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Review

Matrix metalloproteinase-2: Not (just) a “hero” of the past

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ABSTRACT

The 72-kDa type IV collagenase or gelatinase A is the second member of the matrix metalloproteinase family, MMP-2. Since the discovery of its first two substrates within components of the extracellular matrix, denatured interstitial type I collagen and native type IV collagen, the roles and various levels of regulation of MMP-2 have been intensively studied, mainly *in vitro*. Its (over)expression in most if not all tumors was considered a hallmark of cancer aggressiveness and boosted investigations aiming at its inhibition. Unfortunately, the enthusiasm subsided like a *soufflé* after clinical trial failures, mostly because of insufficient knowledge of *in vivo* MMP-2 activities and detrimental side effects of broad-spectrum MMP inhibition.

Nowadays, MMP-2 remains a major topic of interest in research, the second in the MMP family after MMP-9. This review presents a broad overview of the major features of this protease. This knowledge is crucial to identify diagnostic or therapeutic strategies focusing on MMP-2. In this sense, recent publications and clinical trials underline the potential value of measuring circulating or tissular MMP-2 levels as diagnostic or prognostic tools, or as a useful secondary outcome for therapies against other primary targets. Direct MMP-2 inhibition has benefited from substantial progress in the design of more specific inhibitors but their *in vivo* application remains challenging but certainly worth the efforts it receives.

Contents

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1. Introduction

This minireview is not intended to present an extensive review on matrix metalloproteinase (MMP)-2. The purpose is to give an overview of key features of the two lives of MMP-2. Its first life (1980's – 1990's) was rich in biochemical characterization: structure, substrates, regulation, mechanisms of activation and inhibition … But most importantly, MMP-2 emerged as a key player in cancer invasion and metastasis, triggering a craze for strategies aiming at its *in vivo* inhibition. Unfortunately, adverse effects of broad spectrum MMP inhibitors (*i.e.* due to beneficial effects of MMPs) almost rang the bell for the whole field. However, MMP-2, like its close relative MMP-9, still continues to benefit from a sustained interest, as illustrated by the number of publications focusing on, or related with these two MMPs during the last five years (Fig. 1). This second life of MMP-2 (2000's and 2010's) is clearly focused on two major topics: a better knowledge of its precise functions *in vivo* and in pathologies, and the design of more specific inhibitors devoid of adverse effects.

In this minireview, we will summarize key features of MMP-2, in a rather historical (and nostalgic) approach, referring to seminal observations and/or outstanding reviews and we will also give a brief overview of the ongoing research.

2. Discovery

In the early 1970's, Harris and Krane identified in the rheumatoid synovial tissue culture medium an endopeptidase degrading the denatured form of type I collagen or gelatin, but not its native form [1]. By analogy with a previously described endopeptidase called collagenase because of its catalytic activity against native type I collagen [2], the gelatin-degrading enzyme was termed gelatinase. The gelatinase was then purified in a latent 72-kDa form from culture media of various tissues and cells, including rabbit bone [3] and H-ras-transformed human bronchial epithelial cells [4]. The latent gelatinase could be activated to an active form degrading type IV collagen and was therefore also called type IV collagenase [4]. This gelatinase/type IV collagenase exhibited the principal characteristics that conventionally define a member of the MMP family, namely secretion as an inactive proMMP, activation, and metallo-dependent degradation of extracellular macromolecules (for a review [5]). It was named MMP-2 since it was the second enzyme to enter the family after interstitial collagenase/MMP-1 [6]. A 92-kDa endopeptidase also degrading native type IV collagen and gelatin was later reported in SV40-transformed human lung fibroblast cultures [7]. To avoid confusion between these two gelatinases, the 72-kDa enzyme was called gelatinase A whereas the 92-kDa enzyme was called gelatinase B and MMP-9 [6].

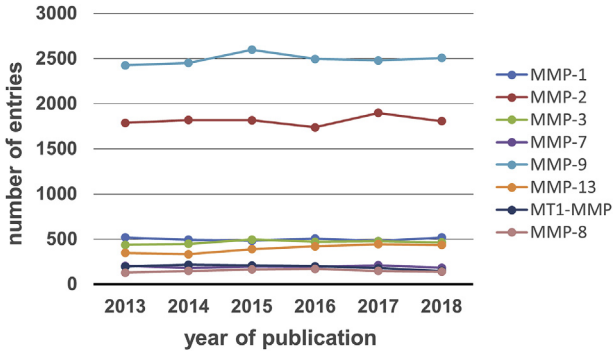

Fig. 1. Number of entries in PubMed per publication year. For each MMP, the number of entries was calculated by searching PubMed for occurrences of the word MMPx or MMP-x (or MT1-MMP for MMP-14) per year, in any field, for the last five years (2014–2018).

3. Biochemical and biological features

MMP-2 is a Zn^{2+}-dependent enzyme encoded by a gene located on the long arm of chromosome 16 at position q12.2. The 27 kb-long *MMP2* gene has 13 exons [8] and is classically transcribed in a 3.1 kb-mRNA [4]. The cDNA for MMP-2 codes for a 660 residues preproenzyme containing a 29 residues signal peptide responsible for translocation to the endoplasmic reticulum and followed by the 72-kDa-proenzyme (Fig. 2). ProMMP-2 is composed of a propeptide followed by a catalytic domain that is connected to a hemopexin (Hpx)-like domain through a linker sequence. A free zinc-ligating thiol group present in the propeptide maintains the enzyme latency until activation (cysteine switch). The Zn^{2+}-binding motif of

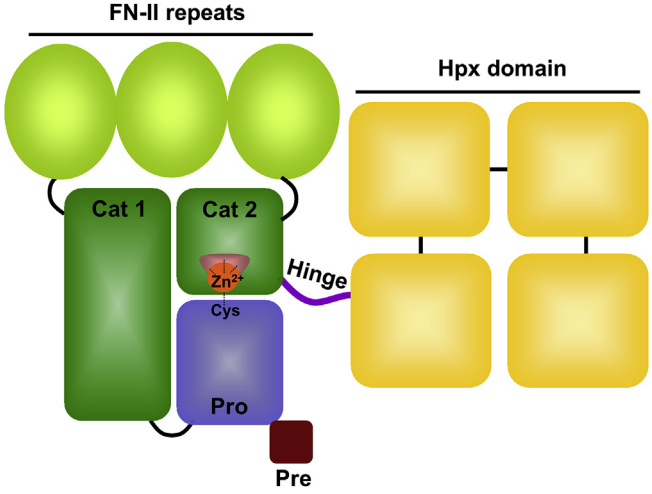

Fig. 2. MMP-2 structure. The signal peptide (Pre, 29 residues) targets the preproMMP-2 to the reticulum endoplasmic and is followed by the prodomain (Pro, 80 residues), which is involved in enzyme latency. A catalytic domain, similar to the one shared by all MMPs, is composed of two parts (Cat 1, 118 residues and Cat 2, 53 residues). Each part binds to a zinc ion (Zn^{2+}) but the figure only shows the Zn^{2+} of the active site (represented by the orange triangle). Inhibition of the catalytic domain in the zymogen form results from its partial coverage by the propeptide through binding of the cysteine switch (represented by Cys) with the Zn^{2+} ion of the active site. Three fibronectin type II (FN-II) repeats (165 residues in total) are inserted between the two parts of the catalytic domain. Four domains similar to hemopexin (Hpx domain, 192 residues in total) are bound to the catalytic domain through a linker sequence (hinge domain, 23 residues).

the catalytic domain is preceded by three cysteine-rich repeats comparable to the collagen-binding fibronectin type II (FN-II) repeats, which are required for recognizing collagen and elastin [9–11].

Different mechanisms contribute to regulate the activity of MMP-2 during its molecular existence: expression, secretion, activation, extra/pericellular localization, inhibition, endocytosis and lysosomal degradation (Fig. 3).

3.1. Expression

According to the Human Protein Atlas [12], the mRNA and the protein are both present essentially in the heart and smooth muscles, in the lung, in the colon, in the kidney and the urinary bladder, in the testis and the prostate, in the uterine cervix and the endometrium, in the placenta, and in all tumors tested. Values of MMP-2 concentration in the blood of healthy individuals were reported in various studies [13–24] summarized in Table 1. It is important to note that a great variability was observed between MMP-2 concentrations. It could be due to the nature of the samples tested (serum *vs* plasma), the anti-clotting agent (sodium citrate *vs* dipotassium EDTA) and/or the molecular MMP-2 forms measured (free *vs* complexed with TIMP-2; latent *vs* active).

Historically, (over)expression of MMP-2 in tumors was quickly linked to increased invasive and metastatic potential, fostering research on its transcriptional control. The human *MMP2* gene lacks a conventional TATA-box or classical transcription response elements found in other MMP genes [25–28]. Constitutive expression of MMP-2 was shown to depend on p53-, Sp1-, Sp3-and AP-2-binding sites [29,30] but the promoter contains other *cis*-regulatory elements including C/EBP, ATF2, PEA3/Ets, c-myc and AP-1 binding sites [29–34]. Epigenetic control also contributes to MMP-2 regulation. For instance, transcriptionally active MMP-2 in invasive cancer cells is characterized by hypomethylation of CpG regions in the *MMP2* promoter and low levels of histone H3 lysine-27 trimethylation [35].

3.2. Secretion or intracellular activity

The N-terminus of preproMMP-2 is a signal peptide responsible for co-translational translocation into the endoplasmic reticulum (ER). Although MMP-2, like all other MMPs, was initially regarded only as a secreted MMP with extracellular activity, this paradigm was progressively modified to account for the accumulating evidence that MMPs are also intracellularly active. Two major mechanisms are proposed to explain intracellular MMP localization. The first one relies on inefficient signal sequence and results in ER translocation of a variable proportion of the proteins being synthesized, while the other ones remain in the cytosol. The other mechanism depends on endocytosis of secreted proteins. MMP-2 can be endocytosed through direct or indirect binding to several membrane proteins (see §3.6). However, its translocation across the endosome membrane towards the cytosol remains unclear. Moreover, besides its transient journey in the secretory pathway (ER, Golgi apparatus and related vesicles), intracellular MMP-2 is not restricted to the cytosol but is also found in organelles including nucleus and mitochondria. Its intracellular life and activities are reviewed in details by Cauwe and Opdenakker [36] and more recently by Jobin et al. [37].

