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External and internal exposome as triggers of biological signalling in systemic sclerosis – A narrative synthesis

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ABSTRACT

Systemic sclerosis (SSc) is an autoimmune chronic connective tissue disorder with a complex pathogenesis and a strong gene-environment interaction. Despite the low prevalence of SSc, with around 100–250 cases per million, the morbidity and mortality are high and disproportionately affecting women. In this context, we review the influence of the external and internal exposome on the "immunome" in SSc. While several studies have addressed aspects of exposure-induced autoimmunity in general, very few have focused on SSc-specific phenotypes. In epidemiological studies, targeted characterization of the external exposome component in relation to SSc has often been limited to a single exposure. Despite the selective characterization of exposure, such studies play an important role in providing evidence that can be used towards reduction of exposure of modifiable factors, and can lead to proper management and prevention of SSc. Additionally, there is an effort towards integration of external exposome data with health data (health records, medical imaging, diagnostic results, etc.), to significantly improve our understanding of the environmental and occupational causes of SSc. A limited number of studies have identified biological processes related to the vascular homeostasis, fibrotic processes and the immune system. The key findings of the current review show advances in our understanding of the SSc disease phenotype and associated biomarkers in relation to specific pathophysiological features, however most often such studies are not supplemented with external exposome data.

1. Introduction

Autoimmune diseases are multigenic, with a strong gene-environment interaction, and a complex pathogenesis [1–3]. In most cases, the triggers and mechanisms leading to the pathogenesis remain largely unknown, thereby reducing the likelihood of evidence-based public health policy implementation, including prevention. While the classical epidemiology studies are unable to dissect the complexity of autoimmune disease pathogenesis, the exposome approach [4,5] promises to study the exposure-disease continuum in its totality. By exploring this continuum, it aims to untangle the interactions between different exposures (external exposome), biological processes, and interactions between the biological processes themselves (internal exposome) (Fig. 1).

1.1. Systemic sclerosis

Systemic sclerosis (SSc) is an autoimmune chronic connective tissue disorder of unknown etiology [7,8], often interchangeably used with the term scleroderma in reference to the specific clinical manifestation of skin fibrosis [9]. Despite the low prevalence of SSc with around 100–250 cases per million [9,10], the morbidity and mortality are high, and disproportionately affect women [10]. Female frequency in SSc could be attributed to genetic or epigenetic differences and X chromosome gene activation [11]. Although existing datasets on SSc are often incomplete, with data from Southeast Asia, South Asia, Latin America, Sub-Saharan Africa largely lacking, SSc appears to have a more rapid onset in Asian and Black patients [12]. A recent literature-based systematic analysis [13] calculated the global incidence density at 8.64 (1.78–23.57) per 100,000 person-years, with 0.67 million newly diagnosed patients

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annually. Countries with the highest incidence were Spain, Italy, Poland and the United Kingdom. A large proportion of incident cases were women, affecting 0.55 million individuals yearly. A recent UK based cohort study of twenty-two million individuals by Conrad et al. [14], calculated a standardized incidence for SSc of 3.3 per 100,000 person-years for the period 2017–2019.

Evidence indicates that SSc is characterized by a common pathological cascade across multiple organs, complemented with organ-specific dysfunction [7]. SSc is characterized by vascular alterations, inflammation, autoimmunity, and fibrosis, which can cause severe organ failure [15]. Skin fibrosis can cause loss of function in the hands and additional esthetical issues, whereas pulmonary fibrosis is a major cause of concern together with pulmonary arterial hypertension, which is the leading cause of death in SSc patients [15–18]. Moreover, recent research pointed towards the development of cerebrovascular and cardiovascular disease as a major comorbidity [19]. The diagnosis of SSc is based on the investigation of different symptoms and signs including imaging [20], and is in accordance to the 2013 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria [9,15,17]. Based on the extent of skin involvement, SSc is often classified into two major subtypes: limited cutaneous SSc (lcSSc), where skin thickening is confined to the extremities, the face, and the neck; and diffuse cutaneous SSc (dcSSc), where skin thickening progresses proximal to elbows and/or knees or affects thorax and/or abdomen at any given time during the disease [21]. lcSSc is often more chronic and slower progressing compared to dcSSc, which generally has a worse prognosis. In the digital arteries and arterioles, transient hypoxia can induce Raynaud's phenomenon (RP), the most observed symptom in SSc.

As a multisystem disease, with variable course and complex pathogenesis, understanding the interplay between environmental/occupational triggers and underlying (epi)genetic factors can aid in the early diagnosis, assessment, and management of SSc. This has been evident throughout the nosological history of the disease. The evolution of SSc nosology has influenced research on the possible causes, identification of serological biomarkers and their association with clinical features; and has been elegantly described by Lescoat et al. [22]. In addition to the evolution of nosology of SSc, the evidence base has stimulated continued

