different placenta decellularization techniques and the applications of decellularized tissue in regenerative medicine. Placenta decellularization techniques include physical, chemical, enzymatic, or their combinations. Depending on its recellularization status, a decellularized placenta can be tailored for various regenerative medicine applications.

structures. Duan et al. [240] utilized human placenta-derived dECM as an ink for bioprinting, enabling the assembly of human umbilical vein endothelial cells and promoting angiogenesis in a mouse model. It can also be processed into nanoparticles or solubilized pre-gels, subsequently forming sheet-like structures upon gelification. Alternatively, a method involves cultivating a layer of cells that produce their own ECM, which can be decellularized to form sheets [244]. However, these forms can be further recellularized or used without cells as a supportive structure.

7.1. dECM application without in vitro recellularization

Since the composition of dECM, including some growth factors and ECM proteins, and its mechanical properties are mostly preserved, it can provide a potential environment for supporting cellular functions [245]. Another advantage of these structures is that they mitigate the challenges associated with long-term storage of cell-based structures and reduce their production costs [232]. The wound-healing properties of placental dECM have been validated through their involvement in skin regeneration and wound closure. Promising outcomes have been documented, encompassing successful migration of keratinocytes and epithelial cells, neovascularization promotion, and facilitation of wound closure following *in vivo* implantation in murine models [232]. In particular, a decellularized human placental sponge has shown great potential as an excellent carrier for human adipose-derived mesenchymal stem cells (MSCs), offering an ideal platform for both cell culture and efficient delivery to skin wounds in mice [246].

In line with these findings, scaffolds composed of sericin and placental dECM have been shown to reduce the size of excision wounds in rat models [247]. The combination of dECM with PEG-based hydrogels has shown significant potential for bone healing in porcine models [241]. Additionally, intact dECM, even before being converted to hydrogel form, can be used as a medical filler, for example, in repairing removed lymph nodes [248].

As another promising approach, decellularized vascular grafts derived from the human placenta, specifically those with diameters less than 1 mm, have been demonstrated in vascular grafting applications. This method shows potential in addressing the issue of host vessel mismatch observed in the arteriovenous loop model. The robust mechanical integrity exhibited by decellularized placental vessels, along with their proficiency in repairing vascular defects, suggests their potential as a viable therapeutic option for various arterial pathologies [249]. Moreover, injection of placenta dECM hydrogel into an ischemic myocardium model not only reduces scar formation but also preserves electrophysiological activity [248].

Additionally, scaffolds derived from the human placenta or bovine placentome can be employed in liver transplants to connect an auxiliary liver to systemic circulation or provide supportive hepatic tissue in the treatment of acute liver failure [250]. In a rat model, transplantation of hepatized bovine placenta maintained perfusion for up to one month. The liver tissue structure was reassembled, and hepatic function remained preserved [251].

7.2. dECM application associated with in vitro recellularization

Recellularization entails repopulating acellular ECM scaffolds from tissues or organs with specific cell types or stem cells. This method seeks to restore the organ's micro-anatomy and specific functions. The ECM, along with its remaining components such as growth factors and structural proteins, is vital in directing the arrangement and maturation of these cells. Notably, it is possible to reconstruct organs by cultivating organ-specific cells within ECMs derived from different organs [252–255]. Placental dECM has emerged as a promising candidate for regenerative medicine applications, owing to its ability to enhance cellular functions, including improved cell attachment and the promotion of endothelial cell formation [232].

In a study by Zhang et al. [243], co-grafting dermal papilla spheres cultured in placenta dECM hydrogel with mouse epidermal cells resulted in the regeneration of hair follicles. Furthermore, Pashuck et al. [256] demonstrated that human dermal cells adhered to and proliferated on the placental dECM, which subsequently stimulated the release of growth factors by the cells. Moreover, placental scaffolds facilitate the adhesion and differentiation of MSCs into chondrogenic and osteogenic lineages, thereby contributing significantly to cartilage and bone engineering [257]. Injectable connective tissue matrices derived from placental sources have also been observed to decrease de-differentiation and mitigate inflammatory responses, thereby promoting the growth and proliferation of tenocytes. These findings provide compelling evidence for the application of placenta-derived materials in tendon healing [225]. Rameshbabu et al. [258] demonstrated the significant impact of human placenta-derived ECM sponges, seeded with amniotic membrane-derived stem cells, on the repair of osteochondral defects in a rabbit model.

Furthermore, placental dECM incorporated into sponges has proven to be an exceptionally effective substrate for the growth and colony formation of spermatogonial stem cells [259]. Another application of the human placenta-derived dECM sponge in male reproduction is its ability to simulate environments like the testis, thereby enhancing the proliferation and differentiation of mouse spermatogonia cells [242].

An innovative approach involved the development of a bioengineered cardiac patch by seeding human-induced pluripotent stem cell-derived cardiomyocytes onto a decellularized placenta scaffold. This approach resulted in a reduction in infarct size, enhanced cell retention, and increased neovascularization following transplantation [228]. Additionally, the establishment of a cardiomyocyte culture system on human placenta-derived dECM enables the exploration of mechanisms underlying cardiac dysfunction, such as arrhythmia, within a 3D culture environment [260], as well as the elucidation of pathways involved in the development of cardiac stem cells [261]. Furthermore, it offers a practical method for screening cardiotoxins, thereby enhancing our understanding of cardiac health and advancing drug discovery efforts in cardiology [260,261].

The placenta-derived dECM can also serve as an effective model for mimicking materno-fetal interactions under physiological conditions, offering a valuable alternative due to the limitations of conducting *in vitro* experiments [262]. Recently, considerable efforts have been made to utilize dECM in developing on-a-chip toxicological models [237]. Moreover, the placenta-derived dECM use as a scaffold for adipogenic progenitors has demonstrated considerable potential in plastic surgery applications, thanks to its resemblance to the native adipose tissue environment [263].

8. Placenta- and placental cell-derived extracellular vesicles

Placenta-derived extracellular vehicles (PEVs) (cell-derived nano-sized particles that transport biomolecules), mainly produced by TCs, play a crucial role in mediating intercellular communication and placental development [264–266]. Notably, PEVs serve as valuable biomarkers for conditions such as pre-eclampsia and gestational diabetes [267,268]. EV membrane and its cargo offer promising targets for novel diagnosis and therapeutic strategies [269,270]. Trophoblast cell-released EVs contain various molecules, including proteins, nucleic acids, and lipids, influencing maternal-fetal communication and significantly contributing to the maintenance of pregnancy and fetal development [266,271]. EVs are formed through the creation of intraluminal vesicles (ILVs) within multivesicular bodies (MVBs), a process that can be either ESCRT (Endosomal Sorting Complex Required for Transport)-dependent or independent. The biogenesis of EVs begins with endocytosis, followed by the fusion of endocytic vesicles with early endosomes, which subsequently develop into MVBs. In the ESCRT-dependent mechanism, the assembly of this complex promotes ILV formation within the MVBs (Fig. 6) [272].

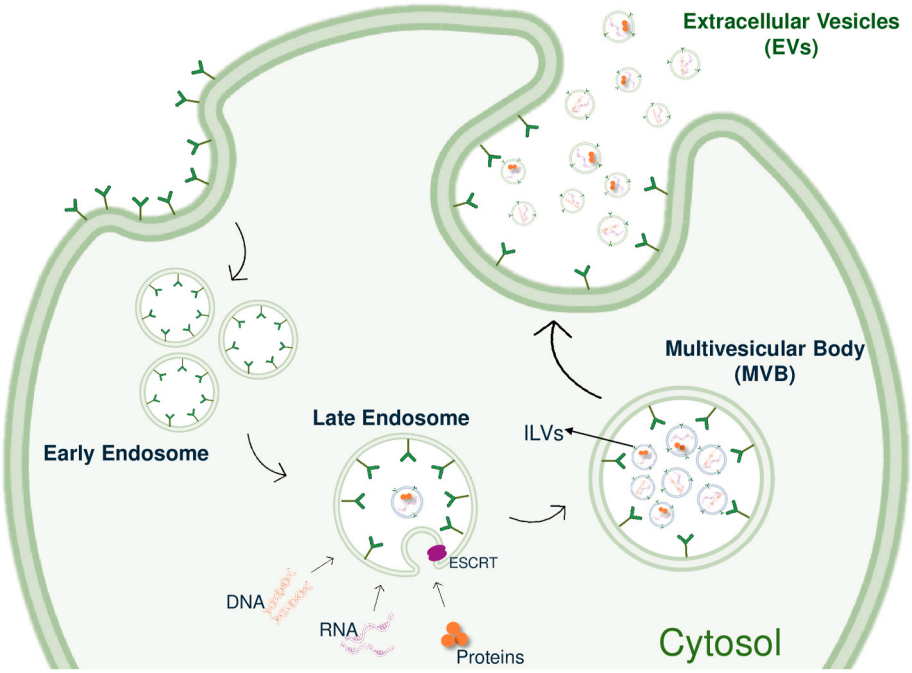


Fig. 6. Illustration of the formation of EVs through the endocytic pathway in placental cells. Endosomes are formed through the inward folding of the plasma membrane. MVBs are generated when these endosomes undergo invaginations of their membrane, leading to the ILVs formation inside. EVs are produced when these ILVs are released from the cells. Abbreviations: Extracellular vehicles, EVs; Intraluminal vesicles, ILVs; Multivesicular bodies, MVBs.

In most studies, PEVs are obtained from CM of placental cells after their *in vitro* culture. However, PEVs can also be directly isolated from peripheral blood circulation [273] or plasma [274], where they reflect the physiological state of the placenta *in vivo* during the pregnancy. Additionally, it is possible to isolate these vesicles directly dissociating the placental extracts, providing a more comprehensive profile of EVs present within the placental tissue [275]. PEVs, particularly from CM, allow for controlled study conditions, while those from plasma and placental extract offer insights into the *in vivo* environment, capturing the natural physiological state and interactions. PEVs can be invaluable tools in reproductive medicine, and research, acting as valuable biomarkers and a possible safeguard for the healthcare of women and babies.

8.1. PEVs immune modulation

EVs from placental cells have been shown to preserve the morphology and angiogenesis of the placenta, as well as improve preeclampsia symptoms [276], modulate immune response [277], and be used as a powerful research tool in regenerative medicine. EVs play a crucial role in mediating cell-cell communication, particularly in the context of maternal immune tolerance during pregnancy. PEVs are notably involved in modulating the maternal immune response to ensure a successful pregnancy. This modulation occurs through different pathways to ensure a successful pregnancy, by maintaining a balanced immune environment. The maternal immune system must be competent against pathogens yet tolerant to the fetus. PEVs contribute to immune tolerance and the prevention of adverse pregnancy outcomes by influencing several immune cell types [277]. Bai et coworkers demonstrated that human PEVs directly modulate monocytes via miRNA-29a-3p [278]. This miRNA has a suppressive effect on the PTEN signaling pathway, triggering PD-L1 expression in monocytes [278]. Additionally, these monocytes transition to an intermediate CD14+CD16 stage, enhancing their migratory and pro-inflammatory capacities [277]. Therefore, it is described that PEVs promote the polarization of macrophages to an M2 phenotype, which is known for its immunosuppressive properties [277,278]. This shift helps create a tolerant immune environment necessary for fetal development. T cells are another target of placental EV. PEVs directly isolated from peripheral circulation of pregnant women showed expression of FasL and TRAIL on their surface, promoting the apoptosis of Jurkat T and inhibiting T cell activation and proliferation by downregulating NF-κB, CD3ζ, and Janus kinase 3 [273]. This modulation helps reduce the maternal immune response against the fetus. It is described that immune tolerance by the placental EVs can also be regulated by different molecules, such as MHC, which help recognize and regulate immune responses [279]. These vesicles can also promote the differentiation of Treg cells [280]. On the other hand, a recent study suggests that miRNA-518-3p carried by PEVs may contribute to pregnancy complications by disrupting the balance of Th17/Treg differentiation and promoting Jurkat T cell proliferation [281].

NK cells, another abundant immune cell found in the mother's body, are also modulated by placental exosomes. These vesicles, carrying NKG2D ligand, are internalized by NK cells, reducing their cytotoxicity [279]. They also increase caspase-3 activity in $CD56^{dim}$ NK cells, inducing their apoptosis. PEVs are crucial for modulating the cytotoxicity of immune cells and inducing immune tolerance, further protecting the fetus from the mother's immune response [274,277]. Recently, Thiruvenkataraman et al., demonstrated that EVs derived from placenta MSCs have a protective effect against lung injury caused by lipopolysaccharide, by increasing the cellular viability of alveolar epithelial cells and modulating the release of pro-inflammatory cytokines such as IL-6 and IL-8 [282].

8.2. PEVs antiviral activity

By inhibiting T cell activation and promoting macrophage polarization, placenta-derived EVs have been described to confer antiviral potential to other cell types. Delorme-Axford et al. conducted a study where they cultured non-placenta cells with placenta-derived EVs and subsequently infected these cells with different viruses [283]. They observed a significant decrease in infection rate compared to cells that were not exposed to the EVs. Further analysis revealed that C19MC miRNAs, within the EVs, induced autophagy and antiviral response in the recipient cells. These miRNAs target specific mRNAs involved in

autophagy, leading to the activation of autophagy-associated genes [283,284]. Additionally, EVs derived from the plasma of pregnant women demonstrated a greater ability to decrease vesicular stomatitis virus infection compared to EVs from non-pregnant women, highlighting the enhanced antiviral properties of placental EVs [285]. All these findings suggest that placenta-derived EVs may play a crucial role in antiviral defense during pregnancy and show their potential use as antiviral therapies.

8.3. PEVs therapeutic applications in regenerative medicine

Placenta-derived EVs hold significant potential for therapeutic applications in regenerative medicine due to their unique properties and enrichment in growth factors, cytokines, and miRNAs that promote tissue repair and regeneration. EVs isolated from placenta extract have been identified as promising therapeutic candidates for osteogenesis and bone repair, by promoting chondrocyte migration and proliferation and reducing the inflammatory genes in a cellular model of osteoarthritis [275]. The research by Jia et al. demonstrated that exosomes from maternal and **UCBS** promote the proliferation and migration of endothelial cells [286]. For the first time, Go et al. studied the regenerative capacity of human trophoblasts as a cell-free EV therapy. They showed that EVs derived from trophoblasts were able to promote the rejuvenation, modulation of extracellular components expression, and chemokine activation in human skin fibroblasts highlighting their potential as anti-aging factors [287]. In addition to the trophoblasts, many studies have reported the importance of EVs secreted by placenta stem cells, such as TSCs and MSCs. Ni et al., demonstrated that TSC-derived EVs could attenuate cardiac injury in patients that are in cancer treatment with doxorubicin [288]. Numerous have highlighted the potential of MSC-derived EVs in regenerative medicine [289]. For instance, MSC-derived EVs have been shown to accelerate wound healing in keratocytes *in vitro* and in rat wound models, potentially by inhibiting the activation of engrailed-1 [290–292]. They have also been shown to protect neurons from damage in neurodegenerative diseases and promote differentiation and proliferation of neural stem cells, aiding in the repair of neural tissues [293–295]. Recently, Soleimani and colleagues demonstrated that EVs from placenta MSCs could improve functional recovery and prevent chronicity after spinal cord injury after injection in an animal model. The EVs diminished apoptosis of the neurons at the boundary of the injury, showcasing their neuroprotective properties [296]. Moreover, combining these EVs with hyperbaric oxygen therapy has been shown to significantly enhance sciatic nerve regeneration following injury in a rat model, promoting tissue repair and functional recovery [297].

Placenta MSCs-derived exosomes can also be used as anti-fibrotic agents. Zheng et al. used a liver organoid model for fibrosis cultured with EVs secreted from placental MSCs and observed attenuation of fibrotic phenotypes. They attributed this effect to miR-3378c which has the potential to inactivate hepatic stellate cells by inhibiting epithelial-mesenchymal transition thought the stabilization of E-cadherin [104]. Furthermore, within the reproductive system, placental EVs have demonstrated therapeutic potential in treating ovarian and endometrial cancer [298], as well as inhibiting the growth of prostate cancer cells [299]. Recently, Liu et al. demonstrated that placenta-derived EVs carrying miRNA-23a-3p, miRNA-125b-5p, and miRNA-30c-5p can downregulate the TGF-β/Smad pathway. By inhibiting this signaling pathway, these EVs reduced fibrosis, promoted endometrial thickening, and enhanced uterine receptivity, ultimately improving fertility outcomes [300].

8.4. PEVs as drug delivery systems

Vesicular nanocarriers have gained significant attention as efficient drug delivery systems due to their ability to encapsulate therapeutic agents and target specific tissues. These carriers can be classified into synthetic and natural types, with each offering distinct advantages in terms of stability, biocompatibility, and targeted delivery [289,301]. EVs derived from stem cells and other sources serve as natural vesicular nanocarriers, offering significant promise for drug delivery applications. These vesicles are demonstrating increasing therapeutic potential in the treatment of a wide range of disorders, thanks to their ability to encapsulate bioactive molecules and target specific tissues with minimal immunogenicity [289]. The unique characteristics of EVs make them ideal vectors for cell reprogramming, as they can selectively target specific cells and efficiently deliver their cargo. Their ability to transfer bioactive molecules, including proteins, lipids, and RNA, enhances their potential for precise modulation of cellular functions and therapeutic applications [275,298,302]. Numerous studies have explored the use of placenta-derived EVs as drug delivery systems, particularly for gene therapy applications aimed at altering the phenotype of target cells. These EVs offer a unique advantage due to their ability to carry genetic material, efficiently to specific cells, potentially enabling targeted and precise modifications in therapeutic interventions. Therefore, by modifying EVs-producing cells, researchers can engineer EVs with tailored cargoes, such as specific miRNAs or plasmids, capable of silencing interest genes in the target cells [303]. Recently, Kang et al. developed a protocol for the large-scale production of placenta-derived EVs and demonstrated efficient loading of plasmid DNA into these vesicles. This protocol not only addresses the challenge of scalable production but also ensures the functional integrity of the loaded genetic material [304]. Their findings corroborate the potential of placenta-derived EVs as versatile and effective drug delivery systems for gene therapy.

9. Amniotic and chorionic membranes

The human amniotic membrane (AM) and chorion constitute the fetal components of the placental membrane. The AM, which is in direct contact with the amniotic fluid, serves as the innermost layer, while the chorion is adjacent to the uterine lining. Transparent and lacking blood vessels, the AM typically ranges in thickness from 0.02 to 0.50 mm. It consists of five distinct layers: the epithelial cell layer, basement membrane, compact layer, fibroblast layer, and spongy layer. The compact, fibroblast, and spongy layers are collectively known as the stromal layers. The AM contains amniotic MSCs and AECs, which produce ECM, cytokines, and growth factors [305–307]. The epithelial layer is a single layer of cuboidal cells derived from the embryonic ectoderm. It synthesizes various enzymes and expresses antigens such as HLA I and CA125. Additionally, this layer secretes growth factors and cytokines, including EGF, HGF, bFGF, TGF-β1, TGF-β2, TGF-α, and keratinocyte growth factor, while also releasing cholinergic receptors, lysosomes, and other neurotransmitters that facilitate tissue regeneration [308].

The basement membrane possesses a considerable thickness and is composed of collagen types IV and VII, fibronectin, laminin, and hyaluronic acid, which promote cell migration and adhesion [309]. The stromal layer is avascular and contains high levels of TGF-β, anti-inflammatory factors (such as IL-1, IL-2, IL-8, IFN-γ, and TNF-β), anti-angiogenic proteins, and protease inhibitors. These components contribute to immune modulation and tissue repair. The compact layer contains type I and III collagen, providing mechanical strength, while the fibroblast layer contains macrophages and fibroblasts, which produce collagen fibers, elastic fibers, reticular fibers, and various glycoproteins and proteoglycans in the matrix [307]. Additionally, the spongy layer allows the human AM to glide over the chorion [310].

A thick basement membrane and avascular stroma are key AM structural features. The thick basement membrane facilitates epithelial cell migration, enhances basal epithelial cell adhesion, promotes epithelialization, and prevents epithelial cell apoptosis. The avascular stroma prevents the excessive formation of fibrous scar tissue and controls the occurrence of immune rejection responses.

The chorion, thicker than the amnion, comprises the reticular layer, basement membrane, and trophoblast layer, which attach to the decidua

[311,312]. The reticular layer consists of collagen types I, III, IV, V, and VI and contacts the amniotic spongy layer. The basement membrane contains collagen IV, fibronectin, and laminin, anchoring the trophoblast layer to the reticular layer. The trophoblast layer interfaces with the decidua [313,314]. The chorion is a significant source of growth factors, cytokines, MSCs, and ECM proteins, including tissue inhibitors of metalloproteinases that inhibit matrix metalloproteinases [315–317]. It also contains various immunomodulatory molecules, such as IL-10, TGF-β, and HLA-G, which help suppress the maternal immune response, protecting the fetus from rejection [318]. While the placental membranes have been extensively researched and used clinically as a whole, independent evaluations of the chorion's potential value are limited.

9.1. Advancements in AM modifications for biomedical engineering

The rapid degradation rate and limited mechanical properties of natural AM restrict its clinical applications. Various physical, chemical, and biological modifications have been employed to enhance the mechanical stability, biocompatibility, and bioactivity of human AM. Cryopreservation and lyophilization are common AM preservation techniques; however, both methods preserve AM along with its epithelial layer, which may be more immunogenic. This limits its application in cell culture and tissue regeneration, as the presence of epithelial cells may hinder cell migration and differentiation on AM [319]. One approach to overcoming this limitation is AM decellularization, which removes cells and cellular debris while preserving ECM structural proteins. This process reduces antigenicity while maintaining the structural and bioactive properties of ECM, thereby retaining human AM's potential for recellularization. Decellularized AM, also referred to as a "scaffold", is recognized for its porous structure and bioactive molecules, which make it an ideal biological scaffold by minimizing immunogenic responses and the risk of disease transmission [320].

Several decellularization methods have been developed using EDTA, trypsin, dispase, urea, Triton X-100, and thermolysin. It is crucial to ensure that the chosen method preserves the biomechanical and physicochemical properties of the ECM to maintain its regenerative potential. However, decellularization also leads to the removal of growth factors from AM, thereby diminishing its natural reparative properties. Crosslinking is one of the strategies used to enhance the stability of AM by improving its mechanical properties and biodegradation rate. Crosslinking techniques for AM can be categorized into chemical crosslinking (e.g., glutaraldehyde [321], 1,4-butanediol diglycidyl ether [322] and 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC)/N-hydroxysuccinimide (NHS) [323]), physical crosslinking (e.g., ultraviolet or gamma radiation [324], and dehydrothermal treatment [325]), and enzymatic crosslinking (e.g., transglutaminase crosslinking [326]). Crosslinked AM has demonstrated promising applications in ocular surface repair, wound healing, vaginal tissue engineering, and bone tissue engineering. For instance, EDC/NHS crosslinked AM exhibits enhanced mechanical strength, reduced degradation rates, and improved corneal regeneration capacity [327].

Electrospinning, a physical modification technique, enhances human AM's mechanical strength and structural integrity, making it suitable for load-bearing scaffold applications [328]. Electrospinning is an advanced technology that mimics the natural ECM by producing scaffolds with fibers ranging from nanometers to micrometers in diameter, closely resembling ECM fibers. Lotfi et al. [329] fabricated an innovative polycaprolactone (PCL)/AM scaffold via electrospinning, where AM was incorporated into PCL nanofibers, leading to improved tensile strength, cellular viability, proliferation, adhesion, and elastic-plastic behavior.

3D printing and rapid prototyping technologies have also emerged as alternative approaches for scaffold fabrication. For example, Dehghani et al. [330] developed a 3D-printed biomembrane composed of gelatin, elastin, and sodium hyaluronate, which was compared with native AM for conjunctival reconstruction in a rabbit model. This approach exhibited more predictable degradation patterns, reduced inflammation, and decreased scar tissue formation. However, 3D-printed biomembranes still face challenges in replicating the multi-layered ECM structure of AM, as post-printing issues such as interlayer delamination and morphological instability may affect their long-term performance. Lyophilization is another widely used technique that preserves the ECM structure while maintaining porosity, which facilitates cell infiltration and tissue integration. Niknejad et al. [331] demonstrated that lyophilized AM significantly improved endothelial cell adhesion and viability.

AM-based hydrogels, derived from decellularized tissue, are typically composite hydrogels in which AM is modified by crosslinking its proteins with various synthetic or natural chemical agents. Compared with AM or decellularized AM, AM-based hydrogels offer several advantages, including greater stability, ease of handling, suitable mechanical properties, and uniform composition. Various fabrication methods for AM-based hydrogels have been reported, and their integration with 3D printing and nanotechnology has been explored. G. Kafili et al. developed a printable, nanoengineered composite hydrogel based on human AM, supplemented with sodium alginate and Laponite nanosheets, highlighting its therapeutic potential for wound healing applications [332].

In addition to physical modifications, chemical treatments such as redox processing, enzymatic digestion, and growth factor immobilization have been investigated to tailor human AM's biological properties. These approaches allow precise control over its degradation rate, cell adhesion properties, and immunogenicity, thereby facilitating targeted tissue regeneration. Moreover, biological modifications, including enzyme-mediated ECM remodeling, MSC seeding, and genetic engineering, enhance human AM's regenerative potential by promoting ECM remodeling in response to specific tissue microenvironments. Overall, these advancements significantly expand human AM's applications in wound healing, ophthalmology, soft tissue repair, and nerve regeneration, reinforcing its value as a next generation bioengineered therapeutic material.

