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Sylvie Ricard-Blum, Sylvain Vallet

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Sylvie Ricard-Blum and Sylvain Vallet

Univ Lyon, University Claude Bernard Lyon 1, CNRS, INSA Lyon, CPE, Institute of Molecular and Supramolecular Chemistry and Biochemistry, UMR 5246, F-69622 Villeurbanne cedex, France.

sylvie.ricard-blum@univ-lyon1.fr sylvain.vallet@univ-lyon1.fr

Corresponding author:

Prof. Sylvie RICARD-BLUM

Institut de Chimie et Biochimie Moléculaires et Supramoléculaires UMR 5246

Bâtiment Raulin - Université Lyon 1

43 Boulevard du 11 novembre 1918

F - 69622 Villeurbanne cedex, France

e-mail: Sylvie.ricard-blum@univ-lyon1.fr

Phone: +33(0)472448232

Abstract

The remodeling of the extracellular matrix (ECM) by several protease families releases a number of bioactive fragments, which regulate numerous biological processes such as autophagy, angiogenesis, adipogenesis, fibrosis, tumor growth, metastasis and wound healing. We review here the proteases which generate bioactive ECM fragments, their ECM substrates, the major bioactive ECM fragments, together with their biological properties and their receptors. The translation of ECM fragments into drugs is challenging and would take advantage of an integrative approach to optimize the design of pre-clinical and clinical studies. This could be done by building the contextualized interaction network of the ECM fragment repertoire including their parent proteins, remodeling proteinases, and their receptors, and by using mathematical disease models.

Keywords: Extracellular matrix; Remodeling; Matrikines; Proteases; Receptors; Drugs;

Abbreviations: ADAM, a disintegrin and metalloproteinase; ADAMTS, a disintegrin and metalloproteinase with thrombospondin motifs; CD, Cluster Differentiation; CUB, complement C1r/C1s, Uegf, Bmp1 domain; CXCL4L1, chemokine platelet factor-4 variant; CXCR2, C-X-C chemokine receptor type 2; ECM, extracellular matrix; ED, ectodomain; EGFR, Epidermal Growth Factor Receptor; ERK, extracellular signal-regulated protein kinase; FN, fibronectin; HER2, Tyrosine kinase-type cell surface receptor HER2 or Receptor tyrosine-protein kinase erbB-2; IGFR, Insulin Growth Factor Receptor; MMP, matrix metalloproteinase; MT-MMP, membrane-type matrix metalloproteinases; NC, non collageneous domain; NTR, netrin-like domain; PEX, hemopexin domain; SDC, syndecan; SPARC, secreted protein acidic and rich in cysteine; SSTN, synstatin; TGFβR1, Transforming Growth Factor β Receptor-1/Activin receptor-like kinase 5 (ALK5); TLR2, Toll-like Receptor-2; VEGFR2, Vascular endothelial growth factor receptor 2).

Introduction

Extracellular matrix (ECM) remodeling is a dynamic process, which involves neosynthesis and degradation and occurs both in physiological and pathological states. ECMis thus a key player in tissue failure [1]. This mini-review focuses on the bioactive fragments called matricryptins or matrikines, which are proteolytically released from ECM proteins and glycosaminoglycans in the course of matrix remodeling, and regulate numerous biological processes in physiological and pathological situations. These fragments have been termed matricryptins [2–6] and/or matrikines [2,7–11] and/or ECM fragments [12]. Initially the term "matricryptin" has been proposed for ECM fragments with biological activities that differ

from those of their parent molecules [13], and the term "matrikine" for ECM-derived peptides able to regulate cell activity [14,15]. Several ECM fragments (e.g. anastellin, arresten, canstatin, endorepellin, endostatin, endotrophin, tumstatin, vastatin) are named based on their biological activity and/or their cellular target(s), whereas peptides are named after their sequences (e.g. PGP or prolyl-glycyl-proline [10]). Matricryptins, matrikines and other ECM-derived peptides will be collectively referred to as ECM fragments in this review.

Several proteinase families, mostly zinc metalloproteinases and serine or cysteine proteases generate bioactive fragments in the course of ECM remodeling. These fragments interact with growth factor receptors, toll-like receptors and integrins to exert their biological activities and a number of them share common cell surface receptors (see [5] for review). Some ECM fragments bind to each other, which leads to the formation of a dense and highly connected fragment-receptor network at the surface of cells such as endothelial and tumor cells. This network regulates major biological processes such angiogenesis, tumor growth, metastasis, fibrosis, wound healing, and adipogenesis. Several biological processes may be regulated by different ECM fragments, and ECM fragments have various molecular functions modulating gene expression, cell signaling, and acting as enzymes, proenzyme activators or enzyme inhibitors. ECM fragments are potential drugs. One of them (endostatin) has been approved in China for the treatment of small-cell lung cancer in combination with chemotherapy and has been tested in several clinical trials. Furthermore ECM proteolytic fragments released in biological fluids are used as diagnostic and prognostic disease markers [16]. A complete review of the ECM bioactive fragments is beyond the scope of this mini-review, which provides an overview of the ECM fragment repertoire, its generation and its biological activities based on examples and highlights of recent findings. General reviews of ECM fragments generated from collagens and proteoglycans [3,4,8], the proteases which generates them [6,11], and their receptors [5] provide a more detailed and comprehensive

view of previous studies. An overview of the ECM bioactive fragments repertoire, including several examples of ECM fragments, ECM fragments sources, proteases releasing ECM fragments, and major biological processes and diseases they regulate are provided in **Table 1**.