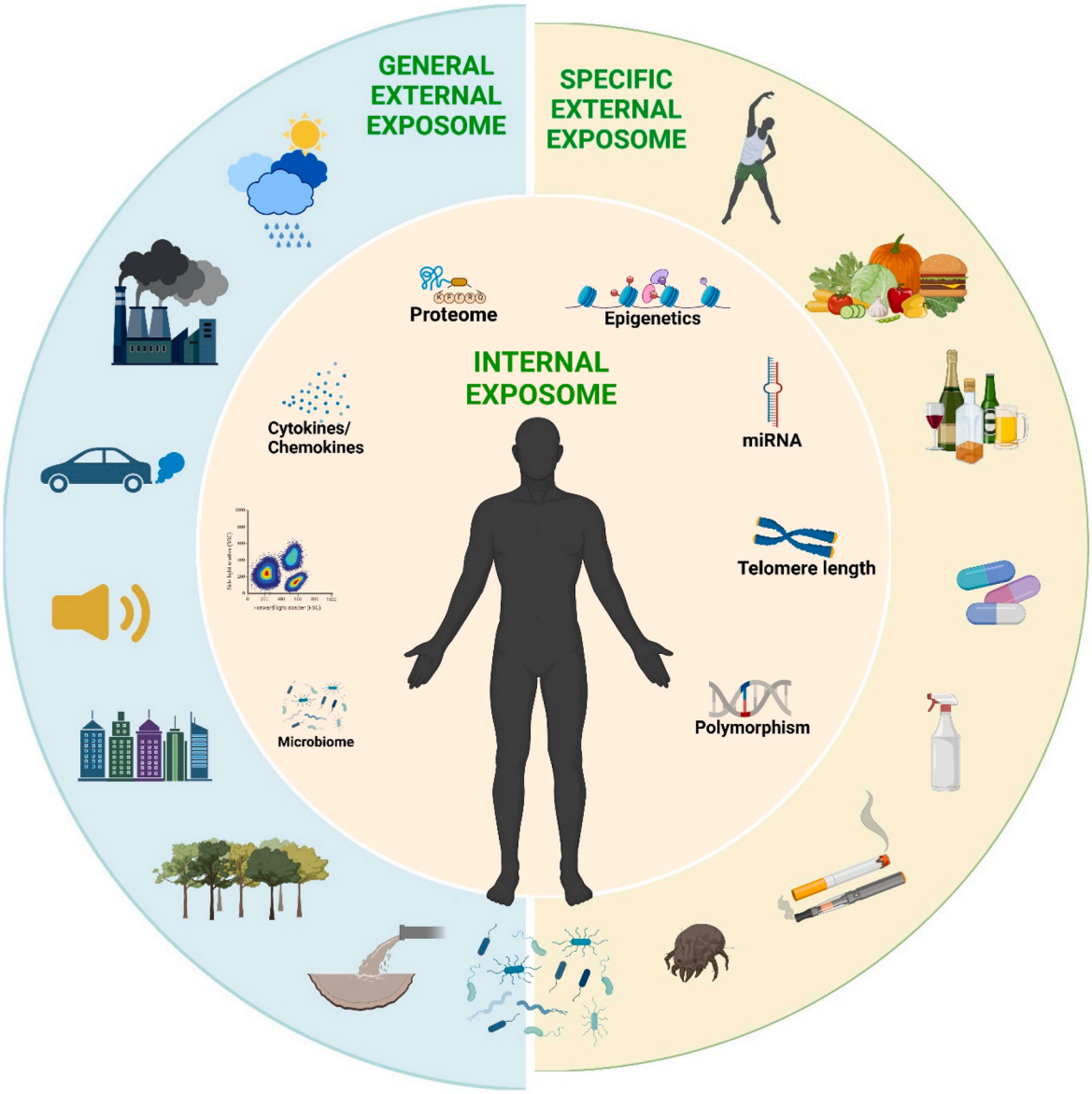


Fig. 1. Schematic overview of the exposome concept, towards a better understanding of exposome-immunome interaction in systemic sclerosis (Created with BioRender.com).

discussion on the importance and relevance of SSc subsets at different points in time [22–26].

This continued interest and the emerging evidence base, form the foundation for the current scoping review, where we use a combination of narrative approaches, systematic screening of literature and bio-informatic analysis on existing datasets.

2. Contribution of external exposome- environmental and occupational risk factors of SSc

The SSc-cascade is thought to be caused by environmental events in a genetically susceptible individual, triggering a chronic and self-amplifying multifocal process. In addition to the critical impact of genetic factors [27] which has been discussed in a later section, recent studies have increasingly highlighted the importance of environmental factors and their impact on both latency and severity of SSc [28,29]. A systematic review and meta-analysis conducted by Rubio-Rivas et al., in 2017 reported a significant increase in the overall risk of developing SSc after exposure to silica, solvents, silicone breast implants, epoxy resins, pesticides and welding fumes [29]. This risk appears to increase with high cumulative exposures [30]. Furthermore, occupational exposure to toxic agents has been associated with severity markers of systemic sclerosis, which include the extent of skin involvement, pulmonary involvement, and severe microangiopathy among others [31].

2.1. Occupational exposure to silica

It is estimated that approximately 5 million workers in Europe, and millions more around the world, are exposed to respirable crystalline silica (RCS) (also referred to as “silica”) [32,33]. Occupational exposure to silica occurs in a wide array of industries and settings, including mining, stone quarries, granite production, ceramic and pottery industries, agriculture, foundries and textile transformation [34]. To a lesser extent, inhalation of silica dust might happen in daily life activities such as handling and washing of dusty clothes and manual hobbies, performed repeatedly without any type of protection [35]. The first description of systemic sclerosis associated with silica exposure, was made by Erasmus in 1957 [36]. Several meta-analyses [29,34] have reported that occupational exposure to silica significantly increases the risk of systemic sclerosis. Rubio-Rivas et al. [29] reported an OR of 2.81, based on 15 case-control studies and an RR of 17.52 based on 4 cohort studies. Mc Cormic et al. [34], on the other hand, reported a combined estimator of relative risk (CERR) of 3.02. An Australian national study including over 1500 patients with systemic sclerosis has shown that over 30 % of male patients had prior silica exposure [37]. A retrospective Belgian study performed by the Cliniques Universitaires de Saint-Luc and University Hospitals Leuven concluded that about 50% of male patients suffering from SSc had a history of occupational silica exposure [38]. Various other epidemiological studies have consolidated these

