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Cell-matrix interactions: focus on proteoglycan-proteinase interplays and pharmacological targeting in cancer

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Abstract

Proteoglycans are major constituents of the extracellular matrices as well as the cell surfaces and basement membranes. They play key roles in supporting the dynamic extracellular matrix by generating complex structural networks with other macromolecules and by regulating cellular phenotypes and signaling. It is becoming evident, however, that proteolytic enzymes are required partners for matrix remodeling and for modulating cell signaling via matrix constituents. Proteinases contribute to all stages of diseases, particularly in cancer development and progression, and contextually participate in either the removal of damaged products or in the processing of matrix molecules and signaling receptors. Indeed, the dynamic interplay between proteoglycans and proteolytic enzymes is a crucial biological step that contributes to the pathophysiology of cancer and inflammation. Moreover, proteoglycans are implicated in the expression and secretion of proteolytic enzymes and often modulate their activities. In this review we present emerging biological roles of proteoglycans and proteinases with special emphasis on their complex interplay. We critically evaluate this important proteoglycan-proteinase interactome and discuss future challenges of potentially targeting this axis in the treatment of cancer.

Graphical Abstract

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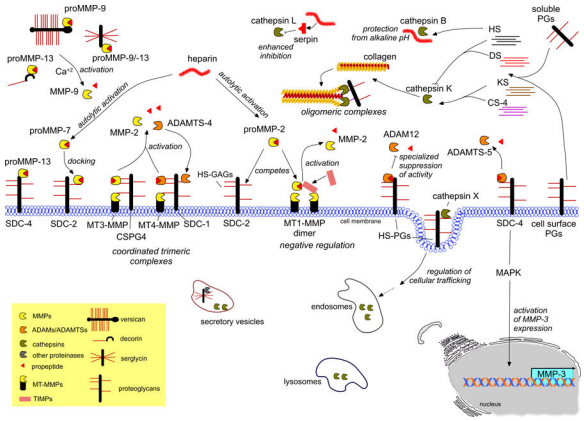

Proteolysis is a highly regulated and specific process. Here, we highlight recent findings, which suggest that PGs/GAG interplay regulates proteinases' activity, stability, substrate specificity and localization. The interaction between proteinases and proteoglycans may occur either through the GAG chains or the core protein of PGs. Such findings introduce a new avenue for specific cancer therapeutics.

Keywords

matrix metalloproteinases; proteoglycans; glycosaminoglycans; cathepsins; syndecans; serglycin; versican

INTRODUCTION

Extracellular matrix (ECM) is a highly dynamic and functional network, which is assembled from a variety of molecules. This network creates the scaffold where cells are hosted forming certain tissues and organs. ECM varies in composition among tissues and is continuously remodeled under physiological and pathological conditions. The changes in the expression of matrix molecules and the compositional alterations among them markedly affect the assembly of ECM and its ability to regulate a multitude of cellular functions. Among major ECM components are proteoglycans (PGs) as well as fibrillar proteins, like collagens and elastin, and other (glyco)proteins [1]. In cancer, PG expression is often altered in the stroma and this might contribute to disease progression or do quite the opposite. ECM remodeling is also a hallmark of cancer progression and in this process matrix proteinases play a central role [2]. Indeed, proteinases contribute to all stages of cancer development and progression. The intracellular proteases participate in the removal of damaged or undesirable products, whereas the extracellular proteases are actively involved in tumor progression and metastasis by degrading the majority of ECM macromolecules. Moreover, there are transmembrane proteases, which mostly target transmembrane receptors and signaling molecules [2–4]. Thus the interaction of PG and proteases is complex and often multifactorial, and generally operates in a cell- and tissue-contextual manner.

PROTEINASES: STRUCTURE, FUNCTIONS AND TARGETING IN CANCER

The term “proteinase” encompasses a large family of enzymes that catalyze the hydrolytic breakdown of proteins into peptides or amino acids at their terminal ends (exopeptidases) or inside the peptide chain (endopeptidases) [5]. According to the MEROPS database, the human degradome contains at least 569 proteinases distributed intra- and extracellularly, and classified based on the chemical moiety that participates in the hydrolysis (aspartic, cysteine, threonine, serine, and metallo-proteinases) [6]. This is in contrast to the PG family, which contains less than fifty genes. Thus a single PG would be expected to interact and modulate, on the average, more than ten proteases.

It is well recognized that proteinases contribute to all stages of tumor progression including tumor growth and survival, angiogenesis, cell invasion, cell adhesion, migration, EMT, immune surveillance and are produced not only by the tumor cells themselves, but also by the tumor microenvironment [2, 7, 8]. Metalloproteinases and cathepsins are among the major families of proteinases implicated in cancer cell biology. These two categories in terms of structure, function and possibilities for their targeting are described in detail below.

Metalloproteinases

The metzincin family of metalloproteinases is characterized by the presence of the conservative methionine residue at the active site and the use of a zinc ion in the enzymatic reaction [9]. This family comprises matrix mettalloproteinases (MMPs), a disintegrin and metalloproteinases (ADAMs) [4] and ADAMs with thrombospondin motifs (ADAMTSs) [10], the bacterial serralysins, and proteases such as the astacins (including the meprins) [10]. The most well studied representatives of this super-family are MMPs, as well as ADAMs and ADAMTSs. All members of the metalloproteinases family share domain structure similarities. The current MMP classification, based on substrate specificity, sequence similarity and domain organization categorize MMPs into six groups; collagenases, gelatinases, stromelysins, matrilysins, membrane type MMPs (MT-MMPs) and other MMPs [11]. A typical MMP structure involves several conserved distinct domains involving a N-terminal signal peptide responsible for secretion or plasma membrane insertion and a propeptide (containing highly conserved PRCGVPDV sequence) that following its proteolytic cleavage the enzyme is activated. The catalytic domain is defined by a 3-His motif (HEXXHXXGXXH) to which the catalytic zinc ion is held followed by a hemopexin domain responsible for the substrate specificity (except in MMP-7), and the interactions with other MMPs and tissue inhibitors of metalloproteinases (TIMPs) [12]. Furthermore, most ADAMs are type I transmembrane proteins that possess disintegrin, cysteine-rich, and EGF domains instead of MMP hemopexin domain, whereas ADAMTSs are secreted proteins that contain thrombospondin I motifs instead of the EGF and transmembrane domain [13].