ECM proteins or protein families generating ECM fragments	**References**
Collagens	[3,6]
Basement membrane collagens	[9]
Elastin	[17–19]
Fibronectin	[20–24] and references therein
Laminins	[25]
Laminin-111	[26]
Laminin-332	[27]
Proteoglycans	[3,6]
Versican	[28]
Osteopontin	[29–31] and references therein
Tenascin C	[32]
Hyaluronan	[33–36]

Individual ECM fragments	**References**
Endostatin	[37–43]
Endorepellin	[43–46] and references therein
Endotrophin	[47,48] and references therein
Tumstatin	[49–51]
Proline-Glycine-Proline	[10]
Syndecan ectodomains	[52]
Synstatins	[53,54] and references therein

Protease or protease families generating ECM fragments	**References**
Several protease families	[6]
MMPs	[11]
MMP-12	[17]

Biological processes and diseases regulated by ECM fragments	**References**
Angiogenesis	[38,41–43,55]
Atherosclerosis	[56]
Autophagy	[43,45,46]
Cancer	[5,26,30,31,43,57,58]
Breast cancer	[47]
Skin cancer (melanoma)	[2,50,59]
Cartilage destruction	[20,22]
Embryogenesis	[28]

Inflammation	[12,34,36,60]
Lung diseases	[7,36]
Chronic obstructive pulmonary disease	[10,60,61]
Wound repair	[2,25]
Skin rejuvenation	[33,62]
Regenerative medicine	[63]
Neuronal regeneration	[64]
Obesity/diabetes	[58,65]
Diabetic retinopathy	[41]

Table 1. **Overview of the ECM fragment repertoire.** Several examples of ECM fragments generated from a single ECM protein or by an ECM protein family, by a protease family or regulating a biological process or involved in a disease are listed with reviews, or major papers when no review is available. (MMP: matrix metalloproteinase). Further ECM fragments are listed in Table 2.

1. The ECM as a source of bioactive fragments regulating numerous biological processes

Numerous fragments are released upon degradation of major ECM proteins (e.g. collagens, elastin, fibronectin, laminins and matricellular proteins) and proteoglycans (e.g. perlecan and versican). Those listed in Table 2 are named according to their parent protein, biological activity and/or target cell(s). They regulate angiogenesis, apoptosis, autophagy, tumor growth and metastasis [9], fibrosis, wound healing, adipogenesis, synaptogenesis and inflammation [5,6]. Some examples and recent findings are summarized below.

Endostatin plays a role in the organization of brain synapses through α3β1 integrins [66] and synaptic plasticity [67]. The NC1 domain of the α2 (canstatin), α3 (tumstatin) and α6 chains of collagen IV cluster synaptic vesicles [68] whereas the NC1 domain of collagen XIX induces the formation of inhibitory synapses *via* integrin receptors [69]. The matrikine N-acetylated proline-glycine-proline induces premature senescence of nucleus pulposus cells [70] and increases vascular inflammation [71]. The C-1158/59 peptide (14 residues) recapitulating the activity of the Iα1 C-1158/59 fragment released from collagen I by MMP-2 and MMP-9 increases angiogenesis and promotes would healing after myocardial infection [72]. In contrast the fragments derived from the C-terminus of collagens associated with

basement membranes (IV, VIII, XV, XVIII, and XIX) are anti-angiogenic and/or anti-tumoral [4,6,9,42]. Collagen fragments may have opposite activity. Indeed endostatin inhibits angiogenesis, tumor growth [6,42,43] and fibrosis [73] whereas endotrophin is pro-angiogenic, and promotes adipose tissue fibrosis and tumor progression [58,74]. ECM fragments stimulate wound healing by modulating angiogenesis as reported for the SVVYGLR peptide (SV-peptide) of osteopontin, which also stimulates the differentiation of fibroblasts into myofibroblasts [75], for lumikine (a peptide from lumican [76,77] and for hyaluronan fragments [78,79]. It should be noted that size matters for the biological activities of hyaluronan fragments [35,80]. In contrast endostatin has been reported to impair blood vessel maturation during wound healing [81] and to delay wound healing when overexpressed [82] although it has no effect according to another study [83].

Proteoglycans are also a source of bioactive ECM fragments. Endorepellin, the C-terminus of perlecan, inhibits angiogenesis and induces autophagy in endothelial cells [43,44]. Peptides derived from lumican, a small leucine-rich proteoglycan, such as lumcorin (a leucine-rich repeat 9-derived peptide) inhibit melanoma cell growth and migration [84,85]. The 13 C-terminal amino acid residues of lumican (YEALRVANEVTLN, LumC13 or lumikine) and its derivatives promote wound healing [76,77]. Proapoptotic fragments, released from versican by ADAMTSs (A Disintegrin And Metalloproteinases with Thrombospondin motifs, ADAMTS 5, 9, 20 and possibly 1) regulate interdigital regression [86]. Versikine, the N-terminal G1 domain of the versican V1 isoform, generated by 5 [28], is a novel damage associated molecular pattern, which induces T-cell inflammation in a myeloma microenvironment [87]. It also promotes the differentiation of pre-dendritic cell toward Batf3-dependent dendritic cells that are of crucial importance for T cell immunity [88]. The ectodomains of syndecan-1, -2, -3 are anti-angiogenic [52,54]. Peptides derived from syndecan ectodomains are called synstatins (SSTN, **Table 2**). Two synstatins, $SSTN_{82-}$

$_{130}$ and $SSTN_{92-119}$, inhibit angiogenesis *in vitro* and *in vivo* and $SSTN_{82-130}$ decreases tumor growth in mice [89]. $SSTN_{92-119}$ also inhibits the ternary complex comprised of syndecan-1, IGF1R and αvβ3/αvβ5 integrins in tumorigenesis and angiogenesis [53,90]. Furthermore SSTN peptides capturing the β1 integrin subunit or VEGFR2 inhibit activation of VEGFR2 and the invasive phenotype induced by heparanase expression in myeloma and endothelial cells [91].