GLOSSARY

- **Systemic sclerosis** [scleroderma; *MeSH descriptor:D012595*[#]]: A chronic multi-system disorder of connective tissue. It is characterized by sclerosis in the skin, the lungs, the heart, the gastrointestinal tract, the kidneys, and the musculoskeletal system. Other important features include diseased small blood vessels and autoantibodies. The disorder is named for its most prominent feature (hard skin) and classified into subsets by the extent of skin thickening: limited scleroderma and diffuse scleroderma.
- **Raynaud’s phenomenon** [*MeSH descriptor:D011928*[#]]: An idiopathic vascular disorder characterized by bilateral Raynaud phenomenon, the abrupt onset of digital paleness or cyanosis in response to cold exposure or stress.
- **Exposome** [*MeSH descriptor:D000081413*[#]]: The measure of all the exposures of an individual from all sources, including environmental and occupational sources, in a lifetime and how those exposures relate to health.
- **Exposome** (expanded definition, Miller 2020 [6]): The cumulative measure of environmental influences and associated biological responses throughout the lifespan including exposures from the environment, diet, behaviour and endogenous processes.
- **Exposome (Internal;** Wild 2012 [5]**):** Metabolism, endogenous hormones, body morphology, physical activity, gut microflora, inflammation, lipid peroxidation, oxidative stress, ageing etc.
- **Exposome (General external;** Wild 2012 [5]**)**: Social capital, education, financial status, psychological and mental stress, urban–rural environment, climate, etc.
- **Exposome (Specific external;** Wild 2012 [5]: Radiation, infectious agents, chemical contaminants and environmental pollutants, diet, lifestyle factors (e.g., tobacco, alcohol), occupation, medical interventions, etc.
- **Biomarkers** [*MeSH descriptor:D015415*[#]]: Measurable and quantifiable biological parameters (e.g., specific enzyme concentration, specific hormone concentration, specific gene phenotype distribution in a population, presence of biological substances) which serve as indices for health- and physiology-related assessments, such as disease risk, psychiatric disorders, environmental exposure and its effects, disease diagnosis, metabolic processes, substance abuse; pregnancy cell line development; epidemiologic studies; etc.
- **Immunome**: All the genes and proteins that constitute the immune system are collectively known as the immunome.
- **Genome-Wide Association Study** [*MeSH descriptor: D055106*[#]]: An analysis comparing the allele frequencies of all available (or a whole genome representative set of) polymorphic markers to identify gene candidates or quantitative trait loci associated with a specific organism trait or specific disease or condition.
- **Epigenomics** [*MeSH descriptor: D057890* [#]]: The systematic study of the global gene expression changes due to epigenetic processes and not due to DNA base sequence changes.
- **Proteomics** [*MeSH descriptor: D040901*[#]]: The systematic study of the complete complement of proteins (proteome) of organisms.
- **Metabolomics** [*MeSH descriptor: D055432*[#]]: The systematic identification and quantitation of all the metabolic products of a cell, tissue, organ, or organism under varying conditions. The metabolome of a cell or organism is a dynamic collection of metabolites which represent its net response to current conditions.
- **Secretome** [*MeSH descriptor: D000089282*[#]]: The set of all the soluble factors and extracellular vesicles secreted into the extracellular space by cells, or an organ or organism. In some studies, the secretome only refers to the proteins secreted into the extracellular space.
- **Exosome** [*MeSH descriptor: D055354* [#]]: A type of extracellular vesicle, containing RNA and proteins, that is secreted into the extracellular space by exocytosis when multivesicular bodies fuse with the plasma membrane.
- **Cell-Derived Microparticles** [*MeSH descriptor: D055252* [#]]: Extracellular vesicles generated by the shedding of cell membrane blebs.

NIH, National library of medicine, MeSH Descriptor Data.

findings by showing that the percentage of people exposed to silica was significantly higher in SSc affected patients than in the general population. In addition, a recent study has demonstrated that systemic sclerosis patients with occupational exposure have significantly higher serum levels of silica nanoparticles than controls, and that there was an association between high serum silicon levels and specific clinico-serological features associated with a worse prognosis of the disease [39]. Remarkably, the causal link connecting silica and systemic sclerosis appears to be weaker in women [34]. This might be because the majority of workers in dusty trades are men, and women are much more likely to suffer from systemic sclerosis through other causal pathways involving sex hormones and pregnancy-related events, diluting the cases of SSc due to silica exposure. While several of the mechanistic questions remain unanswered, a general hypothesis includes the release of nucleic acids and other damage-associated molecular patterns (DAMP) due to silica-induced tissue damage, leading to inflammation, the release and modification of self-antigens, which could lead to humoral and cellular autoimmunity in a genetically susceptible individual [40].

2.2. Exposure to solvents

Apart from respirable crystalline silica, solvent exposure has also been associated with a higher risk of developing SSc. Besides their regular use in occupational settings, solvents are also utilized at home, in offices, laboratories, and various other environments due to their presence in a wide array of products, including paints, adhesives, degreasing agents, and cleaning agents. Main solvent composition in these products include benzene, toluene, xylene, acetone, trichloroethylene, ethanol and isopropyl alcohol, among others. Exposure to solvents can happen via inhalation, ingestion, as well as transdermal routes, and it can lead to a plethora of health effects, both acute and chronic [41]. Acute exposure typically leads to irritation of the airways and skin, neurotoxic symptoms like headaches and drowsiness, or organ-specific toxicity like nephro- and hepatotoxicity. While chronic exposure can result in cognitive dysfunction, impaired reproductive function, cardiomyopathy and suppression of the hematopoietic system [42,43]. Two characteristics of solvents play an important role in their pathogenicity, namely their volatility and their lipophilicity [44]. The volatility of solvents facilitates their entry in the body through inhalation, and their lipophilicity allows for skin penetration. In addition, the latter characteristic enables them to cross cell membranes and the blood brain barrier easily and results in bioaccumulation in adipose rich tissues and organs such as the brain, liver and bone marrow. Furthermore, solvents are regarded as harmful substances by the body and thus require metabolization and excretion through the liver and kidneys, with these organs becoming targets of solvent toxicity due to extended contact. Besides, certain solvents are also associated with different cancers, and the development of autoimmune diseases [42]. Numerous epidemiological studies have investigated the role of solvent exposure in the development and occurrence of autoimmune diseases, such as SSc [45–52]. Their exact role in these diseases are theorized to be the introduction of protein modifications, where enzymatically transformed (more reactive metabolites of) solvents bind to cellular proteins, membranes or DNA [53] and serve as neoantigens to stimulate an autoimmune response [54,55]. Although these studies can give an indication of the pathophysiology, further research is needed to establish causal relationships and unravel the pathophysiological mechanisms of specific solvents in specific situations.