3.3. ProMMP-2 activation

The latent proform of most MMPs is generally processed in the extracellular compartment by proteolytic removal of the ~10-kDa

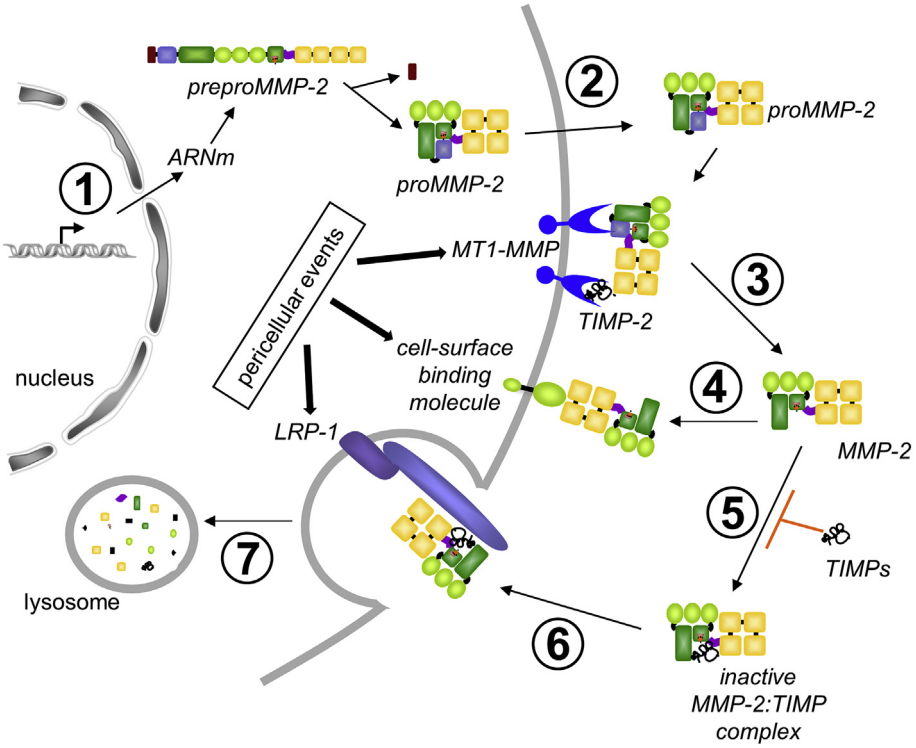

Fig. 3. Levels of control of extra/pericellular MMP-2. After expression (1), preproMMP-2 is usually translocated into the secretion pathway and converted into proMMP-2 by removal of the signal peptide. After secretion (2) into the extracellular space, proMMP-2 is activated (3) at the cell surface by MT1-MMP. Active MMP-2 can bind to various cell-surface molecules (4). Active MMP-2 can also be inhibited by TIMPs (5). The inactive complex can be endocytosed by a member of the LRP family, namely LRP-1 (6) and then be degraded in lysosomes (7).

Table 1
MMP-2 levels in human serum and/or plasma. Values are expressed in ng/ml, as means or medians and standard deviation (SD), standard error (SE), interquartile range or global range ([–]). A-C: anti-clotting agent added into plasma. FMAP: Fluorokine MultiAnalyte Profiling. NT: not tested.

Serum	Plasma	A-C	Technique	Molecular forms assayed	Ref.
160.0 ± 14.8 (SD)	140.1 ± 21,7 (SD)	EDTA	FMAP	forms and complexes not specified	[13]
340 (252) (IQ)	288 (216) (IQ)	citrate	FMAP	pro and active; complexes not specified	[14]
235 [108–384]	NT		ELISA	forms and complexes not specified	[15]
582.5 ± 139.3 (SD)	NT		ELISA	free and complexed	[16]
610 ± 25.9 (SE)	405.5 ± 54.3 (SE)	citrate	ELISA	forms and complexes not specified	[17]
	569.9 ± 26.5 (SE)	heparin	ELISA	forms and complexes not specified	[17]
	86.5 ± 15.6 (SE)	EDTA	ELISA	forms and complexes not specified	[17]
NT	753 ± 126 (SD)	unknown	ELISA	pro but not active; free and complexed	[18]
625 [588–662]	NT		ELISA	MMP-2/TIMP-2 complex	[19]
1259.9 [793.9–1881.9]	1195.5 [770.6–1791.2]	EDTA	ELISA	free proMMP-2	[20]
29.4 [10.8–68.1]	NT		ELISA	free active MMP-2	[20]
1456.4 [749.8–2168.7]	1119.1 [641.6–1780.6]	EDTA	ELISA	MMP-2/TIMP-2 complex	[20]
49.0 ± 10.8 (SD)	NT		ELISA	forms and complexes not specified	[21]
NT	781.4 ± 190.7 (SD)	EDTA	ELISA	forms and complexes not specified	[22]
593.3 ± 134.0 (SD)	NT		ELISA	forms and complexes not specified	[23]
61.17 (14.02) (IQ)	NT		EIA	forms and complexes not specified	[24]

propeptide, resulting in an intermediate form which is further activated by another proteinase into a fully active form [38]. However, proMMP-2 cannot be fully activated by most extracellular proteinases. For example, thrombin alone is unable to fully activate proMMP-2 [39] and activation of proMMP-2 by neutrophil elastase, cathepsin G or proteinase-3 depends on the expression of membrane-type 1 MMP (MT1-MMP) [40]. A prominent mechanism for proMMP-2 activation occurs at the cell surface and depends on the MT-MMPs, mainly MT1-MMP. The six MT-MMPs are associated to cell membranes by either a type I transmembrane domain (MT1-, MT2-, MT3-and MT5-MMPs) or a glycosylphosphatidylinositol (GPI) anchor (MT4- and MT6-MMPs). Their pericellular activities are diverse and include ECM degradation and shedding and activation processes (for recent reviews [41,42]).

Among the six MT-MMPs tested *in vitro*, only MT4-MMP does not activate proMMP-2 [43] while MT6-MMP appears not to be very efficient [44,45]. The recombinant catalytic domain of MT5-MMP generates the active form of MMP-2 [46]. Activation of proMMP-2 by MT3-MMP requires a preliminary interaction between chondroitin sulfate glycosaminoglycans expressed at the cell surface and the Hpx-like domain of proMMP-2 [47]. MT2-MMP activates proMMP-2 by directly interacting with the Hpx-like domain of the proenzyme [48].

Mechanisms of proMMP-2 activation by MT1-MMP have been extensively studied and involve tissue inhibitor of metalloproteinases-2 (TIMP-2), a physiological inhibitor of MMPs [41,49]. Briefly, proMMP-2 can be secreted either in a free form or already complexed with TIMP-2 through its C-terminal domain [50]. In the first case, a TIMP-2 that inhibits a cell membrane-anchored MT1-MMP by interaction between its N-terminal inhibitory domain and the catalytic domain of MT1-MMP, acts as a binding site for free proMMP-2 by interaction between the proMMP-2 Hpx-like domain and the TIMP-2 C-terminal domain. ProMMP-2 present in the resulting MT1-MMP-TIMP-2-proMMP-2 complex can then be activated by another adjacent TIMP-2-free MT1-MMP. In the second case, the N-terminal inhibitory domain of TIMP-2 in the proMMP-2-TIMP-2 complex can interact with a cell membrane-anchored MT1-MMP. This proMMP-2 is then activated by an adjacent free MT1-MMP. To illustrate this process, it has been shown that proMMP-2 colocalizes with TIMP-2 and MT1-MMP inside caveolae on the surface of endothelial cells [51]. However, a recent study performed both *in vitro* and *in vivo* suggests that extracellular association of proMMP-2 and TIMP-2 would depend on TIMP-2 phosphorylation by extracellular c-Src tyrosine kinase [52], thereby highlighting that the proMMP-2 activation process is not yet fully understood. Moreover, as noted by Ra and Parks, mechanisms deduced from *in vitro* studies investigating proMMP activation show « how a zymogen can be activated, not how it is activated » [53]. Interestingly, TIMP-2-deficient mice revealed that TIMP-2 is required for efficient *in vivo* activation of proMMP-2 by MT1-MMP [54,55]. Moreover, a good correlation between active MMP-2 and increasing tumor grade exists [56]. These seminal data could confer on MT1-MMP the title of the « *in vivo* activator » of proMMP-2, at least in a malignant disease context.

When proMMP-2 is not secreted, it can also be activated by proteolytic cleavage or alternatively by oxidation (by H_2O_2), S-nitrosylation and S-glutathiolation (reviewed in Ref. [36]). For instance, it was shown that intracellular activation of proMMP-2 by oxidative stress contributes to cardiovascular pathologies (reviewed in Ref. [57]).

3.4. Extra- and peri-cellular substrates

First characterized as a proteinase present in the extracellular compartment for degrading denatured type I collagen [1] and intact type IV collagen [4], cell-membrane-associated MMP-2 was also reported since the late 1980's (for examples, see Refs. [58–62]). Analysis of the litterature [*e.g.* 36,63–70] and of the Peptidase Database MEROPS [71] reveals that MMP-2 has more than 1,200 extra-, peri- and intra-cellular substrates based on the determination of their cleavage site(s). Intracellular substrates were mentioned in §3.2. Table 2 presents a selection of extra- and pericellular MMP-2 substrates associated with ECM and its degradation [72–89].

3.4.1. Cell-surface molecules binding (pro)MMP-2

Besides MT-MMPs, which efficiently bind proMMP-2 to induce its activation (see §3.3), a limited number of cell-surface molecules have been shown to contribute to enhance proteolytic activity at the migrating front of invasive cells by clustering active MMP-2 at the cell membrane. Among them the heat shock protein HSP90α expressed at the surface of tumor cells promotes MMP-2 activity and tumor invasion [90] by binding to the Hpx-like domain of MMP-2 [91]. The $\alpha_v\beta_3$ integrin was first identified as a binding site for the C-terminal Hpx-like domain of MMP-2 in studies investigating *in vivo* and *in vitro* interactions between angiogenic blood vessels and melanoma cells [92,93]. This $\alpha_v\beta_3$/MMP-2 interaction was further identified in many other invasive cells such as endothelial cells [94], mesenchymal cells [95], lung cancer cells [96] and glioblastoma cells [97]. However, the direct interaction between

Table 2
Selected extra- and peri-cellular MMP-2 substrates.

Substrates	Ref.
Collagens	
type I collagen α1 chain	[66,70,72,73]
type I collagen α2 chain	[66,72,73]
type II collagen α1 chain	[73]
type III collagen α1 chain	[66,70,73]
type IV collagen α2 chain	[66,70]
type V collagen α1 chain	[74]
type V collagen α2 chain	[66,70]
type V collagen α3 chain	[66]
type VI collagen α1 chain	[74]
type VI collagen α2 chain	[66,70]
type VI collagen α3 chain	[70]
Other (glyco)proteins	
elastin	[75]
fibrillin 1	[76]
fibronectin	[66,70]
laminin β1 subunit	[70]
laminin γ1 subunit	[70]
laminin-5 γ2 subunit	[77]
nidogen-1	[70]
osteopontin	[78]
Proteoglycans	
aggrecan	[79]
biglycan	[73]
decorin	[70,73,80]
Matricellular proteins	
SPARC, osteonectin, BM-40	[70,81]
thrombospondin-2	[66,70]
(Co)-receptors	
dystroglycan	[70]
syndecan 1	[82]
syndecan 4	[82]
Cytokines	
interleukin-1β	[83]
Proteases and inhibitors	
- Proforms	
procathepsin B	[66]
procathepsin L1	[66]
proMMP-2 (auto-activation)	[67]
proMMP-9 (activation)	[68]
proMMP-13 (activation)	[69]
- Active forms	
cathepsin A	[70]
cathepsin B	[70]
cathepsin L	[70]
MMP-2	[70]
MMP-12	[70]
- Inhibitors	
α2M	[71]
TIMP-1	[70]
TIMP-2	[70]

MMP-2 and $\alpha_v\beta_3$ integrin was challenged [98]. Regardless of these proposed molecules, MT-MMPs represent the major proMMP-2 binding partners at the cell surface (see §3.3). Notably, MT1-MMP-mediated proMMP-2 activation on the cell surface promotes tumor cell invasion [99].