MMPs represent one of the most-well studied classes and the main group of regulating proteinases in ECM. MMPs are responsible for the turnover and degradation of almost all ECM components [14], including collagens, fibronectin and laminins etc, as well as non-ECM cell regulators such as numerous cell-surface receptors, integrins, kinases, chemokines and cytokines [15, 16]. Thus, they are central regulators not only in physiological processes,

such as embryogenesis, remodeling, wound healing and angiogenesis, but also in pathological conditions.

Along with ADAMS, MMPs exert their actions in cancer progression not only by degrading the physical barriers that cancer cells encounter but also by increasing the availability of signaling effectors like growth factors and cytokines to the tumor milieu. They also act on ECM macromolecules such as collagen, PGs, integrins, cell surface receptors, generating regulatory molecules and modulating cell-cell and cell-matrix interactions [2, 17, 18]. However, some MMPs are anchored to the cell surface [i.e. MT-MMPs, ADAMS], following their intracellular activation, whereas most are produced as secreted proteins and activated extracellularly. As mentioned above, secreted metalloproteinases are produced as inactive zymogens that generally need to be proteolytically activated, involving removal of the propeptide by other proteinases or by autoactivation. It is well documented that pro-forms of metalloproteinases may be activated through allosteric interactions with other molecules "revealing" the active site form the propeptide. In the case of membrane bound metalloproteinases, a furin recognition sequence between their propeptide and catalytic domains allows the cleavage and activation by furin convertase enzymes in the Golgi apparatus [19].

ADAMTSs exert various functions such as angiogenesis inhibition, degradation of proteoglycans; aggrecan, versican and brevican, collagen processing, and blood coagulation, among others [20]. In the case of cancer, ADAMTSs may have dual effect either promoting or suppressing tumor growth. ADAMTS -1, -2 and -8 exert antiangiogenic effects and suppression of ADAMTS -1 stimulates breast cancer cell migration and invasion [20, 21]. Also ADAMTS -9 is down-regulated in liver metastasis of colorectal tumors [22]. On the other hand, ADAMTS -4 and -5 are up-regulated in gliomas [23].

Based on the critical importance of metalloproteinases in cancer progression, numerous metalloproteinases inhibitors have been developed with goal to target their synthesis, secretion, activation and enzymatic activity. Many strategies have been employed involving synthetic MMPIs like peptidomimetics, mimicking metalloproteinases substrates and functioning as competitive inhibitors, non-peptidomimetic compounds interacting with the catalytic zinc ion and inhibiting enzymatic activity, as well as chemical derivatives of tetracycline group of drugs which lack antimicrobial action to antibody-based inhibitors and tetracycline like derivatives. The use of natural MMPs' inhibitors like genistein contradicted the high toxicity profile observed with the synthetic MMPIs. In that line, antibody-based MMP inhibitors, as well as novel mechanism-based inhibitors were introduced to the field. Last, several off-target inhibitors such as bisphosphonates are documented in the literature to inhibit indirectly MMPs [3, 4, 24–28]. Bisphosphonates are used in clinical practice for treatment of osteoporosis and bone metastasis. It has been found that zolendronic acid, a third generation bisphosphonate used in clinical practice, can modulate expression of ECM genes [29, 30].

The various targeting strategies developed though time involve at first the generation of wide-spectrum inhibitors reaching nowadays to more selective targeting. Batimastat (BB94) and Ilomastat (GM-6001) peptidomimetics, followed by improved second-generation

inhibitors Marimastat (BB2516), Prinomastat (AG3340), BAY12-9566) were the first anticancer MMP inhibitors that entered cancer clinical trials. Several clinical trials of such inhibitors have been carried tested alone and in combination with standard chemotherapeutic drugs. The outcomes were controversial resulting in the discontinuation of Phase III clinical trials due to lack of efficacy or severe musculoskeletal side effects in some patients [2, 25, 31–33]. The clinical failures are attributed to the multiple and in some cases dual roles of metalloproteinases at different stages of cancer progression, such as tumor stage, site, enzyme localization and substrate profile [34]. Despite significant clinical interest, it has proven difficult to achieve selective inhibition of metalloproteinases due their common active site [35]. However, the emerging evolution of proteinases degradomics leads to novel inhibition strategies of metalloproteinases based on blocking exosite-mediated cell surface interactions and activation as well as multifunctional inhibitors able to interact with both the active site and exosites, unique to individual metalloproteinases [36–39]. Although ADAMTSs have a structure similar to MMPs, unlike the other metalloproteinases, they have a narrow substrate specificity [40]. This characteristic might give an advantage to ADAMTSs inhibitors vis-à-vis other metalloproteinase inhibitors. Although targeting of ADAMTSs to fight cancer is promising, more mechanistic studies need to be done to fully understand how each ADAMTS is implicated in cancer development and progression [41]. Current efforts focus on designing inhibitors of ADAMTS-4 and -5 that could fight arthritis [40]. Pentosan polysulfate, a chemically-sulfated xylanopyranose, is a multifaceted exosite inhibitor of ADAMTS-4 and -5. It interacts with the noncatalytic spacer domain of ADAMTS-4 and the cysteine-rich domain of ADAMTS-5, blocking their activity. It also mediates the formation of a high-affinity trimolecular complex with ADAMTS-5 and TIMP-3 improving the efficacy of TIMP-3 as an aggrecanase inhibitor [42, 43]. Notably, some inhibitors of ADAMs used in clinical cancer trials were interrupted because of liver toxicity. Despite this handicap, ADAMs inhibitors remain a promising target for cancer treatment. Selective inhibitors, such as INCB3619 [44] G1254023X [45] and KB-R7785 [46], have generated promising results in pre-clinical studies.

