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**FRAGMENTS GENERATED UPON EXTRACELLULAR MATRIX REMODELING:  
BIOLOGICAL REGULATORS AND POTENTIAL DRUGS**

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**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; TGF $\beta$ R1, Transforming Growth Factor  $\beta$  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. ECM is 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**.

| <b>ECM proteins or protein families generating ECM fragments</b>    | <b>References</b>              |
|---|--------------------------------|
| 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]                        |
| <b>Individual ECM fragments</b>                                     | <b>References</b>              |
| 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 |
| <b>Protease or protease families generating ECM fragments</b>       | <b>References</b>              |
| Several protease families   | [6]                            |
| MMPs  | [11]                           |
| MMP-12  | [17]                           |
| <b>Biological processes and diseases regulated by ECM fragments</b> | <b>References</b>              |
| 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  $\alpha 3\beta 1$  integrins [66] and synaptic plasticity [67]. The NC1 domain of the  $\alpha 2$  (canstatin),  $\alpha 3$  (tumstatin) and  $\alpha 6$  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 I $\alpha$ 1 C-1158/59 fragment released from collagen I by MMP-2 and MMP-9 increases angiogenesis and promotes wound 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<sub>82</sub>-

<sup>130</sup> and SSTN<sub>92-119</sub>, inhibit angiogenesis *in vitro* and *in vivo* and SSTN<sub>82-130</sub> decreases tumor growth in mice [89]. SSTN<sub>92-119</sub> also inhibits the ternary complex comprised of syndecan-1, IGF1R and  $\alpha\beta 3/\alpha\beta 5$  integrins in tumorigenesis and angiogenesis [53,90]. Furthermore SSTN peptides capturing the  $\beta 1$  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  $\alpha 5\beta 1$  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].



| <b>PARENT PROTEIN</b> | <b>ECM FRAGMENTS</b>             | <b>(CO)-RECEPTORS</b>  | <b>REFERENCES</b>             |
|-----------------------|----------------------------------|--|-------------------------------|
| <b>ECM Proteins</b>   |                                  |  |                               |
| Collagen I            | Proline-Glycine-Proline          | CXCR2  | [101,102]                     |
|                       | I $\alpha$ 1 C-1158/59 fragment  | -  | [72]                          |
|                       | C-propeptide                     | $\alpha$ 1 $\beta$ 1 integrin<br>$\alpha$ 2 $\beta$ 1 integrin   | [103–107]                     |
| Collagen II           | N-propeptide                     | $\alpha$ v $\beta$ 3 integrin<br>$\alpha$ v $\beta$ 5 integrin   | [108–110]                     |
|                       | C-propeptide (chondrocalcin)     | Anchorin CII   | [111–113]                     |
| Collagen IV           | Arresten ( $\alpha$ 1 chain)     | $\alpha$ 1 $\beta$ 1 integrin  | [114,115]                     |
|                       | Canstatin ( $\alpha$ 2 chain)    | $\alpha$ 3 $\beta$ 1 integrin<br>$\alpha$ v $\beta$ 3 integrin<br>$\alpha$ v $\beta$ 5 integrin  | [114,116,117]                 |
|                       | Tumstatin ( $\alpha$ 3 chain)    | $\alpha$ 3 $\beta$ 1 integrin<br>$\alpha$ 6 $\beta$ 1 integrin<br>$\alpha$ v $\beta$ 3 integrin<br>$\alpha$ v $\beta$ 5 integrin                             | [118–121]                     |
|                       | Tetrastatin ( $\alpha$ 4 chain)  | $\alpha$ v $\beta$ 3 integrin  | [122]                         |
|                       | NC1 domain ( $\alpha$ 6 chain)   | $\alpha$ v $\beta$ 3 integrin  | [116]                         |
| Collagen VI           | Endotrophin ( $\alpha$ 3 chain)  | -  | [123]                         |
| Collagen VIII         | Vastatin ( $\alpha$ 1 chain)     | -  | [124–126]                     |
| Collagen XIII         | Ectodomain ( $\alpha$ 1 chain)   | $\alpha$ 1 $\beta$ 1 integrin  | [127,128]                     |
| Collagen XV           | Restin ( $\alpha$ 1 chain)       | -  | [129]                         |
| Collagen XVII         | Peptide p561 ( $\alpha$ 1 chain) | -  | [130]                         |
|                       | Ectodomain ( $\alpha$ 1 chain)   | -  | [131]                         |
| Collagen XVIII        | Endostatin ( $\alpha$ 1 chain)   | $\alpha$ 5 $\beta$ 1 integrin<br>$\alpha$ v $\beta$ 3 integrin<br>$\alpha$ v $\beta$ 5 integrin<br>VEGFR1<br>VEGFR2<br>Glypican-1<br>Glypican-4<br>Nucleolin | [132–141]                     |
|                       | *G10T peptide<br>* K15T peptide  | -  | [142]                         |
|                       | Neostatins 7 and 14              | -  | [143,144]                     |
|                       | Collagen XIX                     | NC1 domain ( $\alpha$ 1 chain)   | $\alpha$ v $\beta$ 3 integrin |
| Collagen XXIII        | Ectodomain ( $\alpha$ 1 chain)   | $\alpha$ 2 $\beta$ 1 integrin  | [146,147]                     |
| Collagen XXV          | Ectodomain ( $\alpha$ 1 chain)   | -  | [148]                         |
| Elastin               | Elastokines                      | $\alpha$ v $\beta$ 3 integrin<br>Elastin Receptor<br>Complex<br>Galectin-3 receptor  | [19,149–151]                  |

|  |  | Lactose-insensitive receptor                             |  |
|--|--|--|--|
| Fibronectin                                | FN-gelatinase  |  |  |
|  | FN-lamininase  | -  | [21,152,153]   |
|  | FN-fibronectinase  |  |  |
|  | FN-type IV collagenase                                   |  |  |
|  | Anastellin   | -  | [154]  |
| Gliomedin                                  | Fibstatin (C-terminal heparin binding domain)            | -  | [96]   |
|  | Ectodomain   |  |  |
| Procollagen C-proteinase-enhancer-1        | Olfactomedin domain                                      | -  | [155,156]  |
|  | CUB1-CUB2 domain   | -  | [157]  |
|  | NTR domain   | Syndecan-1<br>Syndecan-2<br>Syndecan-3                   | [157,158]  |
|  | <b>Proteoglycans</b>                                     |  |  |
|  | Lumcorin   |  | [84]   |
| Lumican                                    | Lumikines (LumC <sub>13</sub> )                          | TGFβR1<br>(Activin receptor-like kinase 5 ALK5)          | [76,77]  |
|  | Perlecan<br>*Generated from endorepellin                 | Endorepellin   | α2β1 integrin<br>VEGFR1<br>VEGFR2                      |
| *LG3 domain                                |  |  | [162,163]  |
| Syndecan-1                                 | Ectodomain   | HER2<br>α3β1 integrin<br>αvβ3 integrin<br>IGFR<br>VEGFR2 | [53,89,91,164–168]                                     |
|  | Synstatin <sub>92-119</sub> (or SSTN <sub>IGF-1R</sub> ) | -  | [53,90,168]  |
|  | SSTN <sub>82-130</sub>                                   | -  | [89]   |
|  | SSTN <sub>210-240</sub>                                  | -  | [91,168]   |
|  | Syndecan-2   | Ectodomain   | CD148 (Receptor-type tyrosine-protein phosphatase eta) |
| Syndecan-3                                 | Ectodomain   | -  | [171]  |
| Syndecan-4                                 | Ectodomain   | EGFR<br>α3β1 integrin                                    | [164,168,172]  |
|  | SSTN <sub>87-131</sub>                                   | -  | [168]  |
| Versican                                   | Versikine  | TLR2 (+ other unidentified receptors?)                   | [28,87,173]  |
| <b>Cross-linking and degrading enzymes</b> |  |  |  |
| Lysyl oxidase                              | Propeptide   | -  | [174,175]  |
| MMP-2                                      | PEX (hemopexin)  | αvβ3 integrin  | [176]  |

|        |                        |  |           |
|--------|------------------------|--|-----------|
|        | domain)                |  |           |
| MMP-9  | PEX (hemopexin domain) | $\alpha 4\beta 1$ integrin<br>$\alpha 5\beta 1$ integrin<br>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, TGF $\beta$ R1: Transforming Growth Factor  $\beta$  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<sup>TM</sup>) 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 ECM protein 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  $\beta$ 1 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 TGF $\beta$ R1 to promote

wound healing [76,77]. The role played by receptors is context-dependent. Anastellin requires heparan sulfate proteoglycans and integrins (likely  $\alpha 5\beta 1$  integrin) to promote aortic smooth muscle cell adhesion and to activate ERK1/2 [203], but activates p38 MAP kinase independently of  $\beta 1$  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 glycosphosphatidyl 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 ECM in 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 sensitizers (balaglitazone and pioglitazone) in patients with diabetes (~300 patients) and identify those who may take advantage from PPAR $\gamma$  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 ECM by 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.

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## References

- [1] M.A. Karsdal, M.J. Nielsen, J.M. Sand, K. Henriksen, F. Genovese, A.-C. Bay-Jensen, V. Smith, J.I. Adamkewicz, C. Christiansen, D.J. Leeming, Extracellular matrix remodeling: the common denominator in connective tissue diseases. Possibilities for evaluation and current understanding of the matrix as more than a passive architecture, but a key player in tissue failure, *Assay Drug Dev Technol.* 11 (2013) 70–92. doi:10.1089/adt.2012.474.
- [2] K.T. Tran, P. Lamb, J.-S. Deng, Matrikines and matricryptins: Implications for cutaneous cancers and skin repair, *J. Dermatol. Sci.* 40 (2005) 11–20. doi:10.1016/j.jdermsci.2005.05.001.
- [3] S. Ricard-Blum, L. Ballut, Matricryptins derived from collagens and proteoglycans, *Front Biosci (Landmark Ed)*. 16 (2011) 674–697.
- [4] S. Ricard-Blum, R. Salza, Matricryptins and matrikines: biologically active fragments of the extracellular matrix, *Exp. Dermatol.* 23 (2014) 457–463. doi:10.1111/exd.12435.
- [5] S. Ricard-Blum, S.D. Vallet, Matricryptins Network with Matricellular Receptors at the Surface of Endothelial and Tumor Cells, *Front Pharmacol.* 7 (2016) 11. doi:10.3389/fphar.2016.00011.
- [6] S. Ricard-Blum, S.D. Vallet, Proteases decode the extracellular matrix cryptome, *Biochimie.* 122 (2016) 300–313. doi:10.1016/j.biochi.2015.09.016.
- [7] J.K. Burgess, M. Weckmann, Matrikines and the lungs, *Pharmacol. Ther.* 134 (2012) 317–337. doi:10.1016/j.pharmthera.2012.02.002.
- [8] C. Bonnans, J. Chou, Z. Werb, Remodelling the extracellular matrix in development and disease, *Nat. Rev. Mol. Cell Biol.* 15 (2014) 786–801. doi:10.1038/nrm3904.
- [9] J.C. Monboisse, J.B. Oudart, L. Ramont, S. Brassart-Pasco, F.X. Maquart, Matrikines from basement membrane collagens: a new anti-cancer strategy, *Biochim. Biophys. Acta.* 1840 (2014) 2589–2598. doi:10.1016/j.bbagen.2013.12.029.
- [10] M. Abdul Roda, A.M. Fernstrand, F.A. Redegeld, J.E. Blalock, A. Gaggar, G. Folkerts, The matrikine PGP as a potential biomarker in COPD, *Am. J. Physiol. Lung Cell Mol. Physiol.* 308 (2015) L1095–1101. doi:10.1152/ajplung.00040.2015.
- [11] J.M. Wells, A. Gaggar, J.E. Blalock, MMP generated matrikines, *Matrix Biol.* 44–46 (2015) 122–129. doi:10.1016/j.matbio.2015.01.016.
- [12] L. Sorokin, The impact of the extracellular matrix on inflammation, *Nat. Rev. Immunol.* 10 (2010) 712–723. doi:10.1038/nri2852.