MMP-2 binding to members of the low-density lipoprotein receptor-related protein (LRP) family to induce endocytic clearance of MMP-2 is presented in details below (see §3.6).

3.4.2. Cell-surface targets of MMP-2

An extensive review published a decade ago listed the main cell-surface molecules degraded or shed by MMP-2 [100]. It notably included cytokines and growth factors that can be activated or degraded by MMP-2. Since then, other targets have been identified. As an example, recruitment of MMP-2 by the β_1 integrin, concomitant with an altered processing of the β_1 integrin, was first reported in apoptotic HUVEC cells [101]. Kryczka et al. later reported that MMP-2 degraded β_1 integrin in colon cancer cells by shedding its I-like domain [102]. They concluded that sheddase activity promoted cell motility by reducing their adhesion to collagen or fibronectin substrates. MMP-2 also binds and cleaves the transmembrane proteoglycans syndecans 1 and 4, members of the syndecan family that exerts important roles in cell proliferation, differentiation, adhesion and migration [88]. The MMP-2-mediated shedding of human leukocyte antigen-G proteins affects control of pregnancy immune regulation and inflammation [103]. The α-dystroglycan, a subunit of the dystroglycan receptor, was recently identified as a target of MMP-2. Interestingly, α-dystroglycan degradation contributes to progression of cancer and muscular dystrophies [104].

From maturation and activation to shedding or degradation, activity of MMP-2 on its various targets on the cell-surface has profound consequences on cell behavior in term of proliferation, differentiation, adhesion and migration, notably in cancer pathologies.

3.4.3. Non enzymatic membrane-associated activity

Cell membrane-bound MMPs can also act as transducers and trigger outside-in signaling [105]. For instance, binding of proMMP-2 to $\alpha_v\beta_3$ integrin on the surface of lung cancer cells stimulates tumor angiogenesis by activating PI3K/AKT pathway and HIF-1α, leading to VEGF-A expression [96].

3.5. Inhibition of MMP-2 activity

3.5.1. TIMPs

Like all active endoproteinases, MMPs are inhibited by the "universal" plasma proteinase inhibitor α_2-macroglobulin (α_2M) [106]. MMP activity can also be moderately inhibited by other proteins including domains of netrins, the procollagen C-terminal proteinase enhancer (PCPE), the reversion-inducing cysteine-rich protein with Kazal motifs (RECK), and tissue factor pathway inhibitor (TFPI-2), but their physiological significance remains to be clarified (reviewed in Ref. [107]).

However the most important inhibitors of MMPs and their close relatives "a disintegrin and metalloproteinases" (ADAMs) and ADAMs with thrombospondin motifs (ADAMTSs) are the tissue inhibitors of metalloproteinases (TIMPs) (reviewed in Ref. [108]). Four members, TIMP-1 to TIMP-4, make up the TIMP family [108]. All members inhibit active MMP-2 with a binding constant in the low picomolar range. This binding also involves interaction between TIMP and the MMP-2 Hpx-like domain [109].

While TIMP-2, TIMP-3 and TIMP-4 are able to strongly interact with proMMP-2 [107,110], TIMP-2 is the only one contributing to cell-surface activation of the proenzyme by MT1-MMP (see §3.3). Such antagonistic properties of TIMP-2 (inhibition *vs* activation) highlight its seminal role in the control of pericellular MMP-2 activity [111].

3.5.2. Synthetic MMP inhibitors

The relationship between MMP activity and tumor aggressiveness and metastatic potential [112,113] prompted laboratories and pharmaceutical companies to undergo massive research activity aimed at designing and developing synthetic MMP inhibitors (MMPIs). Most of these molecules were characterized by their capacity to bind the MMP active site [114]. Unfortunately, these broad spectrum MMPIs presented major side effects and thus failed to pass successfully the phase III clinical trials [115,116]. Different reasons can be pinpointed for explaining such a failure. Among them, the design of these MMPIs was essentially based on *in vitro* data that did not completely reflect the *in vivo* complexity. Moreover, besides contributing to cancer progression (drug targets),

some MMPs, such as MMP-8, can also act as antitumor agents and must be considered as anti-targets in cancer therapy [117–119]. Despite these issues MMP-1, MMP-2 and MMP-7 are still the subjects of research aimed at anti-tumor therapies. Studies are in progress to improve specificity towards MMP-2 target versus MMP anti-targets in cancer [120,121].

3.5.3. "Exotic" natural inhibitors

Natural compounds represent a promising source of MMPIs [122,123]. While the crucial problem to be solved is their selectivity, some of them already present moderate natural specificity. For instance, unsaturated long-chain fatty acids inhibit preferentially MMP-2 and -9 with micromolar Ki values but their inhibition of MMP-1 activity is weak [124].

3.6. MMP-2 endocytic clearance

Endocytosis allows the transport of material from extracellular environment into intracellular space for its elimination. This mechanism is well known for the clearance of active proteinases complexed to α_2M via the α_2M receptor [125]. The α_2M receptor has been identified as the low-density lipoprotein receptor-related protein (LRP) [126]. LRP, now noted LRP-1, is the first member of an endocytic receptor family related to the LDL receptor [127]. Three members of this scavenger receptor family, LRP-1, LRP-1b and LRP-2, are able to endocytose MMP-2 and thus participate in the regulation of extracellular MMP-2 levels [128].

3.6.1. LRP-1

Binding of (pro)MMP-2 to thrombospondin-2 (TSP-2), which is a ligand of LRP-1 [129] allows efficient clearance of MMP-2 [130]. When complexed with TIMP-2, proMMP-2 can also be endocytosed by LRP-1 [131]. The involvement of TIMP-2 in both activation of proMMP-2 by MT1-MMP and uptake of proMMP-2 by LRP-1 strongly suggests the existence of a competition between these two processes. In contrast, the proMMP-2 activator MT1-MMP is able to shed LRP-1 [132,133]. Consequently it would impede MMP-2 endocytosis by LRP-1 [131] and thus would favor the cell-surface bioavailability of MMP-2. Endocytosis of TIMP-1 [134] and TIMP-3 [135], both able to bind and inhibit active MMP-2 [108], also contributes to the clearance of MMP-2. Moreover, a recent study demonstrates that different glycosaminoglycans including hyaluronan and sulfated hyaluronan impact negatively or positively on MMP-2/TIMP-3 complex formation [136].

The net effect of all these mechanisms on regulation of active MMP-2 at the cell surface depends on the cell type, the extracellular environment and the physio-pathological context.

3.6.2. LRP-1b

LRP-1b inactivation in cultured thyroid cancer cells modifies their growth and invasive capacities [137]. Interestingly, restoration of LRP-1b is accompanied by a reduction of MMP-2 in the conditioned medium without concomitant difference in MMP-2 mRNA levels. These data suggest that LRP-1b has the ability to mediate endocytic clearance of MMP-2.

3.6.3. LRP-2/megalin

Using an *in vitro* model of BN16 cell cultures, we recently showed that LRP-2 was able to bind and endocytose proMMP-2 complexed to TIMP-2 [138]. Moreover conditional renal invalidation of LRP-2 in mice resulted in accumulation of proMMP-2 and TIMP-2 in their urine, highlighting the physiological relevance of the binding of the complex to LRP-2. As hypothesized for LRP-1, LRP-2 could also represent an additional mechanism to regulate active MMP-2 at the cell surface depending on the cell type, the extracellular environment and the physio-pathological context.

4. Pathologies

From the first correlation established between metastatic potential and degradation of basement membrane type IV collagen by a 65-kDa endopeptidase [139] up to the discovery of MT1-MMP [140], MMP-2 overexpression was considered as a hallmark of cancer aggressiveness. Meta-analyses found that MMP-2 expression could be correlated (and often proposed to be used as prognostic marker) with pituitary adenomas [141], breast cancer [142], ovarian cancer [143], endometrial cancer [144], gastric cancer [145], and non-small cell lung cancer [146].

However extra/pericellular MMP-2 is also involved in other degenerative pathologies, often in association with other MMPs. MMP-2 is thus involved in neurological disorders including Parkinson's and Alzheimer's diseases and glaucoma (for review, see for instance Refs. [147,148]). MMP-2 is associated with inflammation of various origins, such as parasitic diseases [149] and osteoarthritis [150]. MMP-2 also contributes to the rupture of atherosclerotic plaques [151]. Meta-analyses also found that MMP-2 is associated with renal fibrosis [152] and thoracic aortic aneurysm [153].

Most of the MMP-2 deleterious activities are associated with up-regulation of its expression/activity. In contrast, a recent review presents important data that demonstrate impact of MMP-2 underactivity, either MMP-2 deficiency or insufficiency, on inflammation, metabolic dysregulation and cardiovascular and skeletal pathologies [154].

Several mutations in the *MMP2* gene can cause Multicentric Osteolysis, Nodulosis, and Arthropathy (MONA), a rare skeletal dysplasia characterized by progressive osteolysis (particularly of the carpal and tarsal bones), osteoporosis, subcutaneous nodules on the palms and soles, and progressive arthropathy (OMIM gene entry 120360) [155].

Another genetic disease, the Winchester syndrome (OMIM entry 277650) is also linked to deficient MMP-2 activity since it is caused by mutations in the *MT1-MMP* gene, thereby affecting proMMP-2 activation. Without surprise, the Winchester syndrome shares common symptoms with MONA, including osteolysis and arthropathy.

Moreover, recent meta-analyses have concluded that the −1306 C/T and −735 C/T polymorphisms are potentially linked to increased cancer risk [156,157].

5. Perspectives and conclusion

As our knowledge progresses, the original "gelatinase", described as being able to degrade denatured interstitial type I collagen, has grown considerably in importance. In this sense, it has followed the same route as other members of the MMP family: from basic proteinases degrading components of the extracellular matrix, they have become major actors with extra-, peri- and intracellular functions. As a predictable consequence, they have been implicated in many pathologies. In particular, MMP-2 has emerged as a key player in tumor development. About 40% of the PubMed entries reporting on MMP-2 in 2018 (MMP2, MMP-2 or gelatinase A in the title) were focusing on cancer. Unquestionably, the *in vitro* approach has greatly improved our fundamental knowledge about its expression, activation and substrates. However, future investigations will have to focus on its *in vivo* features.