Cathepsins

Cathepsins belong to a large family of proteases found in mammals as well as other organisms. Depending on their structure, their catalytic type and the proteins they cleave, cathepsins are classified in three different groups: (I) Aspartic proteases, including cathepsins D and E; (II) Serine proteases, including cathepsins A and G; and (III) Cysteine proteases, consisting of 11 papain-like lysosomal cathepsins (B, C, F, H, L, K, O, S, V, X and W) [6]. The majority of cathepsins and more specifically cysteine cathepsins are optimally active efficient in acidic compartments, and, thus, are often located within lysosomes and acidic endosomes [47, 48]. However, cathepsins are also present within secretory vesicles, cytosol and nuclei [49–53]. Several cathepsins. i.e., cathepsins B, H, L, X, are ubiquitously expressed, whereas cathepsins S, V, F, C and W are specifically expressed by particular tissues or cell types [54]. For instance, cathepsin K is strongly expressed in osteoclasts [55] and cathepsin W is mainly expressed in CD8 and natural killer cells [56]. As mentioned above, the structure and the mechanism of action of the cathepsins differ among the three groups.

All papain-like cysteine cathepsins consist of three functional regions. The signal peptide, the propeptide, which contributes in several functions such as the proper folding of the active enzyme and finally the catalytic site of the enzyme [54]. Their catalytic mechanism is in common with other cysteine proteases. Through their proteolytic action, cathepsins regulate vital processes in both physiological and pathological conditions. Therefore, cathepsins are involved in processes such as the collagen turnover in bone and cartilage [57, 58], hormone production [59] and the regulation of antigen presentation in the immune system [60]. However, a variety of cathepsins play a regulatory role in several diseases. For example, cathepsins K, L, S and B are expressed in patients with bone and cartilage diseases such as rheumatoid arthritis and osteoarthritis, contributing to bone destruction [61–64]. In addition, cathepsins are also implicated in cardiovascular diseases, immune defects, lung diseases and cancer. Particularly in cancer, the role of cathepsins in the progression of the diseases has been reviewed [65, 66]. Although it has been suggested that a variety of cathepsins are implicated in cancer, most studies focus on the action of cathepsins B, S and L. Cathepsins demonstrate elevated expression and activity levels in many tumor cells contributing to cancer cell invasion, migration and metastasis, commonly through ECM degradation or by promoting the availability of several growth factors. For example, cathepsin B is over-expressed in many tumor cells including breast, colon, brain, lung and prostate [67–77]. Among its oncogenic effects, cathepsin B leads in enhanced MMPs activity through degradation of TIMPs [78] and is suggested to assist in the activation of oncogenic signaling of TGF-β [79]. In breast cancer cells, activation of ErbB2 receptor induces cathepsin B expression promoting invasiveness [75]. Cathepsin B over-expression increases ECM degradation fostering collective cell invasion into adjacent tissue [68]. Cathepsin B and pro-uPA are located on tumor cells surface together with their receptors in a caveolin-1 dependent manner thus mediating cell-surface proteolytic events associated with invasion of colon cancer cells [69]. The importance of uPAR and cathepsin B in the regulation of malignant stem cell self-renewal through regulation of hedgehog signaling components, Bmi1 and Sox2, has been also highlighted [72]. Selective inhibition of cathepsin B leads to limited breast to bone metastasis [77] and reduced invasion of breast cancer cells [76]. Moreover, the inhibition of cathepsin S significantly reduced the migration of aggressive lung adenocarcinoma and melanoma cells [80].

Several inhibitors specifically targeting particular cathepsins have been developed. The majority of them are peptidic or peptidomimetic molecules which covalently interact with the active site of the cysteine cathepsins. Apart from general inhibitor of cysteine cathepsins, inhibitors of higher specificity need to developed and tested for their efficiency in targeting particular enzymes of this family. The most recent inhibitors against cathepsin K include balicatib and odanacatib, which are nitrile-based inhibitors, relacatib, a non-basic azepanone analogue, as well as ONO-5334 and MIV-711. These inhibitors have been used in preclinical and clinical trials inhibiting bone resorption and increasing bone mineral density [65, 81, 82]. Targeting cathepsin B may be valuable for treatment of cancer progression. CA-074, a small molecule inhibitor of cathepsin B, reduces metastasis in tumor-bearing animals indicating a pro-metastatic role for cathepsin B in breast cancer and therefore illustrating the therapeutic benefits of its inhibition *in vivo* [77]. Similarly, CA-074 also prevents human melanoma growth as wells as lung metastasis [83]. The majority of cathepsins inhibitors

target the active site of the enzyme blocking their catalytic activity. As cathepsins are ubiquitously expressed, direct inhibition of a given cathepsin could affect its physiological action in other tissues, causing significant off-target effects. In addition, the selectivity of the inhibitor is crucial for the appearance of side effects. For example two cathepsin K inhibitors, relicatib and balicatib were excluded from clinical trial due to lack of specificity. Balicatib is selective for cathepsin K in enzyme assays, while it is not in whole-cells assays. Furthermore, balicatib may cause skin rashes and morphea-like skins incidences [84].