- [13] G.E. Davis, K.J. Bayless, M.J. Davis, G.A. Meininger, Regulation of tissue injury responses by the exposure of matricryptic sites within extracellular matrix molecules, *Am. J. Pathol.* 156 (2000) 1489–1498. doi:10.1016/S0002-9440(10)65020-1.
- [14] F.X. Maquart, A. Siméon, S. Pasco, J.C. Monboisse, [Regulation of cell activity by the extracellular matrix: the concept of matrikines], *J. Soc. Biol.* 193 (1999) 423–428.
- [15] F.-X. Maquart, S. Pasco, L. Ramont, W. Hornebeck, J.-C. Monboisse, An introduction to matrikines: extracellular matrix-derived peptides which regulate cell activity. Implication in tumor invasion, *Crit. Rev. Oncol. Hematol.* 49 (2004) 199–202. doi:10.1016/j.critrevonc.2003.06.007.
- [16] F. Genovese, M.A. Karsdal, Protein degradation fragments as diagnostic and prognostic biomarkers of connective tissue diseases: understanding the extracellular matrix message and implication for current and future serological biomarkers, *Expert Rev Proteomics.* 13 (2016) 213–225. doi:10.1586/14789450.2016.1134327.
- [17] S. Taddese, A.S. Weiss, G. Jahreis, R.H.H. Neubert, C.E.H. Schmelzer, In vitro degradation of human tropoelastin by MMP-12 and the generation of matrikines from domain 24, *Matrix Biol.* 28 (2009) 84–91. doi:10.1016/j.matbio.2008.12.002.
- [18] A.C. Mora Huertas, C.E.H. Schmelzer, W. Hoehenwarter, F. Heyroth, A. Heinz, Molecular-level insights into aging processes of skin elastin, *Biochimie.* 128–129 (2016) 163–173. doi:10.1016/j.biochi.2016.08.010.
- [19] A. Heinz, M.C. Jung, L. Duca, W. Sippl, S. Taddese, C. Ihling, A. Rusciani, G. Jahreis, A.S. Weiss, R.H.H. Neubert, C.E.H. Schmelzer, Degradation of tropoelastin by matrix metalloproteinases--cleavage site specificities and release of matrikines, *FEBS J.* 277 (2010) 1939–1956. doi:10.1111/j.1742-4658.2010.07616.x.
- [20] M.L. Barilla, S.E. Carsons, Fibronectin fragments and their role in inflammatory arthritis, *Semin. Arthritis Rheum.* 29 (2000) 252–265.
- [21] M.A. Liz, M.M. Sousa, Deciphering cryptic proteases, *Cell. Mol. Life Sci.* 62 (2005) 989–1002. doi:10.1007/s00018-005-4544-2.
- [22] T. Yasuda, Cartilage destruction by matrix degradation products, *Mod Rheumatol.* 16 (2006) 197–205. doi:10.1007/s10165-006-0490-6.
- [23] M. Pagano, M. Reboud-Ravaux, Cryptic activities of fibronectin fragments, particularly cryptic proteases, *Front Biosci (Landmark Ed).* 16 (2011) 698–706.
- [24] R.S. Aziz-Seible, C.A. Casey, Fibronectin: functional character and role in alcoholic liver disease, *World J. Gastroenterol.* 17 (2011) 2482–2499. doi:10.3748/wjg.v17.i20.2482.
- [25] V. Iorio, L.D. Troughton, K.J. Hamill, Laminins: Roles and Utility in Wound Repair, *Adv Wound Care (New Rochelle).* 4 (2015) 250–263. doi:10.1089/wound.2014.0533.
- [26] Y. Kikkawa, K. Hozumi, F. Katagiri, M. Nomizu, H.K. Kleinman, J.E. Koblinski, Laminin-111-derived peptides and cancer, *Cell Adh Migr.* 7 (2013) 150–256. doi:10.4161/cam.22827.
- [27] P. Rousselle, K. Beck, Laminin 332 processing impacts cellular behavior, *Cell Adh Migr.* 7 (2013) 122–134. doi:10.4161/cam.23132.
- [28] S. Nandadasa, S. Foulcer, S.S. Apte, The multiple, complex roles of versican and its proteolytic turnover by ADAMTS proteases during embryogenesis, *Matrix Biol.* 35 (2014) 34–41. doi:10.1016/j.matbio.2014.01.005.
- [29] Y.A. Gao, R. Agnihotri, C.P.H. Vary, L. Liaw, Expression and characterization of recombinant osteopontin peptides representing matrix metalloproteinase proteolytic fragments, *Matrix Biol.* 23 (2004) 457–466. doi:10.1016/j.matbio.2004.09.003.
- [30] T.E. Kruger, A.H. Miller, A.K. Godwin, J. Wang, Bone sialoprotein and osteopontin in bone metastasis of osteotropic cancers, *Crit. Rev. Oncol. Hematol.* 89 (2014) 330–341. doi:10.1016/j.critrevonc.2013.08.013.

- [31] L.M. Castello, D. Raineri, L. Salmi, N. Clemente, R. Vaschetto, M. Quaglia, M. Garzaro, S. Gentili, P. Navalesi, V. Cantaluppi, U. Dianzani, A. Aspesi, A. Chiocchetti, Osteopontin at the Crossroads of Inflammation and Tumor Progression, *Mediators Inflamm.* 2017 (2017) 4049098. doi:10.1155/2017/4049098.
- [32] M. Hasegawa, T. Yoshida, A. Sudo, Role of tenascin-C in articular cartilage, *Mod Rheumatol.* (2017) 1–6. doi:10.1080/14397595.2017.1349560.
- [33] K.L. Aya, R. Stern, Hyaluronan in wound healing: rediscovering a major player, *Wound Repair Regen.* 22 (2014) 579–593. doi:10.1111/wrr.12214.
- [34] A.C. Petrey, C.A. de la Motte, Hyaluronan, a crucial regulator of inflammation, *Front Immunol.* 5 (2014) 101. doi:10.3389/fimmu.2014.00101.
- [35] J.M. Cyphert, C.S. Trempus, S. Garantziotis, Size Matters: Molecular Weight Specificity of Hyaluronan Effects in Cell Biology, *Int J Cell Biol.* 2015 (2015) 563818. doi:10.1155/2015/563818.
- [36] S. Ghosh, S.A. Hoselton, G.P. Dorsam, J.M. Schuh, Hyaluronan fragments as mediators of inflammation in allergic pulmonary disease, *Immunobiology.* 220 (2015) 575–588. doi:10.1016/j.imbio.2014.12.005.
- [37] S.A. Wickström, K. Alitalo, J. Keski-Oja, Endostatin signaling and regulation of endothelial cell-matrix interactions, *Adv. Cancer Res.* 94 (2005) 197–229. doi:10.1016/S0065-230X(05)94005-0.
- [38] J. Folkman, Antiangiogenesis in cancer therapy--endostatin and its mechanisms of action, *Exp. Cell Res.* 312 (2006) 594–607. doi:10.1016/j.yexcr.2005.11.015.
- [39] A.V. Digtyar, N.V. Pozdnyakova, N.B. Feldman, S.V. Lutsenko, S.E. Severin, Endostatin: current concepts about its biological role and mechanisms of action, *Biochemistry Mosc.* 72 (2007) 235–246.
- [40] Y. Fu, H. Tang, Y. Huang, N. Song, Y. Luo, Unraveling the mysteries of endostatin, *IUBMB Life.* 61 (2009) 613–626. doi:10.1002/iub.215.
- [41] T. Behl, A. Kotwani, Possible role of endostatin in the antiangiogenic therapy of diabetic retinopathy, *Life Sci.* 135 (2015) 131–137. doi:10.1016/j.lfs.2015.06.017.
- [42] A. Walia, J.F. Yang, Y.-H. Huang, M.I. Rosenblatt, J.-H. Chang, D.T. Azar, Endostatin's emerging roles in angiogenesis, lymphangiogenesis, disease, and clinical applications, *Biochim. Biophys. Acta.* 1850 (2015) 2422–2438. doi:10.1016/j.bbagen.2015.09.007.
- [43] C. Poluzzi, R.V. Iozzo, L. Schaefer, Endostatin and endorepellin: A common route of action for similar angiostatic cancer avengers, *Adv. Drug Deliv. Rev.* 97 (2016) 156–173. doi:10.1016/j.addr.2015.10.012.
- [44] S. Douglass, A. Goyal, R.V. Iozzo, The role of perlecan and endorepellin in the control of tumor angiogenesis and endothelial cell autophagy, *Connect. Tissue Res.* 56 (2015) 381–391. doi:10.3109/03008207.2015.1045297.
- [45] M.A. Gubbiotti, R.V. Iozzo, Proteoglycans regulate autophagy via outside-in signaling: an emerging new concept, *Matrix Biol.* 48 (2015) 6–13. doi:10.1016/j.matbio.2015.10.002.
- [46] M.A. Gubbiotti, T. Neill, R.V. Iozzo, A current view of perlecan in physiology and pathology: A mosaic of functions, *Matrix Biol.* 57–58 (2017) 285–298. doi:10.1016/j.matbio.2016.09.003.
- [47] J. Park, P.E. Scherer, Endotrophin in the tumor stroma: a new therapeutic target for breast cancer?, *Expert Rev Anticancer Ther.* 13 (2013) 111–113. doi:10.1586/era.12.164.
- [48] B. Cabilia, S. Andrade, M.C. Carreira, F.F. Casanueva, A.B. Crujeiras, A role for novel adipose tissue-secreted factors in obesity-related carcinogenesis, *Obes Rev.* 17 (2016) 361–376. doi:10.1111/obr.12377.

- [49] Y. Hamano, R. Kalluri, Tumstatin, the NC1 domain of alpha3 chain of type IV collagen, is an endogenous inhibitor of pathological angiogenesis and suppresses tumor growth, *Biochem. Biophys. Res. Commun.* 333 (2005) 292–298. doi:10.1016/j.bbrc.2005.05.130.
- [50] W. Hornebeck, A. Robinet, L. Duca, F. Antonicelli, J. Wallach, G. Bellon, The elastin connection and melanoma progression, *Anticancer Res.* 25 (2005) 2617–2625.
- [51] A. Sudhakar, C.S. Boosani, Inhibition of tumor angiogenesis by tumstatin: insights into signaling mechanisms and implications in cancer regression, *Pharm. Res.* 25 (2008) 2731–2739. doi:10.1007/s11095-008-9634-z.
- [52] G. De Rossi, J.R. Whiteford, A novel role for syndecan-3 in angiogenesis, *F1000Res.* 2 (2013) 270. doi:10.12688/f1000research.2-270.v1.
- [53] A.C. Rapraeger, Synstatin: a selective inhibitor of the syndecan-1-coupled IGF1R- $\alpha$ v $\beta$ 3 integrin complex in tumorigenesis and angiogenesis, *FEBS J.* 280 (2013) 2207–2215. doi:10.1111/febs.12160.
- [54] G. De Rossi, A.R. Evans, E. Kay, A. Woodfin, T.R. McKay, S. Nourshargh, J.R. Whiteford, Shed syndecan-2 inhibits angiogenesis, *J. Cell. Sci.* 127 (2014) 4788–4799. doi:10.1242/jcs.153015.
- [55] G. Bellon, L. Martiny, A. Robinet, Matrix metalloproteinases and matrikines in angiogenesis, *Crit. Rev. Oncol. Hematol.* 49 (2004) 203–220. doi:10.1016/j.critrevonc.2003.10.004.
- [56] P. Maurice, S. Blaise, S. Gayral, L. Debelle, M. Laffargue, W. Hornebeck, L. Duca, Elastin fragmentation and atherosclerosis progression: the elastokine concept, *Trends Cardiovasc. Med.* 23 (2013) 211–221. doi:10.1016/j.tcm.2012.12.004.
- [57] B. Coquerel, F. Poyer, F. Torossian, V. Dulong, G. Bellon, I. Dubus, A. Reber, J.-P. Vannier, Elastin-derived peptides: matrikines critical for glioblastoma cell aggressiveness in a 3-D system, *Glia.* 57 (2009) 1716–1726. doi:10.1002/glia.20884.
- [58] J. Park, P.E. Scherer, Endotrophin - a novel factor linking obesity with aggressive tumor growth, *Oncotarget.* 3 (2012) 1487–1488. doi:10.18632/oncotarget.796.
- [59] S. Pasco, L. Ramont, F.-X. Maquart, J.C. Monboisse, Control of melanoma progression by various matrikines from basement membrane macromolecules, *Crit. Rev. Oncol. Hematol.* 49 (2004) 221–233. doi:10.1016/j.critrevonc.2003.09.006.
- [60] S. Akthar, D.F. Patel, R.C. Beale, T. Peiró, X. Xu, A. Gaggar, P.L. Jackson, J.E. Blalock, C.M. Lloyd, R.J. Snelgrove, Matrikines are key regulators in modulating the amplitude of lung inflammation in acute pulmonary infection, *Nat Commun.* 6 (2015) 8423. doi:10.1038/ncomms9423.
- [61] A. Gaggar, N. Weathington, Bioactive extracellular matrix fragments in lung health and disease, *J. Clin. Invest.* 126 (2016) 3176–3184. doi:10.1172/JCI83147.
- [62] C. Aldag, D. Nogueira Teixeira, P.S. Leventhal, Skin rejuvenation using cosmetic products containing growth factors, cytokines, and matrikines: a review of the literature, *Clin Cosmet Investig Dermatol.* 9 (2016) 411–419. doi:10.2147/CCID.S116158.
- [63] T.H. Barker, The role of ECM proteins and protein fragments in guiding cell behavior in regenerative medicine, *Biomaterials.* 32 (2011) 4211–4214. doi:10.1016/j.biomaterials.2011.02.027.
- [64] S. Meiners, M.L.T. Mercado, Functional peptide sequences derived from extracellular matrix glycoproteins and their receptors: strategies to improve neuronal regeneration, *Mol. Neurobiol.* 27 (2003) 177–196. doi:10.1385/MN:27:2:177.
- [65] S. Blaise, B. Romier, C. Kawecki, M. Ghirardi, F. Rabenoelina, S. Baud, L. Duca, P. Maurice, A. Heinz, C.E.H. Schmelzer, M. Tarpin, L. Martiny, C. Garbar, M. Dauchez, L. Debelle, V. Durlach, Elastin-derived peptides are new regulators of insulin resistance development in mice, *Diabetes.* 62 (2013) 3807–3816. doi:10.2337/db13-0508.