9.2. a.m. application in ocular surface reconstruction

The use of the AM in ocular surface reconstruction has been studied for decades and has shown significant efficacy in treating various ocular surface diseases due to its unique biological properties. The AM shares structural similarities with human conjunctival tissue and contains essential substances for conjunctival and corneal epithelial cell growth. It is smooth, avascular, neural, and elastic, providing high safety, repair scaffolding, anti-inflammatory, antibacterial, tissue repair promotion, scar formation inhibition, and semipermeable membrane functions [333]. Consequently, AM is widely used in ocular surface reconstruction [334,335], including conjunctival reconstruction (for pterygium [336], acute Steven-Johnson syndrome [337], conjunctival tumors [338], symblepharon [339], and ocular surface squamous neoplasia [340]), corneal reconstruction (for persistent corneal epithelial defects [341], neurotrophic corneal ulcers [342], infectious keratitis [343], bullous keratopathy [344], and chemical burns [345]), limbal stem cell reconstruction [346], and glaucoma surgery [347].

The first documented use of AM in ophthalmology was by de Rotth in 1940 for conjunctival defect repair [348]. However, the initial application faced setbacks due to immune rejection caused by the highly antigenic chorion, leading to transplantation failure. The resurgence of AM in ophthalmology occurred in 1995 when Kim and Tseng reported successful ocular surface reconstruction using modified and preserved AM [349].

In AM transplantation, the primary function of the AM graft is to provide a basement membrane that supports the growth of ocular surface epithelium, thereby facilitating ocular surface reconstruction. The AM basement membrane closely resembles the ocular surface epithelial basement membrane, promoting epithelial cell migration, inducing differentiation, and preventing apoptosis [350–352]. When used as a

covering, AM protects new epithelial tissue from eyelid abrasion and reduces contact between inflammatory cells, tear proteins, and the corneal stroma [353]. Additionally, AM secretes various growth factors that promote epithelial growth and contains neurotrophic factors beneficial for corneal nerves [354]. Moreover, AM can suppress IL expression, modulate inflammatory chemokines, induce polymorphonuclear cell apoptosis, and reduce the expression of corneal matrix metalloproteinases 1, 2, and 9, thus mitigating corneal inflammation and preventing corneal melting. By inhibiting the mRNA expression of TGF-β, AM reduces fibroblast activity, thereby minimizing corneal scarring [355]. The anti-angiogenic proteins in AM, including thrombospondin-1, endostatin, and all four tissue inhibitors of metalloproteinases (TIMP-1, 2, 3, and 4), help inhibit neovascularization [356]. The absence of HLA-A, B, C, and DR antigens and β2-microglobulin in AM results in low antigenicity and minimal rejection in allogeneic transplantation [357].

Recent advancements in bioengineering have led to the development of engineered AM to optimize its physical and biological properties, enhancing its efficacy in ocular surface reconstruction. For instance, a novel 3D biomimetic corneal model combining corneal cells and multilayer ultra-thin AM has been developed, allowing corneal stromal-like tissue maturation *in vitro* [358]. Additionally, AM extracts are being studied for use in eye drops or gels for ocular surface disease treatment. Studies have shown that eye drops containing AM extract can significantly reduce inflammation, indicating promising clinical applications [359].

In recent years, the development of engineered amniotic membranes (EAMs) has emerged as a crucial strategy for enhancing the therapeutic efficacy of AM-based treatments. The application of nanotechnology and growth factors in biomedical research has introduced new possibilities for EAMs. For instance, AM loaded with silver nanoparticles exhibits excellent antibacterial properties, accelerates wound healing in rat burn models, and reduces the risk of postoperative infections [332]. Similarly, EAMs incorporating zinc oxide nanoparticles or titanium dioxide nanoparticles not only enhance antimicrobial activity but also generate reactive oxygen species upon UV light exposure, thereby improving membrane stability and resistance to degradation [360,361]. Additionally, AM combined with EGF has been shown to promote corneal epithelial cell proliferation and accelerate wound healing [362].

The application of commercial EAMs in ocular surface reconstruction has become increasingly well-established, with products such as PROKERA®, AmbioDisk®, Omnigen®, and Aril® gaining clinical adoption. PROKERA®, developed by Bio-Tissue, is a commercial AM-based bioproduct that integrates cryopreserved AM with a biodegradable polycarbonate ring scaffold. It can be directly applied to the ocular surface and has been approved by the FDA for the treatment of corneal injuries, dry eye syndrome, chemical burns, and other ocular surface disorders. Compared with traditional AM transplantation, commercial AM products (e.g., PROKERA®) exhibit significant anti-inflammatory, anti-scarring, and pro-healing effects in ocular surface reconstruction. However, challenges remain regarding their cost, comfort during wear, and broader clinical applicability, necessitating further optimization [363].

9.3. a.m. application in vaginal reconstruction

AMs are ideal grafts for vaginal reconstruction surgery, used to create a new vagina, and they show promising prospects due to their anti-inflammatory, anti-fibrotic, and wound-healing properties, as well as their ability to promote epithelialization. In the 1980s, researchers began exploring the application of AM in vaginal reconstruction [364,365], particularly in the treatment of patients with Mayer-Rokitansky-Küster-Hauser syndrome (MRKH), a condition characterized by the absence of a uterus and vagina. Treatment typically involves surgically creating a new vagina and it serves as biologically active dressings or grafts, facilitating vaginal epithelium growth and enhancing tissue integration. This approach facilitates the development of a functional vaginal lining, providing a promising alternative to traditional techniques and demonstrating success in clinical practice. A retrospective 6.5-year study included 50 MRKH patients who underwent vaginoplasty, resulting in high postoperative satisfaction [366].

AMs present a compelling alternative for graft selection. Unlike skin grafts [367] and autologous buccal mucosa grafts [368], which may cause additional trauma, and autologous *in vitro* cultured vaginal tissue [369], which is costly, AM are low-cost, widely available, and easy to handle during surgery. They have proven effective in achieving complete epithelialization of vaginal tissue, particularly beneficial in developing countries. However, it is essential to recognize the risk of viral infection transmission, necessitating thorough screening before the procedure [323].

9.4. Amnion/chorion membrane as scaffolds in tissue engineering

Tissue engineering aims to induce tissue growth by combining cells, scaffolds, and growth factors or biomolecules. An ideal scaffold should exhibit appropriate biocompatibility, biodegradability, and sufficient mechanical strength. Additionally, a porous structure is advantageous for facilitating cell attachment and proliferation. Depending on specific requirements, scaffolds can carry and gradually release growth factors to promote cell proliferation, differentiation, tissue regeneration, and support angiogenesis [370].

As a surgical waste product, the AM presents advantages in terms of easy accessibility, low cost, and free from ethical concerns. Human AM demonstrates outstanding biocompatibility and low immunogenicity, making it less likely to cause immune rejection upon transplantation and allowing for good integration with host tissues. The AM is rich in anti-inflammatory factors (such as IL-10 and TGF-β) and anti-fibrotic factors (tissue inhibitors of metalloproteinases), which can suppress inflammatory responses and excessive fibrous tissue proliferation, promoting normal tissue healing [371]. The presence of immunoregulatory molecules in the AM, such as HLA-G and Fas ligand [372], along with low or absent expression of HLA class I and II molecules [373], can reduce post-transplant immune rejection, enhancing the biocompatibility of tissue-engineered materials. Studies have shown that fresh, preserved, or bone-differentiated AM exhibits biocompatibility and induces lower inflammatory responses compared to controls [374,375].

AM can serve as a scaffold to promote the proliferation of various stem cells. For instance, it has been used to culture corneal limbal stem cells, oral epithelium, urothelial cells, chondrocytes, and bladder and vaginal epithelial cells. With its structural similarity to normal human skin, the AM can function as a scaffold for living skin, serving as a biological dressing for treating skin injuries and burns while demonstrating efficacy in wound healing [376]. One study indicated that human AM containing AECs and amniotic MSCs exhibited appropriate blood compatibility [377].

AM is rich in cytokines and growth factors which promote cell proliferation, differentiation, and migration, contributing significantly to tissue regeneration. In tendon repair, AM supports the attachment and proliferation of various cell types at epithelial and stromal sites, facilitating the transfer of autologous/allogeneic cells [378]. Moreover, AM has demonstrated efficacy in promoting skin regeneration showing efficacy in wound healing, burns, junctional epidermolysis bullosa, urethral defects, and calcification defense [379]. It has also been observed that human AECs can differentiate into stratified epithelium on the de-epidermized dermis, indicating their potential role in skin regeneration [380].

As a nerve regeneration scaffold, human AM has shown the ability to promote regeneration in damaged nerves. Human AECs can increase the survival rate of neural stem cells, induce their proliferation and differentiation, and promote the growth of primary neurites, exhibiting significant pro-survival and pro-regeneration effects on neural cells [381]. Additionally, these cells can regulate the expression of miR-141 and

mediate miR-410 inhibition, thus promoting axonal regeneration in dopaminergic neuron-like cells and retinal ganglion cells, respectively [382,383]. In the domain of angiogenesis, human AECs have displayed significant pro-angiogenic effects *in vitro* under hypoxic conditions by expressing angiogenic cell-activity factors, owing to their anti-inflammatory and regenerative properties. However, the underlying mechanisms of these effects are yet to be fully elucidated [384].

Studies have shown that decellularized human chorion membrane exhibits noteworthy biocompatibility when implanted subcutaneously *in vitro* and *in vivo*, making it a promising scaffold for tissue engineering [385]. This approach can prevent unfavorable interactions between cells and the host while preserving crucial ECM proteins such as collagen types I and IV, fibronectin, and laminin, according to *in vitro* research. Notably, removing cellular components during the decellularization process is essential for reducing immune rejection responses. In contrast, using intact chorion as in ophthalmology application can provoke adverse immune reactions, as the host immune system recognizes the remaining cellular elements as foreign tissue [386]. This distinction underscores the critical role of decellularization in improving the biocompatibility of chorion-derived scaffolds. Furthermore, decellularized ECM scaffolds derived from human chorion have been found to support the tight adhesion and osteogenic differentiation of human placental MSCs, while offering potential as a versatile tool for vascularization experiments and as a potent graft material for future *in vivo* applications [387,388].

9.5. Lyophilized placental composite sheets

It is essential to note the potential of human AM in preparing lyophilized placental composite sheets, a biomaterial processed through lyophilization that incorporates AM and placental tissue. These sheets retain the bioactivity of growth factors, cytokines, anti-inflammatory, and immunoregulatory factors, and exhibit good biocompatibility and storage stability. Deegan et al. developed a lyophilized placental composite as a tissue graft in wound care to promote wound healing and tissue regeneration. This composite sheet, including amniotic and processed chorionic layers, is prepared by lyophilization to retain the biological activity of its components. These properties support cell attachment, viability, and proliferation, making it a promising approach for supporting tissue regeneration. Additionally, compared to thermal drying, lyophilization retains higher levels of essential growth factors such as HGF, PDGF, bFGF, and EGF [389]. Therefore, the innovative use of lyophilized placental composites presents a significant advancement in tissue engineering and regenerative medicine.

9.6. Dehydrated human amnion/chorion membrane allografts

Research increasingly provided evidence supporting the clinical efficacy of dehydrated human amnion/chorion membrane (dHACM) in facilitating the healing process of surgical or chronic wounds. Notably, dHACM has been observed to promote the proliferation and migration of periodontal ligament-derived cells and angiogenesis, facilitating periodontal healing [390]. Furthermore, dHACM has exhibited the capacity to enhance the healing of partial-thickness burns, venous leg ulcers, and diabetic foot ulcers, reducing scar formation [391–393]. The use of dHACM allografts has demonstrated notable improvements in wound healing associated with dermatological conditions, reduced wound pain, increased convenience of wound dressing, and lower infection risks [394]. In a study conducting a propensity score matching analysis on 58 patients who underwent nerve-sparing robotic-assisted laparoscopic radical prostatectomy with the placement of dHACM around the neurovascular bundles. The implantation of dHACM contributed to the early recovery of urinary and sexual function, and no adverse reactions, which is undoubtedly promising [395]. Moreover, dHACM patches to reinforce esophageal anastomoses after esophagectomy may help reduce esophageal anastomotic complications [396]. dHACM has demonstrated biocompatibility and efficacy in various clinical settings, and its future applications may extend beyond wound healing and tissue regeneration to areas such as organ repair, nerve regeneration, and the treatment of complex surgical defects. The inherent properties of dHACM, including its ability to retain bioactive factors, suggest its potential utility in regenerative medicine, particularly for conditions that require enhanced angiogenesis and cell proliferation. Standardized processing protocols, thorough characterization, and multicenter long-term clinical trials are necessary steps to optimize and promote its application, maximizing the potential of dHACM in biomedical research.

10. Amniotic fluid and its derivatives

Amniotic fluid (AF) is a bioactive fluid that is abundant in growth factors (FGF, EGF, TGFβ), ECM proteins, and anti-inflammatory agents (Fig. 7). It plays a crucial role in processes such as wound healing, tissue regeneration, fibrosis attenuation, and antimicrobial defense [397]. The composition of AF dynamically changes throughout gestation, providing essential support for fetal development and protection [398–400]. In the early stages of pregnancy, AF primarily consists of water, electrolytes, and proteins derived from maternal serum [399,401]. As pregnancy progresses, AF increasingly resembles fetal extracellular fluid due to the production of fetal urine (600–1200 mL/day) and pulmonary secretions (60–100 mL/kg/day) [402–404]. The volume of AF peaks at around the 33rd week of gestation before gradually decreasing [405]. AF serves to deliver nutrients, growth factors, and antimicrobial components, while also preventing umbilical cord compression and minimizing fetal-maternal friction [399,406]. Furthermore, AF promotes fibroblast attachment and collagen secretion through adhesion proteins such as fibronectin [407]. AF derivatives, including stem cells and exosomes, further support tissue repair and modulate inflammatory responses.

10.1. Biomedical applications of amniotic fluid

Despite its relative underutilization compared to other placental-derived materials, AF demonstrates considerable therapeutic potential in fields such as orthopedics, neurology, cardiology, and wound healing. It has been shown to accelerate bone repair [408] and foster cartilage regeneration. In the field of neurology, AF has been observed to reduce nerve scarring and promote regeneration in spina bifida models [409–411], nerve tissue regeneration [412], and prevention of epidural fibrosis [413].

In cardiovascular applications, AF provides protective effects to the heart following injury [414], reduces inflammation, and enhances elasticity in vocal fold therapy [415]. Furthermore, AF has been shown to protect bone marrow-derived stem cells from radiation-induced damage [416], preserve its antimicrobial properties after processing [417], and alleviate inflammation induced by colitis [418]. Moreover, AF plays a role in preserving tear secretion in chronic graft-versus-host disease [419] and stimulates hair growth while mitigating inflammation in models of hair loss [420].

10.2. Amniotic fluid and bioengineering

AF plays a pivotal role in regenerative medicine and the development of biomaterials. Electrospun silk fibroin-alginate hydrogels incorporating AF have been shown to enhance wound healing by promoting fibroblast activity [421]. AF has also demonstrated its potential in preventing scarring during fetal wound healing, making it a promising candidate for scar-free tissue repair [422]. AF-derived nanofibers exhibit superior mechanical properties, including stiffness and strength, when compared to AMs, while maintaining flexibility [423]. Chick-derived AF plays a significant role in epidermal barrier formation, although its effects are diminished under heat exposure [424]. Furthermore, AF is involved in the development of the fetal larynx and the separation of the vocal folds [425], and its use has been proposed to

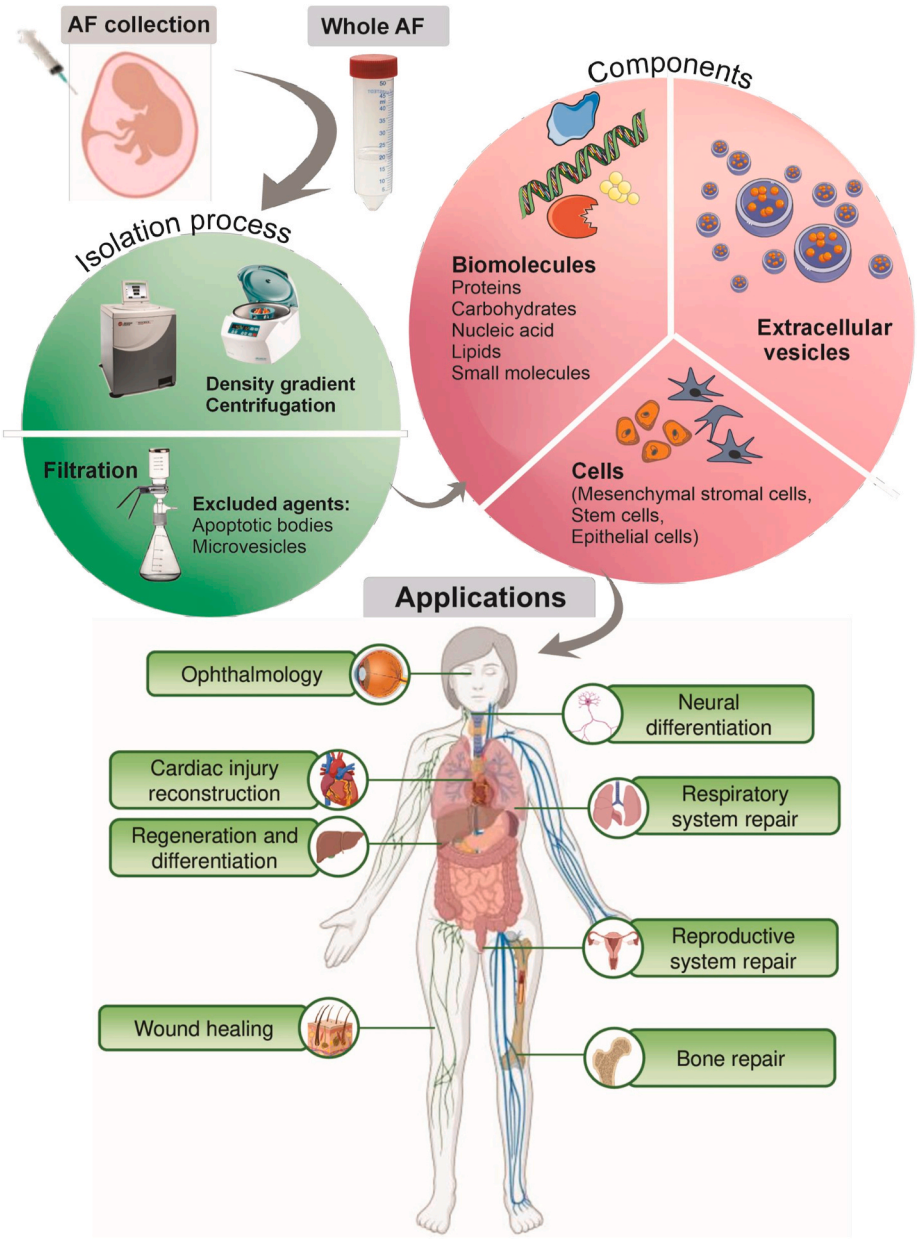


Fig. 7. Sampling, isolation, components, and applications of AF derivatives. Comprehensive overview of AF derivatives, including the processes of sampling and isolation, characterization of key components, and their diverse therapeutic and biomedical applications. Abbreviation: Amniotic fluid, AF.

improve the viscoelasticity of vocal folds in therapeutic applications [415]. AF progenitor cells, when combined with transglutaminase FXIII-modified PEG hydrogels, hold promise for use in bone replacement applications [426]. AF-based biomaterials, including patches, have been proposed for the treatment of neural tube defects [427]. Preliminary studies using ovine models have demonstrated the feasibility of prenatal implantation of tissue-engineered heart valves comprising biodegradable matrices seeded with autologous amniotic fluid cells. These valves exhibited functional integrity and were thrombosis-free *in vivo* [410].

10.3. Amniotic fluid-derived stem cells

AF-derived stem cells (AFSCs) possess significant regenerative capacity and have been investigated for a wide range of therapeutic applications (Table 2). They have been shown to facilitate myocardial regeneration [428], protect against renal ischemia-reperfusion injury [429], and are under investigation for potential treatments for ovarian dysfunction and infertility [430]. During the COVID-19 pandemic, AFSCs exhibited immunomodulatory effects, including the reduction of viral-induced lung damage [431]. In musculoskeletal regeneration, AFSCs contribute to the repair of large skeletal defects by promoting bone and cartilage formation [432]. In models of fetal myelomeningocele, intra-amniotic injections of AFSCs improved skin defect closure, promoted neurogenesis, and reduced astrogliosis, highlighting their potential in treating congenital neural defects [433,434].

10.4. Amniotic fluid stem cell-derived extracellular vesicles

AFSCs-derived EVs have demonstrated diverse applications in biomedical research across various physiological systems and pathological conditions (Table 2). In azoospermia models, AFSC-EVs have been shown to restore spermatogenesis and testicular function [435]. In chick embryo models of autism, AFSC-EVs facilitate the delivery of sulforaphane for gene regulation [436]. In neonatal hypoxic

Table 2
AF derivatives applications in biomedical research.

AF Derivative	Area	Condition	Model	Advantages	Ref.
AFSC	Heart	Cardiomyoplasty	Rat	Exhibiting some electrophysiological properties	[428]
	Kidney	Acute ischemia-reperfusion Acute tubular necrosis	Mice	Ability to differentiate into kidney cells	[429]
	Female reproductive	Dystrophy and fertility	Cow	Alleviating bovine ovarian dystrophy and restoring fertility	[430]
	Musculoskeletal	Muscular dystrophy	Mice	Cell therapy for the damaged sphincter	[441]
	Lung	COVID 19	Mice	Adaption to different lung injuries by expressing specific markers	[431]
	Bone and cartilage	Extensive bone defect disease	Rat	Correcting large cranial defects; neovascularization during skeletal defect reconstruction	[432]
	Brain	Cerebral ischemia	Rat	Tissue engineering; therapeutic cell transplantation	[442]
	Fetal	Congenital diaphragmatic hernia abdominal Congenital heart	Rat	Effective treatment for myelomeningocele	[443, 444]
	Inflammatory and autoimmune diseases	Inflammatory bowel disease Systemic lupus erythematosus Encephalomyelitis	Mice	Modulating cellular immune response; distancing organ damage during sublethal endotoxemia	[445]
AF-EVs	Testis	Azoospermia	Rat	Enhancing spermatogenesis and sperm quality Increasing testicular function	[435]
	Pregnancy	Preeclampsia (PE)	Rat	Promoting trophoblast proliferation via miR-146a-5p, and protecting against PE	[446]
	Brain	Autism	Chick embryo	Effective drug delivery vehicles; successful unloading of sulforaphane resulted in gene expression regulation	[436]
	Lung	Bronchopulmonary dysplasia	Rat	Enhancing pro-inflammatory cytokines production Reducing free-radical quenching Conserving alveolar growth	[438]
		Neonatal hypoxic encephalopathy	Mouse	Improving angiogenesis Increasing performance of the spatial memory Eased hypoxic encephalopathy	[437]
AFSC-EVs	Female reproductive	Ovarian failure due to chemotherapy	Mice	MiR-146a and miR-10a dominant effect on reducing apoptosis in ovarian cells	[447]
				miR-369-3p down-regulated apoptosis of ovarian granulosa cells	[448]
			Rat	Restored total follicular counts, anti-Müllerian hormone levels, regular estrous cycles and conception; EV-borne miRNA-21 acts by regulating PTEN and caspase 3 apoptotic pathways	[449]
	Brain	Ischemic stroke	Rat	Activated anti-apoptotic and pro-survival pathways	[450]
		Alzheimer's disease	Murine	Enhancing progression of Amyloid-β-induced neuronal death and ↑Neuron morphology and viability	[451]
			Human	Declining neuroinflammation, significantly recovering cells from neurotoxicity	[452]
		Multiple sclerosis	Mouse	Educate type conventional dendritic cells to rescue autoimmune disorders	[453]
		Neural Tube Defects (NTDs)	Mouse	As potential therapeutics for NTD prevention	[454]
	Lung	Fetal pulmonary hypoplasia	Rabbit	Modulating gene expression Increasing branching morphogenesis alveolarization Enhancing cellular homeostasis and tissue maturation	[439]
			Rat	Improving airspace density and branching morphogenesis promoting differentiation of lung cells during both canalicular and saccular stages of fetal lung development	[440]
		Oligohydramnios-induced lung hypoplasia	Rat	Increasing airspace, lung branching, modulating TGF-beta signaling via miR-93-5p	[455]
		Nitrofen and bisdiamine-exposed fetal lungs	Mouse	Improving lung branching, angiogenesis, reduced fetal lung inflammation	[456]
	Gastrointestinal	NEC	Rat	Declining incidence and disease severity of experimental necrotizing enterocolitis	[457]
				Reducing bowel condition	[458]
			Mouse	Reducing intestinal injury and inflammation Enhancing Intestinal cell proliferation	[459]
				Declining Intestinal injury and NEC score Reducing NEC-associated brain injury Declining systemic and ileal inflammation	[460]
	Heart	Cardiac injury	Mouse	↑Tissue regeneration	[461]
			Rodent	Maintained myocardial renewal with significant improvement of cardiac function	[462]
		Ischemia-reperfusion injury	Rat	Enhancing Cardio-protection and angiogenesis	[463]
		Cardiac fibrosis	Rat	Improving angiogenesis	[464]
		Myocardial infarction	Mouse	Enhancing cardiomyocyte renewal and cell cycle re-entry	[465]
	Inflammatory and metabolic disorders	IBD	Human	Regulating inflammatory cytokines	[466]
		Cystinosis	Mice	Reducing Lysosomal cystine accumulation in target cells	[467]
		Osteoarthritis	Rat	Produced near-complete restoration of cartilage Polarized macrophages into EV-treated knee joints	[468]
		Neuromuscular junction integrity during muscle atrophy	Human	Declining disease progression	[469]
		Alport Syndrome	Mice	Reducing cellular damage Demonstrating glomerulus-targeted disease intervention	[470]

(*continued on next page*)

Table 2 (*continued*)

AF Derivative	Area	Condition	Model	Advantages	Ref.
	Wound healing and tissue regeneration	Wound healing	Rat	Enhancing Wound healing rate ↑Regeneration of hair follicles, blood vessels and nerves. ↑Cutaneous cell proliferation and collagen distribution Reducing scar formation and fibrosis	[471] [472]

Abbreviations: Amniotic fluid, AF; Amniotic fluid-derived stem cell, AFSC; Amniotic fluid stem cell-derived extracellular vesicle, AFSC-EV; Inflammatory bowel disease, IBD; Necrotizing enterocolitis, NEC.

encephalopathy, AFSC-EVs promote angiogenesis and improve cognitive function in mice [437]. They also reduce inflammation and oxidative stress while promoting alveolar development in models of bronchopulmonary dysplasia [438]. Furthermore, in models of fetal pulmonary hypoplasia, AFSC-EVs support lung maturation and maintain cellular homeostasis in rabbits [439] and enhance lung differentiation in fetal rats [440]. These findings underscore the regenerative and immunomodulatory potential of AFSCs and AFSC-EVs across a range of biomedical applications.