Several proteolytic fragments of various molecular weight are generated from fibronectin [23] in addition to anastellin, a fragment from the first fibronectin III domain, which inhibits angiogenesis. The N-terminal heparin-, N-terminal gelatin-, and central cell-binding fibronectin fragments induce cartilage degradation [22] and the N-terminal 30 kDa fragment triggers the degeneration of the intervertebral disc [92]. The catabolic activity of the 29 kDa N-terminal heparin-binding fragment is increased at low oxygen tension [93]. Trypsin- and chymotrypsin fibronectin fragments promote the migration of prostate cancer cells towards bone marrow mesenchymal stromal cells via the α5β1 integrin [94]. A 42-kDa fragment, consisting of fibronectin III domains 7–10 and including the cell-binding domain, also promotes an increase in S-sulfenylation in the tyrosine kinase Src and in Src activity in normal chondrocytes [95]. Fibstatin, the fibronectin III domains 12-14 of fibronectin [96], inhibits tumor angiogenesis, lymphangiogenesis and metastasis in cooperation with CXCL4L1 [97].

Matricellular proteins such as osteopontin and SPARC are also a source of bioactive fragments (**Table 1**). SPARC peptides inhibit fibroblast and endothelial cell spreading [98], angiogenesis and progression of neuroblastoma tumors [99]. Furthermore ON29, an acidic peptide of SPARC regulates bone mineralization by decreasing the amount of water in the disordered phase [100].

PARENT PROTEIN	ECM FRAGMENTS	(CO)-RECEPTORS	REFERENCES
ECM Proteins			
Collagen I	Proline-Glycine-Proline	CXCR2	[101,102]
	Iα1 C-1158/59 fragment	-	[72]
	C-propeptide	α1β1 integrin α2β1integrin	[103–107]
Collagen II	N-propeptide	αvβ3 integrin αvβ5 integrin	[108–110]
	C-propeptide (chondrocalcin)	Anchorin CII	[111–113]
Collagen IV	Arresten (α1 chain)	α1β1 integrin	[114,115]
	Canstatin (α2 chain)	α3β1 integrin αvβ3 integrin αvβ5 integrin	[114,116,117]
	Tumstatin (α3 chain)	α3β1 integrin α6β1 integrin αvβ3 integrin αvβ5 integrin	[118–121]
	Tetrastatin (α4 chain)	αvβ3 integrin	[122]
	NC1 domain (α6 chain)	αvβ3 integrin	[116]
Collagen VI	Endotrophin (α3 chain)	-	[123]
Collagen VIII	Vastatin (α1 chain)	-	[124–126]
Collagen XIII	Ectodomain (α1 chain)	α1β1 integrin	[127,128]
Collagen XV	Restin (α1 chain)	-	[129]
Collagen XVII	Peptide p561 (α1 chain)	-	[130]
	Ectodomain (α1 chain)	-	[131]
Collagen XVIII	Endostatin (α1 chain)	α5β1 integrin αvβ3 integrin αvβ5 integrin VEGFR1 VEGFR2 Glypican-1 Glypican-4 Nucleolin	[132–141]
	*G10T peptide * K15T peptide	-	[142]
	Neostatins 7 and 14	-	[143,144]
Collagen XIX	NC1 domain (α1 chain)	αvβ3 integrin	[145]
Collagen XXIII	Ectodomain (α1 chain)	α2β1integrin	[146,147]
Collagen XXV	Ectodomain (α1 chain)	-	[148]
Elastin	Elastokines	αvβ3 integrin Elastin Receptor Complex Galectin-3 receptor	[19,149–151]

		Lactose-insensitive receptor	
Fibronectin	FN-gelatinase FN-lamininase FN-fibronectinase FN-type IV collagenase	-	[21,152,153]
	Anastellin	-	[154]
	Fibstatin (C-terminal heparin binding domain)	-	[96]
Gliomedin	Ectodomain Olfactomedin domain	-	[155,156]
Procollagen C-proteinase-enhancer-1	CUB1-CUB2 domain	-	[157]
	NTR domain	Syndecan-1 Syndecan-2 Syndecan-3	[157,158]

Proteoglycans			
Lumican	Lumcorin		[84]
	Lumikines ($LumC_{13}$)	TGFβR1 (Activin receptor-like kinase 5 ALK5)	[76,77]
Perlecan *Generated from endorepellin	Endorepellin	α2β1integrin VEGFR1 VEGFR2	[159–161]
	*LG3 domain		[162,163]
Syndecan-1	Ectodomain	HER2 α3β1 integrin αvβ3 integrin IGFR VEGFR2	[53,89,91,164–168]
	$Synstatin_{92-119}$ (or $SSTN_{IGF-1R}$	-	[53,90,168]
	$SSTN_{82-130}$	-	[89]
	$SSTN_{210-240}$	-	[91,168]
Syndecan-2	Ectodomain	CD148 (Receptor-type tyrosine-protein phosphatase eta)	[169,170]
Syndecan-3	Ectodomain	-	[171]
Syndecan-4	Ectodomain	EGFR α3β1 integrin	[164,168,172]
	$SSTN_{87-131}$	-	[168]
Versican	Versikine	TLR2 (+ other unidentified receptors?)	[28,87,173]

Cross-linking and degrading enzymes			
Lysyl oxidase	Propeptide	-	[174,175]
MMP-2	PEX (hemopexin	αvβ3 integrin	[176]

	domain)		
MMP-9	PEX (hemopexin domain)	α4β1 integrin α5β1 integrin CD44	[177–180]
MMP-14	PEX (hemopexin domain)	CD44	[181,182]

Table 2: **Names, parent proteins and receptors of major ECM fragments.** (CD: Cluster Differentiation, CXCR2: C-X-C chemokine receptor type 2, EGFR: Epidermal Growth Factor Receptor, FN: fibronectin, HER2: Tyrosine kinase-type cell surface receptor HER2 or Receptor tyrosine-protein kinase erbB-2, IGFR: Insulin Growth Factor Receptor, PEX: hemopexin domain, SSTN: synstatin, TGFβR1: Transforming Growth Factor β receptor-1/Activin receptor-like kinase 5 (ALK5), TLR2: Toll-like Receptor-2, VEGFR2: Vascular endothelial growth factor receptor 2).