PROTEOGLYCANS: BIOLOGICAL ROLES, THEIR RELATIONS WITH PROTEINASES AND TARGETING IN CANCER

PGs are complex macromolecules, which are composed of a core protein that carries one or more covalently linked glycosaminoglycan (GAG) chains. GAGs are linear polysaccharides, which are composed of repeating disaccharides of hexosamines (N-acetyl-galactosamine or N-acetyl-glucosamine) and uronic acids (D-glucuronic acid or L-iduronic acid) being sulfated at various positions. Keratan sulfate (KS) is the only GAG to be comprised of repeating disaccharides containing N-acetyl-glucosamine and galactose. Notably, hyaluronan (HA) is the only GAG which is not covalently bound to PG protein core, and it has been shown that its synthesis is epigenetically regulated [85]. The number and the type of GAG chains as well as the specific structure of each GAG chain covalently linked to protein cores may greatly differ [86, 87]. These variations in the overall PG structure may be cell- and tissue-specific but may also depend on the differentiation stage and the action of various stimuli on the cells. The structural diversity of PGs determines their functional heterogeneity making them biological chameleons [86, 88]. According to their localization, PGs are categorized as ECM-secreted, cell surface associated and intracellular ones. They can interact with almost all proteins in ECM with different affinities. Their GAGs chains are mainly implicated in these interactions although their protein cores are sometimes involved. Apart from their participation in the organization of ECM and regulation of its mechanical properties, PGs interact with growth factors, cytokines and chemokines protecting them from degradation and form effective gradients of these components in ECM [86]. Furthermore, PGs act as co-receptors for these molecules promoting their signaling. The proven ability of PGs to form complexes with growth factor receptors results in the regulation of their signaling properties. PGs regulate cell behavior and phenotype. They are involved in cell proliferation, adhesion, migration and invasion. In this context, certain PGs affect the expression of bioactive molecules, their secretion, localization and activity [86, 88]. PGs are well established as key players in the regulation of physiological and pathological conditions, such as cardiovascular diseases including myocardial dysfunction and failure as well as cancer development and progression [86, 89]. The major PG families involved in cancer progression and have been also related to certain proteinases are presented below.

Versican

Versican is a chondroitin sulfate (CS)/dermatan sulfate (DS) proteoglycan (CS/DSPG), which is present in ECM of many tissues. It belongs to subfamily of hyalectans, for hyaluronan and lectin binding proteoglycans [90]. Versican is essentially composed of three

modular domains: an N-terminal domain with the ability to bind hyaluronan (HA) through its globular domain (G1), a central domain that harbors CS or/and DS, and a C-terminal globular domain (G3), which exhibits lectin-like activity, located in the C-terminal. Versican exist as a full-length proteoglycan (named V0) and three splice variants (V1, V2 and V3). They differ in the central domain and carry different number of GAG chains (V0, V1 and V2), whereas the third splice variant V3 lacks completely the GAG attachment region and it should be considered as a protein and not as true PG [86, 91, 92]. Versican is highly expressed in most malignancies and has been associated with cancer relapse and poor patient outcome in breast, prostate and other cancer types [86, 88, 93–99]. Versican is predominantly secreted by the activated peritumoral stromal cells in malignancies in response to various stimuli. Its expression is up-regulated in cancer associated fibroblasts upon TGF-β treatment and promotes the motility and invasion of ovarian cancer cells by activating the NF-κB signaling pathway and by up-regulating expression of CD44, MMP-9, and the HA-mediated motility receptor [100]. However, some cancer cells can also secrete versican [86, 101–105]. Versican modulates the adhesion of cancer cells to ECM and increases their motility, proliferation and metastasis [86]. Versican is highly expressed in sporadic clear cell renal cell carcinoma [101]. Its expression is associated with the expression of CD26 on T-anaplastic large cell lymphoma. Abrogation of versican expression results in decreased levels of MT1-MMP and CD44 and marked suppression of T-cell adhesion and invasion [102]. Versican is substrate for ADAMTS and the use of antibodies against to ADAMTS specific versican cleavage site inhibits glioma cell migration [106]. ADAMTS are often over-expressed in various tumors and the formation of neo-epitopes of versican fragments within tumor stroma may be used for targeted therapy. In this context, a novel versican isoform V4 is highly expressed in breast cancer [107], whereas versican is also differentially glycosylated in breast cancer since it contains more sialic acid [108]. This alternative splice variant of versican or the presence of unusual glycosylation may be possible targets for therapeutic intervention with antibody-related agents. Furthermore, disruption of the HA–CD44 interaction with HA oligomers may be also used for targeting tumor progression. HA oligomers can block the acquisition of a HA-versican pericellular matrix by ovarian cancer cells that increases their metastatic potential and are promising inhibitors of cancer dissemination [109].

Decorin

Another important class of matrix PGs is the small leucine-rich PG (SLRP) family, with decorin being the most studied member of this family with well-documented implication in cancer [110]. Decorin is a CS/DSPG that plays an important role in tumor progression by affecting both the composition of the tumor stroma as well as tumor cell growth [86, 88, 94–96, 98, 99, 111]. Specifically, decorin protein core has a potent antitumor effect by interfering with several signaling pathways and repressing and attenuating tumor cell survival, growth, migration and angiogenesis. Soluble decorin is a robust pan-RTK inhibitor targeting not only EGFR, but also Met, IGF-IR, VEGFR2 and PDGFR [112–117]. Indeed, soluble decorin can be considered a tumor repressor [118] that possesses anti-oncogenic and anti-metastatic [119] properties and, thus, it has been proposed to be a “guardian from the matrix” [120]. Decorin protein core binds to EGFR leading to rapid caveolar endocytosis and lysosomal degradation [121]. This interaction also promotes ERK1/2 signaling and

transcription of p21 leading to tumor cell growth arrest [122] as well as caspase-3 activation and induction of apoptosis [123]. Notably, decorin inhibits angiogenesis [120] by directly antagonizing the pro-angiogenic Met and simultaneous suppression of HIF-1α and VEGFA transcription [124, 125]. Decorin favors angiostasis by rapidly inducing the secretion of thrombospondin-1 [126], a key antiangiogenic factor [127, 128]. Thus, soluble decorin is an endogenous anti-oncogenic agent [86, 110], a notion supported by robust genetic evidence indicating that targeted deletion of the decorin gene is permissive for tumorigenesis [129, 130]. Adenoviral-mediated gene delivery of decorin or systemic administration human recombinant decorin or decorin protein core to various tumor xenograft models (breast and prostate carcinomas), suppress tumor growth [131–135]. The recent discoveries that decorin is pro-inflammatory and interacts with Toll-like receptors [136] together with induction of autophagy in endothelial cells [137] and mitophagy in breast cancer cells [138] indicate that decorin can affect both the tumor stroma and the tumor proper in a variety of ways. As decorin interacts with various metalloproteases, directly or indirectly by modulating their production, it is likely that this important endogenous factor might be involved in the turnover not only of matrix molecules, but, most importantly, in the cleavage and processing of cell surface receptors.