Recent publications and clinical trials suggest that MMP-2 levels will become useful biomarkers for diagnostic or prognostic evaluation [158–163]. For instance, variations of circulating or tissular MMP-2 levels are measured as a secondary outcome in trials with a different primary target (*e.g.* VEGF). However, variability between

assays will require tightly standardized procedures. Despite a significant progress in the design of more specific MMP-2 inhibitors, their therapeutic usage remains a challenge, due to the reverse effects of systematic MMP-2 inhibition.

In conclusion, we believe that MMP-2 clearly deserves the amount of energy it receives from the scientific community, due to the ever-growing complexity of its physiological functions, and therefore (potential) implication in (severe) pathologies.

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Conflict of interest

We have no conflict of interest to declare.

References

[1] E.D. Harris Jr., S.M. Krane, An endopeptidase from rheumatoid synovial tissues culture, Biochim. Biophys. Acta 258 (1972) 566–576. https://doi.org/10.1016/0005-2744(72)90249-5.
[2] J. Gross, C.M. Lapiere, Collagenolytic activity in amphibian tissues: a tissue culture assay, Proc. Natl. Acad. Sci. U.S.A. 48 (1962) 1014–1022. https://doi.org/10.1073/pnas.48.6.1014.
[3] G. Murphy, C.G. McAlpine, C.T. Poll, J.J. Reynolds, Purification and characterization of a bone metalloproteinase that degrades gelatin and types IV and V collagen, Biochim. Biophys. Acta 831 (1985) 49–58. https://doi.org/10.1016/0167-4838(85)90148-7.
[4] I.E. Collier, S.M. Wilhelm, A.Z. Eisen, B.L. Marmer, G.A. Grant, J.L. Seltzer, A. Kronberger, C.S. He, E.A. Bauer, G.I. Goldberg, H-ras oncogene-transformed human bronchial epithelial cells (TBE-1) secrete a single metalloprotease capable of degrading basement membrane collagen, J. Biol. Chem. 263 (1988) 6579–6587.
[5] H. Nagase, J.F. Woessner Jr., Matrix metalloproteinases, J. Biol. Chem. 274 (1999) 21491–21494. https://doi.org/10.1074/jbc.274.31.21491.
[6] H. Nagase, A.J. Barrett, J.F. Woessner Jr., Nomenclature and glossary of the matrix metalloproteinases, Matrix Suppl. 1 (1992) 421–424.
[7] S.M. Wilhelm, I.E. Collier, B.L. Marmer, A.Z. Eisen, G.A. Grant, G.I. Goldberg, SV40-transformed human lung fibroblasts secrete a 92-kDa type IV collagenase which is identical to that secreted by normal human macrophages, J. Biol. Chem. 264 (1989) 17213–17221.
[8] P. Huhtala, L.T. Chow, K. Tryggvason, Structure of the human type IV collagenase gene, J. Biol. Chem. 265 (1990) 11077–11082.
[9] G. Murphy, Q. Nguyen, M.I. Cockett, S.J. Atkinson, J.A. Allan, C.G. Knight, F. Willenbrock, A.J. Docherty, Assessment of the role of the fibronectin-like domain of gelatinase A by analysis of a deletion mutant, J. Biol. Chem. 269 (1994) 6632–6636.
[10] J.M. Shipley, G.A. Doyle, C.J. Fliszar, Q.Z. Ye, L.L. Johnson, S.D. Shapiro, H.G. Welgus, R.M. Senior, The structural basis for the elastolytic activity of the 92-kDa and 72-kDa gelatinases. Role of the fibronectin type II-like repeats, J. Biol. Chem. 271 (1996) 4335–4341. https://doi.org/10.1074/jbc.271.8.4335.
[11] S.R. Van Doren, Matrix metalloproteinase interactions with collagen and elastin, Matrix Biol. 44–46 (2015) 224–231. https://doi.org/10.1016/j.matbio.2015.01.005.
[12] www.proteinatlas.org/ENSG00000087245-MMP2. (Accessed 7 March 2019).
[13] K. Thrailkill, G. Cockrell, P. Simpson, C. Moreau, J. Fowlkes, R.C. Bunn, Physiological matrix metalloproteinase (MMP) concentrations: comparison of serum and plasma specimens, Clin. Chem. Lab. Med. 44 (2006) 503–504.
[14] A. Jonsson, C. Hjalmarsson, P. Falk, M.L. Ivarsson, Levels of matrix metalloproteinases differ in plasma and serum - aspects regarding analysis of biological markers in cancer, Br. J. Canc. 115 (2016) 703–706. https://doi.org/10.1038/bjc.2016.127.
[15] M. Groblewska, B. Mroczko, M. Gryko, A. Pryczynicz, K. Guzińska-Ustymowicz, B. Kędra, A. Kemona, M. Szmitkowski, Serum levels and tissue expression of matrix metalloproteinase 2 (MMP-2) and tissue inhibitor of metalloproteinases 2 (TIMP-2) in colorectal cancer patients, Tumour Biol 35 (2014) 3793–3802. https://doi.org/10.1007/s13277-013-1502-8.
[16] G.A. Preston, C.V. Barrett, D.A. Alcorta, S.L. Hogan, L. Dinwiddie, J.C. Jennette, R.J. Falk, Serum matrix metalloproteinases MMP-2 and MMP-3 levels in dialysis patients vary independently of CRP and IL-6 levels, Nephron 92 (2002) 817–823. https://doi.org/10.1159/000065464.
[17] A. Meisser, M. Cohen, P. Bischof, Concentrations of circulating gelatinases (matrix metalloproteinase-2 and -9) are dependent on the conditions of blood collection, Clin. Chem. 51 (2005) 274–276. https://doi.org/10.1373/clinchem.2004.041707.
[18] K.M. Walsh, P. Timms, S. Campbell, R.N. MacSween, A.J. Morris, Plasma levels of matrix metalloproteinase-2 (MMP-2) and tissue inhibitors of metalloproteinases -1 and -2 (TIMP-1 and TIMP-2) as noninvasive markers of liver disease in chronic hepatitis C: comparison using ROC analysis, Dig. Dis. Sci. 44 (1999) 624–630.
[19] A. Talvensaari-Mattila, T. Turpeenniemi-Hujanen, Levels of Circulating TIMP-2 and MMP2-TIMP2 complex are decreased in squamous cervical carcinoma, Obstet. Gynecol. Int. 2010 (2010) 179351. https://doi.org/10.1155/2010/179351.
[20] P. Kuvaja, A. Talvensaari-Mattila, T. Turpeeniemi-Hujanen, The sample type used affects the levels of gelatinases (MMP-2 and -9) and their inhibitors (TIMP-1 and -2) in circulating blood of healthy controls and breast cancer patients, Biomark. Insights 2 (2007) 117–127.
[21] R. Zeng, F. Wen, X. Zhang, Y. Su, Serum levels of matrix metalloproteinase 2 and matrix metalloproteinase 9 elevated in polypoidal choroidal vasculopathy but not in age-related macular degeneration, Mol. Vis. 19 (2013) 729–736.
[22] L. Incorvaia L, G. Badalamenti, G. Rini, C. Arcara, S. Fricano, C. Sferrazza, D. Di Trapani, N. Gebbia, G. Leto, MMP-2, MMP-9 and activin A blood levels in patients with breast cancer or prostate cancer metastatic to the bone, Anticancer Res. 27 (2007) 1519–1525.
[23] S.M. Sheen-Chen, H.S. Chen, H.L. Eng, C.C. Sheen, W.J. Chen, Serum levels of matrix metalloproteinase 2 in patients with breast cancer, Cancer Lett. 173 (2001) 79–82. https://doi.org/10.1016/S0304-3835(01)00657-7.
[24] Y. Shi, C. Su, H. Hu, H. Yan, W. Li, G. Chen, D. Xu, X. Du, P. Zhang, Serum MMP-2 as a potential predictive marker for papillary thyroid carcinoma, PLoS One 13 (2018), e0198896. https://doi.org/10.1371/journal.pone.0198896.
[25] M. Fanjul-Fernández, A.R. Folgueras, S. Cabrera, C. López-Otín, Matrix metalloproteinases: evolution, gene regulation and functional analysis in mouse models, Biochim. Biophys. Acta 1803 (2010) 3–19. https://doi.org/10.1016/j.bbamcr.2009.07.004.
[26] I.M. Clark, T.E. Swingler, C.L. Sampieri, D.R. Edwards, The regulation of matrix metalloproteinases and their inhibitors, Int. J. Biochem. Cell Biol. 40 (2008) 1362–1378. https://doi.org/10.1016/j.biocel.2007.12.006.
[27] J. Gaffney, I. Solomonov, E. Zehorai, I. Sagi, Multilevel regulation of matrix metalloproteinases in tissue homeostasis indicates their molecular specificity in vivo, Matrix Biol. 44–46 (2015) 191–199. https://doi.org/10.1016/j.matbio.2015.01.012.
[28] C. Yan, D.D. Boyd, Regulation of matrix metalloproteinase gene expression, J. Cell. Physiol. 211 (2007) 19–26. http://doi.org/10.1002/jcp.20948.
[29] H. Qin, Y. Sun, E.N. Benveniste, The transcription factors Sp1, Sp3, and AP-2 are required for constitutive matrix metalloproteinase-2 gene expression in astroglioma cells, J. Biol. Chem. 274 (1999) 29130–29137.
[30] E. Staun-Ram, S. Goldman, E. Shalev, p53 mediates epidermal growth factor (EGF) induction of MMP-2 transcription and trophoblast invasion, Placenta 30 (2009) 1029–1036. https://doi.org/10.1016/j.placenta.2009.09.010.
[31] J. Reisdorff J, A. En-Nia, I. Stefanidis, J. Floege, D.H. Lovett, P.R. Mertens, Transcription factor Ets-1 regulates gelatinase a gene expression in mesangial cells, J. Am. Soc. Nephrol. 13 (2002) 1568–1578.
[32] H. Song, S.H. Ki, S.G. Kim, A. Moon, Activating transcription factor 2 mediates matrix metalloproteinase-2 transcriptional activation induced by p38 in breast epithelial cells, Cancer Res. 66 (2006) 10487–10496. https://doi.org/10.1158/0008-5472.CAN-06-1461.
[33] M.R. Bergman, S. Cheng, N. Honbo, L. Piacentini, J.S. Karliner, D.H. Lovett, A functional activating protein 1 (AP-1) site regulates matrix metalloproteinase 2 (MMP-2) transcription by cardiac cells through interactions with JunB-Fra1 and JunB-FosB heterodimers, Biochem. J. 369 (2003) 485–496. https://doi.org/10.1042/BJ20020707.
[34] H. Hasegawa, T. Senga, S. Ito, T. Iwamotot, M. Hamaguchi, A role for AP-1 in matrix metalloproteinase production and invadopodia formation of v-Crk-transformed cells, Exp. Cell Res. 315 (2009) 1384–1392. https://doi.org/10.1016/j.yexcr.2009.02.019.
[35] A.V. Chernov, N.E. Sounni, A.G. Remacle, A.Y. Strongin, Epigenetic control of the invasion-promoting MT1-MMP/MMP-2/TIMP-2 axis in cancer cells, J. Biol. Chem. 284 (2009) 12727–12734. https://doi.org/10.1074/jbc.M900273200.
[36] B. Cauwe, G. Opdenakker, Intracellular substrate cleavage: a novel dimension in the biochemistry, biology and pathology of matrix metalloproteinases, Crit. Rev. Biochem. Mol. Biol. 45 (2010) 351–423. https://doi.org/10.3109/10409238.2010.501783.
[37] P.G. Jobin, G.S. Butler, C.M. Overall, New intracellular activities of matrix metalloproteinases shine in the moonlight, Biochim. Biophys. Acta Mol. Cell Res. 1864 (2017) 2043–2055. https://doi.org/10.1016/j.bbamcr.2017.05.013.
[38] H. Birkedal-Hansen, W.G. Moore, M.K. Bodden, L.J. Windsor, B. Birkedal-Hansen, A. DeCarlo, J.A. Engler, Matrix metalloproteinases: a review, Crit. Rev. Oral Biol. Med. 4 (1993) 197–250. https://doi.org/10.1177/10454411930040020401.
[39] S. Zucker, C. Conner, B.I. DiMassmo, H. Ende, M. Drews, M. Seiki, W.F. Bahou, Thrombin induces the activation of progelatinase A in vascular endothelial cells. Physiologic regulation of angiogenesis, J. Biol. Chem. 270 (1995) 23730–23738. https://doi.org/10.1074/jbc.270.40.23730.
[40] P. Shamamian, J.D. Schwartz, B.J. Pocock, S. Monea, D. Whiting, S.G. Marcus,