2. A complex interplay between ECM bioactive fragments and proteases

Several proteinase families are able to release bioactive fragments from most, if not all, ECM proteins and proteoglycans including collagens, elastin, fibronectin, laminins, matricellular proteins (e.g. SPARC, and osteopontin), remodeling and cross-linking enzymes (MMP-2/-9/-14, and lysyl oxidase), procollagen C-proteinase-enhancer-1 [157], hyalectans (e.g. aggrecan), small leucine-rich proteoglycans (e.g. lumican [84]), perlecan and membrane proteoglycans (syndecan ectodomains and glypican-3 peptides).

The major proteinases, which cleave the above proteins, belong to the metzincin superfamily and are mostly matrix metalloproteinases (MMPs [11,183], ADAMs [184–186], ADAMTSs and tolloid proteases [187,188] (**Figure 1**). Cysteine and aspartate proteinases (cathepsins E, L, B, and S) and serine proteases (plasmin, thrombin, elastase, furin and cathepsin G) also participate in the release of matricryptins/matrikines (**Figure 1**). Some ECM fragments are further enzymatically processed into bioactive peptides as shown for endorepellin, which is cleaved by a tolloid protease, Bone Morphogenetic Protein-1, into the LG3 bioactive fragment [163] (**Figure 1**). Moreover, proteinases not only generate ECM fragments, but may also regulate their activity, as shown for cathepsins S and L, which cleave

endostatin in two peptides with increased anti-angiogenic properties compared to uncleaved endostatin [142].

The ECM fragment repertoire generated during ECM physiological and pathological remodeling varies according to the regulation of proteases. Indeed MMPs are tightly regulated *in vivo* at several levels, gene expression, activation of proenzyme and inhibition of enzymatic activities [189,190]. The expression profiles of the degradome, which can be analyzed in different tissues with a DNA microarray chip (CLIP-CHIP^{TM}) for 1561 human and murine proteases, inactive homologues and inhibitors [191,192], would be helpful to evaluate the composition and the amount of the ECM fragment repertoire in a particular tissue, whether in a physiological or pathological state. ECM fragment repertoires are context-dependent, even those generated from a single ECMprotein such as elastin. The abundance of several elastin peptides either decreases or increases upon aging. Furthermore the cleavage pattern of elastin is affected in a different way in chronological aging and photoaging, the N-terminal and central part of elastin being more susceptible to proteolysis in photoaging [18].

The interplay of ECM fragments with proteases is further strengthened because the ECM fragments themselves regulate protease expression, activation and/or activity. MMP-9 expression is induced in monocyte/macrophages by a laminin peptide (SIKVIV) and in fibroblasts by a fibronectin fragment containing the cell binding region [193,194]. The expression of MMP-2 in cardiac fibroblasts is increased by canstatin [195], which also increases the secretion of MMP-2 and MMP-9 by myofibroblasts [196]. MMP-1 and MMP-10 are up-regulated in airway smooth muscle cells by tumstatin [197]. MT1-MMP is upregulated by elastin peptides in endothelial cells [198], whereas endostatin downregulates MMP-1 and MMP-2 expression in these cells [199]. The 29-kDa fragment of fibronectin increases MMP-1, MMP-3, and MMP-13 expression in chondrocytes [200].

The activation of MT1-MMP is markedly decreased by tetrastatin [122], and endostatin, which also blocks the activation of proMMP-2, proMMP-13, and proMMP-9. The activation of proMMP-2 is also inhibited by tumstatin [6] and references therein. Furthermore endostatin inhibits the enzymatic activity of MMP-2 and MT1-MMP [6]. Whereas endostatin may act as a MMP inhibitor, it increases the activity of the proteases ADAM-10 and neprilysin in breast cancer cell lines [201]. Several fibronectin fragments display enzymatic activities acting as aspartic proteases (gelatinase and lamininase), metalloprotease (type IV collagenase) and serine protease (fibronectinase [21]) and a 90-kDa fragment has a streptokinase-like activity [20]. Furthermore the 29- and 50-kDa fragments of fibronectin mediate release of proteoglycan from articular cartilage [20] and tenascin C fragments (EGF-L and FN type III domains 3–8) have aggrecanase activity [202]. ECM fragments generated by proteolysis may thus act as enzymes, proenzyme activators, and inhibitors or activators of enzyme activity.