2.3. Other environmental agents

Besides silica and solvents, many other substances have been reported to be associated with features of autoimmunity and systemic sclerosis in human populations [56]. These include vinyl chloride, dioxins, asbestos, and components of air pollution [57–60]. It has also been underscored that metals (such as mercury, silver and gold) can induce autoimmunity [61] and exposure to antimony, cadmium, lead and mercury has been associated to SSc [62]. Furthermore, there is some evidence suggesting that physical exposures, such as UV radiation and hand-transmitted vibration, might be associated with an elevated risk of developing SSc. Nevertheless, their precise role in the development of SSc remains a subject of ongoing debate [63]. In addition, infection with Parvovirus B19, Cytomegalovirus [64] and Helicobacter pylori have been suggested to be associated with SSc onset, given that the incidence of these infections is surprisingly high in patients with systemic sclerosis. However, evidence is insufficient to conclude that infection is a significant risk factor for SSc.

3. Contribution of internal exposome – (epi)-genetic, immunological and metabolic factors

Studies have indicated that the clinically classified subsets of systemic sclerosis are often distinct compared to their subsets that are determined by characterization of molecular markers, including the genomics and epigenomics [65–67]. Additionally, the combination of clinical, serological, and molecular markers, helps us to better understand the distinct features of the different SSc phenotypes and aspects, such as familial and nonfamilial cases and overlap with other disease phenotypes like rheumatoid arthritis [65,68–70]. A growing body of evidence suggests that characterization and identification of several of the internal exposome components, including markers of inflammation and autoantibodies, in the pre-clinical phase, can help develop preventative strategy through the modification of environmental/lifestyle risk factors [71–73]. In this context, complementary characterization of both the external and internal exposome using targeted and untargeted approaches, can provide a better mechanistic understanding of the biological process, and allow more effective and informed means to prevent disease.

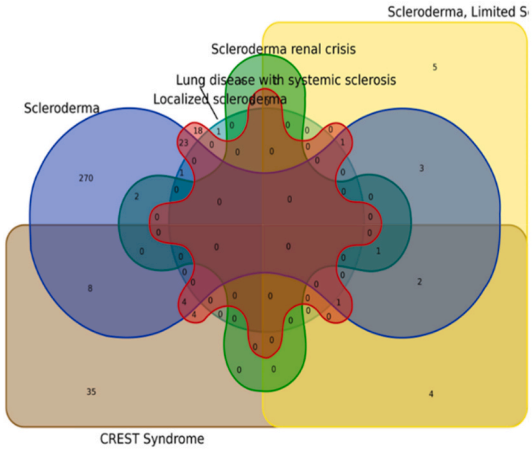
3.1. Influence of genetic and transcriptomic factors

3.1.1. Genetic factors

Several genes have been identified for their key role in the pathogenesis of SSc [27], including, but not limited to, Interferon regulatory factor 5 (IRF5), Signal transducer and activator of transcription 4 (STAT4), interleukin-1 receptor-associated kinase 1 (IRAK1), and angiopoietin 1 (ANGPT1) which were also confirmed in the study by López-Isac et al. [74]. Moreover, it has long been established that major histocompatibility complex (MHC) gene families play a key role in the development of several autoimmune diseases, including SSc [69,74–86]. Additionally, given that SSc is a multigenic disease, affecting multiple biological processes – including vascular homeostasis, fibrotic processes, and the immune system – a large number of genetic polymorphisms are shared between different phenotypes of SSc, and between other autoimmune diseases [3,87,88] (see Fig. 1).

In order to better understand and visualize the genetic heterogeneity among SSc disease phenotypes, the current review consulted datasets from the DisGeNET database [89,90] for Systemic Scleroderma (UMLS CUI[2]: C0036421); Scleroderma (UMLS CUI: C0011644); Localized scleroderma (UMLS CUI: C0036420); Generalized morphea (UMLS CUI: C0263664); Scleroderma renal crisis (UMLS CUI: C1262147); Scleroderma, Limited (UMLS CUI: C0748540); CREST Syndrome (UMLS CUI: C0206138), and Reynolds syndrome (UMLS CUI: C0748397). The DisGeNET datasets revealed the clear overlaps, unique genetic signatures and the complexity of the disease phenotypes (Fig. 2). This was also evident from datasets downloaded from MalaCards - human disease database (Version 5.16) [91] for Systemic Scleroderma (MCID: SYS005) and Localized Scleroderma (MCID: LCL006), with 18 overlapping genes

[2] Unified Medical Language System (UMLS) controlled biomedical vocabulary unique identifier (CUI).



Systemic Scleroderma (UMLS CUI: C0036421)

GO:0000165	MAPK cascade
GO:0000302	response to reactive oxygen species
GO:0001503	ossification
GO:0001525	angiogenesis
GO:0001568	blood vessel development
GO:0001666	response to hypoxia
GO:0001667	ameboidal-type cell migration
GO:0001775	cell activation
GO:0001816	cytokine production
GO:0001817	regulation of cytokine production

Fig. 2. Venn diagram showing the overlap between gene sets for Systemic Scleroderma (UMLS CUI: C0036421); Scleroderma (UMLS CUI: C0011644); Localized scleroderma (UMLS CUI: C0036420); Generalized morphea (UMLS CUI); Scleroderma renal crisis (UMLS CUI: C1262147); Scleroderma, Limited (UMLS CUI: C0748540); CREST Syndrome (UMLS CUI: C0206138); Reynolds syndrome (UMLS CUI: C0748397) obtained from DisGeNET, Table in inset summarizes the enrichment of biological process for Systemic Scleroderma (UMLS CUI: C0036421) performed using WebGestalt.

(Supplementary Fig. 1) over-representing biological process associated with cell differentiation, cytokine production and regulations of immune processes (GO:0045597, GO:0002682, GO:0050776, GO:0001817). Additional analysis of the DisGeNET gene set using WebGestalt [92] for Systemic Scleroderma (UMLS CUI: C0036421) indicated enrichment of biological processes related to MAPK cascade (GO:0000165), ossification (GO:0001503), angiogenesis (GO:0001525), among others (Fig. 2, Supplementary Fig. 2). The enrichment of many of these biological processes are reflective of the phenotypic traits exhibited by SSc, for instance diffuse pulmonary ossification has been studied in idiopathic pulmonary fibrosis (IPF) and SSc [93,94]. Additionally, other well described processes such as oxidative stress response, angiogenesis and vasculopathy in SSc are also reflected in the enrichment of biological processes [95–98].