Syndecans

Syndecans are type 1 transmembrane heparan sulfate (HS) PGs (HSPGs) that have important roles during development, wound healing, neural and glioma stem cell differentiation as well as in tumor progression [139–141]. There are four syndecans in mammals with different distribution among tissues. Syndecan-1 is expressed at early stages during development, in epithelial and cancer cells in adults as well as in some leukocytes. Syndecan-2 is synthesized in mesenchymal tissues, fibroblasts, liver and neuronal cells. Syndecan-3 is present in neural and musculoskeletal tissues, whereas syndecan-4 is ubiquitously distributed. Syndecan-1 and syndecan-3 may also carry CS apart from HS chains. Syndecans interact with numerous ECM molecules, growth factors, chemokines and cytokines primarily via their HS chains. Thus, they influence cell proliferation, differentiation, adhesion and migration often in co-operation with other cell surface receptors [139, 140].

Syndecans are expressed in various tumor types possessing diverse roles according to tumor type and stage of the disease, acting either as promoters or inhibitors of tumor progression [139]. Synstatin, a syndecan-derived peptide inhibitor, interferes with syndecan-1/αvβ3 integrin interaction and indirectly attenuates angiogenesis and impairs mammary tumor growth in a mouse tumor model suggesting that syndecan-1 might be involved in regulating angiogenesis and tumorigenesis [142, 143]. Syndecan-1 plays important role in supporting α2β1 integrin-mediated adhesion to collagen. The formation of syndecan-1/α2β1 integrin contributes to proper organization of cortical actin and enhances the transcription of MMP-1 in response to collagen binding [144]. Activation of K-Ras in tumor cells correlates with increased expression of α2β1 integrin, MT1-MMP, syndecan-1, and syndecan-4. α2β1 integrin and MT1-MMP are positive regulators of invasion, whereas syndecans inhibit cell invasion into 3D collagen matrix [145]. Syndecan-1 serves as collagen receptor in squamous cancer cells in addition to α2β1 integrin and promotes strong cell adhesion. Lowering syndecan-1 levels results in enhanced cell spreading and motility on collagen I by

modulating RhoA and Rac activity, but does not affect cell motility on other ECM substrates [146]. Syndecan levels at the cell surface are regulated by a fine-tuned proteolytic cleavage, which is called shedding. Syndecans are cleaved by various proteases such as MMPs, ADAMTS and ADAMS, in their extracellular domain near the plasma membrane [139, 147]. This process is regulated by a variety of stimuli such as growth factors, chemokines, oxidative stress, heparanase and others [139, 147]. Shed syndecan ectodomains are implicated in several steps of cancer progression. For example soluble syndecan-1 may bind growth factors and chemokines protecting them from inactivation and promote their signaling in tumor microenvironment or may sequester inhibitory signals for tumor cells [86, 139].

Syndecans may be potential targets for tumor therapy due to their well-documented implication in tumorigenesis. A possibility is to directly target syndecans by using therapeutic antibodies in malignancies where these molecules are highly expressed [86, 139, 148–150]. Another option is to target the formation of functional syndecan complexes with other receptors such as integrins and growth factor receptors by using synthetic molecules such as synstatin [151]. Blocking of syndecans shedding either by inhibiting heparanase activity using specific inhibitors or proteinase inhibitors may be also of interest [152–154]. It is worth noticing that many drugs used in cancer therapy can regulate the expression levels of syndecans and may benefit patients [29, 30, 155, 156]. Furthermore, syndecans' function in cancer is regulated by miRNAs and this open a new area of research [157].

CSPG4/NG2

Neuron-glial antigen 2 (NG2) also known as chondroitin sulfate proteoglycan 4 (CSPG4) or melanoma associated CSPG, is a transmembrane PG, which is up-regulated in several tumor types and play important role in tumor cell proliferation, survival, migration and tumor progression [158]. Expression of CSPG4 enhances integrin-mediated cell spreading, FAK phosphorylation, and activation of ERK1/2 through independent mechanisms [159]. Furthermore, CSPG4 is implicated in the activation of pro-MMP-2 by MT3-MMP [160, 161]. CSPG4 mediates tumor cell adhesion and spreading on collagen VI by cooperating with $\alpha 2\beta 1$ integrin and activating PI-3K [162]. CSPG4 is an attractive target for antibody-based cancer immunotherapy because of its proven role in tumor cell biology, its high expression on tumor and cancer stem cells and its restricted distribution in normal tissues [158, 163]. The development and use of several therapeutic antibodies give promising results in cancer treatment [158, 163–166]. Furthermore, T lymphocytes genetically modified with a CSPG4-specific chimeric antigen receptor controlled tumor growth *in vitro* and *in vivo* in mice engrafted with various tumor cells. This suggests that CSPG4-redirected T cells should provide an effective treatment modality for a variety of solid tumors [167].