- [66] J. Su, R.S. Stenbjorn, K. Gorse, K. Su, K.F. Hauser, S. Ricard-Blum, T. Pihlajaniemi, M.A. Fox, Target-derived matricryptins organize cerebellar synapse formation through  $\alpha 3\beta 1$  integrins, *Cell Rep.* 2 (2012) 223–230. doi:10.1016/j.celrep.2012.07.001.
- [67] T. Wang, A.G. Hauswirth, A. Tong, D.K. Dickman, G.W. Davis, Endostatin is a trans-synaptic signal for homeostatic synaptic plasticity, *Neuron.* 83 (2014) 616–629. doi:10.1016/j.neuron.2014.07.003.
- [68] M.A. Fox, J.R. Sanes, D.-B. Borza, V.P. Eswarakumar, R. Fässler, B.G. Hudson, S.W.M. John, Y. Ninomiya, V. Pedchenko, S.L. Pfaff, M.N. Rheault, Y. Sado, Y. Segal, M.J. Werle, H. Umemori, Distinct target-derived signals organize formation, maturation, and maintenance of motor nerve terminals, *Cell.* 129 (2007) 179–193. doi:10.1016/j.cell.2007.02.035.
- [69] J. Su, J. Chen, K. Lippold, A. Monavarfeshani, G.L. Carrillo, R. Jenkins, M.A. Fox, Collagen-derived matricryptins promote inhibitory nerve terminal formation in the developing neocortex, *J. Cell Biol.* 212 (2016) 721–736. doi:10.1083/jcb.201509085.
- [70] C. Feng, Y. Zhang, M. Yang, M. Lan, H. Liu, J. Wang, Y. Zhou, B. Huang, The matrikine N-acetylated proline-glycine-proline induces premature senescence of nucleus pulposus cells via CXCR1-dependent ROS accumulation and DNA damage and reinforces the destructive effect of these cells on homeostasis of intervertebral discs, *Biochim. Biophys. Acta.* 1863 (2017) 220–230. doi:10.1016/j.bbadis.2016.10.011.
- [71] G.A. Payne, J. Li, X. Xu, P. Jackson, H. Qin, D.M. Pollock, J.M. Wells, S. Oparil, M. Leesar, R.P. Patel, J.E. Blalock, A. Gaggar, The Matrikine Acetylated Proline-Glycine-Proline Couples Vascular Inflammation and Acute Cardiac Rejection, *Sci Rep.* 7 (2017) 7563. doi:10.1038/s41598-017-07610-0.
- [72] M.L. Lindsey, R.P. Iyer, R. Zamilpa, A. Yabluchanskiy, K.Y. DeLeon-Pennell, M.E. Hall, A. Kaplan, F.A. Zouein, D. Bratton, E.R. Flynn, P.L. Cannon, Y. Tian, Y.-F. Jin, R.A. Lange, D. Tokmina-Roszyk, G.B. Fields, L.E. de Castro Brás, A Novel Collagen Matricryptin Reduces Left Ventricular Dilation Post-Myocardial Infarction by Promoting Scar Formation and Angiogenesis, *J. Am. Coll. Cardiol.* 66 (2015) 1364–1374. doi:10.1016/j.jacc.2015.07.035.
- [73] J. Chen, D.-G. Liu, G. Yang, L.-J. Kong, Y.-J. Du, H.-Y. Wang, F.-D. Li, F.-H. Pei, J.-T. Song, Y.-J. Fan, A.-Y. Liu, X.-H. Wang, B.-X. Li, Endostar, a novel human recombinant endostatin, attenuates liver fibrosis in CCl<sub>4</sub>-induced mice, *Exp. Biol. Med. (Maywood).* 239 (2014) 998–1006. doi:10.1177/1535370214532595.
- [74] K. Sun, J. Park, O.T. Gupta, W.L. Holland, P. Auerbach, N. Zhang, R. Goncalves Marangoni, S.M. Nicoloro, M.P. Czech, J. Varga, T. Ploug, Z. An, P.E. Scherer, Endotrophin triggers adipose tissue fibrosis and metabolic dysfunction, *Nat Commun.* 5 (2014) 3485. doi:10.1038/ncomms4485.
- [75] A. Uchinaka, N. Kawaguchi, T. Ban, Y. Hamada, S. Mori, Y. Maeno, Y. Sawa, K. Nagata, H. Yamamoto, Evaluation of dermal wound healing activity of synthetic peptide SVVYGLR, *Biochem. Biophys. Res. Commun.* 491 (2017) 714–720. doi:10.1016/j.bbrc.2017.07.124.
- [76] O. Yamanaka, Y. Yuan, V.J. Coulson-Thomas, T.F. Gesteira, M.K. Call, Y. Zhang, J. Zhang, S.-H. Chang, C. Xie, C.-Y. Liu, S. Saika, J.V. Jester, W.W.-Y. Kao, Lumican binds ALK5 to promote epithelium wound healing, *PLoS ONE.* 8 (2013) e82730. doi:10.1371/journal.pone.0082730.
- [77] T.F. Gesteira, V.J. Coulson-Thomas, Y. Yuan, J. Zhang, H.B. Nader, W.W.-Y. Kao, Lumican Peptides: Rational Design Targeting ALK5/TGFBRI, *Sci Rep.* 7 (2017) 42057. doi:10.1038/srep42057.



- [78] K. Ghazi, U. Deng-Pichon, J.-M. Warnet, P. Rat, Hyaluronan fragments improve wound healing on in vitro cutaneous model through P2X7 purinoreceptor basal activation: role of molecular weight, *PLoS ONE*. 7 (2012) e48351. doi:10.1371/journal.pone.0048351.
- [79] Y. Wang, G. Han, B. Guo, J. Huang, Hyaluronan oligosaccharides promote diabetic wound healing by increasing angiogenesis, *Pharmacol Rep*. 68 (2016) 1126–1132. doi:10.1016/j.pharep.2016.07.001.
- [80] C. Tolg, P. Telmer, E. Turley, Specific sizes of hyaluronan oligosaccharides stimulate fibroblast migration and excisional wound repair, *PLoS ONE*. 9 (2014) e88479. doi:10.1371/journal.pone.0088479.
- [81] W. Bloch, K. Huggel, T. Sasaki, R. Grose, P. Bugnon, K. Addicks, R. Timpl, S. Werner, The angiogenesis inhibitor endostatin impairs blood vessel maturation during wound healing, *FASEB J*. 14 (2000) 2373–2376. doi:10.1096/fj.00-0490fje.
- [82] L. Seppinen, R. Sormunen, Y. Soini, H. Elamaa, R. Heljasvaara, T. Pihlajaniemi, Lack of collagen XVIII accelerates cutaneous wound healing, while overexpression of its endostatin domain leads to delayed healing, *Matrix Biol*. 27 (2008) 535–546. doi:10.1016/j.matbio.2008.03.003.
- [83] A.C. Berger, A.L. Feldman, M.F. Gnant, E.A. Kruger, B.K. Sim, S. Hewitt, W.D. Figg, H.R. Alexander, S.K. Libutti, The angiogenesis inhibitor, endostatin, does not affect murine cutaneous wound healing, *J. Surg. Res*. 91 (2000) 26–31. doi:10.1006/jsre.2000.5890.
- [84] C. Zeltz, S. Brézillon, C. Perreau, L. Ramont, F.-X. Maquart, Y. Wegrowski, Lumcorin: a leucine-rich repeat 9-derived peptide from human lumican inhibiting melanoma cell migration, *FEBS Lett*. 583 (2009) 3027–3032. doi:10.1016/j.febslet.2009.08.012.
- [85] K. Pietraszek, S. Brézillon, C. Perreau, M. Malicka-Błaszkiwicz, F.-X. Maquart, Y. Wegrowski, Lumican - derived peptides inhibit melanoma cell growth and migration, *PLoS ONE*. 8 (2013) e76232. doi:10.1371/journal.pone.0076232.
- [86] D.R. McCulloch, C.M. Nelson, L.J. Dixon, D.L. Silver, J.D. Wylie, V. Lindner, T. Sasaki, M.A. Cooley, W.S. Argraves, S.S. Apte, ADAMTS metalloproteases generate active versican fragments that regulate interdigital web regression, *Dev. Cell*. 17 (2009) 687–698. doi:10.1016/j.devcel.2009.09.008.
- [87] C. Hope, S. Foulcer, J. Jagodinsky, S.X. Chen, J.L. Jensen, S. Patel, C. Leith, I. Maroulakou, N. Callander, S. Miyamoto, P. Hematti, S.S. Apte, F. Asimakopoulos, Immunoregulatory roles of versican proteolysis in the myeloma microenvironment, *Blood*. 128 (2016) 680–685. doi:10.1182/blood-2016-03-705780.
- [88] C. Hope, P.B. Emmerich, A. Papadas, A. Pagenkopf, K.A. Matkowskyj, D.R. Van De Hey, S.N. Payne, L. Clipson, N.S. Callander, P. Hematti, S. Miyamoto, M.G. Johnson, D.A. Deming, F. Asimakopoulos, Versican-Derived Matrikines Regulate Batf3-Dendritic Cell Differentiation and Promote T Cell Infiltration in Colorectal Cancer, *J. Immunol*. 199 (2017) 1933–1941. doi:10.4049/jimmunol.1700529.
- [89] D.M. Beauvais, B.J. Ell, A.R. McWhorter, A.C. Rapraeger, Syndecan-1 regulates  $\alpha$ v $\beta$ 3 and  $\alpha$ v $\beta$ 5 integrin activation during angiogenesis and is blocked by synstatin, a novel peptide inhibitor, *J. Exp. Med*. 206 (2009) 691–705. doi:10.1084/jem.20081278.
- [90] A.C. Rapraeger, B.J. Ell, M. Roy, X. Li, O.R. Morrison, G.M. Thomas, D.M. Beauvais, Vascular endothelial-cadherin stimulates syndecan-1-coupled insulin-like growth factor-1 receptor and cross-talk between  $\alpha$ V $\beta$ 3 integrin and vascular endothelial growth factor receptor 2 at the onset of endothelial cell dissemination during angiogenesis, *FEBS J*. 280 (2013) 2194–2206. doi:10.1111/febs.12134.
- [91] O. Jung, V. Trapp-Stamborski, A. Purushothaman, H. Jin, H. Wang, R.D. Sanderson, A.C. Rapraeger, Heparanase-induced shedding of syndecan-1/CD138 in myeloma and

- endothelial cells activates VEGFR2 and an invasive phenotype: prevention by novel synstatins, *Oncogenesis*. 5 (2016) e202. doi:10.1038/oncsis.2016.5.
- [92] H.-F. Liu, H. Zhang, G.-X. Qiao, B. Ning, Y.-L. Hu, D.-C. Wang, Y.-G. Hu, A novel rabbit disc degeneration model induced by fibronectin fragment, *Joint Bone Spine*. 80 (2013) 301–306. doi:10.1016/j.jbspin.2012.07.009.
- [93] E. Parker, S. Vessillier, B. Pingguan-Murphy, W. Abas, D.L. Bader, T.T. Chowdhury, Low oxygen tension increased fibronectin fragment induced catabolic activities--response prevented with biomechanical signals, *Arthritis Res. Ther.* 15 (2013) R163. doi:10.1186/ar4346.
- [94] R. Joshi, E. Goihberg, W. Ren, M. Pilichowska, P. Mathew, Proteolytic fragments of fibronectin function as matrikines driving the chemotactic affinity of prostate cancer cells to human bone marrow mesenchymal stromal cells via the  $\alpha 5\beta 1$  integrin, *Cell Adh Migr.* 11 (2017) 305–315. doi:10.1080/19336918.2016.1212139.
- [95] S.T. Wood, D.L. Long, J.A. Reisz, R.R. Yammani, E.A. Burke, C. Klomsiri, L.B. Poole, C.M. Furdui, R.F. Loeser, Cysteine-Mediated Redox Regulation of Cell Signaling in Chondrocytes Stimulated With Fibronectin Fragments, *Arthritis & Rheumatology (Hoboken, N.J.)*. 68 (2016) 117–126. doi:10.1002/art.39326.
- [96] C. Bossard, L. Van den Berghe, H. Laurell, C. Castano, M. Cerutti, A.-C. Prats, H. Prats, Antiangiogenic properties of fibstatin, an extracellular FGF-2-binding polypeptide, *Cancer Res.* 64 (2004) 7507–7512. doi:10.1158/0008-5472.CAN-04-0287.
- [97] A.C. Prats, L. Van den Berghe, A. Rayssac, N. Ainaoui, F. Morfoisse, F. Pujol, S. Legonidec, A. Bikfalvi, H. Prats, S. Pyronnet, B. Garmy-Susini, CXCL4L1-fibstatin cooperation inhibits tumor angiogenesis, lymphangiogenesis and metastasis, *Microvasc. Res.* 89 (2013) 25–33. doi:10.1016/j.mvr.2013.05.005.
- [98] T.F. Lane, E.H. Sage, Functional mapping of SPARC: peptides from two distinct Ca(+)-binding sites modulate cell shape, *J. Cell Biol.* 111 (1990) 3065–3076.
- [99] A. Chlenski, L.J. Guerrero, R. Peddinti, J.A. Spitz, P.T. Leonhardt, Q. Yang, Y. Tian, H.R. Salwen, S.L. Cohn, Anti-angiogenic SPARC peptides inhibit progression of neuroblastoma tumors, *Mol. Cancer*. 9 (2010) 138. doi:10.1186/1476-4598-9-138.
- [100] T. Iline-Vul, I. Matlahov, J. Grinblat, K. Keinan-Adamsky, G. Goobes, Changes to the Disordered Phase and Apatite Crystallite Morphology during Mineralization by an Acidic Mineral Binding Peptide from Osteonectin, *Biomacromolecules*. 16 (2015) 2656–2663. doi:10.1021/acs.biomac.5b00465.
- [101] A. Gaggar, P.L. Jackson, B.D. Noerager, P.J. O'Reilly, D.B. McQuaid, S.M. Rowe, J.P. Clancy, J.E. Blalock, A novel proteolytic cascade generates an extracellular matrix-derived chemoattractant in chronic neutrophilic inflammation, *J. Immunol.* 180 (2008) 5662–5669.
- [102] C.S. Hahn, D.W. Scott, X. Xu, M.A. Roda, G.A. Payne, J.M. Wells, L. Viera, C.J. Winstead, P. Bratcher, R.W. Sparidans, F.A. Redegeld, P.L. Jackson, G. Folkerts, J.E. Blalock, R.P. Patel, A. Gaggar, The matrikine N- $\alpha$ -PGP couples extracellular matrix fragmentation to endothelial permeability, *Sci Adv.* 1 (2015). doi:10.1126/sciadv.1500175.
- [103] D. Palmieri, L. Camardella, V. Ulivi, G. Guasco, P. Manduca, Trimer carboxyl propeptide of collagen I produced by mature osteoblasts is chemotactic for endothelial cells, *J. Biol. Chem.* 275 (2000) 32658–32663. doi:10.1074/jbc.M002698200.
- [104] D. Davies, D.S. Tuckwell, D.A. Calderwood, S.A. Weston, M. Takigawa, M.J. Humphries, Molecular characterisation of integrin-procollagen C-propeptide interactions, *Eur. J. Biochem.* 246 (1997) 274–282.