11. Challenges and future perspectives

One of the significant hurdles in utilizing placental derivatives for research lies in the intricacies of replicating its complex and dynamic nature and accounting for donor-to-donor variability. Researchers often address this challenge by pooling tissues obtained from multiple donors to achieve a more representative sample [473]. Another critical issue in the use of placental derivatives in biomedical research is the sterilization process, which requires meticulous attention to avoid compromising the material's integrity and functionality. To ensure the validity and safety of employing these biomaterials, it is imperative to assess their cytocompatibility via *in vitro* cytotoxicity assays. Additionally, their biocompatibility should be evaluated through *in vivo* tests such as subcutaneous implantation. These assessments have been conducted in numerous experiments involving prenatal derivatives, such as chorion membrane and human-derived placenta dECM [474].

Regarding the placental dECM, the decellularization process can affect the structure and the ECM composition [475–477]. Therefore, the concern about using this approach in biomedical applications is the bioactivity of scaffolds. Research on the structure and composition of the ECM post-decellularization has been conducted on various species, including rodents [478,479], canines [480,481], bovines [482,483], and humans [240], highlighting both preserved elements and alterations in the ECM components across different protocols and species. Most studies indicate that the integrity and basement membrane proteins are generally preserved [240,484]. These findings are consistent with those reported by other groups regarding the composition of decellularized human placenta and chorion membranes [232,485]. On the other hand, the decellularization of bovine cotyledons results in no significant difference in ECM protein compared to native tissue [233]. However, some studies have shown a reduction in ECM proteins and the absence of certain cytoplasmic proteins and enzymes in decellularized tissues treated with Triton or SDS. Given the significant influence of ECM architecture and composition on biological activities, such as cell differentiation, proliferation, and migration, ongoing efforts are focused on identifying optimal protocols with minimal destructive effects [476]. Therefore, it is crucial to identify and optimize decellularization methods that maintain the essential characteristics of the ECM to ensure its effectiveness in biomedical applications. Moreover, addressing issues related to the heterogeneity, handling, and plasticity of dECM holds significant promise for future breakthroughs in regenerative medicine.

Looking forward, advancements in bioengineering and material sciences will likely play a critical role in overcoming current limitations. As research progresses, developing standardized protocols and comprehensive guidelines will be essential to mitigate these challenges and harness the full therapeutic potential of placental derivatives. Innovations such as bioprinting, improved decellularization techniques, and enhanced recellularization strategies are expected to enhance the functionality and applicability of placenta-derived biomaterials.

Although the application of placental stem cells in medicine has great potential, several issues need to be carefully considered, particularly in preclinical research. The ability to differentiate stem cells into distinct specialized cell types has advanced quickly, yet existing standard techniques frequently result in mixed populations of cells. One of the biggest obstacles still stands in the way of producing these specialized cells in the required quantity and purity. Furthermore, converting this promise into a therapeutic reality requires a thorough grasp of the intricate mechanisms at play, from cultivating stem cells to effectively transferring differentiated cells into patients [486]. To overcome the challenges of achieving cell purity, quantity, and functionality in stem cell therapies, several innovative methods have emerged. Single-cell RNA sequencing and cell sorting techniques like FACS and MACS allow for precise isolation of specific cell types, while advanced 3D culture systems and organoids improve differentiation efficiency [487,488]. These advancements are making stem cell-based therapies more viable for clinical use.

Despite the numerous advantages of PEVs, including their low immunogenicity, efficient transport of biological cargo, and potential as drug delivery vehicles, several challenges limit their widespread clinical application. One of the primary issues lies in the current methods for isolating and detecting PEVs, such as ultracentrifugation, which is labor-intensive, time-consuming, and often results in impure samples that may reduce the biological activity of the vesicles. While commercially available reagents simplify the extraction process, their high cost restricts them to preclinical research. Researchers are now exploring more cost-effective isolation methods, such as nano-deterministic lateral displacement (Nano-DLD) and resistive pulse sensing (RPS), which offer higher sensitivity and better scalability but still require optimization for broader use [289].

Additionally, the population heterogeneity presents another challenge. Distinguishing between PEV subpopulations and understanding their distinct biological roles remain difficult due to limitations in current isolation and characterization techniques. More research is needed to refine these techniques and fully understand the mechanisms underlying EVs' therapeutic effects, particularly in tissue regeneration and cancer therapies [489]. Furthermore, interdisciplinary collaboration among researchers, clinicians, and regulatory bodies will be vital to translating these scientific advancements into clinical realities, ensuring safe and effective therapies for patients. The future of placental derivatives in biomedical research is promising, with the potential to revolutionize regenerative medicine and tissue engineering.

12. Conclusion remarks

Placental tissue is a rich source of bioactive substances, ECM proteins, and stem cells, available in abundant and sustainable quantities. The structural composition of placental tissues is highly diverse, resulting in a wide range of configurations. A comprehensive analysis of different types of placental derivatives can serve as a valuable guide for selecting suitable products for novel applications. The UC, the placental

disc, and the amnion-chorion membrane are abundant in collagen, fibronectin, laminin, GAGs, elastin, and heparan sulfate, which makes them promising resources for regenerative medicine applications. This valuable organ is also a rich source of growth factors and multipotent stem cells, which have been proposed for various biomedical applications. **AF**, characterized by its immune-privileged nature, contains soluble regulatory elements and cellular components, making it a unique biomaterial option. Moreover, PEVs play a crucial role in cell communication and have emerged as a promising tool for therapeutic applications due to their ability to transfer bioactive molecules. In summary, placental tissue and its derivatives provide a rich source of bioactive substances and stem cells, offering significant potential for innovative biomedical applications.

CRediT authorship contribution statement

Saeid Moghassemi: Writing – review & editing, Writing – original draft, Visualization, Supervision, Project administration, Investigation, Data curation, Conceptualization. **Saba Nikanfar:** Writing – original draft, Investigation. **Arezoo Dadashzadeh:** Writing – original draft, Investigation. **Maria João Sousa:** Writing – original draft, Investigation. **Yuting Wan:** Writing – original draft, Investigation. **Fengxuan Sun:** Writing – original draft, Investigation. **Arthur Colson:** Writing – original draft, Investigation. **Sven De Windt:** Writing – original draft, Investigation. **Lena Kwaspen:** Writing – original draft, Investigation. **Marc Kanbar:** Writing – original draft, Investigation. **Keyvan Sobhani:** Writing – original draft, Investigation. **Jie Yang:** Writing – original draft, Investigation. **Hanne Vlieghe:** Writing – original draft, Investigation. **Yongqian Li:** Writing – original draft, Investigation. **Frédéric Debière:** Writing – review & editing, Resources, Funding acquisition. **Christine Wyns:** Writing – review & editing, Resources, Funding acquisition. **Christiani A. Amorim:** Writing – review & editing, Resources, Funding acquisition.

Ethics approval and consent to participate

No human or animal subjects are in this review, and informed consent is not applicable.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Saeid Moghassemi reports financial support was provided by Fund for Scientific Research. Christiani Andrade Amorim reports a relationship with Foundation Against Cancer that includes: funding grants. Christiani Andrade Amorim reports a relationship with Fund for Scientific Research that includes: funding grants. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgment

This work was supported by research grants from the Belgian Foundation against Cancer (grant OST-2022/2169 awarded to C.A.A.), the Fonds National de la Recherche Scientifique de Belgique (FNRS-PDR convention grant number T.0004.20 awarded to C.A.A. (Ph.D. scholarship awarded to H.V.), FNRS-CR convention grant number J.0057.22 awarded to F.D., and FC 46825 fellowship awarded to S.M.), the UCLouvain's Fonds spéciaux de recherche (IREC FSR22 grant awarded to C.A.A. (Ph.D. scholarship awarded to M.J.S.) and IRE-CFSR23MOVEAND fellowship awarded to S.N.), Fondation Saint-Luc (Fetus for Life awarded to F.D.), the French Community of Belgium (ARC Grant 24/29-137 awarded to F.D., C.W, and C.A.A.) and the China Scholarship Council (Ph.D. scholarship awarded to Y.W., F.S., Y.L, J.Y.).

The figures were partly generated using Servier Medical Art, licensed under a Creative Commons Attribution 3.0 unported license.

References

[1] O. Pogozhykh, V. Prokopyuk, C. Figueiredo, D. Pogozhykh, Placenta and placental derivatives in regenerative therapies: experimental studies, history, and prospects, Stem Cell. Int. 2018 (2018) 4837930.
[2] N. Najafi-Ghalehlou, A. Feizkhah, M. Mobayen, Z. Pourmohammadi-Bejarpasi, S. Shekarchi, A.M. Roushandeh, M.H. Roudkenar, Plumping up a cushion of human biowaste in regenerative medicine: novel insights into a state-of-the-art reserve arsenal, Stem Cell Reviews and Reports 18 (8) (2022) 2709–2739.
[3] J. Davis, Skin transplantation with a review of 550 cases at the johns hopkins hospital, Johns Hopkins Med. J. 15 (307) (1910) 307–398.
[4] A. Roy, M. Mantay, C. Brannan, S. Griffiths, Placental tissues as biomaterials in regenerative medicine, BioMed Res. Int. 2022 (2022) 6751456.
[5] S. Gujjar, A. Tyagi, S. Sainger, P. Bharti, V. Nain, P. Sood, P. Jayabal, J.C. Sharma, P. Sharma, S. Rajput, Biocompatible human placental extracellular matrix derived hydrogels, Advanced Biology 8 (1) (2024) 2300349.
[6] P. Pethe, V. Kale, Placenta: a gold mine for translational research and regenerative medicine, Reprod. Biol. 21 (2) (2021) 100508.
[7] A.C. Duarte, E.C. Costa, H. Filipe, S. Saraiva, T. Jacinto, S. Miguel, M. Ribeiro, P. Coutinho, Animal-derived products in science and current alternatives, Biomater. Adv. (2023) 213428.
[8] C. Yang, P.J. Hillas, J.A. Báez, M. Nokelainen, J. Balan, J. Tang, R. Spiro, J. W. Polarek, The application of recombinant human collagen in tissue engineering, BioDrugs 18 (2004) 103–119.
[9] S. Jung, K.M. Panchalingam, R.D. Wuerth, L. Rosenberg, L.A. Behie, Large-scale production of human mesenchymal stem cells for clinical applications, Biotechnol. Appl. Biochem. 59 (2) (2012) 106–120.
[10] M.P. Francis, E. Breathwaite, A.A. Bulysheva, F. Varghese, R.U. Rodriguez, S. Dutta, I. Semenov, R. Ogle, A. Huber, A.-M. Tichy, Human placenta hydrogel reduces scarring in a rat model of cardiac ischemia and enhances cardiomyocyte and stem cell cultures, Acta Biomater. 52 (2017) 92–104.
[11] A. Higuchi, Q.-D. Ling, S.S. Kumar, M. Munusamy, A.A. Alarfajj, A. Umezawa, G.-J. Wu, Design of polymeric materials for culturing human pluripotent stem cells: progress toward feeder-free and xeno-free culturing, Prog. Polym. Sci. 39 (7) (2014) 1348–1374.
[12] K. Rajala, B. Lindroos, S.M. Hussein, R.S. Lappalainen, M. Pekkanen-Mattila, J. Inzunza, B. Rozell, S. Miettinen, S. Narkilahti, E. Kerkelä, A defined and xeno-free culture method enabling the establishment of clinical-grade human embryonic, induced pluripotent and adipose stem cells, PLoS One 5 (4) (2010) e10246.
[13] B. Liu, S. Chen, Y. Xu, Y. Lyu, J. Wang, Y. Du, Y. Sun, H. Liu, H. Zhou, W. Lai, Chemically defined and xeno-free culture condition for human extended pluripotent stem cells, Nat. Commun. 12 (1) (2021) 3017.
[14] M. Knöfler, S. Haider, L. Saleh, J. Pollheimer, T. Gamage, J. James, Human placenta and trophoblast development: key molecular mechanisms and model systems, Cell. Mol. Life Sci. 76 (18) (2019) 3479–3496.
[15] G.J. Burton, A.L. Watson, J. Hempstock, J.N. Skepper, E. Jauniaux, Uterine glands provide histiotrophic nutrition for the human fetus during the first trimester of pregnancy, J. Clin. Endocrinol. Metab. 87 (6) (2002) 2954–2959.
[16] T. Cindrova-Davies, A.N. Sferruzzi-Perri, Human placental development and function, Semin. Cell Dev. Biol. 131 (2022) 66–77.
[17] I. Brosens, R. Pijnenborg, L. Vercruysse, R. Romero, The "Great Obstetrical Syndromes" are associated with disorders of deep placentation, Am. J. Obstet. Gynecol. 204 (3) (2011) 193–201.
[18] O. Pogozhykh, V. Prokopyuk, C. Figueiredo, D. Pogozhykh, Placenta and placental derivatives in regenerative therapies: experimental studies, history, and prospects, Stem Cell. Int. 2018 (2018).
[19] K. Benirschke, S.G. Driscoll, The Pathology of the Human Placenta, Springer, 1967.
[20] Embryology, Umbilical Cord, 2020.
[21] W. Chatuphonprasert, K. Jarukamjorn, I. Ellinger, Physiology and pathophysiology of steroid biosynthesis, transport and metabolism in the human placenta, Front. Pharmacol. 9 (2018) 384603.
[22] X.-Q. Wang, D.-J. Li, The mechanisms by which trophoblast-derived molecules induce maternal–fetal immune tolerance, Cell. Mol. Immunol. 17 (11) (2020) 1204–1207.
[23] C.-H. Wassmer, E. Berishvili, Immunomodulatory properties of amniotic membrane derivatives and their potential in regenerative medicine, Curr. Diabetes Rep. 20 (2020) 1–10.
[24] A. Moffett, N. Shreeve, Local immune recognition of trophoblast in early human pregnancy: controversies and questions, Nat. Rev. Immunol. 23 (4) (2023) 222–235.
[25] L. Xu, Y. Li, Y. Sang, D.-J. Li, M. Du, Crosstalk between trophoblasts and decidual immune cells: the cornerstone of maternal-fetal immunotolerance, Front. Immunol. 12 (2021) 642392.
[26] M.G. Petroff, Immune interactions at the maternal–fetal interface, J. Reprod. Immunol. 68 (1–2) (2005) 1–13.
[27] M. Takano, Z. Lu, T. Goto, L. Fusi, J. Higham, J. Francis, A. Withey, J. Hardt, B. Cloke, A.V. Stavropoulou, Transcriptional cross talk between the forkhead transcription factor forkhead box O1A and the progesterone receptor coordinates cell cycle regulation and differentiation in human endometrial stromal cells, Mol. Endocrinol. 21 (10) (2007) 2334–2349.

[28] R.R. Nair, P. Verma, K. Singh, Immune-endocrine crosstalk during pregnancy, Gen. Comp. Endocrinol. 242 (2017) 18–23.
[29] A. Alok, D. Mukhopadhyay, A.A. Karande, Glycodelin A, an immunomodulatory protein in the endometrium, inhibits proliferation and induces apoptosis in monocytic cells, Int. J. Biochem. Cell Biol. 41 (5) (2009) 1138–1147.
[30] A.S. Bansal, S.A. Bora, S. Saso, J.R. Smith, M.R. Johnson, M.-Y. Thum, Mechanism of human chorionic gonadotrophin-mediated immunomodulation in pregnancy, Expet Rev. Clin. Immunol. 8 (8) (2012) 747–753.
[31] M.J. van den Heuvel, X. Xie, C. Tayade, C. Peralta, Y. Fang, S. Leonard, V. A. Paffaro Jr., A.K. Sheikhi, C. Murrant, B. Anne Croy, A review of trafficking and activation of uterine natural killer cells, Am. J. Reprod. Immunol. 54 (6) (2005) 322–331.
[32] W. Guo, P. Li, G. Zhao, H. Fan, Y. Hu, Y. Hou, Glucocorticoid receptor mediates the effect of progesterone on uterine natural killer cells, Am. J. Reprod. Immunol. 67 (6) (2012) 463–473.
[33] F. Ietta, N. Bechi, R. Romagnoli, J. Bhattacharjee, M. Realacci, M. Di Vito, C. Ferretti, L. Paulesu, 17β-Estradiol modulates the macrophage migration inhibitory factor secretory pathway by regulating ABCA1 expression in human first-trimester placenta, Am. J. Physiol. Endocrinol. Metabol. 298 (3) (2010) E411–E418.
[34] R.A. Pelekanos, V.S. Sardesai, K. Futrega, W.B. Lott, M. Kuhn, M.R. Doran, Isolation and expansion of mesenchymal stem/stromal cells derived from human placenta tissue, J. Vis. Exp. 112 (2016).
[35] O. Parolini, F. Alviano, G.P. Bagnara, G. Bilic, H.J. Bühring, M. Evangelista, S. Hennerbichler, B. Liu, M. Magatti, N. Mao, T. Miki, F. Marongiu, H. Nakajima, T. Nikaido, C.B. Portmann-Lanz, V. Sankar, M. Soncini, G. Stadler, D. Surbek, T. A. Takahashi, H. Redl, N. Sakuragawa, S. Wolbank, S. Zeisberger, A. Zisch, S. C. Strom, Concise review: isolation and characterization of cells from human term placenta: outcome of the first international Workshop on Placenta Derived Stem Cells, Stem Cell. 26 (2) (2008) 300–311.
[36] M. Wu, R. Zhang, Q. Zou, Y. Chen, M. Zhou, X. Li, R. Ran, Q. Chen, Comparison of the biological characteristics of mesenchymal stem cells derived from the human placenta and umbilical cord, Sci. Rep. 8 (1) (2018) 5014.
[37] O. Parolini, F. Alviano, I. Bergwerf, D. Boraschi, C. De Bari, P. De Waele, M. Dominici, M. Evangelista, W. Falk, S. Hennerbichler, D.C. Hess, G. Lanzoni, B. Liu, F. Marongiu, C. McGuckin, S. Mohr, M.L. Nolli, R. Ofir, P. Ponsaerts, L. Romagnoli, A. Solomon, M. Soncini, S. Strom, D. Surbek, S. Venkatachalam, S. Wolbank, S. Zeisberger, A. Zeitlin, A. Zisch, C.V. Borlongan, Toward cell therapy using placenta-derived cells: disease mechanisms, cell biology, preclinical studies, and regulatory aspects at the round table, Stem Cell. Dev. 19 (2) (2010) 143–154.
[38] B.L. Yen, H.I. Huang, C.C. Chien, H.Y. Jui, B.S. Ko, M. Yao, C.T. Shun, M.L. Yen, M.C. Lee, Y.C. Chen, Isolation of multipotent cells from human term placenta, Stem Cell. 23 (1) (2005) 3–9.
[39] Q. Huang, Y. Yang, C. Luo, Y. Wen, R. Liu, S. Li, T. Chen, H. Sun, L. Tang, An efficient protocol to generate placental chorionic plate-derived mesenchymal stem cells with superior proliferative and immunomodulatory properties, Stem Cell Res. Ther. 10 (1) (2019) 301.
[40] S. Dutta Gupta, A. Sen, P. Priyadarshi, M. Ta, Enzyme-free isolation of mesenchymal stem cells from decidua basalis of the human placenta, STAR Protoc 4 (3) (2023) 102498.
[41] P. Salehinejad, M. Moshrefi, T. Eslaminejad, An overview on mesenchymal stem cells derived from extraembryonic tissues: supplement sources and isolation methods, Stem Cells Cloning 13 (2020) 57–65.
[42] M. Dominici, K. Le Blanc, I. Mueller, I. Slaper-Cortenbach, F. Marini, D. Krause, R. Deans, A. Keating, D. Prockop, E. Horwitz, Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement, Cytotherapy 8 (4) (2006) 315–317.
[43] B. Parekkadan, J.M. Milwid, Mesenchymal stem cells as therapeutics, Annu. Rev. Biomed. Eng. 12 (2010) 87–117.
[44] L.E. Fernández-Garza, S.A. Barrera-Barrera, H.A. Barrera-Saldaña, Mesenchymal stem cell therapies approved by regulatory agencies around the world, Pharmaceuticals 16 (9) (2023) 1334.
[45] C. Li, H. Zhao, L. Cheng, B. Wang, Allogeneic vs. autologous mesenchymal stem/stromal cells in their medication practice, Cell Biosci. 11 (1) (2021) 187.
[46] Q.u.a. khan, B. wasim, K. Haneef, T. Mirza, S. Usman, Isolation of homogenous population of human amniotic epithelial stems cells: same as above, Pakistan Journal of Medicine and Dentistry 11 (3) (2024) 51–58.
[47] T. Miki, Stem cell characteristics and the therapeutic potential of amniotic epithelial cells, Am. J. Reprod. Immunol. 80 (4) (2018) e13003.
[48] M. Zafar, S. Saeed, B. Kant, B. Murtaza, M.F. Dar, N.A. Khan, Use of amnion in vaginoplasty for vaginal atresia, J Coll Physicians Surg Pak 17 (2) (2007) 107–109.
[49] C. Fotopoulou, J. Sehouli, N. Gehrmann, I. Schoenborn, W. Lichtenegger, Functional and anatomic results of amnion vaginoplasty in young women with Mayer-Rokitansky-Küster-Hauser syndrome, Fertil. Steril. 94 (1) (2010) 317–323.
[50] C. Qiu, Z. Ge, W. Cui, L. Yu, J. Li, Human amniotic epithelial stem cells: a promising seed cell for clinical applications, Int. J. Mol. Sci. 21 (20) (2020).
[51] S.M. Vidal Jr., R. Enkhtuya, R. Urrabaz-Garza, R. Menon, Placental trophoblast cell isolation from the term placenta, Methods Mol. Biol. 2781 (2024) 131–142.
[52] P. Bischof, I. Irminger-Finger, The human cytotrophoblastic cell, a mononuclear chameleon, Int. J. Biochem. Cell Biol. 37 (1) (2005) 1–16.
[53] J.L. James, P.R. Stone, L.W. Chamley, The effects of oxygen concentration and gestational age on extravillous trophoblast outgrowth in a human first trimester villous explant model, Hum. Reprod. 21 (10) (2006) 2699–2705.
[54] L. Lunghi, M.E. Ferretti, S. Medici, C. Biondi, F. Vesce, Control of human trophoblast function, Reprod. Biol. Endocrinol. 5 (2007) 6.
[55] M.A. Sheridan, X. Zhao, R.C. Fernando, L. Gardner, V. Perez-Garcia, Q. Li, S.G. E. Marsh, R. Hamilton, A. Moffett, M.Y. Turco, Characterization of primary models of human trophoblast, Development 148 (21) (2021).
[56] H. Okae, H. Toh, T. Sato, H. Hiura, S. Takahashi, K. Shirane, Y. Kabayama, M. Suyama, H. Sasaki, T. Arima, Derivation of human trophoblast stem cells, Cell Stem Cell 22 (1) (2018) 50–63.e6.
[57] T. Hori, H. Okae, S. Shibata, N. Kobayashi, E.H. Kobayashi, A. Oike, A. Sekiya, T. Arima, H. Kaji, Trophoblast stem cell-based organoid models of the human placental barrier, Nat. Commun. 15 (1) (2024) 962.
[58] M.Y. Turco, L. Gardner, R.G. Kay, R.S. Hamilton, M. Prater, M.S. Hollinshead, A. McWhinnie, L. Esposito, R. Fernando, H. Skelton, F. Reimann, F.M. Gribble, A. Sharkey, S.G.E. Marsh, S. O'Rahilly, M. Hemberger, G.J. Burton, A. Moffett, Trophoblast organoids as a model for maternal-fetal interactions during human placentation, Nature 564 (7735) (2018) 263–267.
[59] M.A. Sheridan, R.C. Fernando, L. Gardner, M.S. Hollinshead, G.J. Burton, A. Moffett, M.Y. Turco, Establishment and differentiation of long-term trophoblast organoid cultures from the human placenta, Nat. Protoc. 15 (10) (2020) 3441–3463.
[60] S. Haider, G. Meinhardt, L. Saleh, V. Kunihs, M. Gamperl, U. Kaindl, A. Ellinger, T.R. Burkard, C. Fiala, J. Pollheimer, S. Mendjan, P.A. Latos, M. Knöfler, Self-renewing trophoblast organoids recapitulate the developmental program of the early human placenta, Stem Cell Rep. 11 (2) (2018) 537–551.
[61] S.M. Alatyyat, H.M. Alasmari, O.A. Aleid, M.S. Abdel-maksoud, N. Elsherbiny, Umbilical cord stem cells: background, processing and applications, Tissue Cell 65 (2020) 101351.
[62] S. Kern, H. Eichler, J. Stoeve, H. Klüter, K. Bieback, Comparative analysis of mesenchymal stem cells from bone marrow, umbilical cord blood, or adipose tissue, Stem Cell. 24 (5) (2006) 1294–1301.
[63] S.M. Alatyyat, H.M. Alasmari, O.A. Aleid, M.S. Abdel-Maksoud, N. Elsherbiny, Umbilical cord stem cells: background, processing and applications, Tissue Cell 65 (2020) 101351.
[64] K.J. Moise Jr., Umbilical cord stem cells, Obstet. Gynecol. 106 (6) (2005) 1393–1407.
[65] J. Ropa, W. Van't Hof, The fulfilled promise and unmet potential of umbilical cord blood, Curr. Opin. Hematol. 31 (4) (2024) 168–174.
[66] I.J. Lim, T.T. Phan, Epithelial and mesenchymal stem cells from the umbilical cord lining membrane, Cell Transplant. 23 (4–5) (2014) 497–503.
[67] J. Zhou, Y. Shi, Mesenchymal stem/stromal cells (MSCs): origin, immune regulation, and clinical applications, Cell. Mol. Immunol. 20 (6) (2023) 555–557.
[68] E. Gluckman, H.A. Broxmeyer, A.D. Auerbach, H.S. Friedman, G.W. Douglas, A. Devergie, H. Esperou, D. Thierry, G. Socie, P. Lehn, et al., Hematopoietic reconstitution in a patient with Fanconi's anemia by means of umbilical-cord blood from an HLA-identical sibling, N. Engl. J. Med. 321 (17) (1989) 1174–1178.
[69] X. Zhu, B. Tang, Z. Sun, Umbilical cord blood transplantation: still growing and improving, Stem Cells Transl Med 10 (Suppl 2) (2021) S62–s74.
[70] T.L. Kindwall-Keller, K.K. Ballen, Umbilical cord blood: the promise and the uncertainty, Stem Cells Translational Medicine 9 (10) (2020) 1153–1162.
[71] H. Mayani, P.M. Lansdorp, Biology of human umbilical cord blood-derived hematopoietic stem/progenitor cells, Stem Cell. 16 (3) (1998) 153–165.
[72] L. Gragert, M. Eapen, E. Williams, J. Freeman, S. Spellman, R. Baitty, R. Hartzman, J.D. Rizzo, M. Horowitz, D. Confer, M. Maiers, HLA match likelihoods for hematopoietic stem-cell grafts in the U.S. registry, N. Engl. J. Med. 371 (4) (2014) 339–348.
[73] S. Koestenbauer, A. Zisch, G. Dohr, N.H. Zech, Protocols for hematopoietic stem cell expansion from umbilical cord blood, Cell Transplant. 18 (10–11) (2009) 1059–1068.
[74] M.E. Horwitz, P.J. Stiff, C. Cutler, C. Brunstein, R. Hanna, R.T. Maziarz, A. R. Rezvani, N.A. Karris, J. McGuirk, D. Valcarcel, Omidubicel vs standard myeloablative umbilical cord blood transplantation: results of a phase 3 randomized study, Blood, The Journal of the American Society of Hematology 138 (16) (2021) 1429–1440.
[75] T. Murohara, Cord blood-derived early outgrowth endothelial progenitor cells, Microvasc. Res. 79 (3) (2010) 174–177.
[76] D.A. Ingram, L.E. Mead, H. Tanaka, V. Meade, A. Fenoglio, K. Mortell, K. Pollok, M.J. Ferkowicz, D. Gilley, M.C. Yoder, Identification of a novel hierarchy of endothelial progenitor cells using human peripheral and umbilical cord blood, Blood 104 (9) (2004) 2752–2760.
[77] E.B. Peters, Endothelial progenitor cells for the vascularization of engineered tissues, Tissue Eng., Part B 24 (1) (2018) 1–24.
[78] H. Sun, R. Morihara, T. Feng, Z. Bian, H. Yu, X. Hu, X. Hu, Y. Bian, R. Sasaki, Y. Fukui, Human cord blood–endothelial progenitor cells alleviate intimal hyperplasia of arterial damage in a rat stroke model, Cell Transplant. 32 (2023) 09636897231193069.
[79] Y. Zhou, S.U. Gan, G. Lin, Y.T. Lim, J. Masilamani, F.B. Mustafa, M.L. Phua, L. Rivino, T.T. Phan, K.O. Lee, R. Calne, P.A. Macary, Characterization of human umbilical cord lining-derived epithelial cells and transplantation potential, Cell Transplant. 20 (11–12) (2011) 1827–1841.
[80] H.M. Reza, B.Y. Ng, T.T. Phan, D.T. Tan, R.W. Beuerman, L.P. Ang, Characterization of a novel umbilical cord lining cell with CD227 positivity and unique pattern of P63 expression and function, Stem Cell Rev Rep 7 (3) (2011) 624–638.