3. Cell surface receptors mediate biological activities of ECM fragments

The receptors of ECM fragments at the surface of endothelial and tumor cells and the signaling pathways they induce have been recently reviewed [5]. The activities of ECM fragments are mediated by integrins, tyrosine kinase receptors such as growth factor receptors, membrane proteoglycans and others (**Table 2** and **Figure 2**). The most frequently identified receptors of ECM fragments are integrins, particularly β1 integrins **(Figure 2).** However there might be a research bias towards the integrin family because most studies aiming at identifying receptors of ECM fragments focus on integrins only. Several ECM fragments bind to different receptors and different ECM fragments share the same receptor(s). Endorepellin and endostatin interact with VEGFR2, whereas a single receptor has been identified for lumikine, a peptide derived from lumican), which binds to TGFβR1 to promote

wound healing [76,77]. The role played by receptors is context-dependent. Anastellin requires heparan sulfate proteoglycans and integrins (likely α5β1 integrin) to promote aortic smooth muscle cell adhesion and to activate ERK1/2 [203], but activates p38 MAP kinase independently of β1 integrins in a murine embryo cell line [204]. Cell surface proteins also play a role in the internalization of ECM bioactive fragments by different mechanisms. Nucleolin, which mediates antiangiogenic and antitumor activity of endostatin [205] also mediates its internalization and nuclear translocation in endothelial cells [206]. The propeptide of lysyl oxidase, which is a tumor suppressor, is predominantly internalized by PI3K-dependent macropinocytosis in several cell lines and by a dynamin- and caveola dependent pathway in other cells [175].

ECM bioactive fragments are connected with both the protease web and the receptor network at the cell surface and with ECM proteins, proteoglycans and glycosaminoglycans. Furthermore they may act alone and/or in synergy to regulate the same process by different mechanisms mediated by receptors, which can crosstalk. The building and analysis of their global interaction network will thus allow to better understand their molecular connections and thus to refine the design of therapeutic strategies based on these fragments.

4. ECM bioactive fragments as drugs and biomarkers

The development of ECM bioactive fragments as drugs is challenging as discussed below. Endostatin, considered as a broad spectrum angiogenesis inhibitor [207], will be used as an example because it has been tested in clinical trials and is approved in China since 2005 for the treatment of non-small-cell lung cancer in combination with vinorelbine-cisplatin (phase III trial [208]). Several phase I [209,210], and II [211–219] clinical trials have been conducted these last five years in patients with melanoma [213], nasopharyngeal carcinoma

[215], head and neck carcinoma [218] lung [211,216,217,219,220], pancreatic [209], colorectal [210], breast [212,214] and gastric cancer [221].

A single ECM fragment may modulate different biological processes, which may lead to unwanted side effects if it is used to target a particular process. Endostatin for example regulates angiogenesis, adipogenesis, and autophagy and exert various molecular activities at the molecular level (see [6,42] for reviews). Endostatin has ATPase activity, which mediates its antiangiogenic and antitumor activities [222], and acts as an inhibitor of MMPs and an activator of proMMP as discussed above. Furthermore the effects of ECM fragments may depend on the molecular, cellular and tissue microenvironment. Endotrophin, derived from the C-terminus of collagen VI, upregulates different gene sets in different cell populations of adipose tissue [223]. It upregulates collagen genes and downregulates hormone-sensitive lipolysis gene in adipocytes, increases the expression of lysyl oxidase, which initiates cross-linking of collagens and elastin, and of proinflammatory genes in macrophages from white adipose tissue and upregulates profibrotic and proinflammatory genes in the stromal vascular fraction of adipose tissue [223]. The molecular context determines the immunological activity of the fibronectin fragment containing the extra domain A (FNIII EDA), which has an agonist effect on tolloid-like receptor 4 (TLR4) [224]. The presence of fibronectin III domains 9-11 at the N-terminus increases its agonist activity of TLR4 whereas the presence of fibronectin III domains 12-14 at the C-terminus abolishes it [224]. Some ECM fragments inhibit tumor cell proliferation [9,225] whereas other or identical ECM fragments sensitize cell lines and/or tumors to chemotherapy as shown for endostatin in *in vitro* and *in vivo* models of p53-deficient non-small cell lung cancer [226] and for the N-terminal peptide of SPARC, that resensitizes chemoresistant tumors *in vivo* [227]. Furthermore endostatin radiosensitizes non-small cell lung cancer cells by inhibiting VEGFR2 expression [228].

ECM proteins or proteoglycans may be needed for several ECM fragments to be active, which makes therapeutic use of ECM fragments more complicated. To inhibit angiogenesis *in vivo* anastellin requires either plasma fibronectin and endostatin both plasma fibronectin and vitronectin [229]. The silencing of the proteoglycan versican improves the anti-tumoral activity of endostatin by diminishing the inflammatory and immunosuppressive changes that endostatin triggers in the tumor microenvironment [230]. The expression and function of endostatin during fracture repair are negatively altered by the proteoglycan biglycan to favor angiogenesis required for bone repair [231].

Furthermore several ECM fragments may regulate the same biological process via different or common mechanisms suggesting that they may be more efficient in combination. Endostatin and anastellin inhibit angiogenesis by regulating different steps of this process and additively inhibit the migration of endothelial cells induced by VEGF [232]. However it is not always the case. Endostatin and endorepellin bind to integrins and VEGFR2, are both anti-angiogenic and anti-tumoral, are internalized by endothelial cells [43] and bind to each other but endorepellin counteracts the anti-angiogenic activity of endostatin [159]. It is thus important to take into account the full repertoire of ECM fragments comprising fragments with identical or opposite biological activities and their interaction networks as discussed above to predict interferences and/or possible synergies. It is also important when designing therapeutic strategies to integrate the biological context, *i.e.* growth factors and cytokines modulating the process targeted by the ECM fragments [233]. If the combination of ECM fragments is not always an efficient therapeutic strategy, one of them, endostatin, has been successfully used in combination with chemotherapy or radiotherapy *in vitro* on esophageal squamous cell carcinoma [234] and melanoma cell lines [235] and in patients with advanced non-small cell lung cancer [217,236–238] and breast cancer [239]. Endostatin, when associated with an antibody directed against placental growth factor, inhibits ocular

hemangiomas [240]. Another aspect to take into account for using ECM fragments as drugs is their delivery. Most of them have been delivered by injection for *in vivo* assays. However an endostatin peptide has been found to be anti-fibrotic when administered orally in a model of pulmonary fibrosis [241] and osteopontin fragments delivered intranasally confer neuroprotection in stroke [242,243]. Their engineering, delivery and targeting have been recently reviewed [5] and recent studies emphasize the use of gold and chitosan nanoparticles for endostatin delivery [244–246].