- [105] S.A. Weston, D.J. Hulmes, A.P. Mould, R.B. Watson, M.J. Humphries, Identification of integrin alpha 2 beta 1 as cell surface receptor for the carboxyl-terminal propeptide of type I procollagen, *J. Biol. Chem.* 269 (1994) 20982–20986.
- [106] M. Bhattacharyya-Pakrasi, S.K. Dickeson, S.A. Santoro, Alpha2beta1 integrin recognition of the carboxyl-terminal propeptide of type I procollagen: integrin recognition and feed-back regulation of matrix biosynthesis are mediated by distinct sequences, *Matrix Biol.* 17 (1998) 223–232.
- [107] S.K. Dickeson, M. Bhattacharyya-Pakrasi, N.L. Mathis, P.H. Schlesinger, S.A. Santoro, Ligand binding results in divalent cation displacement from the alpha 2 beta 1 integrin I domain: evidence from terbium luminescence spectroscopy, *Biochemistry.* 37 (1998) 11280–11288. doi:10.1021/bi9727848.
- [108] R.J. Fernandes, S. Hirohata, J.M. Engle, A. Colige, D.H. Cohn, D.R. Eyre, S.S. Apte, Procollagen II amino propeptide processing by ADAMTS-3. Insights on dermatosparaxis, *J. Biol. Chem.* 276 (2001) 31502–31509. doi:10.1074/jbc.M103466200.
- [109] N. Fukui, A. McAlinden, Y. Zhu, E. Crouch, T.J. Broekelmann, R.P. Mecham, L.J. Sandell, Processing of type II procollagen amino propeptide by matrix metalloproteinases, *J. Biol. Chem.* 277 (2002) 2193–2201. doi:10.1074/jbc.M105485200.
- [110] Z. Wang, J. Bryan, C. Franz, N. Havlioglu, L.J. Sandell, Type IIB procollagen NH(2)-propeptide induces death of tumor cells via interaction with integrins alpha(V)beta(3) and alpha(V)beta(5), *J. Biol. Chem.* 285 (2010) 20806–20817. doi:10.1074/jbc.M110.118521.
- [111] M. Van der Rest, L.C. Rosenberg, B.R. Olsen, A.R. Poole, Chondrocalcin is identical with the C-propeptide of type II procollagen, *Biochem. J.* 237 (1986) 923–925.
- [112] E. Kessler, K. Takahara, L. Biniaminov, M. Brusel, D.S. Greenspan, Bone morphogenetic protein-1: the type I procollagen C-proteinase, *Science.* 271 (1996) 360–362.
- [113] T. Kirsch, M. Pfäffle, Selective binding of anchorin CII (annexin V) to type II and X collagen and to chondrocalcin (C-propeptide of type II collagen). Implications for anchoring function between matrix vesicles and matrix proteins, *FEBS Lett.* 310 (1992) 143–147.
- [114] I.T. Rebutini, C. Myers, K.S. Lassiter, A. Surmak, L. Szabova, K. Holmbeck, V. Pedchenko, B.G. Hudson, M.P. Hoffman, MT2-MMP-dependent release of collagen IV NC1 domains regulates submandibular gland branching morphogenesis, *Dev. Cell.* 17 (2009) 482–493. doi:10.1016/j.devcel.2009.07.016.
- [115] A. Sudhakar, P. Nyberg, V.G. Keshamouni, A.P. Mannam, J. Li, H. Sugimoto, D. Cosgrove, R. Kalluri, Human alpha1 type IV collagen NC1 domain exhibits distinct antiangiogenic activity mediated by alpha1beta1 integrin, *J. Clin. Invest.* 115 (2005) 2801–2810. doi:10.1172/JCI24813.
- [116] E. Petitclerc, A. Boutaud, A. Prestayko, J. Xu, Y. Sado, Y. Ninomiya, M.P. Sarras, B.G. Hudson, P.C. Brooks, New functions for non-collagenous domains of human collagen type IV. Novel integrin ligands inhibiting angiogenesis and tumor growth in vivo, *J. Biol. Chem.* 275 (2000) 8051–8061.
- [117] C. Magnon, A. Galaup, B. Mullan, V. Rouffiac, C. Bouquet, J.-M. Bidart, F. Griscelli, P. Opolon, M. Perricaudet, Canstatin acts on endothelial and tumor cells via mitochondrial damage initiated through interaction with alphavbeta3 and alphavbeta5 integrins, *Cancer Res.* 65 (2005) 4353–4361. doi:10.1158/0008-5472.CAN-04-3536.
- [118] Y. Hamano, M. Zeisberg, H. Sugimoto, J.C. Lively, Y. Maeshima, C. Yang, R.O. Hynes, Z. Werb, A. Sudhakar, R. Kalluri, Physiological levels of tumstatin, a fragment

- of collagen IV alpha3 chain, are generated by MMP-9 proteolysis and suppress angiogenesis via alphaV beta3 integrin, *Cancer Cell*. 3 (2003) 589–601.
- [119] C.M. Borza, A. Pozzi, D.-B. Borza, V. Pedchenko, T. Hellmark, B.G. Hudson, R. Zent, Integrin alpha3beta1, a novel receptor for alpha3(IV) noncollagenous domain and a trans-dominant Inhibitor for integrin alphavbeta3, *J. Biol. Chem.* 281 (2006) 20932–20939. doi:10.1074/jbc.M601147200.
- [120] Y. Maeshima, P.C. Colorado, R. Kalluri, Two RGD-independent alpha vbeta 3 integrin binding sites on tumstatin regulate distinct anti-tumor properties, *J. Biol. Chem.* 275 (2000) 23745–23750. doi:10.1074/jbc.C000186200.
- [121] V. Pedchenko, R. Zent, B.G. Hudson, Alpha(v)beta3 and alpha(v)beta5 integrins bind both the proximal RGD site and non-RGD motifs within noncollagenous (NC1) domain of the alpha3 chain of type IV collagen: implication for the mechanism of endothelia cell adhesion, *J. Biol. Chem.* 279 (2004) 2772–2780. doi:10.1074/jbc.M311901200.
- [122] S. Brassart-Pasco, K. Sénéchal, J. Thevenard, L. Ramont, J. Devy, L. Di Stefano, A. Dupont-Deshorgue, S. Brézillon, J. Feru, J.-F. Jazon, M.-D. Diebold, S. Ricard-Blum, F.-X. Maquart, J.C. Monboisse, Tetrastatin, the NC1 domain of the  $\alpha 4$ (IV) collagen chain: a novel potent anti-tumor matrikine, *PLoS ONE*. 7 (2012) e29587. doi:10.1371/journal.pone.0029587.
- [123] J. Park, P.E. Scherer, Adipocyte-derived endotrophin promotes malignant tumor progression, *J. Clin. Invest.* 122 (2012) 4243–4256. doi:10.1172/JCI63930.
- [124] R. Xu, Z.Y. Yao, L. Xin, Q. Zhang, T.P. Li, R.B. Gan, NC1 domain of human type VIII collagen (alpha 1) inhibits bovine aortic endothelial cell proliferation and causes cell apoptosis, *Biochem. Biophys. Res. Commun.* 289 (2001) 264–268. doi:10.1006/bbrc.2001.5970.
- [125] Z. Shen, C. Yao, Z. Wang, L. Yue, Z. Fang, H. Yao, F. Lin, H. Zhao, Y.-J. Sun, X.-W. Bian, W. Jiang, X. Wang, Y. Li, G. Lu, W.S. Poon, H.-F. Kung, M.C.-M. Lin, Vastatin, an Endogenous Antiangiogenesis Polypeptide That Is Lost in Hepatocellular Carcinoma, Effectively Inhibits Tumor Metastasis, *Mol. Ther.* 24 (2016) 1358–1368. doi:10.1038/mt.2016.56.
- [126] Y. Li, J. Li, Y.M. Woo, Z. Shen, H. Yao, Y. Cai, M.C.-M. Lin, W.S. Poon, Enhanced expression of Vastatin inhibits angiogenesis and prolongs survival in murine orthotopic glioblastoma model, *BMC Cancer*. 17 (2017) 126. doi:10.1186/s12885-017-3125-8.
- [127] A. Snellman, H. Tu, T. Väisänen, A.P. Kvist, P. Huhtala, T. Pihlajaniemi, A short sequence in the N-terminal region is required for the trimerization of type XIII collagen and is conserved in other collagenous transmembrane proteins, *EMBO J.* 19 (2000) 5051–5059. doi:10.1093/emboj/19.19.5051.
- [128] J. Dennis, D.T. Meehan, D. Delimont, M. Zallocchi, G.A. Perry, S. O'Brien, H. Tu, T. Pihlajaniemi, D. Cosgrove, Collagen XIII induced in vascular endothelium mediates alpha1beta1 integrin-dependent transmigration of monocytes in renal fibrosis, *Am. J. Pathol.* 177 (2010) 2527–2540. doi:10.2353/ajpath.2010.100017.
- [129] R. Ramchandran, M. Dhanabal, R. Volk, M.J. Waterman, M. Segal, H. Lu, B. Knebelmann, V.P. Sukhatme, Antiangiogenic activity of restin, NC10 domain of human collagen XV: comparison to endostatin, *Biochem. Biophys. Res. Commun.* 255 (1999) 735–739. doi:10.1006/bbrc.1999.0248.
- [130] L. Lin, T. Betsuyaku, L. Heimbach, N. Li, D. Rubenstein, S.D. Shapiro, L. An, G.J. Giudice, L.A. Diaz, R.M. Senior, Z. Liu, Neutrophil elastase cleaves the murine hemidesmosomal protein BP180/type XVII collagen and generates degradation products that modulate experimental bullous pemphigoid, *Matrix Biol.* 31 (2012) 38–44. doi:10.1016/j.matbio.2011.09.003.

- [131] C.-W. Franzke, K. Tasanen, H. Schäcke, Z. Zhou, K. Tryggvason, C. Mauch, P. Zigrino, S. Sunnarborg, D.C. Lee, F. Fahrenholz, L. Bruckner-Tuderman, Transmembrane collagen XVII, an epithelial adhesion protein, is shed from the cell surface by ADAMs, *EMBO J.* 21 (2002) 5026–5035.
- [132] U. Felbor, L. Dreier, R.A. Bryant, H.L. Ploegh, B.R. Olsen, W. Mothes, Secreted cathepsin L generates endostatin from collagen XVIII, *EMBO J.* 19 (2000) 1187–1194. doi:10.1093/emboj/19.6.1187.
- [133] M. Ferreras, U. Felbor, T. Lenhard, B.R. Olsen, J. Delaissé, Generation and degradation of human endostatin proteins by various proteinases, *FEBS Lett.* 486 (2000) 247–251.
- [134] R. Heljasvaara, P. Nyberg, J. Luostarinen, M. Parikka, P. Heikkilä, M. Rehn, T. Sorsa, T. Salo, T. Pihlajaniemi, Generation of biologically active endostatin fragments from human collagen XVIII by distinct matrix metalloproteinases, *Exp. Cell Res.* 307 (2005) 292–304. doi:10.1016/j.yexcr.2005.03.021.
- [135] D.H.-K. Ma, J.-Y. Yao, M.-T. Kuo, L.-C. See, K.-Y. Lin, S.-C. Chen, J.-K. Chen, A.-S. Chao, S.-F. Wang, K.-K. Lin, Generation of endostatin by matrix metalloproteinase and cathepsin from human limboconal epithelial cells cultivated on amniotic membrane, *Invest. Ophthalmol. Vis. Sci.* 48 (2007) 644–651. doi:10.1167/iovs.06-0884.
- [136] W. Wen, M.A. Moses, D. Wiederschain, J.L. Arbiser, J. Folkman, The generation of endostatin is mediated by elastase, *Cancer Res.* 59 (1999) 6052–6056.
- [137] M. Rehn, T. Veikkola, E. Kukk-Valdre, H. Nakamura, M. Ilmonen, C. Lombardo, T. Pihlajaniemi, K. Alitalo, K. Vuori, Interaction of endostatin with integrins implicated in angiogenesis, *Proc. Natl. Acad. Sci. U.S.A.* 98 (2001) 1024–1029. doi:10.1073/pnas.031564998.
- [138] Y.-M. Kim, S. Hwang, Y.-M. Kim, B.-J. Pyun, T.-Y. Kim, S.-T. Lee, Y.S. Gho, Y.-G. Kwon, Endostatin blocks vascular endothelial growth factor-mediated signaling via direct interaction with KDR/Flk-1, *J. Biol. Chem.* 277 (2002) 27872–27879. doi:10.1074/jbc.M202771200.
- [139] S.A. Karumanchi, V. Jha, R. Ramchandran, A. Karihaloo, L. Tsiokas, B. Chan, M. Dhanabal, J.I. Hanai, G. Venkataraman, Z. Shriver, N. Keiser, R. Kalluri, H. Zeng, D. Mukhopadhyay, R.L. Chen, A.D. Lander, K. Hagihara, Y. Yamaguchi, R. Sasisekharan, L. Cantley, V.P. Sukhatme, Cell surface glypicans are low-affinity endostatin receptors, *Mol. Cell.* 7 (2001) 811–822.
- [140] L. Guo, N. Song, T. He, F. Qi, S. Zheng, X.-G. Xu, Y. Fu, H.-D. Chen, Y. Luo, Endostatin inhibits the tumorigenesis of hemangioendothelioma via downregulation of CXCL1, *Mol. Carcinog.* 54 (2015) 1340–1353. doi:10.1002/mc.22210.
- [141] C. Faye, C. Moreau, E. Chautard, R. Jetne, N. Fukai, F. Ruggiero, M.J. Humphries, B.R. Olsen, S. Ricard-Blum, Molecular interplay between endostatin, integrins, and heparan sulfate, *J. Biol. Chem.* 284 (2009) 22029–22040. doi:10.1074/jbc.M109.002840.
- [142] F. Veillard, A. Saidi, R.E. Burden, C.J. Scott, L. Gillet, F. Lecaille, G. Lalmanach, Cysteine cathepsins S and L modulate anti-angiogenic activities of human endostatin, *J. Biol. Chem.* 286 (2011) 37158–37167. doi:10.1074/jbc.M111.284869.
- [143] H.C. Lin, J.H. Chang, S. Jain, E.E. Gabison, T. Kure, T. Kato, N. Fukai, D.T. Azar, Matrilysin cleavage of corneal collagen type XVIII NC1 domain and generation of a 28-kDa fragment, *Invest. Ophthalmol. Vis. Sci.* 42 (2001) 2517–2524.
- [144] J.-H. Chang, J.A.D. Javier, G.-Y. Chang, H.B. Oliveira, D.T. Azar, Functional characterization of neostatins, the MMP-derived, enzymatic cleavage products of type XVIII collagen, *FEBS Lett.* 579 (2005) 3601–3606. doi:10.1016/j.febslet.2005.05.043.
- [145] J.-B. Oudart, M. Doué, A. Vautrin, B. Brassart, C. Sellier, A. Dupont-Deshorgue, J.-C. Monboisse, F.-X. Maquart, S. Brassart-Pasco, L. Ramont, The anti-tumor NC1 domain