[81] L.P. Ang, P. Jain, T.T. Phan, H.M. Reza, Human umbilical cord lining cells as novel feeder layer for ex vivo cultivation of limbal epithelial cells, Investig. Ophthalmol. Vis. Sci. 56 (8) (2015) 4697–4704.
[82] H.M. Reza, B.Y. Ng, F.L. Gimeno, T.T. Phan, L.P. Ang, Umbilical cord lining stem cells as a novel and promising source for ocular surface regeneration, Stem Cell Rev Rep 7 (4) (2011) 935–947.
[83] J.E.H. Kua, C.W. Siow, W.K. Lim, J. Masilamani, M.S. Tjin, J. Yeong, T.K.H. Lim, T.T. Phan, A.W.C. Chua, Human umbilical cord lining-derived epithelial cells: a potential source of non-native epithelial cells that accelerate healing in a porcine cutaneous wound model, Int. J. Mol. Sci. 23 (16) (2022) 8918.
[84] M. Stubbendorff, T. Deuse, X. Hua, T.T. Phan, K. Bieback, K. Atkinson, T. H. Eiermann, J. Velden, C. Schröder, H. Reichenspurner, R.C. Robbins, H.-D. Volk, S. Schrepfer, Immunological properties of extraembryonic human mesenchymal stromal cells derived from gestational tissue, Stem Cell. Dev. 22 (19) (2013) 2619–2629.
[85] T. Deuse, M. Stubbendorff, K. Tang-Quan, N. Phillips, M.A. Kay, T. Eiermann, T. T. Phan, H.-D. Volk, H. Reichenspurner, R.C. Robbins, S. Schrepfer, Immunogenicity and immunomodulatory properties of umbilical cord lining mesenchymal stem cells, Cell Transplant. 20 (5) (2011) 655–667.
[86] K.C. Yoon, Use of umbilical cord serum in ophthalmology, Chonnam medical journal 50 (3) (2014) 82.
[87] J. Matas, M. Orrego, D. Amenabar, C. Infante, R. Tapia-Limonchi, M.I. Cadiz, F. Alcayaga-Miranda, P.L. González, E. Muse, M. Khoury, F.E. Figueroa, F. Espinoza, Umbilical cord-derived mesenchymal stromal cells (MSCs) for knee osteoarthritis: repeated MSC dosing is superior to a single MSC dose and to hyaluronic acid in a controlled randomized phase I/II trial, Stem Cells Transl Med 8 (3) (2019) 215–224.
[88] L. Wang, S. Huang, S. Li, M. Li, J. Shi, W. Bai, Q. Wang, L. Zheng, Y. Liu, Efficacy and safety of umbilical cord mesenchymal stem cell therapy for rheumatoid arthritis patients: a prospective phase I/II study, Drug Des. Dev. Ther. 13 (2019) 4331–4340.
[89] Y. Xie, Y. Li, J. Yao, X. Song, H. Wang, J. Zhang, X. Li, Protein lactylation modification and proteomics features in cirrhosis patients after UC-MSC treatment, Curr. Issues Mol. Biol. 45 (10) (2023) 8444–8460.
[90] M. Shi, Y.Y. Li, R.N. Xu, F.P. Meng, S.J. Yu, J.L. Fu, J.H. Hu, J.X. Li, L.F. Wang, L. Jin, F.S. Wang, Mesenchymal stem cell therapy in decompensated liver cirrhosis: a long-term follow-up analysis of the randomized controlled clinical trial, Hepatol Int 15 (6) (2021) 1431–1441.
[91] L. Ding, G. Yan, B. Wang, L. Xu, Y. Gu, T. Ru, X. Cui, L. Lei, J. Liu, X. Sheng, B. Wang, C. Zhang, Y. Yang, R. Jiang, J. Zhou, N. Kong, F. Lu, H. Zhou, Y. Zhao, B. Chen, Y. Hu, J. Dai, H. Sun, Transplantation of UC-MSCs on collagen scaffold activates follicles in dormant ovaries of POF patients with long history of infertility, Sci. China Life Sci. 61 (12) (2018) 1554–1565.
[92] M. Meng, W.W. Zhang, S.F. Chen, D.R. Wang, C.H. Zhou, Therapeutic utility of human umbilical cord-derived mesenchymal stem cells-based approaches in pulmonary diseases: recent advancements and prospects, World J. Stem Cell. 16 (2) (2024) 70–88.
[93] S. Moghassemi, A. Dadashzadeh, R.B. de Azevedo, C.A. Amorim, Secure transplantation by tissue purging using photodynamic therapy to eradicate malignant cells, J. Photochem. Photobiol. B Biol. 234 (2022) 112546.
[94] K. Khaddour, C.K. Hana, P. Mewawalla, Hematopoietic Stem Cell Transplantation, StatPearls, StatPearls Publishing Copyright © 2024, StatPearls Publishing LLC., Treasure Island (FL), 2024.
[95] J. Kurtzberg, A history of cord blood banking and transplantation, Stem Cells Transl Med 6 (5) (2017) 1309–1311.
[96] A.O. Gupta, J.E. Wagner, Umbilical cord blood transplants: current status and evolving therapies, Front Pediatr 8 (2020) 570282.
[97] N.H. Zech, N. Broer, I. Ribitsch, M.H. Zech, K.H. Broer, K. Ertan, K.H. Preisegger, The rationale behind collecting umbilical cord blood, J. Turk. Ger. Gynecol. Assoc. 11 (2) (2010) 99–101.
[98] H. Zhou, M.S. Rao, Can cord blood banks transform into induced pluripotent stem cell banks? Cytotherapy 17 (6) (2015) 756–764.
[99] B. Álvarez-Palomo, A. Veiga, A. Raya, M. Codinach, S. Torrents, L. Ponce Verdugo, C. Rodriguez-Aierbe, L. Cuellar, R. Alenda, C. Arbona, D. Hernández-Maraver, C. Fusté, S. Querol, Public Cord Blood Banks as a source of starting material for clinical grade HLA-homozygous induced pluripotent stem cells, Stem Cell Res. Ther. 13 (1) (2022) 408.
[100] B. Kuebler, B. Alvarez-Palomo, B. Aran, J. Castaño, L. Rodriguez, A. Raya, S. Querol Giner, A. Veiga, Generation of a bank of clinical-grade, HLA-homozygous iPSC lines with high coverage of the Spanish population, Stem Cell Res. Ther. 14 (1) (2023) 366.
[101] A. Haase, R. Olmer, K. Schwanke, S. Wunderlich, S. Merkert, C. Hess, R. Zweigerdt, I. Gruh, J. Meyer, S. Wagner, L.S. Maier, D.W. Han, S. Glage, K. Miller, P. Fischer, H.R. Schöler, U. Martin, Generation of induced pluripotent stem cells from human cord blood, Cell Stem Cell 5 (4) (2009) 434–441.
[102] S. Devi, A.M. Bongale, M.A. Tefera, P. Dixit, P. Bhanap, Fresh umbilical cord blood-A source of multipotent stem cells, collection, banking, cryopreservation, and ethical concerns, Life 13 (9) (2023).
[103] S. Yu, X. You, H. Liang, Y. Li, Y. Fu, X. Zhang, X. Hu, J. An, Y. Xu, F. Li, First trimester placental mesenchymal stem cells improve cardiac function of rat after myocardial infarction via enhanced neovascularization, Heliyon 7 (1) (2021) e06120.
[104] W. Zheng, S. Bian, S. Qiu, C.E. Bishop, M. Wan, N. Xu, X. Sun, R.C. Sequeira, A. Atala, Z. Gu, W. Zhao, Placenta mesenchymal stem cell-derived extracellular vesicles alleviate liver fibrosis by inactivating hepatic stellate cells through a miR-378c/SKP2 axis, Inflamm. Regen. 43 (1) (2023) 47.
[105] M. Soleimani, A. Masoumi, B. Momenaei, K. Cheraqpour, R. Koganti, A.Y. Chang, M. Ghassemi, A.R. Djalilian, Applications of mesenchymal stem cells in ocular surface diseases: sources and routes of delivery, Expet Opin. Biol. Ther. 23 (6) (2023) 509–525.
[106] E.H. de Laorden, D. Simón, S. Milla, M. Portela-Lomba, M. Mellén, J. Sierra, P. de la Villa, M.T. Moreno-Flores, M. Iglesias, Human placenta-derived mesenchymal stem cells stimulate neuronal regeneration by promoting axon growth and restoring neuronal activity, Front. Cell Dev. Biol. 11 (2023) 1328261.
[107] S. Garbuzova-Davis, M.C. Rodrigues, S. Mirtyl, S. Turner, S. Mitha, J. Sodhi, S. Suthakaran, D.J. Eve, C.D. Sanberg, N. Kuzmin-Nichols, P.R. Sanberg, Multiple intravenous administrations of human umbilical cord blood cells benefit in a mouse model of ALS, PLoS One 7 (2) (2012) e31254.
[108] C.M. Cotten, K. Fisher, W. Malcolm, K.E. Gustafson, L. Cheatham, A. Marion, R. Greenberg, J. Kurtzberg, A pilot phase I trial of allogeneic umbilical cord tissue-derived mesenchymal stromal cells in neonates with hypoxic-ischemic encephalopathy, Stem Cells Transl Med 12 (6) (2023) 355–364.
[109] J.M. Sun, L.E. Case, C. McLaughlin, A. Burgess, N. Skergan, S. Crane, J.M. Jasien, M.A. Mikati, J. Troy, J. Kurtzberg, Motor function and safety after allogeneic cord blood and cord tissue-derived mesenchymal stromal cells in cerebral palsy: an open-label, randomized trial, Dev. Med. Child Neurol. 64 (12) (2022) 1477–1486.
[110] D.T. Laskowitz, E.R. Bennett, R.J. Durham, J.J. Volpi, J.R. Wiese, M. Frankel, E. Shpall, J.M. Wilson, J. Troy, J. Kurtzberg, Allogeneic umbilical cord blood infusion for adults with ischemic stroke: clinical outcomes from a phase I safety study, Stem Cells Transl Med 7 (7) (2018) 521–529.
[111] N. Ende, R. Chen, Parkinson's disease mice and human umbilical cord blood, J. Med. 33 (1–4) (2002) 173–180.
[112] A. Taguchi, T. Soma, H. Tanaka, T. Kanda, H. Nishimura, H. Yoshikawa, Y. Tsukamoto, H. Iso, Y. Fujimori, D.M. Stern, H. Naritomi, T. Matsuyama, Administration of CD34+ cells after stroke enhances neurogenesis via angiogenesis in a mouse model, J. Clin. Investig. 114 (3) (2004) 330–338.
[113] Y. Moodley, D. Atienza, U. Manuelpillai, C.S. Samuel, J. Tchongue, S. Ilancheran, R. Boyd, A. Trounson, Human umbilical cord mesenchymal stem cells reduce fibrosis of bleomycin-induced lung injury, Am. J. Pathol. 175 (1) (2009) 303–313.
[114] S. Nikfarjam, J. Rezaie, N.M. Zolbanin, R. Jafari, Mesenchymal stem cell derived-exosomes: a modern approach in translational medicine, J. Transl. Med. 18 (1) (2020) 449.
[115] Y.J. Kim, S.M. Yoo, H.H. Park, H.J. Lim, Y.L. Kim, S. Lee, K.W. Seo, K.S. Kang, Exosomes derived from human umbilical cord blood mesenchymal stem cells stimulates rejuvenation of human skin, Biochem. Biophys. Res. Commun. 493 (2) (2017) 1102–1108.
[116] Q. Sun, D. Zhang, Q. Ai, Y. Yue, H. Wang, L. Tang, X. Yi, S. Wang, Y. Zheng, Human umbilical cord mesenchymal stem cells improve uterine incision healing after cesarean delivery in rats by modulating the TGF-β/Smad signaling pathway, Arch. Gynecol. Obstet. 310 (1) (2024) 103–111.
[117] S. Hendrawan, Y. Kusnadi, C.A. Lagonda, D. Fauza, J. Lheman, E. Budi, B. S. Manurung, H.U. Baer, S. Tansil Tan, Wound healing potential of human umbilical cord mesenchymal stem cell conditioned medium: an in vitro and in vivo study in diabetes-induced rats, Vet. World 14 (8) (2021) 2109–2117.
[118] K. Chorath, M. Willis, N. Morton-Gonzaba, A. Moreira, Mesenchymal stem cells for sensorineural hearing loss: a systematic review of preclinical studies, Mol. Biol. Rep. 47 (6) (2020) 4723–4736.
[119] Á. Sierra-Sánchez, T. Montero-Vilchez, M.I. Quiñones-Vico, M. Sanchez-Diaz, S. Arias-Santiago, Current advanced therapies based on human mesenchymal stem cells for skin diseases, Front. Cell Dev. Biol. 9 (2021) 643125.
[120] C. Zhang, L. Huang, X. Wang, X. Zhou, X. Zhang, L. Li, J. Wu, M. Kou, C. Cai, Q. Lian, X. Zhou, Topical and intravenous administration of human umbilical cord mesenchymal stem cells in patients with diabetic foot ulcer and peripheral arterial disease: a phase I pilot study with a 3-year follow-up, Stem Cell Res. Ther. 13 (1) (2022) 451.
[121] F. Ramzan, S. Ekram, T. Frazier, A. Salim, O.A. Mohiuddin, I. Khan, Decellularized human umbilical tissue-derived hydrogels promote proliferation and chondrogenic differentiation of mesenchymal stem cells, Bioengineering (Basel) 9 (6) (2022).
[122] C. Campagnoli, I.A. Roberts, S. Kumar, P.R. Bennett, I. Bellantuono, N.M. Fisk, Identification of mesenchymal stem/progenitor cells in human first-trimester fetal blood, liver, and bone marrow, Blood 98 (8) (2001) 2396–2402.
[123] P. Pethe, V. Kale, Placenta: a gold mine for translational research and regenerative medicine, Reprod. Biol. 21 (2) (2021) 100508.
[124] Y. Liu, X. Zhang, Y. Hu, M. Kang, Y. Wu, Y. Wang, C. Deng, Human placental mesenchymal stem cells regulate inflammation via the NF-κB signaling pathway, Exp. Ther. Med. 24 (5) (2022) 654.
[125] X. Li, W. Ling, A. Pennisi, Y. Wang, S. Khan, M. Heidaran, A. Pal, X. Zhang, S. He, A. Zeitlin, S. Abbot, H. Faleck, R. Hariri, J.D. Shaughnessy Jr., F. van Rhee, B. Nair, B. Barlogie, J. Epstein, S. Yaccoby, Human placenta-derived adherent cells prevent bone loss, stimulate bone formation, and suppress growth of multiple myeloma in bone, Stem Cell. 29 (2) (2011) 263–273.
[126] A. Babajani, A. Manzari-Tavakoli, E. Jamshidi, R. Tarasi, H. Niknejad, Anti-cancer effects of human placenta-derived amniotic epithelial stem cells loaded with paclitaxel on cancer cells, Sci. Rep. 12 (1) (2022) 18148.
[127] S.S. Moonshi, H. Adelnia, Y. Wu, H.T. Ta, Placenta-derived mesenchymal stem cells for treatment of diseases: a clinically relevant source, Adv. Therapeut. 5 (10) (2022) 2200054.
[128] S. Meirelles Lda, A.M. Fontes, D.T. Covas, A.I. Caplan, Mechanisms involved in the therapeutic properties of mesenchymal stem cells, Cytokine Growth Factor Rev. 20 (5–6) (2009) 419–427.