P. Mignatti, Activation of progelatinase A (MMP-2) by neutrophil elastase, cathepsin G, and proteinase-3: a role for inflammatory cells in tumor invasion and angiogenesis, J. Cell. Physiol. 189 (2001) 197–206. https://doi.org/10.1002/jcp.10014.
[41] Y. Itoh, Membrane-type matrix metalloproteinases: their functions and regulations, Matrix Biol. 44–46 (2015) 207–223. https://doi.org/10.1016/j.matbio.2015.03.004.
[42] S.P. Turunen, O. Tatti-Bugaeva, K. Lehti, Membrane-type matrix metalloproteases as diverse effectors of cancer progression, Biochim. Biophys. Acta Mol. Cell Res. 1864 (2017) 1974–1988. https://doi.org/10.1016/j.bbamcr.2017.04.002.
[43] W.R. English, X.S. Puente, J.M. Freije, V. Knauper, A. Amour, A. Merryweather, C. Lopez-Otin, G. Murphy, Membrane type 4 matrix metalloproteinase (MMP17) has tumor necrosis factor-alpha convertase activity but does not activate pro-MMP2, J. Biol. Chem. 275 (2000) 14046–14055. https://doi.org/10.1074/jbc.275.19.14046.
[44] G. Velasco, S. Cal, A. Merlos-Suárez, A.A. Ferrando, S. Alvarez, A. Nakano, J. Arribas, C. López-Otín, Human MT6-matrix metalloproteinase: identification, progelatinase A activation, and expression in brain tumors, Cancer Res. 60 (2000) 877–882.
[45] J. Nie, D. Pei, Direct activation of pro-matrix metalloproteinase-2 by leukolysin/membrane-type 6 matrix metalloproteinase/matrix metalloproteinase 25 at the Asn(109)-Tyr bond, Cancer Res. 63 (2003) 6758–6762.
[46] E. Llano, A.M. Pendás, J.P. Freije, A. Nakano, V. Knäuper, G. Murphy, C. López-Otin, Identification and characterization of human MT5-MMP, a new membrane-bound activator of progelatinase a overexpressed in brain tumors, Cancer Res. 59 (1999) 2570–2576.
[47] J. Iida, K.L. Wilhelmson, J. Ng, P. Lee, C. Morrison, E. Tam, C.M. Overall, J.B. McCarthy, Cell surface chondroitin sulfate glycosaminoglycan in melanoma: role in the activation of pro-MMP-2 (pro-gelatinase A), Biochem. J. 403 (2007) 553–563. https://doi.org/10.1042/BJ20061176.
[48] C.J. Morrison, C.M. Overall, TIMP independence of matrix metalloproteinase (MMP)-2 activation by membrane type 2 (MT2)-MMP is determined by contributions of both the MT2-MMP catalytic and hemopexin C domains, J. Biol. Chem. 281 (2006) 26528–26539. https://doi.org/10.1074/jbc.M603331200.
[49] A.Y. Strongin, I. Collier, G. Bannikov, B.L. Marmer, G.A. Grant, G.I. Goldberg, Mechanism of cell surface activation of 72-kDa type IV collagenase. Isolation of the activated form of the membrane metalloprotease, J. Biol. Chem. 270 (1995) 5331–5338. https://doi.org/10.1074/jbc.270.10.5331.
[50] H. Kolkenbrock, D. Orgel, A. Hecker-Kia, W. Noack, N. Ulbrich, The complex between a tissue inhibitor of metalloproteinases (TIMP-2) and 72-kDa progelatinase is a metalloproteinase inhibitor, Eur. J. Biochem. 198 (1991) 775–781. https://doi.org/10.1111/j.1432-1033.1991.tb16080.x.
[51] A. Puyraimond, R. Fridman, M. Lemesle, B. Arbeille, S. Menashi, MMP-2 colocalizes with caveolae on the surface of endothelial cells, Exp. Cell Res. 262 (2001) 28–36. https://doi.org/10.1006/excr.2000.5069.
[52] J. Sánchez-Pozo, A.J. Baker-Williams, M.R. Woodford, R. Bullard, B. Wei, M. Mollapour, W.G. Stetler-Stevenson, G. Bratslavsky, D. Bourboulia, Extracellular phosphorylation of TIMP-2 by secreted c-Src tyrosine kinase controls MMP-2 activity, iScience 1 (2018) 87–96. https://doi.org/10.1016/j.isci.2018.02.004.
[53] H.J. Ra, W.C. Parks, Control of matrix metalloproteinase catalytic activity, Matrix Biol. 26 (2007) 587–596. https://doi.org/10.1016/j.matbio.2007.07.001.
[54] J.J. Caterina, S. Yamada, N.C. Caterina, G. Longenecker, K. Holmbäck, J. Shi, A.E. Yermovsky, J.A. Engler, H. Birkedal-Hansen, Inactivating mutation of the mouse tissue inhibitor of metalloproteinases-2 (Timp-2) gene alters proMMP-2 activation, J. Biol. Chem. 275 (2000) 26416–26422. https://doi.org/10.1074/jbc.M001271200.
[55] Z. Wang, R. Juttermann, P.D. Soloway, TIMP-2 is required for efficient activation of proMMP-2 in vivo, J. Biol. Chem. 275 (2000) 26411–26415. https://doi.org/10.1074/jbc.M001270200.
[56] B. Davies, D.W. Miles, L.C. Happerfield, M.S. Naylor, L.G. Bobrow, R.D. Rubens, F.R. Balkwill, Activity of type IV collagenases in benign and malignant breast disease, Br. J. Canc. 67 (1993) 1126–1131.
[57] A.L. Jacob-Ferreira, R. Schulz, Activation of intracellular matrix metalloproteinase-2 by reactive oxygen–nitrogen species: consequences and therapeutic strategies in the heart, Arch. Biochem. Biophys. 540 (2013) 82–93. https://dx.doi.org/10.1016/j.abb.2013.09.019.
[58] S. Zucker, J.M. Wieman, R.M. Lysik, D. Wilkie, N.S. Ramamurthy, L.M. Golub, B. Lane, Enrichment of collagen and gelatin degrading activities in the plasma membranes of human cancer cells, Cancer Res. 47 (1987) 1608–1614.
[59] S. Zucker, U.M. Moll, R.M. Lysik, E.I. DiMassimo, W.G. Stetler-Stevenson, L.A. Liotta, J.W. Schwedes, Extraction of type-IV collagenase/gelatinase from plasma membranes of human cancer cells, Int. J. Cancer 45 (1990) 1137–1142. https://doi.org/10.1002/ijc.2910450625.
[60] H.P. Emonard, A.G. Remacle, A.C. Noël, J.A. Grimaud, W.G. Stetler-Stevenson, J.M. Foidart, Tumor cell surface-associated binding site for the M(r) 72,000 type IV collagenase, Cancer Res. 52 (1992) 5845–5848.
[61] J. Lohi, I. Harvima, J. Keski-Oja, Pericellular substrates of human mast cell tryptase: 72,000 dalton gelatinase and fibronectin, J. Cell. Biochem. 50 (1992) 337–349. https://doi.org/10.1002/jcb.240500402.
[62] W.L. Monsky, T. Kelly, C.Y. Lin, Y. Yeh, W.G. Stetler-Stevenson, S.C. Mueller, W.T. Chen, Binding and localization of M(r) 72,000 matrix metalloproteinase at cell surface invadopodia, Cancer Res. 53 (1993) 3159–3164.
[63] P. Schlage, U. auf dem Keller, Proteomic approaches to uncover MMP function, Matrix Biol. 44–46 (2015) 232–238. https://doi.org/10.1016/j.matbio.2015.01.003.
[64] G.A. McQuibban, J.H. Gong, E.M. Tam, C.A. McCulloch, I. Clark-Lewis, C.M. Overall, Inflammation dampened by gelatinase A cleavage of monocyte chemoattractant protein-3, Science 289 (2000) 1202–1206. https://doi.org/10.1126/science.289.5482.1202.
[65] G.A. McQuibban, G.S. Butler, J.H. Gong, L. Bendall, C. Power, I. Clark-Lewis, C.M. Overall, Matrix metalloproteinase activity inactivates the CXC chemokine stromal cell-derived factor-1, J. Biol. Chem. 276 (2001) 43503–43508. https://doi.org/10.1074/jbc.M107736200.
[66] G. Sawicki, H. Leon, J. Sawicka, M. Sariahmetoglu, C.J. Schulze, P.G. Scott, D. Szczesna-Cordary, R. Schulz, Degradation of myosin light chain in isolated rat hearts subjected to ischemia-reperfusion injury: a new intracellular target for matrix metalloproteinase-2, Circulation 112 (2005) 544–552. https://doi.org/10.1161/CIRCULATIONAHA.104.531616.
[67] K.J. Greenlee, D.B. Corry, D.A. Engler, R.K. Matsunami, P. Tessier, R.G. Cook, Z. Werb, F. Kheradmand, Proteomic identification of in vivo substrates for matrix metalloproteinases 2 and 9 reveals a mechanism for resolution of inflammation, J. Immunol. 177 (2006) 7312–7321. https://doi.org/10.4049/jimmunol.177.10.7312.
[68] U. auf dem Keller, A. Prudova, U. Eckhard, B. Fingleton, C.M. Overall, Systems-level analysis of proteolytic events in increased vascular permeability and complement activation in skin inflammation, Sci. Signal. 6 (2013) rs2, https://doi.org/10.1126/scisignal.2003512.
[69] R.A. Dean, G.S. Butler, Y. Hamma-Kourbali, J. Delbé, D.R. Brigstock, J. Courty, C.M. Overall, Identification of candidate angiogenic inhibitors processed by matrix metalloproteinase 2 (MMP-2) in cell-based proteomic screens: disruption of vascular endothelial growth factor (VEGF)/heparin affin regulatory peptide (pleiotrophin) and VEGF/Connective tissue growth factor angiogenic inhibitory complexes by MMP-2 proteolysis, Mol. Cell. Biol. 27 (2007) 8454–8465. https://doi.org/10.1128/MCB.008207.
[70] R.A. Dean, C.M. Overall, Proteomics discovery of metalloproteinase substrates in the cellular context by iTRAQ labeling reveals a diverse MMP-2 substrate degradome, Mol. Cell. Proteom. 6 (2007) 611–623. https://doi.org/10.1074/mcp.M600341-MCP200.
[71] Last accessed on, www.ebi.ac.uk/merops. (Accessed 16 June 2019).
[72] A. Prudova, U. auf dem Keller, G.S. Butler, C.M. Overall, Multiplex N-terminome analysis of MMP-2 and MMP-9 substrate degradomes by iTRAQ-TAILS quantitative proteomics, Mol. Cell. Proteom. 9 (2010) 894–911. https://doi.org/10.1074/mcp.M000050-MCP201.
[73] T. Crabbe, C. Ioannou, A.J. Docherty, Human progelatinase A can be activated by autolysis at a rate that is concentration-dependent and enhanced by heparin bound to the C-terminal domain, Eur. J. Biochem. 218 (1993) 431–438. https://doi.org/10.1111/j.1432-1033.1993.tb18393.x.
[74] R. Fridman, M. Toth, D. Peña, S. Mobashery, Activation of progelatinase B (MMP-9) by gelatinase A (MMP-2), Cancer Res. 55 (1995) 2548–2555.
[75] V. Knäuper, H. Will, C. López-Otin, B. Smith, S.J. Atkinson, H. Stanton, R.M. Hembry, G. Murphy, Cellular mechanisms for human procollagenase-3 (MMP-13) activation. Evidence that MT1-MMP (MMP-14) and gelatinase a (MMP-2) are able to generate active enzyme, J. Biol. Chem. 271 (1996) 17124–17131. https://doi.org/10.1074/jbc.271.29.17124.
[76] U. auf dem Keller, A. Prudova, M. Gioia, G.S. Butler, C.M. Overall, A statistics-based platform for quantitative N-terminome analysis and identification of protease cleavage products, Mol. Cell. Proteom. 9 (2010) 912–927. https://doi.org/10.1074/mcp.M000032-MCP201.
[77] L.F. Arbeláez, U. Bergmann, A. Tuuttila, V.P. Shanbhag, T. Stigbrand, Interaction of matrix metalloproteinases-2 and -9 with pregnancy zone protein and alpha2-macroglobulin, Arch. Biochem. Biophys. 347 (1997) 62–68. https://doi.org/10.1006/abbi.1997.0309.
[78] R.T. Aimes, J.P. Quigley, Matrix metalloproteinase-2 is an interstitial collagenase. Inhibitor-free enzyme catalyzes the cleavage of collagen fibrils and soluble native type I collagen generating the specific 3/4- and 1/4-length fragments, J. Biol. Chem. 270 (1995) 5872–5876. https://doi.org/10.1074/jbc.270.11.5872.
[79] E.Y. Zhen, I.J. Brittain, D.A. Laska, P.G. Mitchell, E.U. Sumer, M.A. Karsda, K.L. Duffin, Characterization of metalloprotease cleavage products of human articular cartilage, Arthritis Rheum. 58 (2008) 2420–2431. https://doi.org/10.1002/art.23654.
[80] O. Kleifeld, A. Doucet, U. auf dem Keller, A. Prudova, O. Schilling, R.K. Kainthan, A.E. Starr, L.J. Foster, J.N. Kizhakkedathu, C.M. Overall, Isotopic labeling of terminal amines in complex samples identifies protein N-termini and protease cleavage products, Nat. Biotechnol. 28 (2010) 281–288. https://doi.org/10.1038/nbt.1611.
[81] R.M. Senior, G.L. Griffin, C.J. Fliszar, S.D. Shapiro, G.I. Goldberg, H.G. Welgus, Human 92- and 72-kilodalton type IV collagenases are elastases, J. Biol. Chem. 266 (1991) 7870–7875.
[82] V.J. Hindson, J.L. Ashworth, M.J. Rock, S. Cunliffe, C.A. Shuttleworth, C.M. Kielty, Fibrillin degradation by matrix metalloproteinases: identification of amino- and carboxy-terminal cleavage sites, FEBS Lett. 452 (1999) 195–198. https://doi.org/10.1016/s0014-5793(99)00623-7.
[83] G. Giannelli, J. Falk-Marzillier, O. Schiraldi, W.G. Stetler-Stevenson, V. Quaranta, Induction of cell migration by matrix metalloprotease-2