To quantify the contribution of specific genes to the probability of developing a disease, genetic risk scores were developed. Genomic risk scores (GRS) and polygenic risk scores (PRS) assess genetic predisposition by combining the weighted effects of multiple risk alleles, aiding in early diagnosis and understanding of the etiology of complex immune mediated diseases like SSc. While being a promising tool, several papers discuss areas of improvement [99–101]. The sensitivity and specificity could be improved by considering factors like serologic subtypes, immune cell counts, age, and sex, in order to be clinically relevant. In addition, they are usually based on GWAS data from predominantly European populations, leaving African, Asian, Latino and Indigenous descent underrepresented. There is also a lack of studies on sex-specific variants and many studies do not take into account the X chromosome. Therefore, refining these scores with more diverse and comprehensive data could enhance their clinical utility and better reflect the genetic complexity of different populations. Furthermore, while cumulative exposure assessment exists, it is usually not considered in combination with genetic risks scores, disregarding the other main etiologic factor in SSc.

3.1.2. *Transcriptomic factors*

To delve deeper into the genes actively expressed in individuals with SSc, transcriptomics offers valuable insights into the molecular heterogeneity and potential treatment responses associated with the disease [102,103]. Notably, single-cell transcriptomics enables the identification of specific cell types contributing to disease pathology, surpassing the resolution of bulk-level analyses. Recent reviews have examined gene expression in various samples from SSc patients, including peripheral blood mononuclear cells (PBMCs), skin lesions, and lung tissue, identifying differentially expressed genes that reflect the disease's heterogeneity and hallmark clinical features [104–106]. Key pathways consistently highlighted include TGF-β/Wnt and interferon signalling, alongside specific markers related to inflammation, immune activity, fibrosis, vascular processes, stress, and cellular senescence. The referenced reviews provide detailed insights into the exact gene expression profiles observed in specific cell types within the analyzed matrix. Collectively, they spotlight gene expression profiles resulting in immune dysregulation, downregulation of angiogenesis, and upregulation of fibrosis, stress, and cellular senescence, mirroring the clinical manifestations characteristic of SSc.

3.2. *Epigenetic factors*

In addition to genetic factors, epigenetic regulation of several key genes and biological processes also plays a key role in SSc pathogenesis. This includes the regulation of DNA methylation and DNA methyl transferases, histone methyltransferase enhancer of zeste homolog 2 (EZH2) and histone methylation among others [84,107–109]. Studies have extensively reported on histone modifications including hyperacetylation of histone H4, hypomethylation of H3K9, demethylation of H3K27me3, dysregulation of HDAC2, HDAC5, HDAC7 among others [110–113]. In a recent study [114], analysis of differentially methylated sites in SSc patients revealed enrichment of processes associated with leukocyte cell-cell adhesion and also T cells related processes, including changes in several key genes- ITGAL, ITGB1, ITGB2, AIRE and IRF1. While extensive discussion of epigenetic regulation of SSc pathogenesis is beyond the scope of the present review, several review articles elegantly present different aspects of the topic, providing an insight into mechanism of disease onset, progression and identification of susceptibility loci [112,115–119].

Next to DNA methylation changes, microRNAs (miRNA) are also part of the internal exposome and epigenetic regulation and are capable of regulating gene expression in response to environmental changes. With regards to SSc, miRNAs are involved in the regulation of gene expression in key disease-specific events like fibrosis, inflammation and vasculopathy. The downregulation or upregulation of certain miRNAs can result in a dysregulation of gene expression leading to hallmark events of SSc.

This was evident from our search of the HMDD (the Human microRNA Disease Database) [120], where a total of twenty-three unique miRNAs were associated with Systemic Scleroderma (HMDD disease ID), as compared to only 3 miRNAs for localized scleroderma (HMDD disease ID) were retrieved. Of the thirty-one unique miRNAs identified for SSc, 2 were found in circulation (hsa-mir-142 and hsa-mir-29a) [121, 122]. Of the identified miRNA, the downregulation of the miR-29 family

and the upregulation of miR-21 can result in increased collagen synthesis and the promotion of fibrosis respectively [123]. Furthermore, the upregulation of miR-155 can result in pro-inflammatory cytokine production [124] and the downregulation of miR-193b can result in vasculopathy [125]. Overexpression of integrins in dermal fibroblasts has also been described in SSc patients with severe clinical manifestations and correlates to lower levels of miR-150 [126]. A study on miRNA expression related to toll like receptor (TLR) pathways have also shown downregulation of miRNA-181a and overexpression of miR-132, miR-143, miR-145, and miR-155 in SSc patients [127]. In addition to directly affecting these hallmark processes of SSc, some miRNAs can also alter DNA methylation and thus act as epigenetic deregulators contributing to the pathogenesis of SSc [123]. Since some miRNAs are specific and important regulators of pathological processes characteristic of SSc, they can be seen as targets for specific therapies and meanwhile represent highly sensitive and specific biomarkers for SSc diagnosis and assessment of SSc progression and has been described in considerable details in a recent review article [128].

3.3. Telomere length

Telomeres are nucleoprotein structures at chromosome ends that play a critical role in preserving genome integrity and stability [129]. Their natural shortening is associated with inflammation and cellular senescence, processes both associated with the pathogenesis of SSc [130,131]. Although results from initial studies were inconsistent, more recent evidence points towards a significant associated between TL and SSc. Usategui et al. [132] showed reduced leukocyte TL in SSc patients particularly in patients with interstitial lung disease (ILD) or anti-topoisomerase I antibodies, whereas Rodriguez-Martin et al. [133] found that longer predicted leukocyte TL being associated with a reduced risk for SSc. Also Liu et al. [134] observed a more significant association of TL shortening with SSc-ILD. To improve the mechanistic understanding of these associations, Adler et al. [135] investigated autoantibodies targeting telomere-associated proteins, and identified autoantibodies targeting telomerase and the sheltering protein telomeric repeat-binding factor 1 (TIRF1) in patients with SSc. These autoantibodies were rarely present in patients with other connective tissue autoimmune diseases and were associated with shorter telomere length and with ILD. Remarkably, TIRF1 autoantibodies highly present in SSc-ILD patients, were almost absent in interstitial pulmonary fibrosis (IPF) patients, despite the overlap in clinical presentation of disease. Moreover, Lakota et al. [136] found that TL shortening in SSc-ILD was specific to lymphocytes, and absent in other types of leukocytes, whereas in IPF, TL shortening was observed in lymphocytes, granulocytes, alveolar epithelial cells and other cell types. In summary, multiple studies highlight the association between telomere shortening and systemic sclerosis, particularly SSc-ILD, with autoantibodies targeting telomere-associated proteins further supporting its involvement in disease pathogenesis. However, the underlying mechanisms remain poorly understood, emphasizing the need for further research to clarify its role as both a biomarker and a potential therapeutic target.