[129] F. Li, C. Gao, G. Song, K. Zhang, G. Huang, H. Liu, Human placenta-derived mesenchymal stem cells combined with artificial dermal scaffold enhance wound healing in a tendon-exposed wound of a rabbit model, Cell Transplant. 33 (2024) 9636897241228922.
[130] J. Huang, Q. Deng, L.L. Tsang, G. Chang, J. Guo, Y.C. Ruan, C.C. Wang, G. Li, H. F. Chan, X. Zhang, X. Jiang, Mesenchymal stem cells from perinatal tissues promote diabetic wound healing via PI3K/AKT activation, Stem Cell Res. Ther. 16 (1) (2025) 59.
[131] J. Jung, J.H. Choi, Y. Lee, J.W. Park, I.H. Oh, S.G. Hwang, K.S. Kim, G.J. Kim, Human placenta-derived mesenchymal stem cells promote hepatic regeneration in CCl4 -injured rat liver model via increased autophagic mechanism, Stem Cell. 31 (8) (2013) 1584–1596.
[132] L. Cacciottola, F. Vitale, J. Donnez, M.M. Dolmans, Use of mesenchymal stem cells to enhance or restore fertility potential: a systematic review of available experimental strategies, Hum Reprod Open 2023 (4) (2023) hoad040.
[133] T. Li, R.W.S. Chan, R.H.W. Li, E.H.Y. Ng, S. Zhang, W.S.B. Yeung, Endometrial mesenchymal stromal/stem cells improve regeneration of injured endometrium in mice, Biol. Res. 57 (1) (2024) 6.
[134] L. Zhang, Y. Li, C.Y. Guan, S. Tian, X.D. Lv, J.H. Li, X. Ma, H.F. Xia, Therapeutic effect of human umbilical cord-derived mesenchymal stem cells on injured rat endometrium during its chronic phase, Stem Cell Res. Ther. 9 (1) (2018) 36.
[135] T.H. Kim, J.H. Choi, Y. Jun, S.M. Lim, S. Park, J.Y. Paek, S.H. Lee, J.Y. Hwang, G. J. Kim, 3D-cultured human placenta-derived mesenchymal stem cell spheroids enhance ovary function by inducing folliculogenesis, Sci. Rep. 8 (1) (2018) 15313.
[136] B. Li, Q. Zhang, J. Sun, D. Lai, Human amniotic epithelial cells improve fertility in an intrauterine adhesion mouse model, Stem Cell Res. Ther. 10 (1) (2019) 257.
[137] B. Çetinkaya Ün, M.A. Ferah, B. Ün, Can mesenchymal stem cells ameliorate testicular damage? Current researches, Journal of Surgery and Medicine 4 (7) (2020) 603–607.
[138] C. Qian, Q. Meng, J. Lu, L. Zhang, H. Li, B. Huang, Human amnion mesenchymal stem cells restore spermatogenesis in mice with busulfan-induced testis toxicity by inhibiting apoptosis and oxidative stress, Stem Cell Res. Ther. 11 (1) (2020) 290.
[139] J. Lu, Z. Liu, M. Shu, L. Zhang, W. Xia, L. Tang, J. Li, B. Huang, H. Li, Human placental mesenchymal stem cells ameliorate chemotherapy-induced damage in the testis by reducing apoptosis/oxidative stress and promoting autophagy, Stem Cell Res. Ther. 12 (1) (2021) 199.
[140] K.H. Kim, K.A. Lee, Metabolic rewiring by human placenta-derived mesenchymal stem cell therapy promotes rejuvenation in aged female rats, Int. J. Mol. Sci. 23 (1) (2022).
[141] T. Yin, S. He, C. Su, X. Chen, D. Zhang, Y. Wan, T. Ye, G. Shen, Y. Wang, H. Shi, L. Yang, Y. Wei, Genetically modified human placenta-derived mesenchymal stem cells with FGF-2 and PDGF-BB enhance neovascularization in a model of hindlimb ischemia, Mol. Med. Rep. 12 (4) (2015) 5093–5099.
[142] M.E. Rhéaume, J. Perreault, D. Fournier, P. Trépanier, Preparation and growth factor characterization of cord blood-derived plasma, serum, growth factor-rich plasma and induced serum, Cytokine 149 (2022) 155756.
[143] Y.A. Romanov, V.V. Vtorushina, T.N. Dugina, A.Y. Romanov, N.V. Petrova, Human umbilical cord blood serum/plasma: cytokine profile and prospective application in regenerative medicine, Bull. Exp. Biol. Med. 168 (1) (2019) 173–177.
[144] N. Orlando, C. Pellegrino, C.G. Valentini, M. Bianchi, O. Barbagallo, S. Sparnacci, F. Forni, T.M. Fontana, L. Teofili, Umbilical cord blood: current uses for transfusion and regenerative medicine, Transfus. Apher. Sci. 59 (5) (2020) 102952.
[145] N. Maharajan, G.-W. Cho, J.H. Choi, C.H. Jang, Regenerative therapy using umbilical cord serum, in vivo 35 (2) (2021) 699–705.
[146] D.A. Sabbah, R. Hajjo, K. Sweidan, Review on epidermal growth factor receptor (EGFR) structure, signaling pathways, interactions, and recent updates of EGFR inhibitors, Curr. Top. Med. Chem. 20 (10) (2020) 815–834.
[147] Y. Liu, Y. Liu, J. Deng, W. Li, X. Nie, Fibroblast growth factor in diabetic foot ulcer: progress and therapeutic prospects, Front. Endocrinol. 12 (2021) 744868.
[148] L. Klimaschewski, P. Claus, Fibroblast growth factor signalling in the diseased nervous system, Mol. Neurobiol. 58 (8) (2021) 3884–3902.
[149] S. Karaman, S. Paavonsalo, K. Heinolainen, M.H. Lackman, A. Ranta, K. A. Hemanthakumar, Y. Kubota, K. Alitalo, Interplay of vascular endothelial growth factor receptors in organ-specific vessel maintenance, J. Exp. Med. 219 (3) (2022).
[150] R.E. Roberts, J. Cavalcante-Silva, M. Del Rio-Moreno, O. Bilgen, R.D. Kineman, T. J. Koh, Liver insulin-like growth factor-1 mediates effects of low-intensity vibration on wound healing in diabetic mice, J. Pathol. 260 (1) (2023) 97–107.
[151] S. Thavapalachandran, S.M. Grieve, R.D. Hume, T.Y.L. Le, K. Raguram, J. E. Hudson, J. Pouliopoulos, G.A. Figtree, R.P. Dye, A.M. Barry, P. Brown, J. Lu, S. Coffey, S.H. Kesteven, R.J. Mills, F.N. Rashid, E. Taran, P. Kovoor, L. Thomas, A.R. Denniss, E. Kizana, N.S. Asli, M. Xaymardan, M.P. Feneley, R.M. Graham, R. P. Harvey, J.J.H. Chong, Platelet-derived growth factor-AB improves scar mechanics and vascularity after myocardial infarction, Sci. Transl. Med. 12 (524) (2020).
[152] R. Li, D. Li, C. Wu, L. Ye, Y. Wu, Y. Yuan, S. Yang, L. Xie, Y. Mao, T. Jiang, Y. Li, J. Wang, H. Zhang, X. Li, J. Xiao, Nerve growth factor activates autophagy in Schwann cells to enhance myelin debris clearance and to expedite nerve regeneration, Theranostics 10 (4) (2020) 1649–1677.
[153] M. Huang, J. Jiao, H. Cai, Y. Zhang, Y. Xia, J. Lin, Z. Shang, Y. Qian, F. Wang, H. Wu, X. Kong, J. Gu, C-C motif chemokine ligand 5 confines liver regeneration by down-regulating reparative macrophage-derived hepatocyte growth factor in a forkhead box O 3a-dependent manner, Hepatology 76 (6) (2022) 1706–1722.
[154] N.G. Frangogiannis, Transforming growth factor-β in myocardial disease, Nat. Rev. Cardiol. 19 (7) (2022) 435–455.
[155] N. Djahanpour, N. Ahsan, B. Li, H. Khan, K. Connelly, H. Leong-Poi, M. Qadura, A systematic review of interleukins as diagnostic and prognostic biomarkers for peripheral artery disease, Biomolecules 13 (11) (2023).
[156] G. Cai, R. Li, X. Chai, X. Cai, K. Zheng, Y. Wang, K. Fan, Z. Guo, J. Guo, W. Jiang, Catalase-templated nanozyme-loaded microneedles integrated with polymyxin B for immunoregulation and antibacterial activity in diabetic wounds, J. Colloid Interface Sci. 667 (2024) 529–542.
[157] P. Ma, J. Liu, J. Qin, L. Lai, G.S. Heo, H. Luehmann, D. Sultan, A. Bredemeyer, G. Bajapa, G. Feng, J. Jimenez, R. He, A. Parks, J. Amrute, A. Villanueva, Y. Liu, C.Y. Lin, M. Mack, K. Amancherla, J. Moslehi, K.J. Lavine, Expansion of pathogenic cardiac macrophages in immune checkpoint inhibitor myocarditis, Circulation 149 (1) (2024) 48–66.
[158] R. Gholikhani-Darbroud, MicroRNA and retinoic acid, Clin. Chim. Acta 502 (2020) 15–24.
[159] A.S. Wolberg, Fibrinogen and fibrin: synthesis, structure, and function in health and disease, J. Thromb. Haemostasis 21 (11) (2023) 3005–3015.
[160] M.A. Gertz, Therapy of transthyretin cardiomyopathy, J. Am. Coll. Cardiol. 74 (3) (2019) 296–298.
[161] G. Giannaccare, A. Carnevali, C. Senni, L. Logozzo, V. Scorcia, Umbilical cord blood and serum for the treatment of ocular diseases: a comprehensive review, Ophthalmology and Therapy 9 (2020) 235–248.
[162] A.A. Tovar, I.A. White, A.L. Sabater, Use of acellular umbilical cord-derived tissues in corneal and ocular surface diseases, Medicines 8 (2) (2021) 12.
[163] R. Huang, C. Su, N. Zhang, C. Shi, G. Pu, Y. Ding, W. Wei, J. Chen, Cord blood-derived biologics lead to robust axonal regeneration in benzalkonium chloride-injured mouse corneas by modulating the Il-17 pathway and neuropeptide Y, Mol. Med. 30 (1) (2024) 2.
[164] B.D. Li, J.X. Jiang, Q. Zhang, Y.R. Chu, Z.Y. Chen, K. Hu, Therapeutic effects of umbilical cord serum for dry eye disease: a systemic review and meta-analysis, Ophthalmic Res. 68 (1) (2025) 71–83.
[165] M.H. Elsawy, H.A. Hasby, M.M. Khater, A.M. Ghoneim, Evaluation of the effect of umbilical cord blood serum therapy in resistant infected corneal ulcer, Digit. J. Ophthalmol. 24 (3) (2023) 141–146.
[166] S. Moradian, M. Ebrahimi, A. Kanaani, A. Faramarzi, S. Safi, Topical umbilical cord serum for corneal epithelial defects after diabetic vitrectomy, J. Ophthalmic Vis. Res. 15 (2) (2020) 160.
[167] S.B. Han, Y.-C. Liu, K. Mohamed-Noriega, J.S. Mehta, Application of novel drugs for corneal cell regeneration, Journal of Ophthalmology 2018 (2018).
[168] N. Sharma, M. Goel, T. Velpandian, J.S. Titiyal, R. Tandon, R.B. Vajpayee, Evaluation of umbilical cord serum therapy in acute ocular chemical burns, Investig. Ophthalmol. Vis. Sci. 52 (2) (2011) 1087–1092.
[169] K.-C. Yoon, H. Heo, S.-K. Im, I.-C. You, Y.-H. Kim, Y.-G. Park, Comparison of autologous serum and umbilical cord serum eye drops for dry eye syndrome, Am. J. Ophthalmol. 144 (1) (2007), 86-92. e2.
[170] E. Afzal, M. Pakzad, M. Nouri, R. Moghadasali, M. Zarrabi, Human umbilical cord serum as an alternative to fetal bovine serum for in vitro expansion of umbilical cord mesenchymal stromal cells, Cell Tissue Bank. 24 (1) (2023) 59–66.
[171] J.-Y. Kim, S.-A. Park, H.-M. Kang, E.-S. Kim, H.-K. Kim, Human cord serum as a fetal bovine serum substitute for the culture of human amnion-derived stem cells, Development and Reproduction 11 (2) (2007) 85–96.
[172] P. Kaokaen, A. Pangjantuk, P. Kunhorm, W. Promjantuek, N. Chaicharoenaudomrung, P. Noisa, Conditioned medium of human umbilical cord-mesenchymal stem cells cultivated with human cord blood serum enhances stem cell stemness and secretome profiles, Toxicol. Vitro 103 (2025) 105973.
[173] P.Q. Viet, N.A. Tu, P.T.-H. Lan, N.T. Sinh, Human umbilical cord blood derived serum and platelet-rich plasma can replace fetal bovine serum to induce human monocytes into dendritic cells, Progress in Biology 2 (1) (2018) 4–19.
[174] F. Sandra, R. Lahirin, Human umbilical cord blood serum has higher potential in inducing proliferation of fibroblast than fetal bovine serum, Molecular and Cellular Biomedical, Sciences 1 (2) (2017) 65–69.
[175] C.H. Jang, Y.B. Cho, M. Yeo, H. Lee, E.J. Min, B.H. Lee, G.H. Kim, Regeneration of chronic tympanic membrane perforation using 3D collagen with topical umbilical cord serum, Int. J. Biol. Macromol. 62 (2013) 232–240.
[176] C.H. Jang, Y.B. Cho, C.H. Choi, Y.S. Jang, W.-K. Jung, H. Lee, G.H. Kim, Effect of umbilical cord serum coated 3D PCL/alginate scaffold for mastoid obliteration, Int. J. Pediatr. Otorhinolaryngol. 78 (7) (2014) 1061–1065.
[177] C.H. Jang, H. Lee, M. Kim, G. Kim, Effect of polycaprolactone/collagen/hUCS microfiber nerve conduit on facial nerve regeneration, Int. J. Biol. Macromol. 93 (2016) 1575–1582.
[178] A. Musiał-Wysocka, M. Kot, M. Majka, The pros and cons of mesenchymal stem cell-based therapies, Cell Transplant. 28 (7) (2019) 801–812.
[179] A. Muntiu, A. Papait, F. Vincenzoni, A. Vitali, W. Lattanzi, P. Romele, A. Cargnoni, A. Silini, O. Parolini, C. Desiderio, Disclosing the molecular profile of the human amniotic mesenchymal stromal cell secretome by filter-aided sample preparation proteomic characterization, Stem Cell Res. Ther. 14 (1) (2023) 339.
[180] K.H. Han, A.K. Kim, G.J. Jeong, H.R. Jeon, S.H. Bhang, D.I. Kim, Enhanced anti-cancer effects of conditioned medium from hypoxic human umbilical cord-derived mesenchymal stem cells, Int J Stem Cells 12 (2) (2019) 291–303.
[181] F. Opo, M. Moulay, G.I. Alrefaei, N.H. Alsubhi, S. Alkarim, M.M. Rahman, Effect of Co-culturing both placenta-derived mesenchymal stem cells and their condition medium in the cancer cell (HepG2) migration, damage through apoptosis and cell cycle arrest, Saudi J. Biol. Sci. 30 (2) (2023) 103519.

[182] B. Un, B. Cetinkaya-Un, M. Akpolat, F. Andic, Y. Yazir, The effects of human amnion membrane-derived mesenchymal stem cells conditioned medium on ionizing radiation-induced premature ovarian failure and endoplasmic reticulum stress-related apoptosis mechanism, Eur. J. Obstet. Gynecol. Reprod. Biol. 288 (2023) 191–197.
[183] P. Danieli, G. Malpasso, M.C. Ciuffreda, E. Cervio, L. Calvillo, F. Copes, F. Pisano, M. Mura, L. Kleijn, R.A. de Boer, G. Viarengo, V. Rosti, A. Spinillo, M. Roccio, M. Gnecchi, Conditioned medium from human amniotic mesenchymal stromal cells limits infarct size and enhances angiogenesis, Stem Cells Transl Med 4 (5) (2015) 448–458.
[184] A. Bier, P. Berenstein, N. Kronfeld, D. Morgoulis, A. Ziv-Av, H. Goldstein, G. Kazimirsky, S. Cazacu, R. Meir, R. Popovtzer, A. Dori, C. Brodie, Placenta-derived mesenchymal stromal cells and their exosomes exert therapeutic effects in Duchenne muscular dystrophy, Biomaterials 174 (2018) 67–78.
[185] Y.J. Choi, W.R. Kim, D.H. Kim, J.H. Kim, J.H. Yoo, Human umbilical cord/placenta mesenchymal stem cell conditioned medium attenuates intestinal fibrosis in vivo and in vitro, Stem Cell Res. Ther. 15 (1) (2024) 69.
[186] L. Du, R. Lv, X. Yang, S. Cheng, T. Ma, J. Xu, Hypoxic conditioned medium of placenta-derived mesenchymal stem cells protects against scar formation, Life Sci. 149 (2016) 51–57.
[187] S.M. Harris, A.L. Su, J.F. Dou, R. Loch-Caruso, E.R. Elkin, S. Jaber, K.M. Bakulski, Placental cell conditioned media modifies hematopoietic stem cell transcriptome invitro, Placenta 145 (2024) 117–125.
[188] Y.Y. Go, C.M. Lee, S.W. Chae, J.J. Song, Osteogenic efficacy of human trophoblasts-derived conditioned medium on mesenchymal stem cells, Int. J. Mol. Sci. 23 (17) (2022).
[189] Q. Zhang, S. Bu, J. Sun, M. Xu, X. Yao, K. He, D. Lai, Paracrine effects of human amniotic epithelial cells protect against chemotherapy-induced ovarian damage, Stem Cell Res. Ther. 8 (1) (2017) 270.
[190] A.D. Theocharis, S.S. Skandalis, C. Gialeli, N.K. Karamanos, Extracellular matrix structure, Adv. Drug Deliv. Rev. 97 (2016) 4–27.
[191] A.K. Emara, H. Anis, N.S. Piuzzi, Human placental extract: the feasibility of translation from basic science into clinical practice, Ann. Transl. Med. 8 (5) (2020) 156.
[192] C. Gwam, C. Ohanele, J. Hamby, N. Chughtai, Z. Mufti, X. Ma, Human placental extract: a potential therapeutic in treating osteoarthritis, Ann. Transl. Med. 11 (9) (2019) 322.
[193] M.E. Marraccini, K.S. Gorman, Exploring placentophagy in humans: problems and recommendations, J. Midwifery Womens Health 60 (4) (2015) 371–379.
[194] S.M. Young, L.K. Gryder, W.B. David, Y. Teng, S. Gerstenberger, D.C. Benyshek, Human placenta processed for encapsulation contains modest concentrations of 14 trace minerals and elements, Nutr. Res. 36 (8) (2016) 872–878.
[195] B. Nair, A.R. Elmore, Final report on the safety assessment of human placental protein, hydrolyzed human placental protein, human placental enzymes, human placental lipids, human umbilical extract, placental protein, hydrolyzed placental protein, placental enzymes, placental lipids, and umbilical extract, Int. J. Toxicol. 21 (Suppl 1) (2002) 81–91.
[196] A.F. Philipps, I.R. Holzman, C. Teng, F.C. Battaglia, Tissue concentrations of free amino acids in term human placentas, Am. J. Obstet. Gynecol. 131 (8) (1978) 881–887.
[197] M.P. Lupo, A.L. Cole, Cosmeceutical peptides, Dermatol. Ther. 20 (5) (2007) 343–349.
[198] G. Tonello, M. Daglio, N. Zaccarelli, E. Sottofattori, M. Mazzei, A. Balbi, Characterization and quantitation of the active polynucleotide fraction (PDRN) from human placenta, a tissue repair stimulating agent, J. Pharm. Biomed. Anal. 14 (11) (1996) 1555–1560.
[199] M. Galeano, G. Pallio, N. Irrera, F. Mannino, A. Bitto, D. Altavilla, M. Vaccaro, G. Squadrito, V. Arcoraci, M.R. Colonna, R. Lauro, F. Squadrito, Polydeoxyribonucleotide: a promising biological platform to accelerate impaired skin wound healing, Pharmaceuticals 14 (11) (2021).
[200] S. Jo, A. Baek, Y. Cho, S.H. Kim, D. Baek, J. Hwang, S.-R. Cho, H.J. Kim, Therapeutic effects of polydeoxyribonucleotide in an in vitro neuronal model of ischemia/reperfusion injury, Sci. Rep. 13 (1) (2023) 6004.
[201] J.M. Bowen, L. Chamley, J.A. Keelan, M.D. Mitchell, Cytokines of the placenta and extra-placental membranes: roles and regulation during human pregnancy and parturition, Placenta 23 (4) (2002) 257–273.
[202] H. Uzumaki, T. Okabe, N. Sasaki, K. Hagiwara, F. Takaku, M. Tobita, K. Yasukawa, S. Ito, Y. Umezawa, Identification and characterization of receptors for granulocyte colony-stimulating factor on human placenta and trophoblastic cells, Proc. Natl. Acad. Sci. U. S. A. 86 (23) (1989) 9323–9326.
[203] V. Shinde, K. Dhalwal, A. Paradkar, K. Mahadik, S. Kadam, Evaluation of in-vitro antioxidant activity of human placental extract, Pharmacologyonline 3 (2006).
[204] S. Togashi, N. Takahashi, M. Iwama, S. Watanabe, K. Tamagawa, T. Fukui, Antioxidative collagen-derived peptides in human-placenta extract, Placenta 23 (6) (2002) 497–502.
[205] H.Y. Choi, S.W. Kim, B. Kim, H.N. Lee, S.-J. Kim, M. Song, S. Kim, J. Kim, Y. B. Kim, J.-H. Kim, S.-G. Cho, Alpha-fetoprotein, identified as a novel marker for the antioxidant effect of placental extract, exhibits synergistic antioxidant activity in the presence of estradiol, PLoS One 9 (6) (2014) e99421.
[206] B. Wo, C. Du, Y. Yang, H. Qi, Z. Liang, C. He, F. Yao, X. Li, Human placental extract regulates polarization of macrophages via IRGM/NLRP3 in allergic rhinitis, Biomed. Pharmacother. 160 (2023) 114363.
[207] S.Y. Park, S. Phark, M. Lee, J.Y. Lim, D. Sul, Anti-oxidative and anti-inflammatory activities of placental extracts in benzo[a]pyrene-exposed rats, Placenta 31 (10) (2010) 873–879.
[208] M. Ghoneum, M.S. El-Gerbed, Human placental extract ameliorates methotrexate-induced hepatotoxicity in rats via regulating antioxidative and anti-inflammatory responses, Cancer Chemother. Pharmacol. 88 (2021) 961–971.
[209] B.Y. Kim, H.R. Park, J.H. Shin, S.W. Kim, S.W. Kim, Human placental extract reduces allergic inflammation in a murine allergic rhinitis model, Laryngoscope 124 (10) (2014) E399–E404.
[210] A. Yamauchi, A. Kamiyoshi, T. Koyama, N. Iinuma, S. Yamaguchi, H. Miyazaki, E. Hirano, T. Kaku, T. Shindo, Placental extract ameliorates non-alcoholic steatohepatitis (NASH) by exerting protective effects on endothelial cells, Heliyon 3 (9) (2017) e00416.
[211] M. Yamagata, M. Tsuchishima, T. Saito, M. Tsutsumi, J. George, Therapeutic implication of human placental extract to prevent liver cirrhosis in rats with metabolic dysfunction-associated steatohepatitis, Clin. Sci. (Lond.) 138 (5) (2024) 327–349.
[212] R. Parida, S. Das, T.R. Raju, T.N. Sathyaprabha, Human placental extract ameliorates cytokine and cytokine receptor signaling in the rat hippocampus upon Benzo[a]Pyrene exposure, J. Chem. Neuroanat. 98 (2019) 8–16.
[213] J. Lee, D. Kim, C.H. Jang, G.H. Kim, Highly elastic 3D-printed gelatin/HA/placental-extract scaffolds for bone tissue engineering, Theranostics 12 (9) (2022) 4051–4066.
[214] S.K. Tiwary, D. Shukla, A.K. Tripathi, S. Agrawal, M.K. Singh, V.K. Shukla, Effect of placental-extract gel and cream on non-healing wounds, J. Wound Care 15 (7) (2006) 325–328.
[215] C.H. Wu, G.Y. Chang, W.C. Chang, C.T. Hsu, R.S. Chen, Wound healing effects of porcine placental extracts on rats with thermal injury, Br. J. Dermatol. 148 (2) (2003) 236–245.
[216] J.W. Hong, W.J. Lee, S.B. Hahn, B.J. Kim, D.H. Lew, The effect of human placenta extract in a wound healing model, Ann. Plast. Surg. 65 (1) (2010) 96–100.
[217] A. Chandanwale, D. Langade, V. Mohod, S. Sinha, A. Ramteke, G.D. Bakhshi, M. Motwani, Comparative evaluation of human placental extract for its healing potential in surgical wounds after orthopaedic surgery: an open, randomised, comparative study, J. Indian Med. Assoc. 106 (6) (2008) 405–408.
[218] L. Huang, L.C. Chin, K. Kimura, Y. Nakahata, Human placental extract delays in vitro cellular senescence through the activation of NRF2-mediated antioxidant pathway, Antioxidants 11 (8) (2022).
[219] P.Y. Chang, L.C. Chin, K. Kimura, Y. Nakahata, Human placental extract activates a wide array of gene expressions related to skin functions, Sci. Rep. 12 (1) (2022) 11031.
[220] M. Nagae, M. Nagata, M. Teramoto, M. Yamakawa, T. Matsuki, K. Ohnuki, K. Shimizu, Effect of porcine placenta extract supplement on skin condition in healthy adult women: a randomized, double-blind placebo-controlled study, Nutrients 12 (6) (2020).
[221] C. Yoshikawa, K. Koike, F. Takano, K. Sugiur, N. Suzuki, Efficacy of porcine placental extract on wrinkle widths below the eye in climacteric women, Climacteric 17 (4) (2014) 370–376.
[222] T.R. Kwon, C.T. Oh, E.J. Choi, H.M. Park, H.J. Han, H.J. Ji, B.J. Kim, Human placental extract exerts hair growth-promoting effects through the GSK-3β signaling pathway in human dermal papilla cells, Int. J. Mol. Med. 36 (4) (2015) 1088–1096.
[223] M.H. Kong, E.J. Lee, S.Y. Lee, S.J. Cho, Y.S. Hong, S.B. Park, Effect of human placental extract on menopausal symptoms, fatigue, and risk factors for cardiovascular disease in middle-aged Korean women, Menopause 15 (2) (2008) 296–303.
[224] J.Y. Lee, C. Lee, S.H. Yoon, H. Choi, Effect of porcine placental extract on menopausal symptoms in postmenopausal women: a prospective, randomized, double-blind, placebo-controlled trial, Taiwan. J. Obstet. Gynecol. 59 (5) (2020) 675–681.
[225] Y. Mao, N. John, N.M. Protzman, A. Kuehn, D. Long, R. Sivalenka, R.A. Junka, A. Gosiewska, R.J. Hariri, S.A. Brigido, A decellularized flowable placental connective tissue matrix supports cellular functions of human tenocytes in vitro, Journal of experimental orthopaedics 9 (1) (2022) 69.
[226] Y. Mao, N.M. Protzman, N. John, A. Kuehn, D. Long, R. Sivalenka, R.A. Junka, A. U. Shah, A. Gosiewska, R.J. Hariri, S.A. Brigido, An in vitro comparison of human corneal epithelial cell activity and inflammatory response on differently designed ocular amniotic membranes and a clinical case study, J. Biomed. Mater. Res. B Appl. Biomater. 111 (3) (2023) 684–700.
[227] X. Zhang, X. Chen, H. Hong, R. Hu, J. Liu, C. Liu, Decellularized extracellular matrix scaffolds: recent trends and emerging strategies in tissue engineering, Bioact. Mater. 10 (2022) 15–31.
[228] Y. Jiang, S.J. Sun, Z. Zhen, R. Wei, N. Zhang, S.Y. Liao, H.F. Tse, Myocardial repair of bioengineered cardiac patches with decellularized placental scaffold and human-induced pluripotent stem cells in a rat model of myocardial infarction, Stem Cell Res. Ther. 12 (1) (2021) 13.
[229] R.A. Hopper, K. Woodhouse, J.L. Semple, Acellularization of human placenta with preservation of the basement membrane: a potential matrix for tissue engineering, Ann. Plast. Surg. 51 (6) (2003) 598–602.
[230] C.P. Chen, J.D. Aplin, Placental extracellular matrix: gene expression, deposition by placental fibroblasts and the effect of oxygen, Placenta 24 (4) (2003) 316–325.
[231] J.J. Lim, T.J. Koob, Placental Cells and Tissues: the Transformative Rise in Advanced Wound Care, Worldwide Wound Healing-Innovation in Natural and Conventional Methods, InTech, Rijeka, Croatia, 2016, pp. 121–151.
[232] J.S. Choi, J.D. Kim, H.S. Yoon, Y.W. Cho, Full-thickness skin wound healing using human placenta-derived extracellular matrix containing bioactive molecules, Tissue engineering, Part. Accel. 19 (3–4) (2013) 329–339.
[233] K.H. Schneider, M. Enayati, C. Grasl, I. Walter, L. Budinsky, G. Zebic, C. Kaun, A. Wagner, K. Kratochwill, H. Redl, A.H. Teuschl, B.K. Podesser, H. Bergmeister,