- of collagen XIX inhibits the FAK/ PI3K/Akt/mTOR signaling pathway through  $\alpha\beta 3$  integrin interaction, *Oncotarget*. 7 (2016) 1516–1528. doi:10.18632/oncotarget.6399.
- [146] J. Banyard, L. Bao, B.R. Zetter, Type XXIII collagen, a new transmembrane collagen identified in metastatic tumor cells, *J. Biol. Chem.* 278 (2003) 20989–20994. doi:10.1074/jbc.M210616200.
- [147] G. Veit, D. Zwolanek, B. Eckes, S. Niland, J. Käpylä, M.C. Zweers, A. Ishada-Yamamoto, T. Krieg, J. Heino, J.A. Eble, M. Koch, Collagen XXIII, novel ligand for integrin  $\alpha 2\beta 1$  in the epidermis, *J. Biol. Chem.* 286 (2011) 27804–27813. doi:10.1074/jbc.M111.220046.
- [148] T. Hashimoto, T. Wakabayashi, A. Watanabe, H. Kowa, R. Hosoda, A. Nakamura, I. Kanazawa, T. Arai, K. Takio, D.M.A. Mann, T. Iwatsubo, CLAC: a novel Alzheimer amyloid plaque component derived from a transmembrane precursor, CLAC-P/collagen type XXV, *EMBO J.* 21 (2002) 1524–1534. doi:10.1093/emboj/21.7.1524.
- [149] P. Pocza, H. Süli-Vargha, Z. Darvas, A. Falus, Locally generated VGVAPG and VAPG elastin-derived peptides amplify melanoma invasion via the galectin-3 receptor, *Int. J. Cancer.* 122 (2008) 1972–1980. doi:10.1002/ijc.23296.
- [150] C.H. Blood, B.R. Zetter, Laminin regulates a tumor cell chemotaxis receptor through the laminin-binding integrin subunit  $\alpha 6$ , *Cancer Res.* 53 (1993) 2661–2666.
- [151] S. Toupance, B. Brassart, F. Rabenoelina, C. Ghoneim, L. Vallar, M. Polette, L. Debelle, P. Birembaut, Elastin-derived peptides increase invasive capacities of lung cancer cells by post-transcriptional regulation of MMP-2 and uPA, *Clin. Exp. Metastasis.* 29 (2012) 511–522. doi:10.1007/s10585-012-9467-3.
- [152] J. Unger, H. Tschesche, The proteolytic activity and cleavage specificity of fibronectin-gelatinase and fibronectin-lamininase, *J. Protein Chem.* 18 (1999) 403–411.
- [153] J. Schnepel, H. Tschesche, The proteolytic activity of the recombinant cryptic human fibronectin type IV collagenase from E. coli expression, *J. Protein Chem.* 19 (2000) 685–692.
- [154] K. Briknarová, M.E. Akerman, D.W. Hoyt, E. Ruoslahti, K.R. Ely, Anastellin, an FN3 fragment with fibronectin polymerization activity, resembles amyloid fibril precursors, *J. Mol. Biol.* 332 (2003) 205–215.
- [155] B. Maertens, D. Hopkins, C.-W. Franzke, D.R. Keene, L. Bruckner-Tuderman, D.S. Greenspan, M. Koch, Cleavage and oligomerization of gliomedin, a transmembrane collagen required for node of ranvier formation, *J. Biol. Chem.* 282 (2007) 10647–10659. doi:10.1074/jbc.M611339200.
- [156] Y. Eshed, K. Feinberg, D.J. Carey, E. Peles, Secreted gliomedin is a perinodal matrix component of peripheral nerves, *J. Cell Biol.* 177 (2007) 551–562. doi:10.1083/jcb.200612139.
- [157] R. Salza, F. Peysselon, E. Chautard, C. Faye, L. Moschovich, T. Weiss, L. Perrin-Cocon, V. Lotteau, E. Kessler, S. Ricard-Blum, Extended interaction network of procollagen C-proteinase enhancer-1 in the extracellular matrix, *Biochem. J.* 457 (2014) 137–149. doi:10.1042/BJ20130295.
- [158] T. Weiss, M. Brusel, P. Rousselle, E. Kessler, The NTR domain of procollagen C-proteinase enhancer-1 (PCPE-1) mediates PCPE-1 binding to syndecans-1, -2 and -4 as well as fibronectin, *Int. J. Biochem. Cell Biol.* 57 (2014) 45–53. doi:10.1016/j.biocel.2014.09.023.
- [159] M. Mongiat, S.M. Sweeney, J.D. San Antonio, J. Fu, R.V. Iozzo, Endorepellin, a novel inhibitor of angiogenesis derived from the C terminus of perlecan, *J. Biol. Chem.* 278 (2003) 4238–4249. doi:10.1074/jbc.M210445200.

- [160] A. Nyström, Z.P. Shaik, D. Gullberg, T. Krieg, B. Eckes, R. Zent, A. Pozzi, R.V. Iozzo, Role of tyrosine phosphatase SHP-1 in the mechanism of endorepellin angiostatic activity, *Blood*. 114 (2009) 4897–4906. doi:10.1182/blood-2009-02-207134.
- [161] A. Goyal, N. Pal, M. Concannon, M. Paul, M. Doran, C. Poluzzi, K. Sekiguchi, J.M. Whitelock, T. Neill, R.V. Iozzo, Endorepellin, the angiostatic module of perlecan, interacts with both the  $\alpha 2\beta 1$  integrin and vascular endothelial growth factor receptor 2 (VEGFR2): a dual receptor antagonism, *J. Biol. Chem.* 286 (2011) 25947–25962. doi:10.1074/jbc.M111.243626.
- [162] J.-F. Cailhier, I. Sirois, P. Laplante, S. Lepage, M.-A. Raymond, N. Brassard, A. Prat, R.V. Iozzo, A.V. Pshezhetsky, M.-J. Hébert, Caspase-3 activation triggers extracellular cathepsin L release and endorepellin proteolysis, *J. Biol. Chem.* 283 (2008) 27220–27229. doi:10.1074/jbc.M801164200.
- [163] E.M. Gonzalez, C.C. Reed, G. Bix, J. Fu, Y. Zhang, B. Gopalakrishnan, D.S. Greenspan, R.V. Iozzo, BMP-1/Tolloid-like metalloproteases process endorepellin, the angiostatic C-terminal fragment of perlecan, *J. Biol. Chem.* 280 (2005) 7080–7087. doi:10.1074/jbc.M409841200.
- [164] T. Manon-Jensen, Y. Itoh, J.R. Couchman, Proteoglycans in health and disease: the multiple roles of syndecan shedding, *FEBS J.* 277 (2010) 3876–3889. doi:10.1111/j.1742-4658.2010.07798.x.
- [165] D. Barbouri, N. Afratis, C. Gialeli, D.H. Vynios, A.D. Theocharis, N.K. Karamanos, Syndecans as modulators and potential pharmacological targets in cancer progression, *Front Oncol.* 4 (2014) 4. doi:10.3389/fonc.2014.00004.
- [166] D.M. Beauvais, B.J. Burbach, A.C. Rapraeger, The syndecan-1 ectodomain regulates  $\alpha v\beta 3$  integrin activity in human mammary carcinoma cells, *J. Cell Biol.* 167 (2004) 171–181. doi:10.1083/jcb.200404171.
- [167] K.J. McQuade, D.M. Beauvais, B.J. Burbach, A.C. Rapraeger, Syndecan-1 regulates  $\alpha v\beta 5$  integrin activity in B82L fibroblasts, *J. Cell. Sci.* 119 (2006) 2445–2456. doi:10.1242/jcs.02970.
- [168] H. Wang, H. Jin, A.C. Rapraeger, Syndecan-1 and Syndecan-4 Capture Epidermal Growth Factor Receptor Family Members and the  $\alpha 3\beta 1$  Integrin Via Binding Sites in Their Ectodomains: NOVEL SYNSTATINS PREVENT KINASE CAPTURE AND INHIBIT  $\alpha 6\beta 4$ -INTEGRIN-DEPENDENT EPITHELIAL CELL MOTILITY, *J. Biol. Chem.* 290 (2015) 26103–26113. doi:10.1074/jbc.M115.679084.
- [169] S. Choi, J.-Y. Kim, J.H. Park, S.-T. Lee, I.-O. Han, E.-S. Oh, The matrix metalloproteinase-7 regulates the extracellular shedding of syndecan-2 from colon cancer cells, *Biochem. Biophys. Res. Commun.* 417 (2012) 1260–1264. doi:10.1016/j.bbrc.2011.12.120.
- [170] J.R. Whiteford, X. Xian, C. Chaussade, B. Vanhaesebroeck, S. Nourshargh, J.R. Couchman, Syndecan-2 is a novel ligand for the protein tyrosine phosphatase receptor CD148, *Mol. Biol. Cell.* 22 (2011) 3609–3624. doi:10.1091/mbc.E11-02-0099.
- [171] V.K. Asundi, R. Erdman, R.C. Stahl, D.J. Carey, Matrix metalloproteinase-dependent shedding of syndecan-3, a transmembrane heparan sulfate proteoglycan, in Schwann cells, *J. Neurosci. Res.* 73 (2003) 593–602. doi:10.1002/jnr.10699.
- [172] S.S. Apte, A disintegrin-like and metalloprotease (reprolysin-type) with thrombospondin type 1 motif (ADAMTS) superfamily: functions and mechanisms, *J. Biol. Chem.* 284 (2009) 31493–31497. doi:10.1074/jbc.R109.052340.
- [173] M. Schmitt, Versican vs versikine: tolerance vs attack, *Blood*. 128 (2016) 612–613. doi:10.1182/blood-2016-06-721092.
- [174] M.I. Uzel, I.C. Scott, H. Babakhanlou-Chase, A.H. Palamakumbura, W.N. Pappano, H.H. Hong, D.S. Greenspan, P.C. Trackman, Multiple bone morphogenetic protein 1-