3.4. The role of different secretory phenotypes

The cellular secretome is classically defined as the complete set of cellular proteins secreted by the cell into the surrounding environment. However, it is now evident that, in addition to protein cargo, non-protein components like miRNA, messenger RNA (mRNA), and lipids play a critical role and, therefore, in the present review these will be collectively considered as part of the secretome. The secretome has been characterized for various tumour microenvironments including non-small cell lung cancer, and has been known to play a deterministic role in cancer progression, metastasis, and towards identification of key therapeutic targets [137–141]. Moreover, the secretome plays a role in understanding hallmarks of disease such as proliferation, apoptosis, immune response and energy metabolism [142], and plays a key role in post-transcriptional regulation of several crucial biological processes [143]. Therefore, it is believed that characterization of the secretome can provide a better understanding of cell-cell and organ crosstalk. Additionally, since the secretome constitutes the entirety of the components secreted by cells, it is potentially a culmination of all major biological processes (at genomic, epigenomic, transcriptomic and proteomics levels) and can provide valuable information of physiological state of the cell/tissue and contribute to a better understanding of SSc pathogenesis. Levels of circulating factors such as the vascular endothelial growth factor (VEGF), angiopoietins, bone sialoprotein osteopontin, and oxidative stress marker 8-isoprostane are amongst the markers studied in relation to SSc [144–147]. In this section we discuss some of the circulatory markers in relation to SSc disease phenotype and pathogenesis.

3.4.1. Inflammatory cytokines

Dysregulation of both innate and adaptive immunity [148] significantly contributes to the pathogenesis of systemic sclerosis. Substantial evidence supports the involvement of (auto)immunity, manifested by the presence of inflammatory cells and inflammatory signatures in affected tissues such as the skin and lungs. Furthermore, alterations in circulating immune cells, including changes in their numbers and functionality, have been observed. Notably, a prominent type I interferon (IFN) signature has been detected in both circulating and tissue-infiltrating immune cells. Additionally, characteristic and distinct serum autoantibodies are commonly detected in the majority of patients, further supporting the role of immune dysregulation in systemic sclerosis.

T_H2 cytokines, particularly IL-4 and IL-13, play crucial roles in systemic sclerosis by stimulating fibroblast proliferation and extracellular matrix synthesis [149,150]. Of specific interest in SSc is IL-6, a multifunctional cytokine that induces T_H2-dominant immunity, inflammation, and fibrotic responses. Elevated levels correlate to skin involvement and poor long-term outcomes [151]. Additionally, chemokines such as CCL2, CCL3, IL-8, and CCL18 are increased in SSc patients, indicating disease severity and progression. Platelet factor 4 (PF4) levels serve as predictors for pulmonary complications [152–154].

3.4.2. Autoantibodies

Disease-specific autoantibodies are considered the most important biomarkers for SSc, due to their ability to stratify patients with different severity and prognosis. More specifically, autoantibodies specific for SSc have been linked to distinct clinical features like organ involvement or comorbidities. Therefore, detecting a particular antibody type is important in predicting prognosis and may have an impact on monitoring and treatment. The vast majority of SSc patients exhibit positive antinuclear antibodies (ANA) or antinuclear factor (ANF) (in about 90 % of SSc patients), accompanied by typically one of the mutually exclusive major SSc-specific antibodies, which are anti-centromere, anti-Th/To, anti-topoisomerase I (anti-Scl70), anti-fibrillarin and anti-RNA polymerase enzyme III (anti-RNAP III) [155]. Many other rare autoantibodies have been discovered in recent years with the use of novel detection methods. In most cases, the autoantibody is present years before the onset of clinical symptoms, which makes them a candidate for disease prediction. Anti-centromere antibodies (against kinetochore proteins that facilitate centromere formation) are associated with limited cutaneous systemic sclerosis (lcSSc) and a more favourable prognosis. Conversely, anti-Th/To antibodies (targeting ribonucleases that degrade RNA) are also linked to lcSSc but indicate a poor prognosis. Anti-topoisomerase I antibodies (against an enzyme crucial for DNA replication and transcription) are associated with diffuse cutaneous systemic sclerosis (dcSSc) and a poorer prognosis. Anti-fibrillarin antibodies (targeting an enzyme involved in pre-ribosomal RNA processing) are linked to muscle involvement, a more severe disease, and a poor prognosis, particularly in black SSc patients. Finally, anti-RNA

polymerase III antibodies (against a protein that transcribes DNA) are associated with dcSSc. Important to mention is that probably not all autoantibodies associated with SSc have been uncovered due to limitations inherent to immunoassays like false positives, the correct determination of titre cutoffs and the underrepresentation of (certain conformations) of antigens in the substrates used [155]. It is believed that some autoantibodies can be considered pathogenic, such as for autoantibodies in organ-specific autoimmune diseases, while others do not (yet) have a clear role in relation to the manifestations and symptoms typical of systemic sclerosis [155]. Most evidence for a pathogenic role exist for anti-topoisomerase I and anti-centromere antibodies [156]. According to Senécal et al., an autoantibody should comply with Bradford Hill's seven criteria to be regarded pathogenic (immunoglobulins contributing or causal for to the development of an autoimmune disease) and thus one must be able to define how it might act and reproduce it experimentally [156]. The pathogenic role of anti-topoisomerase 1 antibodies would lie in their ability to amplify the fibrogenic cascade resulting in continuous healing and continuous fibrosis. And the presence of anti-centromere antibodies would result in a state of continuous vascular remodelling. This aligns with the concept that SSc resembles a perpetual repair process. Although the presence of a certain autoantibody can be associated with certain genetic polymorphisms, the exact reason why and how these autoantibodies are being produced is not completely elucidated.