Serglycin

Serglycin is an intracellular PG that is highly expressed in hematopoietic cells. It is involved in the proper formation of secretory granules and vesicles as well as the storage and secretion of several components in ECM [168]. Serglycin can carry HS, heparin, CS and DS chains and its glycanation depends on the cellular source of serglycin [168]. Several studies have demonstrated the involvement of serglycin in tumorigenesis [169–174]. Serglycin with

different GAG chains and sulfation patterns is expressed in several hematopoietic and non-hematopoietic tumors [168]. The role of serglycin in malignancies is rather intriguing since it seems to participate in tumor development in a manner that at least partially requires interactions between tumor cells and their microenvironment [175]. In mast cells, serglycin is present in intracellular granules where is implicated in the storage of granule-localized proteases such as chymases, tryptases and carboxypaptidase A [176, 177]. Mast cell proteases exert dual roles in the regulation of inflammation and tumorigenesis. Several pro-inflammatory chemokines and cytokines are substrates of mast cell proteases and their cleavage can result in either activation or inactivation of inflammatory mediators. Serglycin is over-expressed and is constitutively secreted in multiple myeloma carrying CS side chains [174, 178]. It is also localized on the cell surface where is attached through its CS-4 chains promoting the adhesion of myeloma cells to collagen I as well as the biosynthesis and secretion of MMP-9 and MMP-2 [173]. Serglycin is involved in the biosynthesis and secretion of proteases. For example, Madin-Darby canine kidney cells stably transfected with serglycin express elevated levels of MMP-9 and urokinase plasminogen activator (uPA) [179]. Recently it has been shown that serglycin bearing CS chains is the major PG that is synthesized and secreted from aggressive breast cancer tumor cells [170]. Ectopic over-expression of serglycin in low aggressive MCF-7 breast cancer cells promotes their anchorage-independent growth, migration and invasion [170] via up-regulation of biosynthesis of proteolytic enzymes (unpublished data). The tumor promoting properties of serglycin are dependent on the overexpression and secretion of glycanated serglycin [170]. Altered biosynthesis of CS chains has been demonstrated in various cancer types [180]. CHST11 gene that specifically mediates 4-O sulfation of CS is highly expressed in MDA-MB-231 breast cancer cells and breast cancer tissues together with CSPG4 another candidate carrier molecule for CS-4. CS-4 chains mediate the binding of breast cancer cells to P-selectin and facilitate the formation of metastasis [181].

INTERPLAY OF MATRIX PROTEINASES WITH PROTEOGLYCANS AND GAGs

Proteolysis is a highly regulated and specific process. Apart from the interactions between the substrate and catalytic domain, non-catalytic sites, called exosites, contribute to substrate cleavage by presenting the substrate to the catalytic domain [37, 39, 182]. In addition, proteinases can form complexes with other macromolecules, like proteins and PGs/GAG in allosteric sites, regulating the activity, stability, substrate specificity and localization of the enzymes. The interacting PGs/GAGs with certain proteinases and the biological roles affected by such interactions are presented in Table 1. An emerging concept is the compartmentalization of proteinases to secretory vesicles and cell membranes. Specifically, the concentrations of both the enzyme and substrate are maintained at catalytically-favorable levels within the pericellular space and are utilized upon cell stimuli rather than diffuse into the extracellular space [183].

It has been shown that MMP-7 co-localizes with HSPGs and heparin increases MMP-7 activity [184]. It is well documented that there is a correlation between GAG sulfation and the regulation of MMP-7 activity. Highly-sulfated GAGs, such as heparin, chondroitin-4,6-

sulfate (CS-E) and DS, enhance MMP-7 activity against specific substrates to a greater extent than low-sulfated forms of CS [185, 186]. Thus, specific GAGs may function as allosteric physiological activators of MMPs. Syndecan-2 can act as a docking site for pro-MMP-7 at the cell surface, and in turn such surface localization is pivotal for its ability to regulate carcinogenesis [37, 187]. MMP/HSPG complexes (MMP-9/HSPG) are also concentrated at the leading edge of highly-metastatic cells, mediating their migration and invasion [188]. However, GAG chains could simultaneously interact with an active MMP and substrate, bringing them together to act as highly-coordinated trimeric complex. For example, trimeric complexes of pro-MMP-2 and MMP-16 (MT3-MMP) and cell-surface CSPG4 can activate MMP-2 and increase cell migration, invasion, and metastasis [160, 161]. In addition, binding of ADAMTS-4 and MMP-17 (MT4-MMP) to syndecan-1 induces the activation of ADAMTS-4. Then, the activated form is located to the cell membrane interacting with the GAG chains of syndecan-1 [189]. Syndecan-4 binding to ADAMTS-5 results in its activation, regulating mitogen-activated protein kinase (MAPK)-dependent synthesis of MMP-3 [190]. On the other hand, syndecan-2 via the HS chains may compete for the binding of pro-MMP-2 interfering with the proper formation of MT1-MMP/TIMP-2/pro-MMP-2 complex that leads to its activation. In this case, syndecan-2 inhibits the activation of pro-MMP-2 suppressing metastasis in mice [191]. Another example of negative regulation is that of HSPGs and pro-ADAM-12. These interactions results in the suppression of ADAM-12 catalytic activity in some substrates but increase the activity of the enzyme against others, such as IGFBP3 [192]. This finding suggests that such inhibition is mediated by the binding of the GAG to basic amino acids in the pro- and catalytic domains of ADAM-12 creating a unique molecular switch [192].

The regulation of the activation/activity of MMPs can be achieved in various ways. The activation mechanism (known as the ‘cysteine switch’) involves proteolytic cleavages of the propeptide causing a destabilization of the cysteine zinc interaction [193]. In the latent state of MMPs, the propeptide “protects” the catalytic site, thereby blocking any interaction with the substrates. Bypassing the common mechanism of activation, the cysteine zinc interaction may be disrupted by an allosteric interaction between the prodomain and the GAG chains of a PG, leading to an active MMP and then the propeptide is either inter- or intra-molecularly cleaved [185]. However, the binding of MMPs to PGs occurs either through specific interactions with the GAG chains or the protein core of the PG. Serglycin and versican isolated from various sources form complexes with proMMP-9 *in vivo* and *in vitro* [194, 195]. Both the hemopexin-like (PEX) domain and the fibronectin-like (FnII) module of proMMP-9 are involved in the interaction with core proteins of PGs. The formation of the complexes alters the mode of activation of proMMP-9 and the interaction of the enzyme with its substrates [194, 196]. ProMMP-9 associated with PGs is activated in the presence of Ca^{2+} and may be important for the activation of pro-enzyme in pathological situation, which are associated with increasing concentrations of this cation such as tumor-induced bone disease [197]. For MMP-13, the PEX domain is responsible for the binding to the protein core of syndecan-4, serglycin, and decorin in chondrocytes [198]. Serglycin interacts with mast cell proteases regulating their activity. Heparin present on serglycin in mast cells forms complexes with chymase and promotes the binding of heparin-binding substrates to the enzyme thus presenting them to chymase and enhancing their proteolysis [199]. Heparin