Another active field of research is to use ECM fragments as vaccines as investigated for fibronectin fragments and glypican-3 peptides [247]. Glypican-3, a cell surface heparan sulfate proteoglycan with a glycophosphatidyl anchor, is overexpressed in hepatocellular carcinoma but not in normal adult tissues. It is a prognostic factor and an immunotherapeutic target in hepatocellular carcinoma (see [248–250] for reviews). Glypican-3 peptides have been screened as peptide vaccines in mice and a glypican-3-derived cytotoxic T-lymphocyte epitope peptide has been identified [251]. Phase I [252] and II [253] clinical trials have been carried out with a glypican-3 vaccine in hepatocellular carcinoma (see [254] for review). This vaccine is safe and well tolerated [254] and improves the one year recurrence rate in a group of 41 patients [253]. Glypican-3 peptide has also been tested in association with other tumor-antigens in patients with hepatocellular carcinoma [255]. Furthermore promising results have been obtained with a cytotoxic T clone specific of the glypican-3 peptide (144-152) in ovarian clear cell carcinoma cell lines [256] and in patients [257,258]. Fragments of fibronectin III extra domain A of fibronectin agonizing TLR4 and immobilized within a fibrin matrix model with antigenic peptides stimulate cytotoxic T cell responses in cancer models, which suggests that they may be used for cancer immunotherapy [224]. In addition the antiangiogenic effect of endostatin is increased in rat glioma by dendritic cell vaccination [259].

ECM fragments released in biological fluids during ECM remodeling can be used to decipher the molecular contribution of the ECMin diseases and as diagnostic or prognostic biomarkers. Numerous studies aiming at measuring ECM fragments/peptides in various diseases and in a variable number of patients have been performed. This requires the development of appropriate assays to measure the concentration of ECM fragments in biological fluids as done for MMP-derived collagen II neoepitope [260], tetrastatin [261] and the NC1 domain of collagen XIX [262]. Most studies focused on measurements of ECM fragments in serum but their presence was also investigated in synovial fluid, bronchoalveolar lavage [261], cerebrospinal fluid [263], amniotic fluid [262], and tissue/tumor extracts [261,262]. Several examples of ECM fragments as promising markers in large-scale studies are given below. A systematic review and meta-analysis of 12 case-control studies, including 736 patients and 350 control subjects, has shown that serum levels of endostatin correlate with the more aggressive type of gastric cancer [264]. Increased serum levels of endotrophin predict response to two insulin sensitisers (balaglitazone and pioglitazone) in patients with diabetes (~300 patients) and identify those who may take advantage from PPARγ agonist treatment [265,266]. The level of endotrophin is also associated with increased mortality in chronic kidney disease as shown in a cohort of 500 patients [267]. Furthermore neoepitopes defined as post-translational modifications of proteins generated by citrullination, nitrosylation, glycosylation and isomerization protease cleavage can be used as serological biomarkers in atherosclerosis [268] portal hypertension [269], muscular dystrophies and other myopathies [270] and in joint degenerative diseases [271] (see [16,272] for reviews). However, all these neoepitopes derived from ECM degradation do not have biological activities of their own in contrast to those described in this review.

Conclusion and perspectives

The remodeling of the ECMby several protease families releases a number of bioactive fragments which regulate biological processes such as autophagy, angiogenesis, adipogenesis, fibrosis, tumor growth, metastasis and wound healing. They are potential drugs but their translation into drugs is challenging and would take advantage of an integrative approach to optimize the design of pre-clinical and clinical studies. This could be done by building the contextualized interaction network of the fragment repertoire including their parent proteins, remodeling proteases, their receptors and their binding partners, as done for endostatin [273,274], and by using mathematical disease models such as the multi-scale model simulating the changes of tumor microvasculature and microenvironment in response to endostatin [275]. A model based on four-variable ordinary differential equations has also been proposed to recapitulate the interactions between pro- and anti-inflammatory cytokines, MMPs and fibronectin fragments released in the course of osteoarthritis [276]. Furthermore, the identification of all ECM substrates of proteinases is a prerequisite in order to build the comprehensive map of the ECM bioactive fragments, and to understand their coordination at the molecular level. Quantitative proteomics and mass spectrometry associated with Isotope-Coded Affinity Tags (ICAT) and Isobaric Tags for Relative and Absolute Quantification (iTRAQ) have been successfully used to identify a broad range of substrates of MMPs in cellular context [277] such as MMP-2 [278], MMP-9 [279], MMP-10 (time-resolved analysis, [280]), MMP-25 [281] and meprin metalloproteinases [282], but the biological activities of the fragments generated by these enzymes remain to be investigated.

Acknowledgements: We are grateful to Adriana E. Miele for her critical reading of the manuscript. The work performed by the authors have been supported by la Fondation pour la Recherche Médicale [Grant n° DBI20141231336 to SRB], and by the Institut Français de

Bioinformatique [Call 2015 to SRB]. We apologize to many colleagues, whose work could not have been cited in due to space limitations.

Contributions: Sylvie Ricard-Blum wrote the paper. Sylvain D. Vallet performed literature searches on ECM fragments in clinical trials, drew the figures and formatted the manuscript. All authors have approved the final version of the article.