cleavage of laminin-5, Science 277 (1997) 225–228. https://doi.org/10.1126/science.277.5323.225.
[84] M.L. Lindsey, F.A. Zouein, Y. Tian, Y.R. Padmanabhan, L.E. de Castro Brás, Osteopontin is proteolytically processed by matrix metalloproteinase 9, Can, J. Physiol. Pharmacol. 93 (2015) 879–886. https://doi.org/10.1139/cjpp-2015-0019.
[85] A.J. Fosang, P.J. Neame, K. Last, T.E. Hardingham, G. Murphy, J.A. Hamilton, The interglobular domain of cartilage aggrecan is cleaved by PUMP, gelatinases, and cathepsin B, J. Biol. Chem. 267 (1992) 19470–19474.
[86] K. Imai, A. Hiramatsu, D. Fukushima, M.D. Pierschbacher, Y. Okada, Degradation of decorin by matrix metalloproteinases: identification of the cleavage sites, kinetic analyses and transforming growth factor-beta1 release, Biochem. J. 322 (1997) 809–814. https://doi.org/10.1042/bj3220809.
[87] T. Sasaki, W. Göhring, K. Mann, P. Maurer, E. Hohenester, V. Knäuper, G. Murphy, R. Timpl, Limited cleavage of extracellular matrix protein BM-40 by matrix metalloproteinases increases its affinity for collagens, J. Biol. Chem. 272 (1997) 9237–9243. https://doi.org/10.1074/jbc.272.14.9237.
[88] T. Manon-Jensen, H.A. Multhaupt, J.R. Couchman, Mapping of matrix metalloproteinase cleavage sites on syndecan-1 and syndecan-4 ectodomains, FEBS J. 280 (2013) 2320–2331. https://doi.org/10.1111/febs.12174.
[89] A. Ito, A. Mukaiyama, Y. Itoh, H. Nagase, I.B. Thogersen, J.J. Enghild, Y. Sasaguri, Y. Mori, Degradation of interleukin 1beta by matrix metalloproteinases, J. Biol. Chem. 271 (1996) 14657–14660. https://doi.org/10.1074/jbc.271.25.14657.
[90] B.K. Eustace, T. Sakurai, J.K. Stewart, D. Yimlamai, C. Unger, C. Zehetmeier, B. Lain, C. Torella, S.W. Henning, G. Beste, B.T. Scroggins, L. Neckers, L.L. Ilag, D.G. Jay, Functional proteomic screens reveal an essential extracellular role for hsp90α in cancer cell invasiveness, Nat. Cell Biol. 6 (2004) 507–514. https://doi.org/10.1038/ncb1131.
[91] X. Song, X. Wang, W. Zhuo, H. Shi, D. Feng, Y. Sun, Y. Liang, Y. Fu, D. Zhou, Y. Luo, The regulatory mechanism of extracellular Hsp90α on matrix metalloproteinase-2 processing and tumor angiogenesis, J. Biol. Chem. 285 (2010) 40039–40049. https://doi.org/10.1074/jbc.M110.181941.
[92] P.C. Brooks, S. Strömblad, L.C. Sanders, T.L. von Schalscha, R.T. Aimes, W.G. Stetler-Stevenson, J.P. Quigley, D.A. Cheresh, Localization of matrix metalloproteinase MMP-2 to the surface of invasive cells by interaction with integrin αvβ3, Cell 85 (1996) 683–693. https://doi.org/10.1016/S0092-8674(00)81235-0.
[93] P.C. Brooks, S. Silletti, T.L. von Schalscha, M. Friedlander, D.A. Cheresh, Disruption of angiogenesis by PEX, a noncatalytic metalloproteinase fragment with integrin binding activity, Cell 92 (1998) 391–400. https://doi.org/10.1016/S0092-8674(00)80931-9.
[94] S. Silletti, T. Kessler, J. Goldberg, D.L. Boger, D.A. Cheresh, Disruption of matrix metalloproteinase 2 binding to integrin αvβ3 by an organic molecule inhibits angiogenesis and tumor growth in vivo, Proc. Natl. Acad. Sci. U.S.A. 98 (2001) 119–124. https://doi.org/10.1073/pnas.98.1.119.
[95] P.A. Rupp, R.P. Visconti, A. Czirók, D.A. Cheresh, C.D. Little, Matrix metalloproteinase 2-integrin αvβ3 binding is required for mesenchymal cell invasive activity but not epithelial locomotion: a computational time-lapse study, Mol. Biol. Cell 19 (2008) 5529–5540. https://doi.org/10.1091/mbc.E07-05-0480.
[96] C. Chetty, S.S. Lakka, P. Bhoopathi, J.S. Rao, MMP-2 alters VEGF expression via αvβ3 integrin-mediated PI3K/AKT signaling in A549 lung cancer cells, Int. J. Cancer 127 (2010) 1081–1095. https://doi.org/10.1002/ijc.25134.
[97] G. Yosef, V. Arkadash, N. Papo, Targeting the MMP-14/MMP-2/integrin αvβ3 axis with multispecific N-TIMP2-based antagonists for cancer therapy, J. Biol. Chem. 293 (2018) 13310–13326. https://doi.org/10.1074/jbc.RA118.004406.
[98] R.E. Nisato, G. Hosseini, C. Sirrenberg, G.S. Butler, T. Crabbe, A.J. Docherty, M. Wiesner, G. Murphy, C.M. Overall, S.L. Goodman, M.S. Pepper, Dissecting the role of matrix metalloproteinases (MMP) and integrin alpha(v)beta3 in angiogenesis in vitro: absence of hemopexin C domain bioactivity, but membrane-Type 1-MMP and alpha(v)beta3 are critical, Cancer Res. 65 (2005) 9377–9387. https://doi.org/10.1158/0008-5472.CAN-05-1512.
[99] Y. Itoh, A. Takamura, N. Ito, Y. Maru, H. Sato, N. Suenaga, T. Aoki, M. Seiki, Homophilic complex formation of MT1-MMP facilitates proMMP-2 activation on the cell surface and promotes tumor cell invasion, EMBO J. 20 (2001) 4782–4793. https://doi.org/10.1093/emboj/20.17.4782.
[100] B. Cauwe, P.E. Van den Steen, G. Opdenakker, The biochemical, biological, and pathological kaleidoscope of cell surface substrates processed by matrix metalloproteinases, Crit. Rev. Biochem. Mol. Biol. 42 (2007) 113–185. https://doi.org/10.1080/10409230701340019.
[101] B. Levkau, R.D. Kenagy, A. Karsan, B. Weitkamp, A.W. Clowes, R. Ross, E.W. Raines, Activation of metalloproteinases and their association with integrins: an auxiliary apoptotic pathway in human endothelial cells, Cell Death Differ. 9 (2002) 1360–1367. https://doi.org/10.1038/sj.cdd.4401106.
[102] J. Kryczka, M. Stasiak, L. Dziki, M. Mik, A. Dziki, C. Cierniewski, Matrix metalloproteinase-2 cleavage of the β1 integrin ectodomain facilitates colon cancer cell motility, J. Biol. Chem. 287 (2012) 36556–36566. https://doi.org/10.1074/jbc.M112.384909.
[103] R. Rizzo, A. Trentini, D. Bortolotti, M.C. Manfrinato, A. Rotola, M. Castellazzi, L. Melchiorri, D. Di Luca, F. Dallocchio, E. Fainardi, T. Bellini, Matrix metalloproteinase-2 (MMP-2) generates soluble HLA-G1 by cell surface proteolytic shedding, Mol. Cell. Biochem. 381 (2013) 243–255. https://doi.org/10.1007/s11010-013-1708-5.