- related mammalian metalloproteinases process pro-lysyl oxidase at the correct physiological site and control lysyl oxidase activation in mouse embryo fibroblast cultures, *J. Biol. Chem.* 276 (2001) 22537–22543. doi:10.1074/jbc.M102352200.
- [175] G.B. Ozdener, M.V. Bais, P.C. Trackman, Determination of cell uptake pathways for tumor inhibitor lysyl oxidase propeptide, *Mol. Oncol.* 10 (2016) 1–23. doi:10.1016/j.molonc.2015.07.005.
- [176] 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.
- [177] E. Roeb, K. Schleinkofer, T. Kernebeck, S. Pötsch, B. Jansen, I. Behrmann, S. Matern, J. Grötzinger, The matrix metalloproteinase 9 (mmp-9) hemopexin domain is a novel gelatin binding domain and acts as an antagonist, *J. Biol. Chem.* 277 (2002) 50326–50332. doi:10.1074/jbc.M207446200.
- [178] A.R. Radjabi, K. Sawada, S. Jagadeeswaran, A. Eichbichler, H.A. Kenny, A. Montag, K. Bruno, E. Lengyel, Thrombin induces tumor invasion through the induction and association of matrix metalloproteinase-9 and beta1-integrin on the cell surface, *J. Biol. Chem.* 283 (2008) 2822–2834. doi:10.1074/jbc.M704855200.
- [179] E. Ugarte-Berzal, E. Bailón, I. Amigo-Jiménez, C.L. Vituri, M.H. del Cerro, M.J. Terol, J.P. Albar, G. Rivas, J.A. García-Marco, A. García-Pardo, A 17-residue sequence from the matrix metalloproteinase-9 (MMP-9) hemopexin domain binds  $\alpha 4\beta 1$  integrin and inhibits MMP-9-induced functions in chronic lymphocytic leukemia B cells, *J. Biol. Chem.* 287 (2012) 27601–27613. doi:10.1074/jbc.M112.354670.
- [180] E. Ugarte-Berzal, E. Bailón, I. Amigo-Jiménez, J.P. Albar, J.A. García-Marco, A. García-Pardo, A novel CD44-binding peptide from the pro-matrix metalloproteinase-9 hemopexin domain impairs adhesion and migration of chronic lymphocytic leukemia (CLL) cells, *J. Biol. Chem.* 289 (2014) 15340–15349. doi:10.1074/jbc.M114.559187.
- [181] 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. doi:10.1093/emboj/20.17.4782.
- [182] H. Mori, T. Tomari, N. Koshikawa, M. Kajita, Y. Itoh, H. Sato, H. Tojo, I. Yana, M. Seiki, CD44 directs membrane-type 1 matrix metalloproteinase to lamellipodia by associating with its hemopexin-like domain, *EMBO J.* 21 (2002) 3949–3959. doi:10.1093/emboj/cdf411.
- [183] S.S. Apte, W.C. Parks, Metalloproteinases: A parade of functions in matrix biology and an outlook for the future, *Matrix Biol.* 44–46 (2015) 1–6. doi:10.1016/j.matbio.2015.04.005.
- [184] M.I. Millichip, D.J. Dallas, E. Wu, S. Dale, N. McKie, The metallo-disintegrin ADAM10 (MADM) from bovine kidney has type IV collagenase activity in vitro, *Biochem. Biophys. Res. Commun.* 245 (1998) 594–598. doi:10.1006/bbrc.1998.8485.
- [185] J. Martin, L.V. Eynstone, M. Davies, J.D. Williams, R. Steadman, The role of ADAM 15 in glomerular mesangial cell migration, *J. Biol. Chem.* 277 (2002) 33683–33689. doi:10.1074/jbc.M200988200.
- [186] R. Roy, U.M. Wewer, D. Zurakowski, S.E. Pories, M.A. Moses, ADAM 12 cleaves extracellular matrix proteins and correlates with cancer status and stage, *J. Biol. Chem.* 279 (2004) 51323–51330. doi:10.1074/jbc.M409565200.
- [187] S. Vadon-Le Goff, D.J.S. Hulmes, C. Moali, BMP-1/tolloid-like proteinases synchronize matrix assembly with growth factor activation to promote morphogenesis and tissue remodeling, *Matrix Biol.* 44–46 (2015) 14–23. doi:10.1016/j.matbio.2015.02.006.



- [188] H. Troilo, C.P. Bayley, A.L. Barrett, M.P. Lockhart-Cairns, T.A. Jowitt, C. Baldock, Mammalian tollid proteinases: role in growth factor signalling, *FEBS Lett.* 590 (2016) 2398–2407. doi:10.1002/1873-3468.12287.
- [189] 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. doi:10.1016/j.matbio.2015.01.012.
- [190] K. Yamamoto, G. Murphy, L. Troeberg, Extracellular regulation of metalloproteinases, *Matrix Biol.* 44–46 (2015) 255–263. doi:10.1016/j.matbio.2015.02.007.
- [191] R. Kappelhoff, U. Auf dem Keller, C.M. Overall, Analysis of the degradome with the CLIP-CHIP microarray, *Methods Mol. Biol.* 622 (2010) 175–193. doi:10.1007/978-1-60327-299-5\_10.
- [192] R. Kappelhoff, X.S. Puente, C.H. Wilson, A. Seth, C. López-Otín, C.M. Overall, Overview of transcriptomic analysis of all human proteases, non-proteolytic homologs and inhibitors: Organ, tissue and ovarian cancer cell line expression profiling of the human protease degradome by the CLIP-CHIP<sup>TM</sup> DNA microarray, *Biochim. Biophys. Acta.* (2017). doi:10.1016/j.bbamcr.2017.08.004.
- [193] M.L. Corcoran, M.C. Kibbey, H.K. Kleinman, L.M. Wahl, Laminin SIKVAV peptide induction of monocyte/macrophage prostaglandin E2 and matrix metalloproteinases, *J. Biol. Chem.* 270 (1995) 10365–10368.
- [194] P. Huhtala, M.J. Humphries, J.B. McCarthy, P.M. Tremble, Z. Werb, C.H. Damsky, Cooperative signaling by alpha 5 beta 1 and alpha 4 beta 1 integrins regulates metalloproteinase gene expression in fibroblasts adhering to fibronectin, *J. Cell Biol.* 129 (1995) 867–879.
- [195] M. Okada, S. Morioka, H. Kanazawa, H. Yamawaki, Canstatin inhibits isoproterenol-induced apoptosis through preserving mitochondrial morphology in differentiated H9c2 cardiomyoblasts, *Apoptosis.* 21 (2016) 887–895. doi:10.1007/s10495-016-1262-1.
- [196] A. Sugiyama, M. Okada, H. Yamawaki, Pathophysiological roles of canstatin on myofibroblasts after myocardial infarction in rats, *Eur. J. Pharmacol.* 807 (2017) 32–43. doi:10.1016/j.ejphar.2017.04.027.
- [197] L.M. Harkness, M. Weckmann, M. Kopp, T. Becker, A.W. Ashton, J.K. Burgess, Tumstatin regulates the angiogenic and inflammatory potential of airway smooth muscle extracellular matrix, *J. Cell. Mol. Med.* (2017). doi:10.1111/jcmm.13232.
- [198] A. Robinet, A. Fahem, J.-H. Cauchard, E. Huet, L. Vincent, S. Lorimier, F. Antonicelli, C. Soria, M. Crepin, W. Hornebeck, G. Bellon, Elastin-derived peptides enhance angiogenesis by promoting endothelial cell migration and tubulogenesis through upregulation of MT1-MMP, *J. Cell. Sci.* 118 (2005) 343–356. doi:10.1242/jcs.01613.
- [199] A. Abdollahi, P. Hahnfeldt, C. Maercker, H.-J. Gröne, J. Debus, W. Ansorge, J. Folkman, L. Hlatky, P.E. Huber, Endostatin's antiangiogenic signaling network, *Mol. Cell.* 13 (2004) 649–663.
- [200] H.S. Hwang, S.J. Park, E.J. Cheon, M.H. Lee, H.A. Kim, Fibronectin fragment-induced expression of matrix metalloproteinases is mediated by MyD88-dependent TLR-2 signaling pathway in human chondrocytes, *Arthritis Res. Ther.* 17 (2015) 320. doi:10.1186/s13075-015-0833-9.
- [201] E.A. Aydemir, E. Şimşek, A.F. Korcum, K. Fişkin, Endostatin and irradiation modifies the activity of ADAM10 and neprilysin in breast cancer cells, *Mol Med Rep.* 14 (2016) 2343–2351. doi:10.3892/mmr.2016.5463.
- [202] N. Sofat, S.D. Robertson, M. Hermansson, J. Jones, P. Mitchell, R. Wait, Tenascin-C fragments are endogenous inducers of cartilage matrix degradation, *Rheumatol. Int.* 32 (2012) 2809–2817. doi:10.1007/s00296-011-2067-8.

- [203] K.O. Mercurius, A.O. Morla, Cell adhesion and signaling on the fibronectin 1st type III repeat; requisite roles for cell surface proteoglycans and integrins, *BMC Cell Biol.* 2 (2001) 18.
- [204] R. You, R.M. Klein, M. Zheng, P.J. McKeown-Longo, Regulation of p38 MAP kinase by anastellin is independent of anastellin's effect on matrix fibronectin, *Matrix Biol.* 28 (2009) 101–109. doi:10.1016/j.matbio.2009.01.003.
- [205] H. Shi, Y. Huang, H. Zhou, X. Song, S. Yuan, Y. Fu, Y. Luo, Nucleolin is a receptor that mediates antiangiogenic and antitumor activity of endostatin, *Blood.* 110 (2007) 2899–2906. doi:10.1182/blood-2007-01-064428.
- [206] N. Song, Y. Ding, W. Zhuo, T. He, Z. Fu, Y. Chen, X. Song, Y. Fu, Y. Luo, The nuclear translocation of endostatin is mediated by its receptor nucleolin in endothelial cells, *Angiogenesis.* 15 (2012) 697–711. doi:10.1007/s10456-012-9284-y.
- [207] G. Limaverde-Sousa, C. Sternberg, C.G. Ferreira, Antiangiogenesis beyond VEGF inhibition: a journey from antiangiogenic single-target to broad-spectrum agents, *Cancer Treat. Rev.* 40 (2014) 548–557. doi:10.1016/j.ctrv.2013.11.009.
- [208] J. Wang, Y. Sun, Y. Liu, Q. Yu, Y. Zhang, K. Li, Y. Zhu, Q. Zhou, M. Hou, Z. Guan, W. Li, W. Zhuang, D. Wang, H. Liang, F. Qin, H. Lu, X. Liu, H. Sun, Y. Zhang, J. Wang, S. Luo, R. Yang, Y. Tu, X. Wang, S. Song, J. Zhou, L. You, J. Wang, C. Yao, [Results of randomized, multicenter, double-blind phase III trial of rh-endostatin (YH-16) in treatment of advanced non-small cell lung cancer patients], *Zhongguo Fei Ai Za Zhi.* 8 (2005) 283–290. doi:10.3779/j.issn.1009-3419.2005.04.07.
- [209] Y. Chen, Y. Du, P. Li, F. Wu, Y. Fu, Z. Li, Y. Luo, Phase I trial of M2ES, a novel polyethylene glycosylated recombinant human endostatin, plus gemcitabine in advanced pancreatic cancer, *Mol Clin Oncol.* 2 (2014) 586–590. doi:10.3892/mco.2014.271.
- [210] Z. Chen, W. Guo, J. Cao, F. Lv, W. Zhang, L. Qiu, W. Li, D. Ji, S. Zhang, Z. Xia, J. Wang, J. Li, Endostar in combination with modified FOLFOX6 as an initial therapy in advanced colorectal cancer patients: a phase I clinical trial, *Cancer Chemother. Pharmacol.* 75 (2015) 547–557. doi:10.1007/s00280-014-2656-9.
- [211] Y. Bao, F. Peng, Q.-C. Zhou, Z.-H. Yu, J.-C. Li, Z.-B. Cheng, L. Chen, X. Hu, Y.-Y. Chen, J. Wang, Y. Wang, H.-L. Ma, Z.-M. Xu, R.-B. Lu, X.-W. Deng, M. Chen, Phase II trial of recombinant human endostatin in combination with concurrent chemoradiotherapy in patients with stage III non-small-cell lung cancer, *Radiother Oncol.* 114 (2015) 161–166. doi:10.1016/j.radonc.2014.11.039.
- [212] J. Chen, Q. Yao, D. Li, J. Zhang, T. Wang, M. Yu, X. Zhou, Y. Huan, J. Wang, L. Wang, Neoadjuvant rh-endostatin, docetaxel and epirubicin for breast cancer: efficacy and safety in a prospective, randomized, phase II study, *BMC Cancer.* 13 (2013) 248. doi:10.1186/1471-2407-13-248.
- [213] C. Cui, L. Mao, Z. Chi, L. Si, X. Sheng, Y. Kong, S. Li, B. Lian, K. Gu, M. Tao, X. Song, T. Lin, X. Ren, S. Qin, J. Guo, A phase II, randomized, double-blind, placebo-controlled multicenter trial of Endostar in patients with metastatic melanoma, *Mol. Ther.* 21 (2013) 1456–1463. doi:10.1038/mt.2013.79.
- [214] Q. Jia, J. Xu, W. Jiang, M. Zheng, M. Wei, J. Chen, L. Wang, Y. Huan, Dynamic contrast-enhanced MR imaging in a phase II study on neoadjuvant chemotherapy combining Rh-endostatin with docetaxel and epirubicin for locally advanced breast cancer, *Int J Med Sci.* 10 (2013) 110–118. doi:10.7150/ijms.5123.
- [215] T. Jin, B. Li, X.-Z. Chen, A phase II trial of Endostar combined with gemcitabine and cisplatin chemotherapy in patients with metastatic nasopharyngeal carcinoma (NCT01612286), *Oncol. Res.* 21 (2013) 317–323. doi:10.3727/096504014X13983417587401.