Acellular vascular matrix grafts from human placenta chorion: impact of ECM preservation on graft characteristics, protein composition and in vivo performance, Biomaterials 177 (2018) 14–26.
[234] K.H. Schneider, P. Aigner, W. Holnthoner, X. Monforte, S. Nürnberger, D. Rünzler, H. Redl, A.H. Teuschl, Decellularized human placenta chorion matrix as a favorable source of small-diameter vascular grafts, Acta Biomater. 29 (2016) 125–134.
[235] R. Sajed, A.H. Zarnani, Z. Madjd, S. Arefi, M.R. Bolouri, S. Vafaei, A. Samadikuchaksaraei, M. Gholipourmalekabadi, N. Haghighipour, R. Ghods, Introduction of an efficient method for placenta decellularization with high potential to preserve ultrastructure and support cell attachment, Artif. Organs 46 (3) (2022) 375–386.
[236] E. Özdemir, A. Emet, R. Hashemihesar, A.C.S. Yürüker, E. Kılıç, D. Uçkan Çetinkaya, E. Turhan, Articular cartilage regeneration utilizing decellularized human placental scaffold, mesenchymal stem cells and platelet rich plasma, Tissue engineering and regenerative medicine 17 (6) (2020) 901–908.
[237] P.K. Parameshwar, L. Sagrillo-Fagundes, N. Azevedo Portilho, W.A. Pastor, C. Vaillancourt, C. Moraes, Engineered models for placental toxicology: emerging approaches based on tissue decellularization, Reprod. Toxicol. 112 (2022) 148–159.
[238] F. Asgari, S. Khosravimelal, M. Koruji, Z. Aliakbar Ahovan, A. Shirani, A. Hashemi, H. Ghasemi Hamidabadi, N.P.S. Chauhan, L. Moroni, R.L. Reis, S. C. Kundu, M. Gholipourmalekabadi, Long-term preservation effects on biological properties of acellular placental sponge patches, Materials science & engineering, C, Materials for biological applications 121 (2021) 111814.
[239] A. Mehrabi, S. Mousazadeh, A. Mollafilabi, N. Nafissi, P.B. Milan, Synthesis and characterization of a silk fibroin/placenta matrix hydrogel for breast reconstruction, Life Sci. 334 (2023) 122236.
[240] Y. Duan, W. Huang, B. Zhan, Y. Li, X. Xu, K. Li, X. Li, X. Liu, S. Ding, S. Wang, J. Guo, Y. Wang, Q. Gu, Bioink derived from human placenta supporting angiogenesis, Biomed. Mater. 17 (5) (2022).
[241] Y. Fan, M. Lüchow, A. Badria, D.J. Hutchinson, M. Malkoch, Placenta powder-infused thiol-ene PEG hydrogels as potential tissue engineering scaffolds, Biomacromolecules 24 (4) (2023) 1617–1626.
[242] F. Asgari, H. Asgari, M. Najafi, S. Hajiaghalou, V. Pirhajati-Mahabadi, A. Mohammadi, M. Gholipourmalekabadi, M. Koruji, In vitro proliferation and differentiation of mouse spermatogonial stem cells in decellularized human placenta matrix, J. Biomed. Mater. Res. B Appl. Biomater. 112 (5) (2024) e35414.
[243] X. Zhang, S. Xiao, B. Liu, Y. Miao, Z. Hu, Use of extracellular matrix hydrogel from human placenta to restore hair-inductive potential of dermal papilla cells, Regen. Med. 14 (8) (2019) 741–751.
[244] Y. Hong, I. Koh, K. Park, P. Kim, On-chip fabrication of a cell-derived extracellular matrix sheet, ACS Biomater. Sci. Eng. 3 (12) (2017) 3546–3552.
[245] S.E. Lobo, L.C. Leonel, C.M. Miranda, T.M. Coelho, G.A. Ferreira, A. Mess, M. S. Abrão, M.A. Miglino, The placenta as an organ and a source of stem cells and extracellular matrix: a review, Cells Tissues Organs 201 (4) (2016) 239–252.
[246] S. Alizadeh, L. Mahboobi, M. Nasiri, Z. Khosrowpour, S. Khosravimelal, F. Asgari, M. Gholipour-Malekabadi, S.M. Taghi Razavi-Toosi, N.P. Singh Chauhan, F. Ghobadi, Decellularized placental sponge seeded with human mesenchymal stem cells improves deep skin wound healing in the animal model, ACS Appl. Bio Mater. 7 (4) (2024) 2140–2152.
[247] J. Bhoopathy, S. Dharmalingam, W.V. Sathyaraj, S. Rajendran, S. Rymbai, R. Senthil, R. Atchudan, Sericin/human placenta-derived extracellular matrix scaffolds for cutaneous wound treatment-preparation, characterization, in vitro and in vivo analyses, Pharmaceutics 15 (2) (2023).
[248] M.P. Francis, E. Breathwaite, A.A. Bulysheva, F. Varghese, R.U. Rodriguez, S. Dutta, I. Semenov, R. Ogle, A. Huber, A.M. Tichy, S. Chen, C. Zemlin, Human placenta hydrogel reduces scarring in a rat model of cardiac ischemia and enhances cardiomyocyte and stem cell cultures, Acta Biomater. 52 (2017) 92–104.
[249] J. Lubsen, B.A. Kirwan, Combined endpoints: can we use them? Stat. Med. 21 (19) (2002) 2959–2970.
[250] Z. Kakabadze, A. Kakabadze, D. Chakhunashvili, L. Karalashvili, E. Berishvili, Y. Sharma, S. Gupta, Decellularized human placenta supports hepatic tissue and allows rescue in acute liver failure, Hepatology 67 (5) (2018) 1956–1969.
[251] Z. Kakabadze, L. Karalashvili, D. Chakhunashvili, N. Havlioglu, M. Janelidze, A. Kakabadze, Y. Sharma, S. Gupta, Decellularized bovine placentome for portacavally-interposed heterotopic liver transplantation in rats, Materials science & engineering, C, Materials for biological applications 97 (2019) 293–301.
[252] K.M. Park, K.H. Hussein, S.H. Hong, C. Ahn, S.R. Yang, S.M. Park, O.K. Kweon, B. M. Kim, H.M. Woo, Decellularized liver extracellular matrix as promising tools for transplantable bioengineered liver promotes hepatic lineage commitments of induced pluripotent stem cells, tissue engineering, Part. Accel. 22 (5–6) (2016) 449–460.
[253] C.A. Batchelder, M.L. Martinez, A.F. Tarantal, Natural scaffolds for renal differentiation of human embryonic stem cells for kidney tissue engineering, PLoS One 10 (12) (2015) e0143849.
[254] K. Kitano, D.M. Schwartz, H. Zhou, S.E. Gilpin, G.R. Wojtkiewicz, X. Ren, C. A. Sommer, A.V. Capilla, D.J. Mathisen, A.M. Goldstein, G. Mostoslavsky, H. C. Ott, Bioengineering of functional human induced pluripotent stem cell-derived intestinal grafts, Nat. Commun. 8 (1) (2017) 765.
[255] W. Yang, Q. Chen, R. Xia, Y. Zhang, L. Shuai, J. Lai, X. You, Y. Jiang, P. Bie, L. Zhang, H. Zhang, L. Bai, A novel bioscaffold with naturally-occurring extracellular matrix promotes hepatocyte survival and vessel patency in mouse models of heterologous transplantation, Biomaterials 177 (2018) 52–66.
[256] E. Pashuck, Y. Mao, K. Kim, A human placenta-derived decellularized connective tissue matrix (CTM) supports cellular functions involved in wound healing processes, in: Symposium on Advanced Wound Care, 2016.
[257] A. Baracho Trindade Hill, A.A. Speri Alves, R. da Silva Nunes Barreto, F. Fernandes Bressan, M.A. Miglino, J. Mansano Garcia, Placental scaffolds have the ability to support adipose-derived cells differentiation into osteogenic and chondrogenic lineages, J Tissue Eng Regen Med 14 (11) (2020) 1661–1672.
[258] A.P. Rameshbabu, P. Ghosh, E. Subramani, K. Bankoti, K. Kapat, S. Datta, P. P. Maity, B. Subramanian, S. Roy, K. Chaudhury, S. Dhara, Investigating the potential of human placenta-derived extracellular matrix sponges coupled with amniotic membrane-derived stem cells for osteochondral tissue engineering, J. Mater. Chem. B 4 (4) (2016) 613–625.
[259] F. Asgari, H.R. Asgari, M. Najafi, B.S. Eftekhari, M. Vardiani, M. Gholipourmalekabadi, M. Koruji, Optimization of decellularized human placental macroporous scaffolds for spermatogonial stem cells homing, J. Mater. Sci. Mater. Med. 32 (5) (2021) 47.
[260] Y.W. Chiu, W.P. Chen, C.C. Su, Y.C. Lee, P.H. Hsieh, Y.L. Ho, The arrhythmogenic effect of self-assembling nanopeptide hydrogel scaffolds on neonatal mouse cardiomyocytes, Nanomed. Nanotechnol. Biol. Med. 10 (5) (2014) 1065–1073.
[261] F. Pampaloni, E.H. Stelzer, A. Masotti, Three-dimensional tissue models for drug discovery and toxicology, Recent Pat. Biotechnol. 3 (2) (2009) 103–117.
[262] J.D. Aplin, Developmental cell biology of human villous trophoblast: current research problems, Int. J. Dev. Biol. 54 (2–3) (2010) 323–329.
[263] L. Flynn, J.L. Semple, K.A. Woodhouse, Decellularized placental matrices for adipose tissue engineering, J. Biomed. Mater. Res., Part A 79 (2) (2006) 359–369.
[264] H. Zeng, S. Guo, X. Ren, Z. Wu, S. Liu, X. Yao, Current strategies for exosome cargo loading and targeting delivery, Cells 12 (10) (2023).
[265] E.E. Burkova, S.E. Sedykh, G.A. Nevinsky, Human placenta exosomes: biogenesis, isolation, composition, and prospects for use in diagnostics, Int. J. Mol. Sci. 22 (4) (2021).
[266] L. Czernek, M. Düchler, Exosomes as messengers between mother and fetus in pregnancy, Int. J. Mol. Sci. 21 (12) (2020).
[267] R. Farrelly, M.G. Kennedy, R. Spencer, K. Forbes, Extracellular vesicles as markers and mediators of pregnancy complications: gestational diabetes, pre-eclampsia, preterm birth and fetal growth restriction, J. Physiol. 601 (22) (2023) 4973–4988.
[268] C.M. Nguyen, M. Sallam, M.S. Islam, K. Clack, N. Soda, N.-T. Nguyen, M.J. A. Shiddiky, Placental exosomes as biomarkers for maternal diseases: current advances in isolation, characterization, and detection, ACS Sens. 8 (7) (2023) 2493–2513.
[269] M. Ghafourian, R. Mahdavi, Z. Akbari Jonoush, M. Sadeghi, N. Ghadiri, M. Farzaneh, A. Mousavi Salehi, The implications of exosomes in pregnancy: emerging as new diagnostic markers and therapeutics targets, Cell Commun. Signal. 20 (1) (2022) 51.
[270] M.D. Mitchell, H.N. Peiris, M. Kobayashi, Y.Q. Koh, G. Duncombe, S.E. Illanes, G. E. Rice, C. Salomon, Placental exosomes in normal and complicated pregnancy, Am. J. Obstet. Gynecol. 213 (4, Supplement) (2015) S173–S181.
[271] A. Nakahara, S. Nair, V. Ormazabal, O. Elfeky, C.E. Garvey, S. Longo, C. Salomon, Circulating placental extracellular vesicles and their potential roles during pregnancy, Ochsner J. 20 (4) (2020) 439–445.
[272] M. Tschuschke, I. Kocherova, A. Bryja, P. Mozdziak, A. Angelova Volponi, K. Janowicz, R. Sibiak, H. Piotrowska-Kempisty, D. Iżycki, D. Bukowska, P. Antosik, J.A. Shibli, M. Dyszkiewicz-Konwińska, B. Kempisty, Inclusion biogenesis, methods of isolation and clinical application of human cellular exosomes, J. Clin. Med. 9 (2) (2020).
[273] A. Sabapatha, C. Gercel-Taylor, D.D. Taylor, Specific isolation of placenta-derived exosomes from the circulation of pregnant women and their immunoregulatory consequences 1, Am. J. Reprod. Immunol. 56 (5-6) (2006) 345–355.
[274] F. da Silva Nardi, T.F. Michelon, J. Neumann, L.F.S. Manvailer, B. Wagner, P. A. Horn, M. da Graça Bicalho, V. Rebmann, High levels of circulating extracellular vesicles with altered expression and function during pregnancy, Immunobiology 221 (7) (2016) 753–760.
[275] C. Huang, Y. Zhao, S. Lin, L. Li, X. Guo, S. Yumiseba, J.D. Yang, R. Hariri, Q. Ye, S. He, A. Kilcoyne, Characterization of human placenta-derived exosome (pExo) as a potential osteoarthritis disease modifying therapeutic, Arthritis Res. Ther. 25 (1) (2023) 229.
[276] Z.H. Xiong, J. Wei, M.Q. Lu, M.Y. Jin, H.L. Geng, Protective effect of human umbilical cord mesenchymal stem cell exosomes on preserving the morphology and angiogenesis of placenta in rats with preeclampsia, Biomed. Pharmacother. 105 (2018) 1240–1247.
[277] K. Bai, X. Li, J. Zhong, E.H.Y. Ng, W.S.B. Yeung, C.L. Lee, P.C.N. Chiu, Placenta-derived exosomes as a modulator in maternal immune tolerance during pregnancy, Front. Immunol. 12 (2021) 671093.
[278] K. Bai, C.-L. Lee, X. Liu, J. Li, D. Cao, L. Zhang, D. Hu, H. Li, Y. Hou, Y. Xu, A.S. Y. Kan, K.-W. Cheung, E.H.Y. Ng, W.S.B. Yeung, P.C.N. Chiu, Human placental exosomes induce maternal systemic immune tolerance by reprogramming circulating monocytes, J. Nanobiotechnol. 20 (1) (2022) 86.
[279] M. Hedlund, A.-C. Stenqvist, O. Nagaeva, L. Kjellberg, M. Wulff, V. Baranov, L. Mincheva-Nilsson, Human placenta expresses and secretes NKG2D ligands via exosomes that down-modulate the cognate receptor expression: evidence for immunosuppressive function, J. Immunol. 183 (1) (2009) 340–351.
[280] Z. Zhu, C. Han, S. Xian, F. Zhuang, F. Ding, W. Zhang, Y. Liu, Placental mesenchymal stromal cells (PMSCs) and PMSC-derived extracellular vesicles (PMSC-EVs) attenuated renal fibrosis in rats with unilateral ureteral obstruction (UUO) by regulating CD4+ T cell polarization, Stem Cell. Int. (2020) 2020.

[281] S.-Q. Cao, T.-X. Jiang, Y.-Y. Guo, R. Lin, L. Lin, MiR-519d-3p from placenta-derived exosomes induce immune intolerance regulating immune cells, contributing to the pathogenesis of preeclampsia, Immunol. Investig. (2025) 1–22.
[282] R.P. Thiruvenkataramani, A. Abdul-Hafez, T. Kesaraju, H. Mohamed, S. A. Ibrahim, A. Othman, H. Arif, A.A. Zarea, M. Abdulmageed, M.G. Arellano, Small extracellular vesicles derived from cord blood plasma and placental mesenchymal stem cells attenuate acute lung injury induced by lipopolysaccharide (LPS), Int. J. Mol. Sci. 26 (1) (2024) 75.
[283] E. Delorme-Axford, R.B. Donker, J.F. Mouillet, T. Chu, A. Bayer, Y. Ouyang, T. Wang, D.B. Stolz, S.N. Sarkar, A.E. Morelli, Y. Sadovsky, C.B. Coyne, Human placental trophoblasts confer viral resistance to recipient cells, Proc. Natl. Acad. Sci. U. S. A. 110 (29) (2013) 12048–12053.
[284] Y. Ouyang, H. Li, K. Krawczynski, J.-F. Mouillet, C. Coyne, A. Sorkin, Y. Sadovsky, B-101 Placental exosomes in maternal-placental-fetal communication and viral resistance, JAIDS Journal of Acquired Immune Deficiency Syndromes 81 (2019).
[285] Y. Ouyang, A. Bayer, T. Chu, V.A. Tyurin, V.E. Kagan, A.E. Morelli, C.B. Coyne, Y. Sadovsky, Isolation of human trophoblastic extracellular vesicles and characterization of their cargo and antiviral activity, Placenta 47 (2016) 86–95.
[286] L. Jia, X. Zhou, X. Huang, X. Xu, Y. Jia, Y. Wu, J. Yao, Y. Wu, K. Wang, Maternal and umbilical cord serum-derived exosomes enhance endothelial cell proliferation and migration, FASEB J. 32 (8) (2018) 4534–4543.
[287] Y.Y. Go, C.M. Lee, W.M. Ju, S.-W. Chae, J.-J. Song, Extracellular vesicles (secretomes) from human trophoblasts promote the regeneration of skin fibroblasts, Int. J. Mol. Sci. 22 (13) (2021) 6959.
[288] J. Ni, Y. Liu, L. Kang, L. Wang, Z. Han, K. Wang, B. Xu, R. Gu, Human trophoblast-derived exosomes attenuate doxorubicin-induced cardiac injury by regulating miR-200b and downstream Zeb1, J. Nanobiotechnol. 18 (1) (2020) 171.
[289] S. Moghassemi, A. Dadashzadeh, M.J. Sousa, H. Vlieghe, J. Yang, C.M. León-Félix, C.A. Amorim, Extracellular vesicles in nanomedicine and regenerative medicine: a review over the last decade, Bioact. Mater. 36 (2024) 126–156.
[290] Y. Zhang, L. Shi, X. Li, Y. Liu, G. Zhang, Y. Wang, Placental stem cells-derived exosomes stimulate cutaneous wound regeneration via engrailed-1 inhibition, Front. Bioeng. Biotechnol. 10 (2022) 1044773.
[291] C. Peng, H. Xu, Q. Zhuang, J. Liu, Y. Ding, Q. Tang, Z. Wang, K. Yao, Placenta-derived mesenchymal stem cells promote diabetic wound healing via exosomal protein interaction networks, Wound Repair Regen. 32 (5) (2024) 638–651.
[292] L. Varyani, N. Ahmadpanah, R. Kasiri, S. Shahzamani, S. Tomraee, A. Jafari, H. Mirjalili, N.S. Asl, Human amniotic membrane hydrogel loaded with exosomes derived from human placental mesenchymal stem cells accelerate diabetic wound healing, Tissue Cell 91 (2024) 102590.
[293] A. Jafari, A.R. Khalatbary, S. Taghiloo, M.S. Mirzaie, E. Nazar, M. Poorhassan, E. Akbari, M. Asadzadeh, A. Raoofi, D. Nasiry, Exosomes derived from human placental mesenchymal stem cells in combination with hyperbaric oxygen synergically alleviates spinal cord ischemia-reperfusion injury, Regenerative Therapy 24 (2023) 407–416.
[294] K. Clark, S. Zhang, S. Barthe, P. Kumar, C. Pivetti, N. Kreutzberg, C. Reed, Y. Wang, Z. Paxton, D. Farmer, F. Guo, A. Wang, Placental mesenchymal stem cell-derived extracellular vesicles promote myelin regeneration in an animal model of multiple sclerosis, Cells 8 (12) (2019).
[295] C. Zhang, C. Zhang, Y. Xu, C. Li, Y. Cao, P. Li, Exosomes derived from human placenta-derived mesenchymal stem cells improve neurologic function by promoting angiogenesis after spinal cord injury, Neurosci. Lett. 739 (2020) 135399.
[296] A. Soleimani, S. Oraee Yazdani, M. Pedram, F. Saadinam, M.J. Rasaee, M. Soleimani, Intrathecal injection of human placental mesenchymal stem cells derived exosomes significantly improves functional recovery in spinal cord injured rats, Mol. Biol. Rep. 51 (1) (2024) 193.
[297] F.T. Amiri, A. Jafari, F. Ahmadi, H. Mokhtari, A. Raoofi, F.M. Kasmaie, M. Omran, M.A. Alimohammadi, D. Nasiry, Exosomes derived from human placental mesenchymal stem cells in combination with hyperbaric oxygen therapy enhance neuroregeneration in a rat model of sciatic nerve crush injury, Regenerative Therapy 28 (2025) 30–40.
[298] Y. Zhang, Y. Tang, X. Chen, X. Sun, M. Zhao, Q. Chen, Therapeutic potential of miRNAs in placental extracellular vesicles in ovarian and endometrial cancer, Hum. Cell 37 (1) (2024) 285–296.
[299] T.C. Peak, P.P. Praharaj, G.K. Panigrahi, M. Doyle, Y. Su, I.R. Schlaepfer, R. Singh, D.J. Vander Griend, J. Alickson, A. Hemal, A. Atala, G. Deep, Exosomes secreted by placental stem cells selectively inhibit growth of aggressive prostate cancer cells, Biochem. Biophys. Res. Commun. 499 (4) (2018) 1004–1010.
[300] H. Liu, X. Zhang, M. Zhang, S. Zhang, J. Li, Y. Zhang, Q. Wang, J.P. Cai, K. Cheng, S. Wang, Mesenchymal stem cell derived exosomes repair uterine injury by targeting transforming growth factor-β signaling, ACS Nano 18 (4) (2024) 3509–3519.
[301] S. Moghassemi, A. Dadashzadeh, H. Jafari, P. Ghaffari-Bohlouli, A. Shavandi, C. A. Amorim, Liposomal oxygen-generating hydrogel for enhancing cell survival under hypoxia condition, Colloids Surf. B Biointerfaces 231 (2023) 113562.
[302] S. Keshtkar, M. Kaviani, S. Soleimanian, N. Azarpira, Z. Asvar, S. Pakbaz, Stem cell-derived exosome as potential therapeutics for microbial diseases, Front. Microbiol. 12 (2021) 786111.
[303] P. Pillay, K. Moodley, J. Moodley, I. Mackraj, Placenta-derived exosomes: potential biomarkers of preeclampsia, Int. J. Nanomed. 12 (2017) 8009–8023.
[304] M. Kang, C. Hisey, B. Tsai, Y. Nursalim, C. Blenkiron, L.W. Chamley, Placental extracellular vesicles can Be loaded with plasmid DNA, Mol. Pharm. 20 (4) (2023) 1898–1913.
[305] N.A. Friel, L. de Girolamo, A.H. Gomoll, K.C. Mowry, J.B. Vines, J. Farr, Amniotic fluid, cells, and membrane application, Operat. Tech. Sports Med. 25 (1) (2017) 20–24.
[306] S. Leal-Marin, T. Kern, N. Hofmann, O. Pogozhykh, C. Framme, M. Borgel, C. Figueiredo, B. Glasmacher, O. Gryshkov, Human Amniotic Membrane: a review on tissue engineering, application, and storage, J. Biomed. Mater. Res. B Appl. Biomater. 109 (8) (2021) 1198–1215.
[307] K. Jirsova, G.L.A. Jones, Amniotic membrane in ophthalmology: properties, preparation, storage and indications for grafting-a review, Cell Tissue Bank. 18 (2) (2017) 193–204.
[308] Q. Zhang, D. Lai, Application of human amniotic epithelial cells in regenerative medicine: a systematic review, Stem Cell Res. Ther. 11 (1) (2020) 439.
[309] F. Sanders, J. Huang, D.B.J. Alió, S. Hamada, C. McAlinden, Amniotic membrane transplantation: structural and biological properties, tissue preparation, application and clinical indications, Eye (Lond) 38 (4) (2024 Mar) 668–679.
[310] A.C. Mamede, M.J. Carvalho, A.M. Abrantes, M. Laranjo, C.J. Maia, M.F. Botelho, Amniotic membrane: from structure and functions to clinical applications, Cell Tissue Res. 349 (2) (2012) 447–458.
[311] W.K. Chua, M.L. Oyen, Do we know the strength of the chorioamnion? A critical review and analysis, Eur. J. Obstet. Gynecol. Reprod. Biol. 144 (Suppl 1) (2009) S128–S133.
[312] H. Niknejad, H. Peirovi, M. Jorjani, A. Ahmadiani, J. Ghanavi, A.M. Seifalian, Properties of the amniotic membrane for potential use in tissue engineering, Eur. Cell. Mater. 15 (2008) 88–99.
[313] B. G., The foetal membranes. A review of the anatomy of normal amnion and chorion and some aspects of their function, Postgrad. Med. J. 38 (438) (1962) 193–201.
[314] S. Parry, J.r. Strauss, Premature rupture of the fetal membranes, N. Engl. J. Med. 338 (10) (1998) 663–670.
[315] T.J. Koob, J.J. Lim, M. Massee, N. Zabek, G. Denoziere, Properties of dehydrated human amnion/chorion composite grafts: implications for wound repair and soft tissue regeneration, J. Biomed. Mater. Res. B Appl. Biomater. 102 (6) (2014) 1353–1362.
[316] T.J. Sabol, G.S. Tran, J. Matuszewski, W.W. Weston, Standardized reporting of amnion and amnion/chorion allograft data for wound care, Health Sci Rep 5 (5) (2022) e794.
[317] T.J. Koob, J.J. Lim, N. Zabek, M. Massee, Cytokines in single layer amnion allografts compared to multilayer amnion/chorion allografts for wound healing, J. Biomed. Mater. Res. B Appl. Biomater. 103 (5) (2015) 1133–1140.
[318] P. Dockery, J. Bermingham, D. Jenkins, Structure-function relations in the human placenta, Biochem. Soc. Trans. 28 (2) (2000) 202–208.
[319] A.J. Shortt, G.A. Secker, R.J. Lomas, S.P. Wilshaw, J.N. Kearney, S.J. Tuft, J. T. Daniels, The effect of amniotic membrane preparation method on its ability to serve as a substrate for the ex-vivo expansion of limbal epithelial cells, Biomaterials 30 (6) (2009) 1056–1065.
[320] R. Sripriya, R. Kumar, Denudation of human amniotic membrane by a novel process and its characterisations for biomedical applications, Prog Biomater 5 (3–4) (2016) 161–172.
[321] E. Spoerl, G. Wollensak, F. Reber, L. Pillunat, Cross-linking of human amniotic membrane by glutaraldehyde, Ophthalmic Res. 36 (2) (2004) 71–77.
[322] B. Ma, X. Wang, C. Wu, J. Chang, Crosslinking strategies for preparation of extracellular matrix-derived cardiovascular scaffolds, Regen Biomater 1 (1) (2014) 81–89.
[323] P.B. Panici, I. Ruscito, M.L. Gasparri, D. Maffucci, C. Marchese, F. Bellati, Vaginal reconstruction with the Abbe-McIndoe technique: from dermal grafts to autologous in vitro cultured vaginal tissue transplant, Semin. Reprod. Med. 29 (1) (2011) 45–54.
[324] J.Y. Lai, Photo-cross-linking of amniotic membranes for limbal epithelial cell cultivation, Mater. Sci. Eng., C 45 (2014) 313–319.
[325] H. Kim, D. Son, T.H. Choi, S. Jung, S. Kwon, J. Kim, K. Han, Evaluation of an amniotic membrane-collagen dermal substitute in the management of full-thickness skin defects in a pig, Arch Plast Surg 40 (1) (2013) 11–18.
[326] D.Y. Chau, S.V. Brown, M.L. Mather, V. Hutter, N.L. Tint, H.S. Dua, F.R. Rose, A. M. Ghaemmaghami, Tissue transglutaminase (TG-2) modified amniotic membrane: a novel scaffold for biomedical applications, Biomed. Mater. 7 (4) (2012) 045011.
[327] M.A. Seyed, K. Vijayaraghavan, Evaluation of an improved chitosan scaffold cross-linked with polyvinyl alcohol and amine coupling through 1-ethyl-3-(3-dimethyl aminopropyl)-carbodiimide (EDC) and 2 N-hydroxysuccinimide (NHS) for corneal applications, Open Access Maced J Med Sci 6 (9) (2018) 1561–1570.
[328] R. Dong, C. Liu, S. Tian, J. Bai, K. Yu, L. Liu, D. Tian, Electrospun polycaprolactone (PCL)-amnion nanofibrous membrane prevents adhesions and promotes nerve repair in a rat model of sciatic nerve compression, PLoS One 15 (12) (2020) e0244301.
[329] Z. Lotfi, M. Khakbiz, N. Davari, S. Bonakdar, J. Mohammadi, M.A. Shokrgozar, S. Derhambakhsh, Fabrication and multiscale modeling of polycaprolactone/amniotic membrane electrospun nanofiber scaffolds for wound healing, Artif. Organs 47 (8) (2023) 1267–1284.
[330] S. Dehghani, M. Rasoulianboroujeni, H. Ghasemi, S.H. Keshel, Z. Nozarian, M. N. Hashemian, M. Zarei-Ghanavati, G. Latifi, R. Ghaffari, Z. Cui, H. Ye, L. Tayebi, 3D-Printed membrane as an alternative to amniotic membrane for ocular surface/conjunctival defect reconstruction: an in vitro & in vivo study, Biomaterials 174 (2018) 95–112.
[331] H. Niknejad, T. Deihim, M. Solati-Hashjin, H. Peirovi, The effects of preservation procedures on amniotic membrane's ability to serve as a substrate for cultivation of endothelial cells, Cryobiology 63 (3) (2011) 145–151.