[104] M. Gioia, G.F. Fasciglione, D. Sbardella, F. Sciandra, M. Casella, S. Camerini, M. Crescenzi, A. Gori, U. Tarantino, P. Cozza, A. Brancaccio, M. Coletta, M. Bozzi, The enzymatic processing of α-dystroglycan by MMP-2 is controlled by two anchoring sites distinct from the active site, PLoS One 13 (2018), e0192651. https://doi.org/10.1371/journal.pone.0192651.
[105] B. Bauvois, New facets of matrix metalloproteinases MMP-2 and MMP-9 as cell surface transducers: outside-in signaling and relationship to tumor progression, Biochim. Biophys. Acta 1825 (2012) 29–36. https://doi.org/10.1016/j.bbcan.2011.10.001.
[106] K. Hibbetts, B. Hines, D. Williams, An overview of proteinase inhibitors, J. Vet. Intern. Med. 13 (1999) 302–308. https://doi.org/10.1111/j.1939-1676.1999.tb02185.x.
[107] A.H. Baker, D.R. Edwards, G. Murphy, Metalloproteinase inhibitors: biological actions and therapeutic opportunities, J. Cell Sci. 115 (2002) 3719–3727. https://doi.org/10.1242/jcs.00063.
[108] V. Arpino, M. Brock, S.E. Gill, The role of TIMPS in regulation of extracellular matrix proteolysis, Matrix Biol. 44–46 (2015) 247–254. https://doi.org/10.1016/j.matbio.2015.03.005.
[109] F. Willenbrock, T. Crabbe, P.M. Slocombe, C.W. Sutton, A.J. Docherty, M.I. Cockett, M. O'Shea, K. Brocklehurst, I.R. Phillips, G. Murphy, The activity of the tissue inhibitors of metalloproteinases is regulated by C-terminal domain interactions: a kinetic analysis of the inhibition of gelatinase A, Biochemistry 32 (1993) 4330–4437. https://doi.org/10.1021/bi00067a023.
[110] K. Brew, H. Nagase, The tissue inhibitors of metalloproteinases (TIMPs): an ancient family with structural and functional diversity, Biochim. Biophys. Acta 1803 (2010) 55–71. https://doi.org/10.1016/j.bbamcr.2010.01.003.
[111] M.M. Bernardo, R. Fridman, TIMP-2 (tissue inhibitor of metalloproteinase-2) regulates MMP-2 (matrix metalloproteinase-2) activity in the extracellular environment after pro-MMP-2 activation by MT1 (membrane type 1)-MMP, Biochem. J. 374 (2003) 739–745. https://doi.org/10.1042/BJ20030557.
[112] V.M. Kähäri, U. Saarialho-Kere, Matrix metalloproteinases and their inhibitors in tumour growth and invasion, Ann. Med. 31 (1999) 34–45.
[113] D.E. Kleiner, W.G. Stetler-Stevenson, Matrix metalloproteinases and metastasis, Cancer Chemother. Pharmacol. 43 (1999) S42–S51.
[114] M. Hidalgo, S.G. Eckhardt, Matrix metalloproteinase inhibitors: how can we optimize their development? Ann. Oncol. 12 (2001) 285–287. https://doi.org/10.1023/A:1011198530099.
[115] B. Fingleton B, Matrix metalloproteinase inhibitors for cancer therapy: the current situation and future prospects, Expert Opin. Ther. Targets 7 (2003) 385–397. https://doi.org/10.1517/14728222.7.3.385.
[116] M. Pavlaki, S. Zucker, Matrix metalloproteinase inhibitors (MMPIs): the beginning of phase I or the termination of phase III clinical trials, Cancer Metastasis Rev. 22 (2003) 177–203. https://doi.org/10.1023/A:1023047431869.
[117] C.M. Overall, O. Kleifeld, Towards third generation matrix metalloproteinase inhibitors for cancer therapy, Br. J. Canc. 94 (2006) 941–946. https://doi.org/10.1038/sj.bjc.6603043.
[118] C.M. Overall, O. Kleifeld, Tumour microenvironment - opinion: validating matrix metalloproteinases as drug targets and anti-targets for cancer therapy, Nat. Rev. Cancer 6 (2006) 227–239. https://doi.org/10.1038/nrc1821.
[119] J. Decock, S. Thirkettle, L. Wagstaff, D.R. Edwards DR, Matrix metalloproteinases: protective roles in cancer, J. Cell Mol. Med. 15 (2011) 1254–1265. https://doi.org/10.1111/j.1582-4934.2011.01302.x.
[120] J.S. Yang, C.W. Lin, S.C. Su, S.F. Yang, Pharmacodynamic considerations in the use of matrix metalloproteinase inhibitors in cancer treatment, Expert Opin, Drug Metab. Toxicol. 12 (2016) 191–200. https://doi.org/10.1517/17425255.2016.1131820.
[121] M. Tauro, C.C. Lynch, Cutting to the chase: how matrix metalloproteinase-2 activity controls breast-cancer-to-bone metastasis, Cancers 10 (2018) e185. https://doi.org/10.3390/cancers10060185.
[122] N.V. Thomas, S.K. Kim, Metalloproteinase inhibitors: status and scope from marine organisms, Biochem. Res. Int. 2010 (2010) 845975. https://doi.org/10.1155/2010/845975.
[123] L. Wang, X. Li, S. Zhang, W. Lu, S. Liao, X. Liu, L. Shan, X. Shen, H. Jiang, W. Zhang, J. Huang, H. Li, Natural products as a gold mine for selective matrix metalloproteinases inhibitors, Bioorg. Med. Chem. 20 (2012) 4164–4171. https://doi.org/10.1016/j.bmc.2012.04.063.
[124] A. Berton, V. Rigot, E. Huet, M. Decarme, Y. Eeckhout, L. Patthy, G. Godeau, W. Hornebeck, G. Bellon, H. Emonard, Involvement of fibronectin type II repeats in the efficient inhibition of gelatinases A and B by long-chain unsaturated fatty acids, J. Biol. Chem. 276 (2001) 20458–20465. https://doi.org/10.1074/jbc.M011664200.
[125] S.K. Moestrup, K. Kaltoft, L. Sottrup-Jensen, J. Gliemann, The human alpha 2-macroglobulin receptor contains high affinity calcium binding sites important for receptor conformation and ligand recognition, J. Biol. Chem. 265 (1990) 12623–12628.
[126] D.K. Strickland, J.D. Ashcom, S. Williams, W.H. Burgess, M. Migliorini, W.S. Argraves, Sequence identity between the alpha 2-macroglobulin receptor and low density lipoprotein receptor-related protein suggests that this molecule is a multifunctional receptor, J. Biol. Chem. 265 (1990) 17401–17404.
[127] N. Etique, L. Verzeaux, S. Dedieu, H. Emonard, LRP-1: a checkpoint for the extracellular matrix proteolysis, BioMed Res. Int. 2013 (2013) 152163. https://doi.org/10.1155/2013/152163.
[128] H. Emonard, E. Marbaix E, Low-density lipoprotein receptor-related protein in metalloproteinase-mediated pathologies: recent insights,