- [216] S. Lu, L. Li, Y. Luo, L. Zhang, G. Wu, Z. Chen, C. Huang, S. Guo, Y. Zhang, X. Song, Y. Yu, C. Zhou, W. Li, M. Liao, B. Li, L. Xu, P. Chen, C. Hu, C. Hu, A multicenter, open-label, randomized phase II controlled study of rh-endostatin (Endostar) in combination with chemotherapy in previously untreated extensive-stage small-cell lung cancer, *J Thorac Oncol.* 10 (2015) 206–211. doi:10.1097/JTO.0000000000000343.
- [217] X.-J. Sun, Q.-H. Deng, X.-M. Yu, Y.-L. Ji, Y.-D. Zheng, H. Jiang, Y.-P. Xu, S.-L. Ma, A phase II study of Endostatin in combination with paclitaxel, carboplatin, and radiotherapy in patients with unresectable locally advanced non-small cell lung cancer, *BMC Cancer.* 16 (2016) 266. doi:10.1186/s12885-016-2234-0.
- [218] W. Ye, R. Liu, C. Pan, W. Jiang, L. Zhang, Z. Guan, J. Wu, X. Ying, L. Li, S. Li, W. Tan, M. Zeng, T. Kang, Q. Liu, G.R. Thomas, M. Huang, W. Deng, W. Huang, Multicenter randomized phase 2 clinical trial of a recombinant human endostatin adenovirus in patients with advanced head and neck carcinoma, *Mol. Ther.* 22 (2014) 1221–1229. doi:10.1038/mt.2014.53.
- [219] X. Zhao, K. Mei, X. Cai, J. Chen, J. Yu, C. Zhou, Q. Li, A randomized phase II study of recombinant human endostatin plus gemcitabine/cisplatin compared with gemcitabine/cisplatin alone as first-line therapy in advanced non-small-cell lung cancer, *Invest New Drugs.* 30 (2012) 1144–1149. doi:10.1007/s10637-011-9631-7.
- [220] R. Zhang, Z.-Y. Wang, Y.-H. Li, Y.-H. Lu, S. Wang, W.-X. Yu, H. Zhao, Dynamic contrast-enhanced MRI to predict response to vinorelbine-cisplatin alone or with rh-endostatin in patients with non-small cell lung cancer and bone metastases: a randomised, double-blind, placebo-controlled trial, *Lancet.* 388 Suppl 1 (2016) S95. doi:10.1016/S0140-6736(16)32022-0.
- [221] R. Xu, N. Ma, F. Wang, L. Ma, R. Chen, R. Chen, M. Kebinu, L. Ma, Z. Han, null Ayixiamu, M. Mayier, P. Su, Y. Naman, H. Jieensi, H. Yang, A. Adili, S. Aili, J. Liu, Results of a randomized and controlled clinical trial evaluating the efficacy and safety of combination therapy with Endostar and S-1 combined with oxaliplatin in advanced gastric cancer, *Onco Targets Ther.* 6 (2013) 925–929. doi:10.2147/OTT.S46487.
- [222] S. Wang, X.-A. Lu, P. Liu, Y. Fu, L. Jia, S. Zhan, Y. Luo, Endostatin has ATPase activity, which mediates its antiangiogenic and antitumor activities, *Mol. Cancer Ther.* 14 (2015) 1192–1201. doi:10.1158/1535-7163.MCT-14-0836.
- [223] Y. Zhao, X. Gu, N. Zhang, M.G. Kolonin, Z. An, K. Sun, Divergent functions of endotrophin on different cell populations in adipose tissue, *Am. J. Physiol. Endocrinol. Metab.* 311 (2016) E952–E963. doi:10.1152/ajpendo.00314.2016.
- [224] Z. Julier, M.M. Martino, A. de Titta, L. Jeanbart, J.A. Hubbell, The TLR4 agonist fibronectin extra domain A is cryptic, exposed by elastase-2; use in a fibrin matrix cancer vaccine, *Sci Rep.* 5 (2015) 8569. doi:10.1038/srep08569.
- [225] S. Ricard-Blum, O. Féraud, H. Lortat-Jacob, A. Rencurosi, N. Fukai, F. Dkhissi, D. Vittet, A. Imberty, B.R. Olsen, M. van der Rest, Characterization of endostatin binding to heparin and heparan sulfate by surface plasmon resonance and molecular modeling: role of divalent cations, *J. Biol. Chem.* 279 (2004) 2927–2936. doi:10.1074/jbc.M309868200.
- [226] L. Jia, X.-A. Lu, G. Liu, S. Wang, M. Xu, Y. Tian, S. Zhang, Y. Fu, Y. Luo, Endostatin Sensitizes p53-Deficient Non-Small Cell Lung Cancer to Genotoxic Chemotherapy by Targeting DNA-PKcs, *J. Pathol.* (2017). doi:10.1002/path.4952.
- [227] M. Rahman, A.P.K. Chan, M. Tang, I.T. Tai, A peptide of SPARC interferes with the interaction between caspase8 and Bcl2 to resensitize chemoresistant tumors and enhance their regression in vivo, *PLoS ONE.* 6 (2011) e26390. doi:10.1371/journal.pone.0026390.

- [228] L. Liu, Y. Qiao, C. Hu, Y. Liu, Y. Xia, L. Wang, B. Liu, H. Chen, X. Jiang, Endostatin exerts radiosensitizing effect in non-small cell lung cancer cells by inhibiting VEGFR2 expression, *Clin Transl Oncol.* 18 (2016) 18–26. doi:10.1007/s12094-015-1319-6.
- [229] M.E. Akerman, J. Pilch, D. Peters, E. Ruoslahti, Angiostatic peptides use plasma fibronectin to home to angiogenic vasculature, *Proc. Natl. Acad. Sci. U.S.A.* 102 (2005) 2040–2045. doi:10.1073/pnas.0409844102.
- [230] Z. Wang, Z. Li, Y. Wang, D. Cao, X. Wang, M. Jiang, M. Li, X. Yan, Y. Li, Y. Liu, F. Luo, Versican silencing improves the antitumor efficacy of endostatin by alleviating its induced inflammatory and immunosuppressive changes in the tumor microenvironment, *Oncol. Rep.* 33 (2015) 2981–2991. doi:10.3892/or.2015.3903.
- [231] M. Myren, D.J. Kirby, M.L. Noonan, A. Maeda, R.T. Owens, S. Ricard-Blum, V. Kram, T.M. Kilts, M.F. Young, Biglycan potentially regulates angiogenesis during fracture repair by altering expression and function of endostatin, *Matrix Biol.* 52–54 (2016) 141–150. doi:10.1016/j.matbio.2016.03.008.
- [232] D.M. Neskey, A. Ambesi, K.M. Pumiglia, P.J. McKeown-Longo, Endostatin and anastellin inhibit distinct aspects of the angiogenic process, *J. Exp. Clin. Cancer Res.* 27 (2008) 61. doi:10.1186/1756-9966-27-61.
- [233] P.N. Bishop, The role of extracellular matrix in retinal vascular development and preretinal neovascularization, *Exp. Eye Res.* 133 (2015) 30–36. doi:10.1016/j.exer.2014.10.021.
- [234] X. Chen, H. Zhang, H. Zhu, X. Yang, Y. Yang, Y. Yang, H. Min, G. Chen, J. Liu, J. Lu, H. Cheng, X. Sun, Endostatin combined with radiotherapy suppresses vasculogenic mimicry formation through inhibition of epithelial-mesenchymal transition in esophageal cancer, *Tumour Biol.* 37 (2016) 4679–4688. doi:10.1007/s13277-015-4284-3.
- [235] A.-W. Zheng, D.-D. Jia, L.-M. Xia, G. Jin, H. Wu, T. Li, Impact of carboplatin plus paclitaxel combined with endostar against A375 melanoma cells: An in vitro and in vivo analysis, *Biomed. Pharmacother.* 83 (2016) 1321–1326. doi:10.1016/j.biopha.2016.08.047.
- [236] B. Rong, S. Yang, W. Li, W. Zhang, Z. Ming, Systematic review and meta-analysis of Endostar (rh-endostatin) combined with chemotherapy versus chemotherapy alone for treating advanced non-small cell lung cancer, *World J Surg Oncol.* 10 (2012) 170. doi:10.1186/1477-7819-10-170.
- [237] Y. Shi, Y. Sun, Medical management of lung cancer: Experience in China, *Thorac Cancer.* 6 (2015) 10–16. doi:10.1111/1759-7714.12168.
- [238] W. Hu, J. Fang, J. Nie, L. Dai, J. Zhang, X. Chen, X. Ma, G. Tian, D. Wu, S. Han, J. Han, Y. Wang, J. Long, Efficacy and safety of extended use of platinum-based doublet chemotherapy plus endostatin in patients with advanced nonsmall cell lung cancer, *Medicine (Baltimore).* 95 (2016) e4183. doi:10.1097/MD.0000000000004183.
- [239] W. Huang, J. Liu, F. Wu, K. Chen, N. Li, Y. Hong, C. Huang, H. Zhen, L. Lin, The efficacy and safety of endostar combined with taxane-based regimens for HER-2-negative metastatic breast cancer patients, *Oncotarget.* 7 (2016) 31501–31507. doi:10.18632/oncotarget.8967.
- [240] H. Jiang, X. Wu, H. Wang, C. Huang, L. Zhang, Combined Anti-PLGF and Anti-Endostatin Treatments Inhibit Ocular Hemangiomas, *Cell. Physiol. Biochem.* 36 (2015) 930–936. doi:10.1159/000430267.
- [241] T. Nishimoto, L. Mlakar, T. Takihara, C. Feghali-Bostwick, An endostatin-derived peptide orally exerts anti-fibrotic activity in a murine pulmonary fibrosis model, *Int. Immunopharmacol.* 28 (2015) 1102–1105. doi:10.1016/j.intimp.2015.07.039.

- [242] K.P. Doyle, T. Yang, N.S. Lessov, T.M. Ciesielski, S.L. Stevens, R.P. Simon, J.S. King, M.P. Stenzel-Poore, Nasal administration of osteopontin peptide mimetics confers neuroprotection in stroke, *J. Cereb. Blood Flow Metab.* 28 (2008) 1235–1248. doi:10.1038/jcbfm.2008.17.
- [243] A.-M. Albertsson, X. Zhang, J. Leavenworth, D. Bi, S. Nair, L. Qiao, H. Hagberg, C. Mallard, H. Cantor, X. Wang, The effect of osteopontin and osteopontin-derived peptides on preterm brain injury, *J Neuroinflammation.* 11 (2014) 197. doi:10.1186/s12974-014-0197-0.
- [244] R.-L. Ding, F. Xie, Y. Hu, S.-Z. Fu, J.-B. Wu, J. Fan, W.-F. He, Y. He, L.-L. Yang, S. Lin, Q.-L. Wen, Preparation of endostatin-loaded chitosan nanoparticles and evaluation of the antitumor effect of such nanoparticles on the Lewis lung cancer model, *Drug Deliv.* 24 (2017) 300–308. doi:10.1080/10717544.2016.1247927.
- [245] F. Pan, W. Yang, W. Li, X.-Y. Yang, S. Liu, X. Li, X. Zhao, H. Ding, L. Qin, Y. Pan, Conjugation of gold nanoparticles and recombinant human endostatin modulates vascular normalization via interruption of anterior gradient 2-mediated angiogenesis, *Tumour Biol.* 39 (2017) 1010428317708547. doi:10.1177/1010428317708547.
- [246] W. Li, X. Zhao, B. Du, X. Li, S. Liu, X.-Y. Yang, H. Ding, W. Yang, F. Pan, X. Wu, L. Qin, Y. Pan, Gold Nanoparticle-Mediated Targeted Delivery of Recombinant Human Endostatin Normalizes Tumour Vasculature and Improves Cancer Therapy, *Sci Rep.* 6 (2016) 30619. doi:10.1038/srep30619.
- [247] Y. Sawada, M. Sakai, T. Yoshikawa, K. Ofuji, T. Nakatsura, A glypican-3-derived peptide vaccine against hepatocellular carcinoma, *Oncoimmunology.* 1 (2012) 1448–1450. doi:10.4161/onci.21351.
- [248] J. Filmus, M. Capurro, Glypican-3: a marker and a therapeutic target in hepatocellular carcinoma, *FEBS J.* 280 (2013) 2471–2476. doi:10.1111/febs.12126.
- [249] K. Ofuji, K. Saito, T. Yoshikawa, T. Nakatsura, Critical analysis of the potential of targeting GPC3 in hepatocellular carcinoma, *J Hepatocell Carcinoma.* 1 (2014) 35–42. doi:10.2147/JHC.S48517.
- [250] Y. Haruyama, H. Kataoka, Glypican-3 is a prognostic factor and an immunotherapeutic target in hepatocellular carcinoma, *World J. Gastroenterol.* 22 (2016) 275–283. doi:10.3748/wjg.v22.i1.275.
- [251] T. Iwama, K. Horie, T. Yoshikawa, D. Nobuoka, M. Shimomura, Y. Sawada, T. Nakatsura, Identification of an H2-Kb or H2-Db restricted and glypican-3-derived cytotoxic T-lymphocyte epitope peptide, *Int. J. Oncol.* 42 (2013) 831–838. doi:10.3892/ijo.2013.1793.
- [252] Y. Sawada, T. Yoshikawa, D. Nobuoka, H. Shirakawa, T. Kuronuma, Y. Motomura, S. Mizuno, H. Ishii, K. Nakachi, M. Konishi, T. Nakagohri, S. Takahashi, N. Gotohda, T. Takayama, K. Yamao, K. Uesaka, J. Furuse, T. Kinoshita, T. Nakatsura, Phase I trial of a glypican-3-derived peptide vaccine for advanced hepatocellular carcinoma: immunologic evidence and potential for improving overall survival, *Clin. Cancer Res.* 18 (2012) 3686–3696. doi:10.1158/1078-0432.CCR-11-3044.
- [253] Y. Sawada, T. Yoshikawa, K. Ofuji, M. Yoshimura, N. Tsuchiya, M. Takahashi, D. Nobuoka, N. Gotohda, S. Takahashi, Y. Kato, M. Konishi, T. Kinoshita, M. Ikeda, K. Nakachi, N. Yamazaki, S. Mizuno, T. Takayama, K. Yamao, K. Uesaka, J. Furuse, I. Endo, T. Nakatsura, Phase II study of the GPC3-derived peptide vaccine as an adjuvant therapy for hepatocellular carcinoma patients, *Oncoimmunology.* 5 (2016) e1129483. doi:10.1080/2162402X.2015.1129483.
- [254] Z. Sun, Y. Zhu, J. Xia, T. Sawakami, N. Kokudo, N. Zhang, Status of and prospects for cancer vaccines against hepatocellular carcinoma in clinical trials, *Biosci Trends.* 10 (2016) 85–91. doi:10.5582/bst.2015.01128.