[332] I.J. Jhumi, T.A. Arafat, P.C. Karmakar, M. Arifuzzaman, M.S. Hossain, N. Akhtar, S.M. Asaduzzaman, Silver nanoparticle incorporated human amniotic membrane gel accelerates second-degree burn wound healing in wister rat, Evid Based Complement Alternat Med 2023 (2023) 9808556.
[333] C. Malhotra, A.K. Jain, Human amniotic membrane transplantation: different modalities of its use in ophthalmology, World J. Transplant. 4 (2) (2014) 111–121.
[334] T. Sc, Amniotic membrane transplantation for ocular surface reconstruction, Biosci. Rep. 21 (4) (2001) 481–489.
[335] M. Fernandes, M.S. Sridhar, V.S. Sangwan, Amniotic membrane transplantation for ocular surface reconstruction, Cornea 24 (6) (2005) 643–653.
[336] H. Wong, J.S. Wang, Y.L. Du, H.T. Xie, M.C. Zhang, Sandwich (Amnion/Conjunctival-Limbal autograft/amnion) transplantation for recurrent pterygium with restrictive strabismus, J. Clin. Med. 11 (23) (2022).
[337] P. Singh, A. Raj, A. Gupta, S. Pradhan, N. Aftab, S. Biswas, Role of amniotic membrane transplantation in treating acute ocular manifestations in Steven-Johnson syndrome and its long-term impact, Indian J. Ophthalmol. 70 (12) (2022) 4470–4471.
[338] A. Furdova, G. Czanner, J. Koller, P. Vesely, R. Furda, Z. Pridavkova, Amniotic membrane application in surgical treatment of conjunctival tumors, Sci. Rep. 13 (1) (2023) 2835.
[339] J. Shimazaki, N. Shinozaki, K. Tsubota, Transplantation of amniotic membrane and limbal autograft for patients with recurrent pterygium associated with symblepharon, Br. J. Ophthalmol. 82 (3) (1998) 235–240.
[340] A. Rahal, D. Meller, A. Manthey, R. Pfortner, S. Lang, N. Bechrakis, H. Westekemper, Midterm results of conjunctival reconstruction with buccal mucosa and amniotic membrane after resecting ocular surface squamous neoplasia of the fornix, Can. J. Ophthalmol. 58 (6) (2023) 543–549.
[341] T. Sc, Amniotic membrane transplantation for persistent corneal epithelial defect, Br. J. Ophthalmol. 85 (12) (2001) 1400–1401.
[342] E. NaPier, M. Camacho, T.F. McDevitt, A.R. Sweeney, Neurotrophic keratopathy: current challenges and future prospects, Ann. Med. 54 (1) (2022) 666–673.
[343] D.S.J. Ting, C. Henein, D.G. Said, H.S. Dua, Amniotic membrane transplantation for infectious keratitis: a systematic review and meta-analysis, Sci. Rep. 11 (1) (2021) 13007.
[344] N.S. Georgiadis, N.G. Ziakas, K.G. Boboridis, C. Terzidou, D.G. Mikropoulos, Cryopreserved amniotic membrane transplantation for the management of symptomatic bullous keratopathy, Clin. Exp. Ophthalmol. 36 (2) (2008) 130–135.
[345] N. Sharma, M. Kaur, T. Agarwal, V.S. Sangwan, R.B. Vajpayee, Treatment of acute ocular chemical burns, Surv. Ophthalmol. 63 (2) (2018) 214–235.
[346] Q. Le, S.X. Deng, The application of human amniotic membrane in the surgical management of limbal stem cell deficiency, Ocul. Surf. 17 (2) (2019) 221–229.
[347] K. Barton, D.L. Budenz, P.T. Khaw, S.C. Tseng, Glaucoma filtration surgery using amniotic membrane transplantation, Investig. Ophthalmol. Vis. Sci. 42 (8) (2001) 1762–1768.
[348] d.R. A, Plastic repair of conjunctival defects with fetal membrane, Arch. Ophthalmol. 23 (1940) 522–525.
[349] J.C. Kim, S.C. Tseng, Transplantation of preserved human amniotic membrane for surface reconstruction in severely damaged rabbit corneas, Cornea 14 (1995) 473–484.
[350] D. Meller, S.C. Tseng, Conjunctival epithelial cell differentiation on amniotic membrane, Investig. Ophthalmol. Vis. Sci. 40 (5) (1999) 878–886.
[351] D. Said, M. Nubile, T. Alomar, A. Hopkinson, T. Gray, J. Lowe, H. Dua, Histologic features of transplanted amniotic membrane: implications for corneal wound healing, Ophthalmology 116 (7) (2009) 1287–1295.
[352] M. Guo, F. Grinnell, Basement membrane and human epidermal differentiation in vitro, J. Invest. Dermatol. 93 (3) (1989) 372–378.
[353] G. Clare, C. Bunce, S. Tuft, Amniotic membrane transplantation for acute ocular burns, Cochrane Database Syst. Rev. 9 (9) (2022) CD009379.
[354] N. Koizumi, N.J. Fullwood, G. Bairaktaris, T. Inatomi, S. Kinoshita, A.J. Quantock, Cultivation of corneal epithelial cells on intact and denuded human amniotic membrane, Investig. Ophthalmol. Vis. Sci. 41 (9) (2000) 2506–2513.
[355] Z. Chen, H.Y. Lao, L. Liang, Update on the application of amniotic membrane in immune-related ocular surface diseases, Taiwan J Ophthalmol 11 (2) (2021) 132–140.
[356] Y. Hao, D.H. Ma, D.G. Hwang, W.S. Kim, F. Zhang, Identification of antiangiogenic and antiinflammatory proteins in human amniotic membrane, Cornea 19 (3) (2000) 348–352.
[357] M. Adinolfi, C.A. Akle, I. McColl, A.H. Fensom, L. Tansley, P. Connolly, B. Hsi, W. P. Faulk, P. Travers, W.F. Bodmer, Expression of HLA antigens, beta 2-microglobulin and enzymes by human amniotic epithelial cells. Nature, Nature 295 (5847) (1982) 325–327.
[358] X. Che, H. Wu, C. Jia, H. Sun, S. Ou, J. Wang, M.V. Jeyalatha, X. He, J. Yu, C. Zuo, Z. Liu, W. Li, A novel tissue-engineered corneal stromal equivalent based on amniotic membrane and keratocytes, Investig. Ophthalmol. Vis. Sci. 60 (2) (2019) 517–527.
[359] L. Liang, W. Li, S. Ling, H. Sheha, W. Qiu, C. Li, Z. Liu, Amniotic membrane extraction solution for ocular chemical burns, Clin. Exp. Ophthalmol. 37 (9) (2009) 855–863.
[360] P. Ramasamy, R. Krishnakumar, R. Rekha, B. Vaseeharan, K. Saraswathi, M. Raj, R.E.B. Hanna, G.P. Brennan, G. Dayanithi, S. Vijayakumar, Bio-fabrication of human amniotic membrane zinc oxide nanoparticles and the wet/dry HAM dressing membrane for wound healing, Front. Bioeng. Biotechnol. 9 (2021) 695710.
[361] M. Islam, P.C. Karmakar, A. Tusher Al, M. Arifuzzaman, N. Karim, N. Akhtar, S. M. Asaduzzaman, Human amniotic membrane and titanium dioxide nanoparticle derived gel for burn wound healing in a rat model, Regenerative Engineering and Translational Medicine 9 (2) (2022) 249–262.
[362] M. Laleh, M. Tahernejad, S. Bonakdar, A. Asefnejad, M. Golkar, F. Kazemi-Lomedasht, M. Habibi-Anbouhi, Positive effect of acellular amniotic membrane dressing with immobilized growth factors in skin wound healing, J. Biomed. Mater. Res. 111 (8) (2023) 1216–1227.
[363] K. Suri, M. Kosker, I.M. Raber, K.M. Hammersmith, P.K. Nagra, B.D. Ayres, C. P. Halfpenny, C.J. Rapuano, Sutureless amniotic membrane ProKera for ocular surface disorders: short-term results, Eye Contact Lens 39 (5) (2013) 341–347.
[364] M.L. Tancer, M. Katz, N.P. Veridiano, Vaginal epithelialization with human amnion, Obstet. Gynecol. 54 (3) (1979) 345–349.
[365] M.F. Ashworth, K.E. Morton, J. Dewhurst, R.J. Lilford, R.G. Bates, Vaginoplasty using amnion, Obstet. Gynecol. 67 (3) (1986) 443–446.
[366] R. Vatsa, J. Bharti, K.K. Roy, S. Kumar, J.B. Sharma, N. Singh, S. Singhal, J. Meena, Evaluation of amnion in creation of neovagina in women with Mayer-Rokitansky-Kuster-Hauser syndrome, Fertil. Steril. 108 (2) (2017) 341–345.
[367] I.A. Mc, The treatment of congenital absence and obliterative conditions of the vagina, Br. J. Plast. Surg. 2 (4) (1950) 254–267.
[368] G.M. Grimsby, L.A. Baker, The use of autologous buccal mucosa grafts in vaginal reconstruction, Curr. Urol. Rep. 15 (8) (2014) 428.
[369] P. Benedetti Panici, D. Maffucci, S. Ceccarelli, E. Vescarelli, G. Perniola, L. Muzii, C. Marchese, Autologous in vitro cultured vaginal tissue for vaginoplasty in women with Mayer-Rokitansky-Kuster-Hauser syndrome: anatomic and functional results, J. Minim. Invasive Gynecol. 22 (2) (2015) 205–211.
[370] M. Fénelon, S. Catros, C. Meyer, J.C. Fricain, L. Obert, F. Auber, A. Louvrier, F. Gindraux, Applications of human amniotic membrane for tissue engineering, Membranes 11 (6) (2021).
[371] E. Ricci, G. Vanosi, A. Lindenmair, S. Hennerbichler, A. Peterbauer-Scherb, S. Wolbank, A. Cargnoni, P.B. Signoroni, M. Campagnol, C. Gabriel, H. Redl, O. Parolini, Anti-fibrotic effects of fresh and cryopreserved human amniotic membrane in a rat liver fibrosis model, Cell Tissue Bank. 14 (3) (2013) 475–488.
[372] M. Kubo, Y. Sonoda, R. Muramatsu, M. Usui, Immunogenicity of human amniotic membrane in experimental xenotransplantation, Investig. Ophthalmol. Vis. Sci. 42 (7) (2001) 1539–1546.
[373] S. Ilancheran, Y. Moodley, U. Manuelpillai, Human fetal membranes: a source of stem cells for tissue regeneration and repair? Placenta 30 (1) (2009) 2–10.
[374] S.P. Wilshaw, J. Kearney, J. Fisher, E. Ingham, Biocompatibility and potential of acellular human amniotic membrane to support the attachment and proliferation of allogeneic cells, Tissue Eng. 14 (4) (2008) 463–472.
[375] T. Nakamura, T. Inatomi, E. Sekiyama, L.P. Ang, N. Yokoi, S. Kinoshita, Novel clinical application of sterilized, freeze-dried amniotic membrane to treat patients with pterygium, Acta Ophthalmol. Scand. 84 (3) (2006) 401–405.
[376] B. Farhadihosseinabadi, M. Farahani, T. Tayebi, A. Jafari, F. Biniazan, K. Modaresifar, H. Moravvej, S. Bahrami, H. Redl, L. Tayebi, H. Niknejad, Amniotic membrane and its epithelial and mesenchymal stem cells as an appropriate source for skin tissue engineering and regenerative medicine, Artif. Cells, Nanomed. Biotechnol. 46 (sup2) (2018) 431–440.
[377] M. Kakavand, G. Yazdanpanah, A. Ahmadiani, H. Niknejad, Blood compatibility of human amniotic membrane compared with heparin-coated ePTFE for vascular tissue engineering, J Tissue Eng Regen Med 11 (6) (2017) 1701–1709.
[378] R.A. Hortensius, J.H. Ebens, M.J. Dewey, B.A.C. Harley, Incorporation of the amniotic membrane as an immunomodulatory design element in collagen scaffolds for tendon repair, ACS Biomater. Sci. Eng. 4 (12) (2018) 4367–4377.
[379] N. Fitriani, G. Wilar, A.C. Narsa, A.F.A. Mohammed, N. Wathoni, Application of amniotic membrane in skin regeneration, Pharmaceutics 15 (3) (2023).
[380] L.W. Jiang, H. Chen, H. Lu, Using human epithelial amnion cells in human de-epidermized dermis for skin regeneration, J. Dermatol. Sci. 81 (1) (2016) 26–34.
[381] A. Sanluis-Verdes, N. Sanluis-Verdes, M.J. Manso-Revilla, A.M. Castro-Castro, J. Pombo-Otero, M. Fraga-Marino, J. Sanchez-Ibanez, N. Domenech, M.E. Rendal-Vazquez, Tissue engineering for neurodegenerative diseases using human amniotic membrane and umbilical cord, Cell Tissue Bank. 18 (1) (2017) 1–15.
[382] T. Liu, H. Zhang, J. Zheng, J. Lin, Y. Huang, J. Chen, Z. Yu, L. Guo, W. Pan, Y. Xiong, C. Chen, SPION-mediated miR-141 promotes the differentiation of HuAESCs into dopaminergic neuron-like cells via suppressing lncRNA-HOTAIR, J. Cell Mol. Med. 22 (4) (2018) 2299–2310.
[383] S.W. Choi, J.J. Kim, M.S. Seo, S.B. Park, T.H. Shin, J.H. Shin, Y. Seo, H.S. Kim, K. S. Kang, Inhibition by miR-410 facilitates direct retinal pigment epithelium differentiation of umbilical cord blood-derived mesenchymal stem cells, J. Vet. Sci. 18 (1) (2017) 59–65.
[384] F. Lebreton, K. Bellofatto, C.H. Wassmer, L. Perez, V. Lavallard, G. Parnaud, D. Cottet-Dumoulin, J. Kerr-Conte, F. Pattou, D. Bosco, V. Othenin-Girard, B. Martinez de Tejada, E. Berishvili, Shielding islets with human amniotic epithelial cells enhances islet engraftment and revascularization in a murine diabetes model, Am. J. Transplant. 20 (6) (2020) 1551–1561.
[385] L.P. Frazao, J. Vieira de Castro, C. Nogueira-Silva, N.M. Neves, Decellularized human chorion membrane as a novel biomaterial for tissue regeneration, Biomolecules 10 (9) (2020).
[386] L.P. Frazão, J. Vieira de Castro, C. Nogueira-Silva, N.M. Neves, Decellularized human chorion membrane as a novel biomaterial for tissue regeneration, Biomolecules 10 (9) (2020) 1208.
[387] S. Mohr, C.B. Portmann-Lanz, A. Schoeberlein, R. Sager, D.V. Surbek, Generation of an osteogenic graft from human placenta and placenta-derived mesenchymal stem cells, Reprod. Sci. 17 (11) (2010) 1006–1015.
[388] K.H. Schneider, P. Aigner, W. Holnthoner, X. Monforte, S. Nurnberger, D. Runzler, H. Redl, A.H. Teuschl, Decellularized human placenta chorion matrix