Metalloproteinases Med. 2 (2015) 9–18, 2015, https://doi.org/10.2147/MNM.S63616.
[129] H. Chen, D.K. Strickland, D.F. Mosher, Metabolism of thrombospondin 2. Binding and degradation by 3T3 cells and glycosaminoglycan-variant Chinese hamster ovary cells, J. Biol. Chem. 271 (1996) 15993–15999. https://doi.org/10.1074/jbc.271.27.15993.
[130] Z. Yang, D.K. Strickland, P. Bornstein, Extracellular matrix metalloproteinase 2 levels are regulated by the low density lipoprotein-related scavenger receptor and thrombospondin 2, J. Biol. Chem. 276 (2001) 8403–8408. https://doi.org/10.1074/jbc.M008925200.
[131] H. Emonard, G. Bellon, L. Troeberg, A. Berton, A. Robinet, P. Henriet, E. Marbaix, K. Kirkegaard, L. Patthy, Y. Eeckhout, H. Nagase, W. Hornebeck, P.J. Courtoy, Low density lipoprotein receptor-related protein mediates endocytic clearance of pro-MMP-2.TIMP-2 complex through a thrombospondin-independent mechanism, J. Biol. Chem. 279 (2004) 54944–54951. https://doi.org/10.1074/jbc.M406792200.
[132] C. Selvais, H.P. Gaide Chevronnay, P. Lemoine, S. Dedieu, P. Henriet, P.J. Courtoy, E. Marbaix, H. Emonard, Metalloproteinase-dependent shedding of low-density lipoprotein receptor-related protein-1 ectodomain decreases endocytic clearance of endometrial matrix metalloproteinase-2 and -9 at menstruation, Endocrinology 150 (2009) 3792–3799. https://doi.org/10.1210/en.2009-0015.
[133] C. Selvais, L. D'Auria, D. Tyteca, G. Perrot, P. Lemoine, L. Troeberg, S. Dedieu, A. Noël, H. Nagase, P. Henriet, P.J. Courtoy, E. Marbaix, H. Emonard, Cell cholesterol modulates metalloproteinase-dependent shedding of LRP-1 (low-density lipoprotein receptor-related protein-1) and clearance function, FASEB J. 25 (2011) 2770–2781. https://doi.org/10.1096/fj.10-169508.
[134] J. Thevenard, L. Verzeaux, J. Devy, N. Etique, A. Jeanne, C. Schneider, C. Hachet, G. Ferracci, M. David, L. Martiny, E. Charpentier, M. Khrestchatisky, S. Rivera, S. Dedieu, H. Emonard, Low-density lipoprotein receptor-related protein-1 mediates endocytic clearance of tissue inhibitor of metalloproteinases-1 and promotes its cytokine-like activities, PLoS One 9 (2014), e103839. https://doi.org/10.1371/journal.pone.0103839.
[135] S.D. Scilabra, L. Troeberg, K. Yamamoto, H. Emonard, I. Thøgersen, J.J. Enghild, D.K. Strickland, H. Nagase, Differential regulation of extracellular tissue inhibitor of metalloproteinases-3 levels by cell membrane-bound and shed low density lipoprotein receptor-related protein 1, J. Biol. Chem. 288 (2013) 332–342. https://doi.org/10.1074/jbc.M112.393322.
[136] G. Ruiz-Gomez, S. Vogel, S. Möller, M.T. Pisabarro, U. Hempel, Glycosaminoglycans influence enzyme activity of MMP2 and MMP2/TIMP3 complex formation – insights at cellular and molecular level, Sci. Rep. 9 (2019) 4905. https://doi.org/10.1038/s41598-019-41355-2.
[137] H. Prazeres, J. Torres, F. Rodrigues, M. Pinto, M.C. Pastoriza, D. Gomes, J. Cameselle-Teijeiro, A. Vidal, T.C. Martins, M. Sobrinho-Simões, P. Soares, Chromosomal, epigenetic and microRNA-mediated inactivation of LRP1B, a modulator of the extracellular environment of thyroid cancer cells, Oncogene 30 (2011) 1302–1317. https://doi.org/10.1038/onc.2010.512.
[138] M. Johanns, P. Lemoine, V. Janssens, G. Grieco, S.K. Moestrup, R. Nielsen, E.I. Christensen, P.J. Courtoy, H. Emonard, E. Marbaix, P. Henriet, Cellular uptake of proMMP-2:TIMP-2 complexes by the endocytic receptor megalin/LRP-2, Sci. Rep. 7 (2017) 4328. https://doi.org/10.1038/s41598-017-04648-y.
[139] L.A. Liotta, K. Tryggvason, S. Garbisa, I. Hart, C.M. Foltz, S. Shafie, Metastatic potential correlates with enzymatic degradation of basement membrane collagen, Nature 284 (1980) 67–68. https://doi.org/10.1038/284067a0.
[140] H. Sato, T. Takino, Y. Okada, J. Cao, A. Shinagawa, E. Yamamoto, M. Seiki, A matrix metalloproteinase expressed on the surface of invasive tumour cells, Nature 370 (1994) 61–65. https://doi.org/10.1038/370061a0.
[141] H.Y. Liu, W.J. Gu, C.Z. Wang, X.J. Ji, Y.M. Mu YM, Matrix metalloproteinase-9 and -2 and tissue inhibitor of matrix metalloproteinase-2 in invasive pituitary adenomas: a systematic review and meta-analysis of case-control trials, Medicine (Baltim.) 95 (2016) e3904. https://doi.org/10.1097/MD.0000000000003904.
[142] F. Ren, R. Tang, X. Zhang, W.M. Madushi, D. Luo, Y. Dang, Z. Li, K. Wei, G. Chen, Overexpression of MMP family members functions as prognostic biomarker for breast cancer patients: a systematic review and meta-analysis, PLoS One 10 (2015), e0135544. https://doi.org/10.1371/journal.pone.0135544.
[143] Z. Fu, S. Xu, Y. Xu, J. Ma, J. Li, P. Xu, The expression of tumor-derived and stromal-derived matrix metalloproteinase 2 predicted prognosis of ovarian cancer, Int. J. Gynecol. Cancer 25 (2015) 356–362. https://doi.org/10.1097/IGC.0000000000000386.
[144] C. Liu, Y. Li, S. Hu, Y. Chen, L. Gao, D. Liu, H. Guo, Y. Yang, Clinical significance of matrix metalloproteinase-2 in endometrial cancer: a systematic review and meta-analysis, Medicine (Baltim.) 97 (2018), e10994. https://doi.org/10.1097/MD.0000000000010994.
[145] H.L. Wang, P.Y. Zhou, Y. Zhang, P. Liu, Relationships between abnormal MMP2 expression and prognosis in gastric cancer: a meta-analysis of cohort studies, Cancer Biother. Radiopharm. 29 (2014) 166–172. https://doi.org/10.1089/cbr.2014.1608.
[146] Q. Qian, Q. Wang, P. Zhan, L. Peng, S.Z. Wei, Y. Shi, Y. Song, The role of matrix metalloproteinase 2 on the survival of patients with non-small cell lung cancer: a systematic review with meta-analysis, Canc. Invest. 28 (2010) 661–669. https://doi.org/10.3109/07357901003735634.
[147] D. Singh, S.K. Srivastava, T.K. Chaudhuri, G. Upadhyay, Multifaceted role of matrix metalloproteinases (MMPs), Front. Mol. Biosci. 2 (2015) 19. https://doi.org/10.3389/fmolb.2015.00019.
[148] M.J. Hannocks, X. Zhang, H. Gerwien, A. Chashchina, M. Burmeister, E. Korpos, J. Song, L. Sorokin, The gelatinases, MMP-2 and MMP-9, as fine tuners of neuroinflammatory processes, Matrix Biol. 75–76 (2019) 102–113. https://doi.org/10.1016/j.matbio.2017.11.007.
[149] N.I. Medeiros, J.A.S. Gomes, R. Correa-Oliveira, Synergic and antagonistic relationship between MMP-2 and MMP-9 with fibrosis and inflammation in Chagas' cardiomyopathy, Parasite Immunol. 39 (2017), e12446. https://doi.org/10.1111/pim.12446.
[150] A. Alunno, E. Falcinelli, F. Luccioli, E. Petito, E. Bartoloni, S. Momi, G. Mirabelli, G.B. Mancini, R. Gerli, P. Gresele, Platelets contribute to the accumulation of matrix metalloproteinase type 2 in synovial fluid in osteoarthritis, Thromb. Haemost. 117 (2017) 2116–2124. https://doi.org/10.1160/TH17-06-0379.
[151] A.C. Newby, Do metalloproteinases destabilize vulnerable atherosclerotic plaques? Curr. Opin. Lipidol. 17 (2006) 556–561.
[152] S.G. Mansour, J. Puthumana, S.G. Coca, M. Gentry, C.R. Parikh, Biomarkers for the detection of renal fibrosis and prediction of renal outcomes: a systematic review, BMC Nephrol. 18 (2017) 72. https://doi.org/10.1186/s12882-017-0490-0.
[153] S.W. Rabkin, Differential expression of MMP-2, MMP-9 and TIMP proteins in thoracic aortic aneurysm - comparison with and without bicuspid aortic valve: a meta-analysis, VASA 43 (2014) 433–442. https://doi.org/10.1024/0301-1526/a000390.
[154] R. Cook, H. Sarker, C. Fernandez-Patron, Pathologies of matrix metalloproteinase-2 underactivity: a perspective on a neglected condition, Can. J. Physiol. Pharmacol. 97 (2019) 486–492. https://doi.org/10.1139/cjpp-2018-0525.
[155] G.S.L. Bhavani, H. Shah, A. Shukla, K.M. Girisha, in: M.P. Adam, H.H. Ardinger, R.A. Pagon, S.E. Wallace, L.J.H. Bean, K. Stephens, A. Amemiya (Eds.), Multicentric Osteolysis Nodulosis and Arthropathy, GeneReviews® [Internet], Seattle, 2016, pp. 1993–2019.
[156] K. Zhang, X. Chen, J. Zhou, C. Yang, M. Zhang, M. Chao, L. Zhang, C. Liang C, Association between MMP2-1306 C/T polymorphism and prostate cancer susceptibility: a meta-analysis based on 3906 subjects, Oncotarget 8 (2017) 45020–45029. https://doi.org/10.18632/oncotarget.16972.
[157] S.K. Kim, S.W. Kang, H.J. Park, J.Y. Ban, C.H. Oh, J.H. Chung, I.H. Oh, K.B. Cho, M.S. Park, Meta-analysis of association of the matrix metalloproteinase 2 (-735 C/T) polymorphism with cancer risk, Int. J. Clin. Exp. Med. 8 (2015) 17096–17101.
[158] L. Shapiro, Phase 2 Study of Bevacizumab in Combination with Docetaxel in Patients with Advanced Breast caCncer, National Cancer Institute (NCI) ClinicalTrials.gov Identifier NCT00055861.
[159] B. Ramaswamy, A.D. Elias, N.T. Kelbick, A. Dodley, M. Morrow, M. Hauger, J. Allen, C. Rhoades, K. Kendra, H.X. Chen, S.G. Eckhardt, C.L. Shapiro, Phase II trial of bevacizumab in combination with weekly docetaxel in metastatic breast cancer patients, Clin. Cancer Res. 12 (2006) 3124–3129. https://doi.org/10.1158/1078-0432.CCR-05-2603.
[160] D. Genre, I. Boquet, Study of the Predictive Impact of MMP2 and MMP9 Levels for Patients with Metastatic Kidney Cancer Treated with Anti-angiogenic Agents Compared to Patients Not Treated with Antiangiogenic (Localized Kidney Cancer and Oligometastatic), National Cancer Institute (NCI) ClinicalTrials.gov Identifier NCT03185039.
[161] E. Tabouret, F. Boudouresque, P. Farina, M. Barrié, C. Bequet, M. Sanson, O. Chinot, MMP2 and MMP9 as candidate biomarkers to monitor bevacizumab therapy in high-grade glioma, Neuro Oncol. 17 (2015) 1174–1176. https://doi.org/10.1093/neuonc/nov094.
[162] E. Tabouret, F. Bertucci, J.Y. Pierga, T. Petit, C. Levy, J.M. Ferrero, M. Campone, J. Gligorov, F. Lerebours, H. Roché, T. Bachelot, S. van Laere, N.T. Ueno, Y. Toiron, P. Finetti, D. Birnbaum, J.P. Borg, P. Viens, O. Chinot, A. Gonçalves, MMP2 and MMP9 serum levels are associated with favorable outcome in patients with inflammatory breast cancer treated with bevacizumab-based neoadjuvant chemotherapy in the BEVERLY-2 study, Oncotarget 7 (2016) 18531–18540. https://doi.org/10.18632/oncotarget.7612.
[163] E. Tabouret, D. Figarella, Prospective Cohort of Patients with Newly Diagnosed Glioblastoma: Analysis of MMP2 and MMP9 Expression and Correlation to Neuro-Imaging Features, National Cancer Institute (NCI) ClinicalTrials.gov Identifier NCT03526822.