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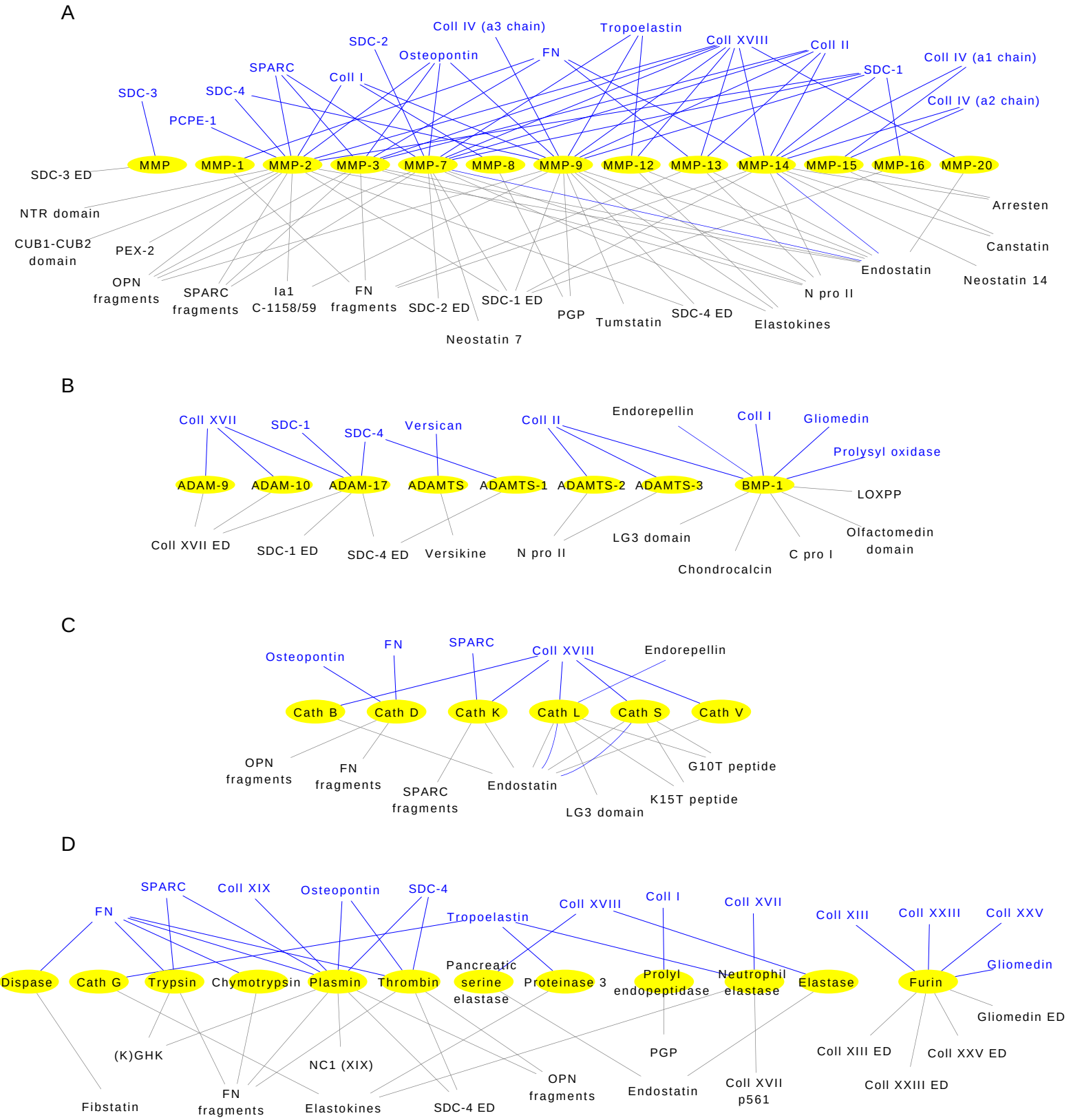
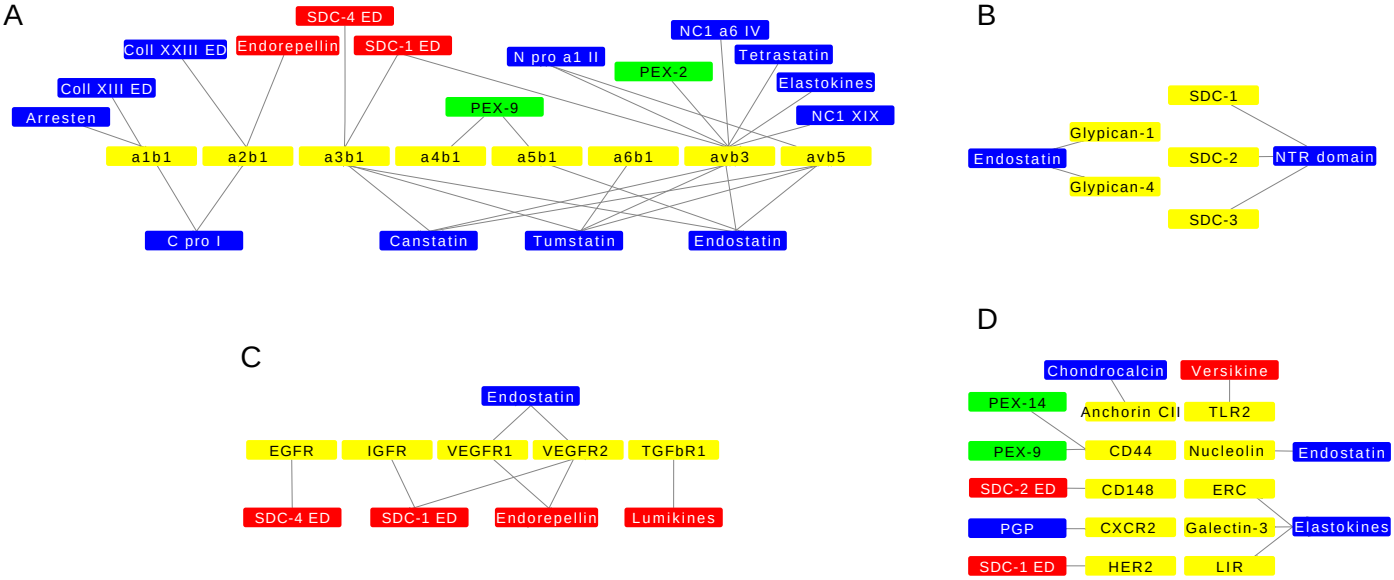
FIGURE LEGENDS