- [255] J.-H. Lee, Y. Lee, M. Lee, M.K. Heo, J.-S. Song, K.-H. Kim, H. Lee, N.-J. Yi, K.-W. Lee, K.-S. Suh, Y.-S. Bae, Y.J. Kim, A phase I/IIa study of adjuvant immunotherapy with tumour antigen-pulsed dendritic cells in patients with hepatocellular carcinoma, *Br. J. Cancer*. 113 (2015) 1666–1676. doi:10.1038/bjc.2015.430.
- [256] S. Suzuki, T. Yoshikawa, T. Hirotsawa, K. Shibata, F. Kikkawa, Y. Akatsuka, T. Nakatsura, Glypican-3 could be an effective target for immunotherapy combined with chemotherapy against ovarian clear cell carcinoma, *Cancer Sci*. 102 (2011) 1622–1629. doi:10.1111/j.1349-7006.2011.02003.x.
- [257] S. Suzuki, K. Shibata, F. Kikkawa, T. Nakatsura, Significant clinical response of progressive recurrent ovarian clear cell carcinoma to glypican-3-derived peptide vaccine therapy: two case reports, *Hum Vaccin Immunother*. 10 (2014) 338–343. doi:10.4161/hv.27217.
- [258] S. Suzuki, J. Sakata, F. Utsumi, R. Sekiya, H. Kajiyama, K. Shibata, F. Kikkawa, T. Nakatsura, Efficacy of glypican-3-derived peptide vaccine therapy on the survival of patients with refractory ovarian clear cell carcinoma, *Oncoimmunology*. 5 (2016) e1238542. doi:10.1080/2162402X.2016.1238542.
- [259] X. Zhou, Y. Liao, H. Li, Z. Zhao, Q. Liu, Dendritic cell vaccination enhances antiangiogenesis induced by endostatin in rat glioma, *J Cancer Res Ther*. 12 (2016) 198–203. doi:10.4103/0973-1482.151430.
- [260] A.-C. Bay-Jensen, Q. Liu, I. Byrjalsen, Y. Li, J. Wang, C. Pedersen, D.J. Leeming, E.B. Dam, Q. Zheng, P. Qvist, M.A. Karsdal, Enzyme-linked immunosorbent assay (ELISAs) for metalloproteinase derived type II collagen neopeptide, CIIM--increased serum CIIM in subjects with severe radiographic osteoarthritis, *Clin. Biochem*. 44 (2011) 423–429. doi:10.1016/j.clinbiochem.2011.01.001.
- [261] A. Dupont-Deshorgue, J.B. Oudart, B. Brassart, G. Deslee, J.M. Perotin, M.D. Diebold, J.C. Monboisse, L. Ramont, S. Brassart-Pasco, A competitive enzyme-linked immunosorbent assay for quantification of tetrastatin in body fluids and tumor extracts, *Anal. Biochem*. 482 (2015) 16–21. doi:10.1016/j.ab.2015.04.023.
- [262] J.B. Oudart, S. Brassart-Pasco, E. Luczka, A. Dupont-Deshorgue, G. Bellon, S.P. Boudko, H.P. Bächinger, J.C. Monboisse, F.X. Maquart, L. Ramont, Analytical methods for measuring collagen XIX in human cell cultures, tissue extracts, and biological fluids, *Anal. Biochem*. 437 (2013) 111–117. doi:10.1016/j.ab.2013.03.007.
- [263] R. Salza, J.-B. Oudart, L. Ramont, F.-X. Maquart, S. Bakchine, H. Thoannès, S. Ricard-Blum, Endostatin level in cerebrospinal fluid of patients with Alzheimer's disease, *J. Alzheimers Dis*. 44 (2015) 1253–1261. doi:10.3233/JAD-142544.
- [264] Z.-H. Wang, Z.-T. Zhu, X.-Y. Xiao, J. Sun, Correlation of serum levels of endostatin with tumor stage in gastric cancer: a systematic review and meta-analysis, *Biomed Res Int*. 2015 (2015) 623939. doi:10.1155/2015/623939.
- [265] M.A. Karsdal, K. Henriksen, F. Genovese, D.J. Leeming, M.J. Nielsen, B.J. Riis, C. Christiansen, I. Byrjalsen, D. Schuppan, Serum endotrophin identifies optimal responders to PPAR $\gamma$  agonists in type 2 diabetes, *Diabetologia*. 60 (2017) 50–59. doi:10.1007/s00125-016-4094-1.
- [266] K. Sun, J. Park, M. Kim, P.E. Scherer, Endotrophin, a multifaceted player in metabolic dysregulation and cancer progression, is a predictive biomarker for the response to PPAR $\gamma$  agonist treatment, *Diabetologia*. 60 (2017) 24–29. doi:10.1007/s00125-016-4130-1.
- [267] A. Fenton, M.D. Jesky, C.J. Ferro, J. Sørensen, M.A. Karsdal, P. Cockwell, F. Genovese, Serum endotrophin, a type VI collagen cleavage product, is associated with increased mortality in chronic kidney disease, *PLoS ONE*. 12 (2017) e0175200. doi:10.1371/journal.pone.0175200.

- [268] H. Skjøt-Arkil, N. Barascuk, T. Register, M.A. Karsdal, Macrophage-mediated proteolytic remodeling of the extracellular matrix in atherosclerosis results in neoepitopes: a potential new class of biochemical markers, *Assay Drug Dev Technol.* 8 (2010) 542–552. doi:10.1089/adt.2009.0258.
- [269] D.J. Leeming, M.A. Karsdal, I. Byrjalsen, F. Bendtsen, J. Trebicka, M.J. Nielsen, C. Christiansen, S. Møller, A. Krag, Novel serological neo-epitope markers of extracellular matrix proteins for the detection of portal hypertension, *Aliment. Pharmacol. Ther.* 38 (2013) 1086–1096. doi:10.1111/apt.12484.
- [270] A. Arvanitidis, K. Henriksen, M.A. Karsdal, A. Nedergaard, Neo-epitope Peptides as Biomarkers of Disease Progression for Muscular Dystrophies and Other Myopathies, *J Neuromuscul Dis.* 3 (2016) 333–346. doi:10.3233/JND-160150.
- [271] A.S. Siebuhr, Y. He, N.S. Gudmann, A. Gram, C.F. Kjølgaard-Petersen, P. Qvist, M.A. Karsdal, A.C. Bay-Jensen, Biomarkers of cartilage and surrounding joint tissue, *Biomark Med.* 8 (2014) 713–731. doi:10.2217/bmm.13.144.
- [272] G.K. Chalikias, D.N. Tziakas, Biomarkers of the extracellular matrix and of collagen fragments, *Clin. Chim. Acta.* 443 (2015) 39–47. doi:10.1016/j.cca.2014.06.028.
- [273] F. Peysselon, S. Ricard-Blum, Heparin-protein interactions: from affinity and kinetics to biological roles. Application to an interaction network regulating angiogenesis, *Matrix Biol.* 35 (2014) 73–81. doi:10.1016/j.matbio.2013.11.001.
- [274] C. Faye, E. Chautard, B.R. Olsen, S. Ricard-Blum, The first draft of the endostatin interaction network, *J. Biol. Chem.* 284 (2009) 22041–22047. doi:10.1074/jbc.M109.002964.
- [275] Y. Cai, J. Zhang, Z. Li, Multi-scale mathematical modelling of tumour growth and microenvironments in anti-angiogenic therapy, *Biomed Eng Online.* 15 (2016) 155. doi:10.1186/s12938-016-0275-x.
- [276] M. Baker, B.S. Brook, M.R. Owen, Mathematical modelling of cytokines, MMPs and fibronectin fragments in osteoarthritic cartilage, *J Math Biol.* (2017). doi:10.1007/s00285-017-1104-y.
- [277] G.S. Butler, R.A. Dean, C.J. Morrison, C.M. Overall, Identification of cellular MMP substrates using quantitative proteomics: isotope-coded affinity tags (ICAT) and isobaric tags for relative and absolute quantification (iTRAQ), *Methods Mol. Biol.* 622 (2010) 451–470. doi:10.1007/978-1-60327-299-5\_26.
- [278] 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 Proteomics.* 6 (2007) 611–623. doi:10.1074/mcp.M600341-MCP200.
- [279] 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 Proteomics.* 9 (2010) 894–911. doi:10.1074/mcp.M000050-MCP201.
- [280] P. Schlage, F.E. Egli, P. Nanni, L.W. Wang, J.N. Kizhakkedathu, S.S. Apte, U. auf dem Keller, Time-resolved analysis of the matrix metalloproteinase 10 substrate degradome, *Mol. Cell Proteomics.* 13 (2014) 580–593. doi:10.1074/mcp.M113.035139.
- [281] A.E. Starr, C.L. Bellac, A. Dufour, V. Goebeler, C.M. Overall, Biochemical characterization and N-terminomics analysis of leukolysin, the membrane-type 6 matrix metalloprotease (MMP25): chemokine and vimentin cleavages enhance cell migration and macrophage phagocytic activities, *J. Biol. Chem.* 287 (2012) 13382–13395. doi:10.1074/jbc.M111.314179.
- [282] T. Jefferson, U. Auf dem Keller, C. Bellac, V.V. Metz, C. Broder, J. Hedrich, A. Ohler, W. Maier, V. Magdolen, E. Sterchi, J.S. Bond, A. Jayakumar, H. Traupe, A. Chalaris, S. Rose-John, C.U. Pietrzik, R. Postina, C.M. Overall, C. Becker-Pauly, The

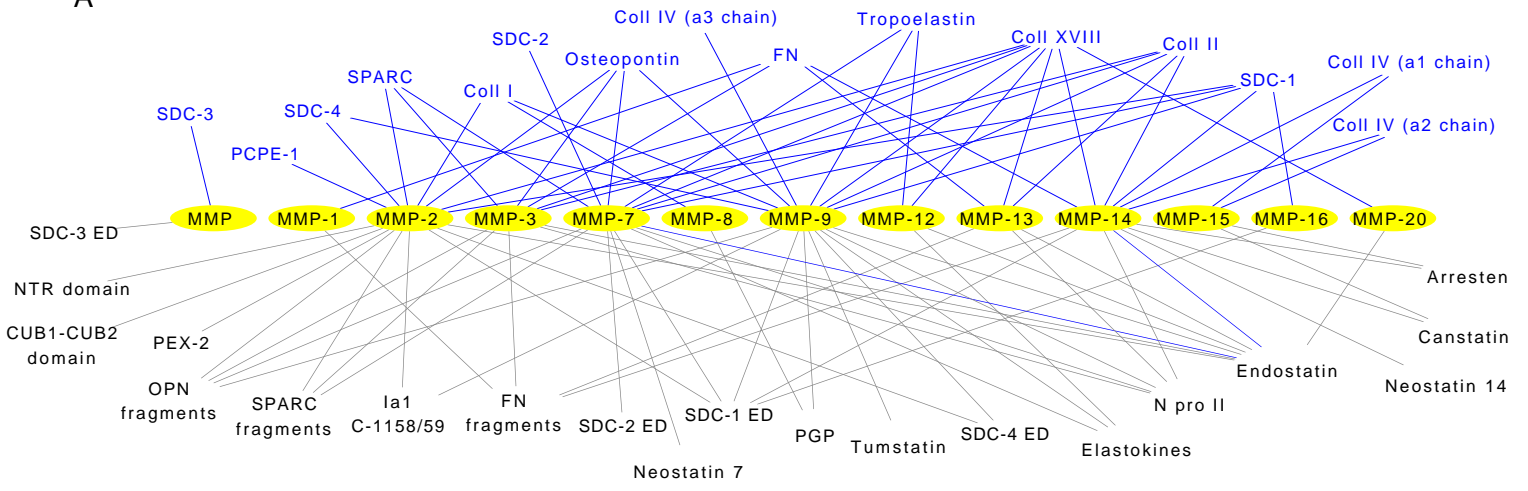
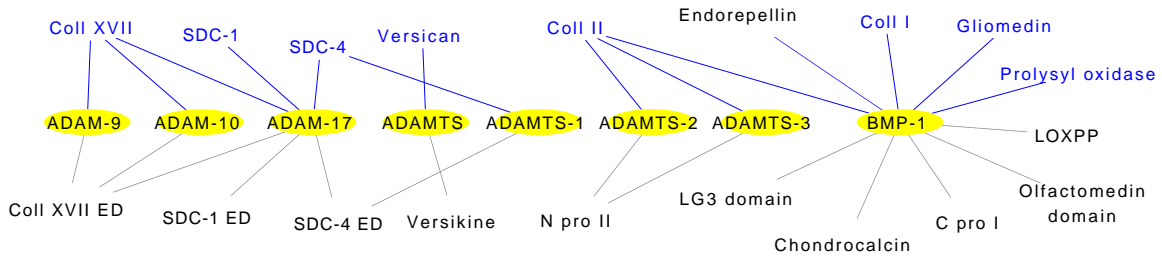
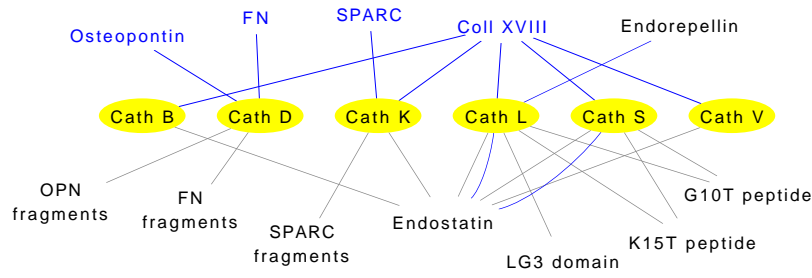
substrate degradome of meprin metalloproteases reveals an unexpected proteolytic link between meprin  $\beta$  and ADAM10, *Cell. Mol. Life Sci.* 70 (2013) 309–333. doi:10.1007/s00018-012-1106-2.

## FIGURE LEGENDS

**Figure 1:** Major protease families generating ECM bioactive fragments from ECM proteins: A) Matrix Metalloproteinases (MMPs), B) Other metalloproteinases (ADAMs, ADMTs, 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  $\beta$ 1, TLR2: toll-like receptor-2).



**A****B****C****D**