as a favorable source of small-diameter vascular grafts, Acta Biomater. 29 (2016) 125–134.
[389] D. Daniel, F. Frank, S.Y. Dana, Lyophilized Placental Composite Sheet and Uses Thereof, USA, 2019.
[390] K. Imamura, Y. Hamada, W. Yoshida, T. Murakami, S. Nakane-Koyachi, K. Yoshikawa, A. Saito, Investigating the effects of dehydrated human amnion-chorion membrane on periodontal healing, Biomolecules 12 (6) (2022).
[391] N. Ahuja, R. Jin, C. Powers, A. Billi, K. Bass, Dehydrated human amnion chorion membrane as treatment for pediatric burns, Adv. Wound Care 9 (11) (2020) 602–611.
[392] T.E. Serena, M.J. Carter, L.T. Le, M.J. Sabo, D.T. DiMarco, V.L.U.S.G. EpiFix, A multicenter, randomized, controlled clinical trial evaluating the use of dehydrated human amnion/chorion membrane allografts and multilayer compression therapy vs. multilayer compression therapy alone in the treatment of venous leg ulcers, Wound Repair Regen. 22 (6) (2014) 688–693.
[393] W. Tettelbach, S. Cazzell, A.M. Reyzelman, F. Sigal, J.M. Caporusso, P.S. Agnew, A confirmatory study on the efficacy of dehydrated human amnion/chorion membrane dHACM allograft in the management of diabetic foot ulcers: a prospective, multicentre, randomised, controlled study of 110 patients from 14 wound clinics, Int. Wound J. 16 (1) (2019) 19–29.
[394] N. Garcia, V. Jiminez, L. Graham, C. Huang, Unique usages of dehydrated human amnion chorion membrane allografts in dermatology, J. Drugs Dermatol. JDD 22 (12) (2023) 1228–1231.
[395] V.R. Patel, S. Samavedi, A.S. Bates, A. Kumar, R. Coelho, B. Rocco, K. Palmer, Dehydrated human amnion/chorion membrane allograft nerve wrap around the prostatic neurovascular bundle accelerates early return to continence and potency following robot-assisted radical prostatectomy: propensity score-matched analysis, Eur. Urol. 67 (6) (2015) 977–980.
[396] D.L. Miller, K.T. Watkins, Dehydrated human amnion-chorion membrane (placenta) reinforcement of esophagectomy anastomosis, Ann. Thorac. Surg. 114 (2) (2022) e137–e139.
[397] A. Bazrafshan, M. Owji, M. Yazdani, M. Varedi, Activation of mitosis and angiogenesis in diabetes-impaired wound healing by processed human amniotic fluid, J. Surg. Res. 188 (2) (2014) 545–552.
[398] R.R. Beloosesky, M. G, Amniotic fluid, in: Encyclopedia of Reproduction, Academic Press, Oxford, UK, 2018.
[399] M.A. Underwood, W.M. Gilbert, M.P. Sherman, Amniotic fluid: not just fetal urine anymore, J. Perinatol. 25 (5) (2005) 341–348.
[400] E.M. Wintour, L. Shandley, Effects of fetal fluid balance on amniotic fluid volume, Semin. Perinatol. 17 (3) (1993) 158–172.
[401] D.M. Sherer, A review of amniotic fluid dynamics and the enigma of isolated oligohydramnios, Am. J. Perinatol. 19 (5) (2002) 253–266.
[402] M. Beall, J. Van Den Wijngaard, M. Van Gemert, M. Ross, Amniotic fluid water dynamics, Placenta 28 (8–9) (2007) 816–823.
[403] J. Suliburska, R. Kocylowski, I. Komorowicz, M. Grzesiak, P. Bogdanski, D. Baralkiewicz, Concentrations of mineral in amniotic fluid and their relations to selected maternal and fetal parameters, Biol. Trace Elem. Res. 172 (1) (2016) 37–45.
[404] X.L. Tong, L. Wang, T.B. Gao, Y.G. Qin, Y.Q. Qi, Y.P. Xu, Potential function of amniotic fluid in fetal development—novel insights by comparing the composition of human amniotic fluid with umbilical cord and maternal serum at mid and late gestation, J. Chin. Med. Assoc. 72 (7) (2009) 368–373.
[405] T.R. Moore, Amniotic fluid dynamics reflect fetal and maternal health and disease, Obstet. Gynecol. 116 (3) (2010) 759–765.
[406] E.D. Fitzsimmons, T. Bajaj, Embryology, Amniotic Fluid, StatPearls, Treasure Island (FL), 2024.
[407] E. Crouch, G. Balian, K. Holbrook, D. Duksin, P. Bornstein, Amniotic fluid fibronectin. Characterization and synthesis by cells in culture, J. Cell Biol. 78 (3) (1978) 701–715.
[408] N. Karaçal, P. Koşucu, Ü.t. Çobanǵlu, N.n. Kutlu, Effect of human amniotic fluid on bone healing, J. Surg. Res. 129 (2) (2005) 283–287.
[409] A. Wang, E.G. Brown, L. Lankford, B.A. Keller, C.D. Pivetti, N.A. Sitkin, M. S. Beattie, J.C. Bresnahan, D.L. Farmer, Placental mesenchymal stromal cells rescue ambulation in ovine myelomeningocele, Stem Cells Transl Med 4 (6) (2015) 659–669.
[410] B. Weber, M.Y. Emmert, L. Behr, R. Schoenauer, C. Brokopp, C. Drogemuller, P. Modregger, M. Stampanoni, D. Vats, M. Rudin, W. Burzle, M. Farine, E. Mazza, T. Frauenfelder, A.C. Zannettino, G. Zund, O. Kretschmar, V. Falk, S.P. Hoerstrup, Prenatally engineered autologous amniotic fluid stem cell-based heart valves in the fetal circulation, Biomaterials 33 (16) (2012) 4031–4043.
[411] G.Y. Özgenel, G. Filiz, Effects of human amniotic fluid on peripheral nerve scarring and regeneration in rats, J. Neurosurg. 98 (2) (2003) 371–377.
[412] G.Y. Ozgenel, G. Filiz, Effects of human amniotic fluid on peripheral nerve scarring and regeneration in rats, J. Neurosurg. 98 (2) (2003) 371–377.
[413] E. Bolat, E. Kocamaz, Z. Kulahcilar, A. Yilmaz, A. Topcu, M. Ozdemir, M. E. Coskun, Investigation of efficacy of mitomycin-C, sodium hyaluronate and human amniotic fluid in preventing epidural fibrosis and adhesion using a rat laminectomy model, Asian Spine Journal 7 (4) (2013) 253.
[414] R. Bia, G. Mitchell, H. Javan, I. Nickel, J. Pierce, C.H. Selzman, S. Franklin, Proteomic characterization of cardioprotective human acellular amniotic fluid, ACS Omega 10 (7) (2025) 6918–6926.
[415] J.L. Pierce, B. Olson, R.M. Merrill, J. Pierce, A. Isom, V. Torrecillas, H. McCrary, A. Aylward, M.E. Smith, M.B. Christensen, Amniotic fluid as a potential treatment for vocal fold scar in a rabbit model, J Voice S0892-1997 (24) (2025) 00445–00454.
[416] M. Kawakatsu, Y. Urata, S. Goto, Y. Ono, T.-S. Li, Placental extract protects bone marrow-derived stem/progenitor cells against radiation injury through anti-inflammatory activity, J. Radiat. Res. 54 (2) (2013) 268–276.
[417] Y. Mao, J. Pierce, A. Singh-Varma, M. Boyer, J. Kohn, J.-A. Reems, Processed human amniotic fluid retains its antibacterial activity, J. Transl. Med. 17 (2019) 1–9.
[418] F. Chen, Y. Zhao, Y. Dai, N. Sun, X. Gao, J. Yin, Z. Zhou, K.-j. Wu, Chick early amniotic fluid alleviates dextran-sulfate-sodium-induced colitis in mice via T-cell receptor pathway, Antioxidants 14 (1) (2025) 51.
[419] Y. Ogawa, H. He, S. Mukai, T. Imada, S. Nakamura, C.-W. Su, M. Mahabole, S. C. Tseng, K. Tsubota, Heavy chain-hyaluronan/pentraxin 3 from amniotic membrane suppresses inflammation and scarring in murine lacrimal gland and conjunctiva of chronic graft-versus-host disease, Sci. Rep. 7 (1) (2017) 42195.
[420] G. Tumentemur, E.G. Aygun, B. Yurtsever, D. Cakirsoy, E. Ovali, Effect of amniotic fluid on hair follicle growth, J. Dermatol. Treat. 36 (1) (2025) 2451389.
[421] S. Ghalei, J. Nourmohammadi, A. Solouk, H. Mirzadeh, Enhanced cellular response elicited by addition of amniotic fluid to alginate hydrogel-electrospun silk fibroin fibers for potential wound dressing application, Colloids Surf. B Biointerfaces 172 (2018) 82–89.
[422] C. Dang, K. Ting, C. Soo, M.T. Longaker, H.P. Lorenz, Fetal wound healing: current perspectives, Clin. Plast. Surg. 30 (1) (2003) 13–23.
[423] H. Beheshti Seresht, P. Akhlaghi, S. Ashouri Sharafshadeh, M.S. Aghajanzadeh, R. Mehdinavaz Aghdam, Mechanical characterization of amniotic-based scaffolds containing silk fibroin and sodium alginate nanofibers, J. Biomed. Mater. Res. B Appl. Biomater. 113 (2) (2025) e35539.
[424] T. Tsuji, R. Onogawa, H. Tatsukawa, A. Murai, K. Hitomi, Potential activity of chicken amniotic fluid in epidermal development by promoting keratinocyte differentiation, Arch. Biochem. Biophys. (2025) 110365.
[425] V. Lungova, K.V. Griffin, T. Lunga, S.L. Thibeault, Drainage of amniotic fluid delays vocal fold separation and induces load-related vocal fold mucosa remodeling, Dev. Biol. 466 (1–2) (2020) 47–58.
[426] Q. Vallmajo-Martin, A.S. Kiveliö, S. Metzger, V. Milleret, P.S. Lienemann, B.M. Carrara, C. Millan, C. Ghayor, N. Ochsenbein-Koelble, M. Ehrbar, Undifferentiated Human Amniotic Fluid Progenitor Cells Promote Bone Regeneration in Vivo, Advanced Healthcare Materials 2300843.
[427] R.S. Khaboushan, S. Mohammadi, A.S. Khaboushan, Advanced Tissue-Engineering Approaches for Prenatal Neurosurgical Management of Spinal Dysraphism, 2024.
[428] A. Di Baldassarre, M.A. D'Amico, P. Izzicupo, G. Gaggi, S. Guarnieri, M. A. Mariggio, I. Antonucci, B. Corneo, D. Sirabella, L. Stuppia, B. Ghinassi, Cardiomyocytes derived from human (Cardiopoietic)Amniotic fluids, Sci. Rep. 8 (1) (2018) 12028.
[429] M. Morigi, P. De Coppi, Cell therapy for kidney injury: different options and mechanisms–mesenchymal and amniotic fluid stem cells, Nephron Exp. Nephrol. 126 (2) (2014) 59.
[430] L.B. Chang, S.Y. Peng, C.J. Chou, Y.J. Chen, J.S. Shiu, P.A. Tu, S.X. Gao, Y. C. Chen, T.K. Lin, S.C. Wu, Therapeutic potential of amniotic fluid stem cells to treat bilateral ovarian dystrophy in dairy cows in a subtropical region, Reprod. Domest. Anim. 53 (2) (2018) 433–441.
[431] G. Carraro, L. Perin, S. Sedrakyan, S. Giuliani, C. Tiozzo, J. Lee, G. Turcatel, S. P. De Langhe, B. Driscoll, S. Bellusci, Human amniotic fluid stem cells can integrate and differentiate into epithelial lung lineages, Stem Cell. 26 (11) (2008) 2902–2911.
[432] T. Maraldi, M. Riccio, A. Pisciotta, M. Zavatti, G. Carnevale, F. Beretti, G.B. La Sala, A. Motta, A. De Pol, Human amniotic fluid-derived and dental pulp-derived stem cells seeded into collagen scaffold repair critical-size bone defects promoting vascularization, Stem Cell Res. Ther. 4 (2013) 1–12.
[433] E. Danzer, L. Zhang, A. Radu, M.W. Bebbington, K.W. Liechty, N.S. Adzick, A. W. Flake, Amniotic fluid levels of glial fibrillary acidic protein in fetal rats with retinoic acid induced myelomeningocele: a potential marker for spinal cord injury, Am. J. Obstet. Gynecol. 204 (2) (2011), 178. e1-178. e11.
[434] D.G. McLone, M.S. Dias, W. Goossens, P.A. Knepper, Pathological changes in exposed neural tissue of fetal delayed splotch (Spd) mice, Childs Nerv. Syst. 13 (1997) 1–7.
[435] H. Mobarak, M. Heidarpour, R. Rahbarghazi, M. Nouri, M. Mahdipour, Amniotic fluid-derived exosomes improved spermatogenesis in a rat model of azoospermia, Life Sci. 274 (2021) 119336.
[436] M. Shahlaei, M. Saeidifar, A. Zamanian, Sustained release of sulforaphane by bioactive extracellular vesicles for neuroprotective effect on chick model, J. Biomed. Mater. Res. B Appl. Biomater. 110 (12) (2022) 2636–2648.
[437] P. Li, X. Lu, J. Hu, M. Dai, J. Yan, H. Tan, P. Yu, X. Chen, C. Zhang, Human amniotic fluid derived-exosomes alleviate hypoxic encephalopathy by enhancing angiogenesis in neonatal mice after hypoxia, Neurosci. Lett. 768 (2022) 136361.
[438] M.A. Bellio, K.C. Young, J. Milberg, I. Santos, Z. Abdullah, D. Stewart, A. Arango, P. Chen, J. Huang, K. Williams, Amniotic fluid-derived extracellular vesicles: characterization and therapeutic efficacy in an experimental model of bronchopulmonary dysplasia, Cytotherapy 23 (12) (2021) 1097–1107.
[439] L. Antounians, V.D. Catania, L. Montalva, B.D. Liu, H. Hou, C. Chan, A.C. Matei, A. Tzanetakis, B. Li, R.L. Figueira, Fetal lung underdevelopment is rescued by administration of amniotic fluid stem cell extracellular vesicles in rodents, Sci. Transl. Med. 13 (590) (2021) eaax5941.
[440] K. Khalaj, L. Antounians, R.L. Figueira, M. Post, A. Zani, Autophagy is impaired in fetal hypoplastic lungs and rescued by administration of amniotic fluid stem cell extracellular vesicles, Am. J. Respir. Crit. Care Med. 206 (4) (2022) 476–487.
[441] S.Y. Chun, J.B. Kwon, S.Y. Chae, J.K. Lee, J.s. Bae, B.S. Kim, H.T. Kim, E.S. Yoo, J. O. Lim, J.J. Yoo, Combined injection of three different lineages of early-

differentiating human amniotic fluid-derived cells restores urethral sphincter function in urinary incontinence, BJU Int. 114 (5) (2014) 770–783.
[442] S. Cipriani, D. Bonini, E. Marchina, I. Balgkouranidou, L. Caimi, G.G. Zucconi, S. Barlati, Mesenchymal cells from human amniotic fluid survive and migrate after transplantation into adult rat brain, Cell Biol. Int. 31 (8) (2007) 845–850.
[443] K. Kajiwara, T. Tanemoto, S. Wada, J. Karibe, N. Ihara, Y. Ikemoto, T. Kawasaki, Y. Oishi, O. Samura, K. Okamura, Fetal therapy model of myelomeningocele with three-dimensional skin using amniotic fluid cell-derived induced pluripotent stem cells, Stem Cell Rep. 8 (6) (2017) 1701–1713.
[444] S.M. Kunisaki, Amniotic fluid stem cells for the treatment of surgical disorders in the fetus and neonate, Stem Cells Transl Med 7 (11) (2018) 767–773.
[445] J.-H. Gosemann, J.F. Kuebler, M. Pozzobon, C. Neunaber, J.H. Hensel, M. Ghionzoli, P. De Coppi, B.M. Ure, G. Holze, Activation of regulatory T cells during inflammatory response is not an exclusive property of stem cells, PLoS One 7 (4) (2012) e35512.
[446] J. Lin, X. Huang, J. Zhang, W. Yang, F. Sun, B. Huang, W. Lu, X. Wang, Amniotic fluid-derived exosomal miR-146a-5p ameliorates preeclampsia phenotypes by inhibiting HIF-1α/FLT-1 expression, Placenta 162 (2025) 35–44.
[447] G.Y. Xiao, C.C. Cheng, Y.S. Chiang, W.T. Cheng, I.H. Liu, S.C. Wu, Exosomal miR-10a derived from amniotic fluid stem cells preserves ovarian follicles after chemotherapy, Sci. Rep. 6 (2016) 23120.
[448] Z. Geng, H. Chen, G. Zou, L. Yuan, P. Liu, B. Li, K. Zhang, F. Jing, X. Nie, T. Liu, Human amniotic fluid mesenchymal stem cell-derived exosomes inhibit apoptosis in ovarian granulosa cell via miR-369-3p/YAF2/PDCD5/p53 pathway, Oxid. Med. Cell. Longev. 2022 (1) (2022) 3695848.
[449] E. Thabet, A. Yusuf, D.A. Abdelmonsif, I. Nabil, G. Mourad, R.A. Mehanna, Extracellular vesicles miRNA-21: a potential therapeutic tool in premature ovarian dysfunction, Mol. Hum. Reprod. 26 (12) (2020) 906–919.
[450] V. Castelli, I. Antonucci, M. d'Angelo, A. Tessitore, V. Zelli, E. Benedetti, C. Ferri, G. Desideri, C. Borlongan, L. Stuppia, Neuroprotective effects of human amniotic fluid stem cells-derived secretome in an ischemia/reperfusion model, Stem Cells Transl Med 10 (2) (2021) 251–266.
[451] M. Gatti, M. Zavatti, F. Beretti, D. Giuliani, E. Vandini, A. Ottani, E. Bertucci, T. Maraldi, Oxidative stress in Alzheimer's disease: in vitro therapeutic effect of amniotic fluid stem cells extracellular vesicles, Oxid. Med. Cell. Longev. 2020 (1) (2020) 2785343.
[452] M. Zavatti, M. Gatti, F. Beretti, C. Palumbo, T. Maraldi, Exosomes derived from human amniotic fluid mesenchymal stem cells preserve microglia and neuron cells from abeta, Int. J. Mol. Sci. 23 (9) (2022).
[453] G. Manni, M. Gargaro, D. Ricciuti, S. Fontana, E. Padiglioni, M. Cipolloni, T. Mazza, J. Rosati, A. di Veroli, G. Mencarelli, B. Pieroni, E.C. Silva Barcelos, G. Scalisi, F. Sarnari, A. di Michele, L. Pascucci, F. de Franco, T. Zelante, C. Antognelli, G. Cruciani, V.N. Talesa, R. Romani, F. Fallarino, Amniotic fluid stem cell-derived extracellular vesicles educate type 2 conventional dendritic cells to rescue autoimmune disorders in a multiple sclerosis mouse model, J. Extracell. Vesicles 13 (6) (2024) e12446.
[454] C.S. Fonteles, J. Enterria-Rosales, Y. Lin, J.W. Steele, R.A. Villarreal-Leal, J. Xiao, D.I. Idowu, B. Burgelin, B.J. Wlodarczyk, R.H. Finnell, Amniotic fluid-derived stem cells: potential factories of natural and mimetic strategies for congenital malformations, Stem Cell Res. Ther. 15 (1) (2024) 1–15.
[455] F. Doktor, R.L. Figueira, V. Fortuna, G. Biouss, K. Stasiewicz, M. Obed, K. Khalaj, L. Antounians, A. Zani, Amniotic fluid stem cell extracellular vesicles promote lung development via TGF-beta modulation in a fetal rat model of oligohydramnios, J. Contr. Release 377 (2025) 427–441.
[456] F. Doktor, E. Lo, V. Fortuna, K. Khalaj, M. Garcia, R.L. Figueira, M. Lacher, L. Antounians, A. Zani, Sex-specific differences in the severity of pulmonary hypoplasia in experimental congenital diaphragmatic hernia and implications for extracellular vesicle-based therapy, Pediatr. Surg. Int. 40 (1) (2024) 1–10.
[457] C.J. McCulloh, J.K. Olson, Y. Wang, Y. Zhou, N.H. Tengberg, S. Deshpande, G. E. Besner, Treatment of experimental necrotizing enterocolitis with stem cell-derived exosomes, J. Pediatr. Surg. 53 (6) (2018) 1215–1220.
[458] B. Li, C. Lee, J.S. O'Connell, L. Antounians, N. Ganji, M. Alganabi, M. Cadete, F. Nascimben, Y. Koike, A. Hock, Activation of Wnt signaling by amniotic fluid stem cell-derived extracellular vesicles attenuates intestinal injury in experimental necrotizing enterocolitis, Cell Death Dis. 11 (9) (2020) 750.
[459] J.S. O'Connell, C. Lee, N. Farhat, L. Antounians, A. Zani, B. Li, A. Pierro, Administration of extracellular vesicles derived from human amniotic fluid stem cells: a new treatment for necrotizing enterocolitis, Pediatr. Surg. Int. 37 (3) (2021) 301–309.
[460] X. Hu, R. Zhang, H. Liang, J. An, Y. Yang, J. Huo, Z. Chen, W. Quan, L. Jiang, C. Li, Comparison and investigation of exosomes from human amniotic fluid stem cells and human breast milk in alleviating neonatal necrotizing enterocolitis, Stem Cell Reviews and Reports 19 (3) (2023) 754–766.
[461] B. Mellows, R. Mitchell, M. Antonioli, O. Kretz, D. Chambers, M.-T. Zeuner, B. Denecke, L. Musante, D.L. Ramachandra, F. Debacq-Chainiaux, Protein and molecular characterization of a clinically compliant amniotic fluid stem cell-derived extracellular vesicle fraction capable of accelerating muscle regeneration through enhancement of angiogenesis, Stem Cell. Dev. 26 (18) (2017) 1316–1333.
[462] C. Balbi, K. Lodder, A. Costa, S. Moimas, F. Moccia, T. van Herwaarden, V. Rosti, F. Campagnoli, A. Palmeri, P. De Biasio, F. Santini, M. Giacca, M.J. Goumans, L. Barile, A.M. Smits, S. Bollini, Reactivating endogenous mechanisms of cardiac regeneration via paracrine boosting using the human amniotic fluid stem cell secretome, Int. J. Cardiol. 287 (2019) 87–95.
[463] K. Takov, Z. He, H.E. Johnston, J.F. Timms, P.V. Guillot, D.M. Yellon, S. M. Davidson, Small extracellular vesicles secreted from human amniotic fluid mesenchymal stromal cells possess cardioprotective and promigratory potential, Basic Res. Cardiol. 115 (3) (2020) 26.
[464] J. Hu, X. Chen, P. Li, X. Lu, J. Yan, H. Tan, C. Zhang, Exosomes derived from human amniotic fluid mesenchymal stem cells alleviate cardiac fibrosis via enhancing angiogenesis in vivo and in vitro, Cardiovasc. Diagn. Ther. 11 (2) (2021) 348.
[465] A. Costa, C. Balbi, P. Garbati, M.E.F. Palamà, D. Reverberi, A. De Palma, R. Rossi, D. Paladini, D. Coviello, P. De Biasio, Investigating the paracrine role of perinatal derivatives: human amniotic fluid stem cell-extracellular vesicles show promising transient potential for cardiomyocyte renewal, Front. Bioeng. Biotechnol. 10 (2022) 902038.
[466] H. Katifelis, E. Filidou, A. Psaraki, F. Yakoub, M.G. Roubelakis, G. Tarapatzi, S. Vradelis, G. Bamias, G. Kolios, M. Gazouli, Amniotic fluid-derived mesenchymal stem/stromal cell-derived secretome and exosomes improve inflammation in human intestinal subepithelial myofibroblasts, Biomedicines 10 (10) (2022) 2357.
[467] D.M. Iglesias, R. El-Kares, A. Taranta, F. Bellomo, F. Emma, M. Besouw, E. Levtchenko, J. Toelen, L. van den Heuvel, L. Chu, Stem Cell Microvesicles Transfer Cystinosin to Human Cystinotic Cells and Reduce Cystine Accumulation in Vitro, 2012.
[468] M. Zavatti, F. Beretti, F. Casciaro, E. Bertucci, T. Maraldi, Comparison of the therapeutic effect of amniotic fluid stem cells and their exosomes on monoiodoacetate-induced animal model of osteoarthritis, Biofactors 46 (1) (2020) 106–117.
[469] M. Gatti, K.S. Dittlau, F. Beretti, L. Yedigaryan, M. Zavatti, P. Cortelli, C. Palumbo, E. Bertucci, L. Van Den Bosch, M. Sampaolesi, Human neuromuscular junction on a chip: impact of amniotic fluid stem cell extracellular vesicles on muscle atrophy and NMJ integrity, Int. J. Mol. Sci. 24 (5) (2023) 4944.
[470] S. Sedrakyan, V. Villani, S. Da Sacco, N. Tripuraneni, S. Porta, A. Achena, M. Lavarreda-Pearce, A. Petrosyan, H. Soloyan, R.E. Filippo, B. Bussolati, L. Perin, Amniotic fluid stem cell-derived vesicles protect from VEGF-induced endothelial damage, Sci. Rep. 7 (1) (2017) 16875.
[471] Y. Zhang, J. Yan, Y. Liu, Z. Chen, X. Li, L. Tang, J. Li, M. Duan, G. Zhang, Human amniotic fluid stem cell-derived exosomes as a novel cell-free therapy for cutaneous regeneration, Front. Cell Dev. Biol. 9 (2021) 685873.
[472] M. Wgealla, H. Liang, R. Chen, Y. Xie, F. Li, M. Qin, X. Zhang, Amniotic fluid derived stem cells promote skin regeneration and alleviate scar formation through exosomal miRNA-146a-5p via targeting CXCR4, J. Cosmet. Dermatol. 21 (10) (2022) 5026–5036.
[473] A.L.F. Castro, Exploring Human Placenta-Derived Hydrogels as a Microenvironment for 3D Cell Culture, Universidade do Porto, Portugal, 2018.
[474] M. Pozzobon, S. D'Agostino, M.G. Roubelakis, A. Cargnoni, R. Gramignoli, S. Wolbank, F. Gindraux, S. Bollini, H. Kerdjoudj, M. Fenelon, R. Di Pietro, M. Basile, V. Borutinskaitė, R. Piva, A. Schoeberlein, G. Eissner, B. Giebel, P. Ponsaerts, General consensus on multimodal functions and validation analysis of perinatal derivatives for regenerative medicine applications, Front. Bioeng. Biotechnol. 10 (2022) 961987.
[475] T.W. Gilbert, T.L. Sellaro, S.F. Badylak, Decellularization of tissues and organs, Biomaterials 27 (19) (2006) 3675–3683.
[476] P.M. Crapo, T.W. Gilbert, S.F. Badylak, An overview of tissue and whole organ decellularization processes, Biomaterials 32 (12) (2011) 3233–3243.
[477] T.J. Keane, I.T. Swinehart, S.F. Badylak, Methods of tissue decellularization used for preparation of biologic scaffolds and in vivo relevance, Methods (San Diego, Calif.) 84 (2015) 25–34.
[478] R.S. Barreto, P. Romagnolli, P. Fratini, A.M. Mess, M.A. Miglino, Mouse placental scaffolds: a three-dimensional environment model for recellularization, J. Tissue Eng. 10 (2019) 2041731419867962.
[479] P.O. Favaron, J. Borghesi, A.M. Mess, P. Castelucci, G.S. Schiavo Matias, R. Barreto, M.A. Miglino, Establishment of 3-dimensional scaffolds from hemochorial placentas, Placenta 81 (2019) 32–41.
[480] G.d.S.S. Matias, A.C.O. Carreira, V.F. Batista, H.J.C. de Carvalho, M.A. Miglino, P. Fratini, In vivo biocompatibility analysis of the recellularized canine tracheal scaffolds with canine epithelial and endothelial progenitor cells, Bioengineered 13 (2) (2022) 3551.
[481] G.d.S.S. Matias, N.N. Rigoglio, A.C.O. Carreira, P. Romagnolli, R.d.S.N. Barreto, A.M. Mess, M.A. Miglino, P. Fratini, Optimization of canine placenta decellularization: an alternative source of biological scaffolds for regenerative medicine, Cells Tissues Organs 205 (4) (2018) 217–225.
[482] R. Barreto, G.S.S. Matias, M.Y. Nishiyama-Jr, A.C.O. Carreira, M.A. Miglino, ECM proteins involved in cell migration and vessel formation compromise bovine cloned placentation, Theriogenology 188 (2022) 156–162.
[483] R.d.S.N. Barreto, P. Romagnolli, A.M. Mess, M.A. Miglino, Decellularized bovine cotyledons may serve as biological scaffolds with preserved vascular arrangement, Journal of tissue engineering and regenerative medicine 12 (4) (2018) e1880–e1888.
[484] G. de Sá Schiavo Matias, R. da Silva Nunes Barreto, A.C.O. Carreira, M.Y. N. Junior, P. Fratini, C.R. Ferreira, M.A. Miglino, Proteomic profile of extracellular matrix from native and decellularized chorionic canine placenta, J. Proteonomics 256 (2022) 104497.
[485] L.P. Frazão, J. Vieira de Castro, C. Nogueira-Silva, N.M. Neves, Decellularized human chorion membrane as a novel biomaterial for tissue regeneration, Biomolecules 10 (9) (2020).
[486] M.S. Oliveira, J.B. Barreto-Filho, Placental-derived stem cells: culture, differentiation and challenges, World J. Stem Cell. 7 (4) (2015) 769.
[487] J.R. Thomas, A. Appios, X. Zhao, R. Dutkiewicz, M. Donde, C.Y. Lee, P. Naidu, C. Lee, J. Cerveira, B. Liu, Phenotypic and functional characterization of first-

trimester human placental macrophages, Hofbauer cells, J. Exp. Med. 218 (1) (2021).
[488] V. Garcia-Flores, Y. Xu, E. Pusod, R. Romero, R. Pique-Regi, N. Gomez-Lopez, Preparation of single-cell suspensions from the human placenta, Nat. Protoc. 18 (3) (2023) 732–754.
[489] L.N. Block, B.D. Bowman, J.K. Schmidt, L.T. Keding, A.K. Stanic, T.G. Golos, The promise of placental extracellular vesicles: models and challenges for diagnosing placental dysfunction in utero, Biol. Reprod. 104 (1) (2021) 27–57.