significantly blocks the inhibition of chymase by natural inhibitors such as α1-protease inhibitor, α1-antichymotrypsin, α2-macroglobulin and soybean trypsin inhibitor [200, 201]. Heparin is also implicated in the formation of active tryptase tetramers [202, 203]. Chymase can activate various MMPs, whereas both tryptase and chymase directly degrade ECM components. Chymase cleaves vitronectin and procollagen, while tryptase degrades collagen IV and both degrade fibronectin [168].

GAGs also interact with cathepsins controlling their activation, stability and activity. It has been shown that the ability of cathepsin K to cleave collagen is highly dependent on the formation of an oligomeric complex with GAGs, in particular, with CS-4. This GAG has no effect on the activity of cathepsin L and MMP-1 [204, 205]. Some GAGs such as KS also enhances cathepsin K activity, while HS and DS inhibit the activity of the protease. These data suggested that the activity of some cathepsins is significantly enhanced by specific GAG chains [206]. Complex formation with GAGs is unique for cathepsin K among other papain-like proteases [205, 206]. It is remarkable that monomeric cathepsin K has no significant collagenase activity [205]. The specific binding of CS-4 to cathepsin K is required to allow the formation of an oligomeric complex capable to digest triple-helical collagen. It is suggested that the main function of this complex is the partial unfolding of triple-helical collagen that increases the accessibility of the scissile bond to the active site of cathepsin K [207].

Recently it has been reported the presence of three positively charged clusters at the bottom part of the protease opposing the active site, which are involved in alternative GAG binding sites. These may play other roles in the formation of collagenolytically active protease complexes, or contribute in a yet unknown manner to the specific binding to collagen [208]. Therefore, any disruption of the complex formation between cathepsin K and GAGs might be of therapeutic value in collagen degradation-related diseases such as cancer. Contrary, CS-4 inhibits the action of cathepsin S and may modulate its collagenase activity *in vivo* [209]. Notably, the interaction of cathepsin B specifically with heparin or HS induces its activity protecting it from alkaline pH [210]. Heparin and HS accelerate the autocatalytic removal of the propeptide, thus activating cathepsin B [211]. In this line of evidence, heparin and HS specifically bind to cathepsin X enhancing its activity [212]. Cathepsin X also binds to cell surface HSPGs in wild-type CHO cells but not in CHO-745 cells, which are deficient in GAG synthesis. In addition, cathepsin X is only endocytosed in CHO cells suggesting that HSPGs may also regulate its cellular trafficking [212]. Although CS-4 significantly enhances the collagenase activity of cathepsin K, the same GAG as well as others, specifically inhibits the potent elastolytic activity of cathepsins V and K [213]. In another study, the activity of pro-cathepsin D is significantly increased in the presence of heparin, HS and CS-E. The regulation of the activity by heparin depends on the sulfation groups and the length of the GAG chain, since more sulfated groups or larger fragments exhibit enhanced activity [214].

Squamous cell carcinoma antigens (SCCA-1 and SCCA-2), members of the high-molecular weight serine proteinase inhibitor (serpin) family, bind to heparin and this significantly enhances the inhibition of cathepsin L-like proteolytic activity secreted from breast and melanoma cancer cell. This finding raises the possibility that the anticancer properties of

heparin may be due, at least partly, to enhanced inhibition of pro-metastatic proteases [215]. The above data highlight the fact that PGs/GAGs are able to control and regulate the activity of many cathepsins. However, this is a complex regulation, since specific GAGs can activate or inhibit specific cathepsins and in addition, a particular GAG may have opposite effects in different cathepsins. Moreover, the length of the GAG and its specific sulfation seems to be of significance.

CONCLUDING REMARKS

Given the central role played by matrix molecules and their processing enzymes, we propose that the interplay between proteoglycans and proteinases could represent a new avenue for specific cancer therapeutics. This hypothesis envisages a novel molecular targeting for treating cancer achieving allosteric inhibition of proteolytic enzyme activity and concurrent compartmentalization of proteinases via proteoglycan modulation. The main axis of regulatory interactions between proteoglycans and proteinases is summarized in Figure 1. The use of modified GAGs or GAG mimetics utilized to modulate GAG-protein interactions [216] alone, or in conjunction with specific proteinases exosites may introduce a new era in cancer therapeutics. One such approach is targeting the exosites of particular cathepsins since GAG chains interact with the exosites of specific cathepsins modulating their catalytic activity. Thus, targeting the exosites could block the proteolytic activity against specific substrates of enzyme without disturbing other processes. Selent *et al.* [217] demonstrated that negatively charged molecules are able to inhibit only the collagenase activity of cathepsin K without affecting the overall proteolytic functions of the enzyme. The inhibitors are negatively charged molecules such as poly-Asp and poly-Glu with ionic properties similar to those of CS-4. These molecules exert their inhibitory effect mainly by interfering with the formation of cathepsin K/CS-4 complex. Therefore, we suggest that the targeting of proteinase exosites, which interact with GAGs, could be a novel mechanism of inhibition. Currently, our knowledge of this field is relatively sparse. Therefore, future targeted studies should be done especially focusing on the development of novel inhibitors, which should selectively inhibit specific proteinase activities and possibly bypass the detrimental side effects caused by present inhibitors.