While considerable amount of evidence is present from the cytokines and autoantibodies, fewer studies have characterized other components of the secretome, namely, proteome, metabolome and exosomes. From this point onward, a systematic approach (Supplementary file) was applied to retrieve literature and summarize the findings.

3.4.3. Proteomic changes associated with SSc

A selected number of studies have characterized the proteome in bronchoalveolar lavage fluid (BALF) and serum samples of SSc patients using both targeted and untargeted approaches. Rottoli et al. [157], used a targeted analysis of protein carbonylation in BALF samples from a diverse group of patients, which included SSc patients. The authors observed an increase in carbonylated proteins (albumin, transferrin, haptoglobin b, IgG heavy chain α) in BALF samples indicating a role of protein oxidation in the pathogenesis of diffuse lung disease. Other studies have shown that oxidation process and resulting protein modification leads to autoantibody production in response to oxidative damage, for instance in type 1 diabetes, Graves' disease and Hashimoto thyroiditis [158–160].

Fietta et al. [161], also analyzed the proteome of BALF samples from SSc patients to understand the role (both protective and causative) in lung fibrogenesis. In SSc patients with lung fibrosis, the authors observed elevated levels of proteins with a role in lung fibrosis (Cal B, cytohesin-2, and calumenin). Other proteins with key roles in maintenance of redox balance and prevention of lung injury such as glutathione S-transferase P (GSTP), Cu–Zn superoxide dismutase (SOD) and cystatin SN were downregulated in patients with fibrosis. Shirahama et al. [162], compared SSc patients with and without lung fibrosis, where the authors observed an increased abundance of α2-macroglobulin, α1-antitrypsin, and pulmonary surfactant protein A in patients with fibrosis. Like the previous study, the authors also observed a decrease in protective proteins such as α2 heat shock protein (HSP) and glutathione S-transferase (GST) in patients with fibrosis.

Carlsson et al. [163] compared the levels of different serum proteins between patients with SSc and systemic lupus erythematosus (SLE). While most of the discussion is based on comparison between SLE and SSc, a limited number of proteins were differentially expressed in SSc patients including IFN-γ, IL-4, MCP-4, and mucin-1. These results have been summarized in Supplementary Table 1.

3.4.4. Metabolomics markers

The use of metabolomics in the field of respiratory diseases has been relatively less explored [164] and is reflective of the relatively fewer studies identified for SSc. A few recent studies identified plasma and serum metabolites in SSc patients (Supplementary Table 1). Fernández-Ochoa et al. [165], studied the plasma and urine metabolome in different systemic autoimmune diseases (SAD). Metabolites distinguishing between healthy controls and SAD included unsaturated fatty acids, acylcarnitines, acylglycines, and amino acids. The higher level of N6-carbamoyl-L-threonyladenosine in controls compared to SAD is especially noteworthy and is likely related to the renal involvement present in these diseases. In a study characterizing serum metabolome [166], the authors reported that some amino acids and purine metabolites (l-tyrosine, l-tryptophan, and 1-methyl-adenosine) could distinguish healthy controls from SSc patients. In another study aimed at identifying an association between intestinal microbiota and SAD, Bellocchi et al. [167], studied faecal microbiota and plasma metabolome in a relatively large number of SSc patients (n = 59). In addition to nine bacteria, seventeen metabolites (including glycerophospholipid metabolites and benzene derivatives) were identified in SSc patients compared to controls. It however remains to be established whether these metabolites can be considered as disease biomarkers and related to specific pathogenic pathways.

3.4.5. Microparticles and exosomes-role in platelet induced immune dysregulation in SSc

Extracellular vesicles (EV) – which were long considered as "waste disposal" devices – are now considered as an important tool in cell-cell communication. Extracellular vesicles (exosomes, microvesicles, and apoptotic bodies; Supplementary Table 2) are ubiquitous in human tissues, circulation, and body fluids; and are now being studied with growing interest across multiple fields. The associated cargo (nucleic acids, proteins and lipids) [168], its function and their crosstalk with other components of the secretome, remains largely unknown. Accumulating data indicate that content, size, and composition of vesicles are dependent on cellular state (apoptosis/autophagy/senescence). While a limited number of studies have reported alteration of the bronchial secretome [169] by exposure to cigarette smoke [170], diesel exhaust [171] and petroleum coke [172], it has not been used thus far to bridge the knowledge gaps related to exposure and prevention strategies in public health. In the current section, we aim to summarize the studies that have explored the role of extracellular vesicles in SSc.

Most of the studies identified through the systematic search, have used a targeted approach to characterize circulatory microparticles (MPs). A large majority of such studies used surface markers (CD molecules) to identify cells of origin. In one of the earlier reports, Guiducci et al. [173], described different cellular sources of microparticles in patients with systemic sclerosis. While the authors observed no significant change in differential cell counts (platelet, erythrocyte, monocyte, and T cell) between control and SSc patients, the latter had a significantly higher number of MPs in plasma. The MPs derived from platelet ($CD42^{+}$), monocytes ($CD14^{+}$), T cells ($CD3^{+}$) and endothelial cells (CD144+), indicating activation of these cell types in SSc patients. Moreover, in the SSc group, patients with modified Rodnan skin score (MRSS) < 10 had significantly higher number of MPs compared to patients with MRSS ≥ 10. In another study, Leleu et al. [174], characterized the expression of platelet- (CD235a-, $CD41^{+}$) and endothelial cell-derived MPs (CD235a-, $CD41^{-}$, $CD31^{+}$). The authors did not observe a difference in endothelial cell derived MPs, but a significant increase in platelet derived MP was observed in SSc patients. Additionally, SSc patients with interstitial lung disease (ILD) and pulmonary fibrosis had higher levels of MPs. The authors reported significantly lower platelet derived MP concentration in patients treated with methotrexate and targeted disease-modifying antirheumatic drugs (tDMARDs). In the same study, the authors demonstrated a profibrotic effect of MPs from SSc patients on dermal fibroblasts *in vitro*. Nomura et al. [175], described elevated levels of platelet- and monocyte-derived MPs in plasma samples from SSc patients, and significantly higher levels