Figure 1: Major protease families generating ECM bioactive fragments from ECM proteins: A) Matrix Metalloproteinases (MMPs), B) Other metalloproteinases (ADAMs, ADMTSs, and BMP-1), C) Cysteine and aspartate proteinases, D) Serine and other proteinases. Blue links connect ECM protein substrates and the proteinases, which cleave them into bioactive fragments. Grey links connect proteinases to the released ECM bioactive fragments. (BMP-1: Bone morphogenetic protein-1, Cath: Cathepsins, Coll: Collagen, C Pro: C-propeptide of procollagen, ED: ectodomain, FN: fibronectin, GPC: glypicans, LOXPP: propeptide of lysyl oxidase, OPN: osteopontin, PCPE-1: procollagen C-proteinase-1, PEX: hemopexin domain of MMPs, NC1: NC1 domain, N-Pro: N-propeptide of procollagen, NTR: netrin, SDC: syndecan, SPARC: Secreted Protein Acidic and Rich in Cysteine).

Figure 2: Major (co)-receptors families interacting with ECM bioactive fragments: A) Integrins, B) Cell surface proteoglycans, C) Growth factor receptors, and D) Miscellaneous cell surface proteins. (CD: cluster differentiation, Coll: Collagen, C Pro: C-propeptide of procollagen, CXCR2: C-X-C chemokine receptor type 2, ED: ectodomain, ERC: elastin complex receptor, GPC: glypicans, HER2: Receptor tyrosine-protein kinase erbB-2, LIR: lactose insensitive receptor, PEX: hemopexin domain of MMPs, NC1: NC1 domain, N-Pro: N-propeptide of procollagen, NTR: netrin, SDC: syndecan, VEGF: vascular endothelial growth factor, TGBb1: transforming growth factor β1, TLR2: toll-like receptor-2).


A
Coll IV (a3 chain)
Tropoelastin
SDC-2
Coll XVIII
Coll II
Osteopontin
FN
Coll IV (a1 chain)
SPARC
Coll I
SDC-1
SDC-3
SDC-4
Coll IV (a2 chain)
PCPE-1
MMP
MMP-1
MMP-2
MMP-3
MMP-7
MMP-8
MMP-9
MMP-12
MMP-13
MMP-14
MMP-15
MMP-16
MMP-20
SDC-3 ED
Arresten
NTR domain
CUB1-CUB2 domain
PEX-2
Canstatin
Endostatin
OPN fragments
SPARC fragments
Ia1 C-1158/59
FN fragments
SDC-2 ED
SDC-1 ED
N pro II
Neostatin 14
PGP
Tumstatin
SDC-4 ED
Elastokines
Neostatin 7
B
Coll XVII
SDC-1
SDC-4
Versican
Coll II
Endorepellin
Coll I
Gliomedin
Prolysyl oxidase
ADAM-9
ADAM-10
ADAM-17
ADAMTS
ADAMTS-1
ADAMTS-2
ADAMTS-3
BMP-1
LOXPP
Coll XVII ED
SDC-1 ED
SDC-4 ED
Versikine
N pro II
LG3 domain
Olfactomedin domain
Chondrocalcin
C pro I
C
Osteopontin
FN
SPARC
Coll XVIII
Endorepellin
Cath B
Cath D
Cath K
Cath L
Cath S
Cath V
OPN fragments
FN fragments
SPARC fragments
Endostatin
G10T peptide
K15T peptide
LG3 domain
D
SPARC
Coll XIX
Osteopontin
SDC-4
FN
Tropoelastin
Coll XVIII
Coll I
Coll XVII
Coll XIII
Coll XXIII
Coll XXV
Pancreatic serine elastase
Gliomedin
Dispase
Cath G
Trypsin
Chymotrypsin
Plasmin
Thrombin
Proteinase 3
Prolyl endopeptidase
Neutrophil elastase
Elastase
Furin
Gliomedin ED
(K)GHK
NC1 (XIX)
PGP
Coll XIII ED
Coll XXV ED
Coll XXIII ED
OPN fragments
Endostatin
Coll XVII p561
Fibstatin
FN fragments
Elastokines
SDC-4 ED


A
SDC-4 ED
Coll XXIII ED
Endorepellin
SDC-1 ED
NC1 a6 IV
N pro a1 II
Tetrastatin
PEX-2
Elastokines
Coll XIII ED
Arresten
PEX-9
NC1 XIX
a1b1
a2b1
a3b1
a4b1
a5b1
a6b1
avb3
avb5
C pro I
Canstatin
Tumstatin
Endostatin
B
SDC-1
Glypican-1
Endostatin
SDC-2
NTR domain
Glypican-4
SDC-3
C
Endostatin
EGFR
IGFR
VEGFR1
VEGFR2
TGFbR1
SDC-4 ED
SDC-1 ED
Endorepellin
Lumikines
D
Chondrocalcin
Versikine
PEX-14
Anchorin CII
TLR2
PEX-9
CD44
Nucleolin
Endostatin
SDC-2 ED
CD148
ERC
PGP
CXCR2
Galectin-3
Elastokines
SDC-1 ED
HER2
LIR