of MP in patients with interstitial pneumonia. Oyabu et al. [176], also observed an elevated level of platelet-derived MPs in SSc patients and suggested a role of platelet activation and possible role in chronic vascular damage. Iversen et al. [177], on the other hand reported lower levels of MPs, derived from platelet-poor plasma of SSc patients as compared to control. While the authors observed an overall decrease in MPs (derived from platelets, leucocytes, and endothelial cells), there was a significantly higher level of AnxV non-binding MPs in SSc patients, with a role in vascular activation.

Michalska-Jakubus et al. [178] also studied the levels of endothelial cell derived MPs in platelet poor plasma of SSc patients. The mean concentrations of endothelial derived MPs were significantly higher including activated (CD62E+/AnnV−) and apoptotic (CD62E+/AnnV+ and $CD51^{+}$) MPs, in SSc patients compared to healthy control. An inverse correlation was observed between the number of MPs and the MRSS score. In a later study from the same group, an increase in endothelial cell derived MP in SSc patients was reported by Małgorzata et al. [179]. The authors also observed elevated levels of apoptotic endothelial-derived MPs (CD62E+/AnnV+ and $CD51^{+}$) in patients with higher anti-endothelial cell antibodies (AECAs) which is associated with vascular injury and plays a key role in vascular diseases by affecting bone marrow derived endothelial progenitor cells (EPCs). Benyamine et al. [180], described an increased level of endothelial MP in platelet poor plasma of SSc patients, which were significantly correlated with levels of VEGF, endothelin-1 and s-Fractalkine as markers of vascular activation and disease severity. McCarthy et al. [181] also characterized endothelial- and platelet-derived MP in platelet poor plasma from SSc patients to understand the role of MPs in vascular dysfunction. The authors observed a significant increase in platelet derived MPs, potentially indicative of platelet activation and has been elaborately discussed by Scherlinger et al. in their review [182].

While most of the studies described thus far only identified the cellular origin of microparticles (MPs), a few additional studies attempted to characterize the content of such MPs. In one study, Wermuth et al. [183] characterized exosomes from serum samples of SSc patients for surface protein markers (CD63, CD81, ALIX, FLOT1, ICAM1, EpCam, ANXA5 or TSG101) and miRNA. While the study was performed in a small group of patients (n = 6), six profibrotic and twelve antifibrotic miRNAs were significantly dysregulated in exosomes isolated from SSc patient. In another study, Østergaard et al. [184] characterized the proteome of MPs in serum. While the main objective of the study was to characterize unique proteome signature of MPs from patients with SLE, the authors included a small subset of SSc patients (n = 6) for comparison. In the MPs isolated from platelet poor plasma of SSc patients, seven proteins were unique to SSc alone and 20 were unique when compared to control, however, no further interpretation of such findings was provided. Chouri et al. [185], characterized the miRNA content of exosomes obtained from serum samples of SSc patients, in which twenty-nine miRNAs were differentially expressed compared to controls. Some of these miRNAs, including expression of miR-483-5p, were further validated and were found to be stably embedded in the exosome.

4. Summary

The studies discussed in the present review clearly show advances in understanding of SSc disease phenotype and associated biomarkers in relation to specific pathophysiological features and biological processes. However, most of the reviewed studies evaluating internal exposome markers are not supplemented with external exposome data. A more clear association between different exposure conditions and features of autoimmunity, including elevated levels of specific autoantibodies, toll-like receptor imbalance, markers of vasculopathy, cell death and fibrosis, come from a limited number of studies in rodent models [186–190]. While many of these studies have addressed aspects of exposure-induced autoimmunity, only few have focused on SSc specific phenotypes. In epidemiological studies on the other hand, characterization of external exposome components is mostly targeted, often characterizing a single exposure component in relation to SSc. Studies in SLE patients have shown that longer duration of exposure to silica dust is associated with greater risks. Therefore, despite the selective characterization of exposure, such studies play an important role in providing evidence that can be used towards reduction of exposure of modifiable factors and can lead to proper management and prevention of SSc.

In this context, in the EXIMIOUS project, a major emphasis has been placed on characterization of a large number of external exposome parameters covering different aspects of current occupational exposures (measured and modelled), occupational history, socioeconomic factors, hobbies, housing condition and air pollution modelling [191]. Additionally, there is a huge effort towards integration of these external exposome data with multiple health data (health records, medical imaging, diagnostic results etc), to significantly improve our understanding of the environmental and occupational cause of SSc. Additionally, a large amount of internal exposome (genomic, epigenomic, transcriptomic and secretome) data is being generated and integrated in the EXIMIOUS project, for a better mechanistic understanding of SSc etiology and progression. We aim to integrate internal exposome data (including genetic risk scores) together with the external exposome data to facilitate early identification of persons at risk for diseases like SSc. EXIMIOUS additionally uses the “meet-in-the-middle” approach where characterization of the internal exposome markers in occupational and disease cohorts can further improve our understanding of both clinical and pre-clinical phases of autoimmunity. As a result, the complex exercise of external exposome-health-internal exposome data is expected to provide valuable information towards prevention and contribute towards European health policies and improved health care systems.

CRediT authorship contribution statement

Lisa MF. Janssen: Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Frauke Lemaire:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Chiara Longo Sanchez-Calero:** Writing – review & editing, Writing – original draft. **François Huaux:** Writing – review & editing. **Steven Ronsmans:** Writing – review & editing. **Peter HM. Hoet:** Writing – review & editing, Writing – original draft, Supervision, Funding acquisition, Conceptualization. **Manosij Ghosh:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Methodology, Funding acquisition, Formal analysis, Data curation, Conceptualization.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jaut.2024.103342.

Data availability

No data was used for the research described in the article.

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