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Abbreviations

ADAM	a disintegrin and metalloproteinase
ADAMTS	a disintegrin and metalloproteinase with thrombospondin motifs
CS	chondroitin sulfate
DS	dermatan sulfate

ECM	extracellular matrix
GAG	glycosaminoglycan
HA	hyaluronan
HS	heparan sulfate
MMP	matrix metalloproteinase
MT-MMP	membrane type-MMP
PG	proteoglycan
TIMP	tissue inhibitors of MMPs

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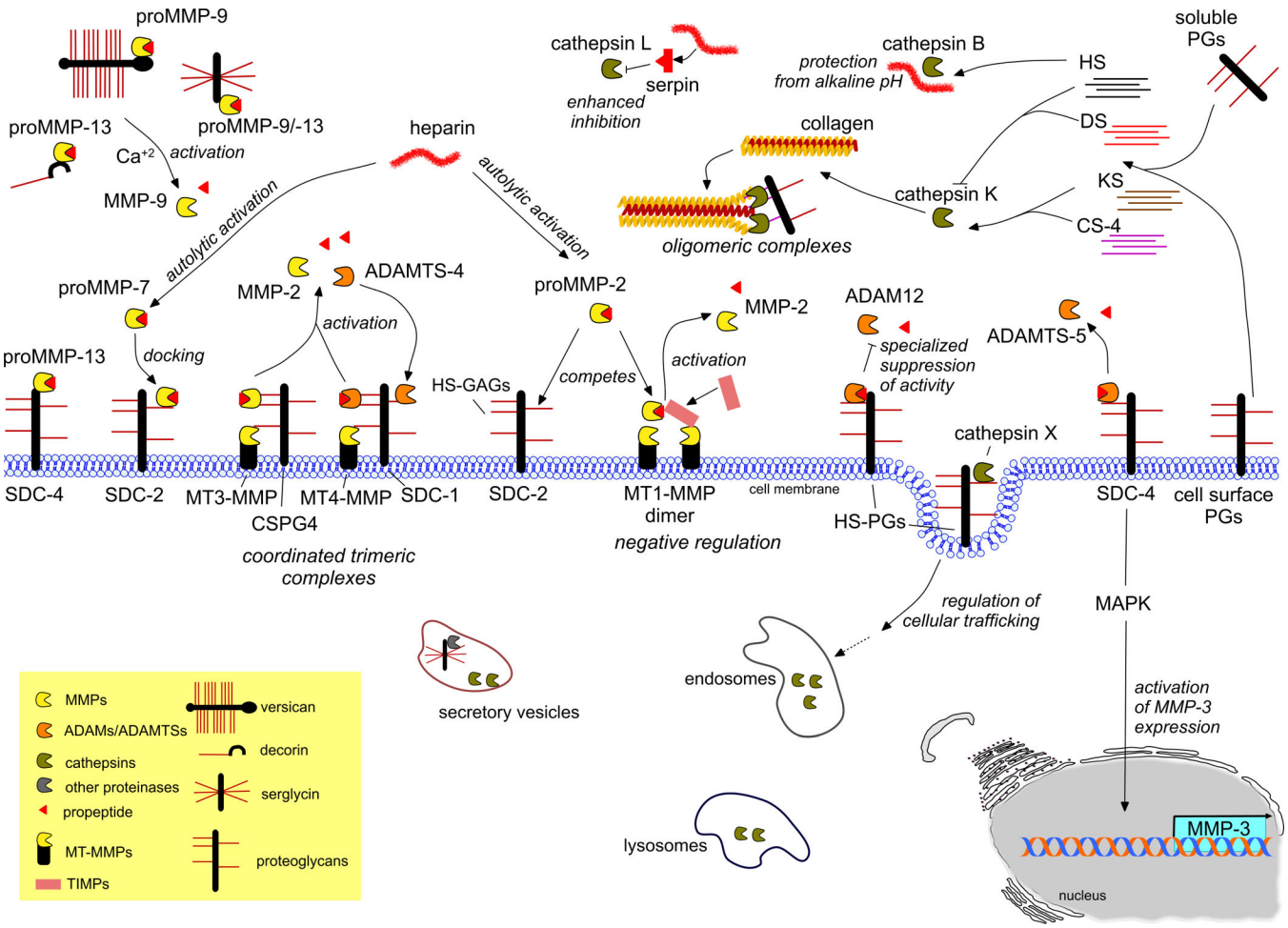

Figure 1. Main axis of proteinases regulation by proteoglycans action

The interaction between proteinases and proteoglycans occurs either through the GAG chains or the core protein of PGs. One main outcome of such interactions is the compartmentalization of proteinases confined to secretion vesicles and especially to cell membrane as well as stored in confined spaces within the extracellular space. Thus, proMMPs (proMMP-9, proMMP-13) bind to the core protein of several PGs secreted or membrane bound, like serglycin, decorin, versican and SDC-4 or interact with the GAG chains of SDC-2 acting as a docking site (*top-left panel*). HSPGs also represent a binding site for cathepsins at the cell surface, implicating them also to their cellular trafficking in the case of cathepsin X. The activation and activity of proteinases is strongly regulated by GAGs in either positive or negative mode. CS-4 chains of cell-surface CSPG4 are able to simultaneously interact with active MT3-MMP and its substrate pro-MMP-2, leading to the formation of a coordinated trimeric complex and subsequent activation of MMP-2 (*left-middle panel*). Similarly, the complex of ADAMTS-4/MT4-MMP/SDC-1 induces the activation of ADAMTS-4, further located to the cell membrane via interacting with the GAG chains of SDC-1 (*left-middle panel*). On the other hand, SDC-2 HS chains compete with MT1-MMP for the binding of pro-MMP2, which prevents the activation of the proMMP2 via cell membrane ternary complex, which also involves MT1-MMP dimer and TIMP-2 (*middle panel*). Another example of negative regulation is that of HSPGs and pro-

ADAM-12, resulting in the specialized suppression of ADAM-12 catalytic activity against some substrates (*right-middle panel*). SDC-4 is also able to control the ADAMTS-5 activation through direct interaction, leading also to MAPK-mediated activation of MMP-3 expression (*right panel*). In the case of cathepsins, the formation of oligomeric complexes with GAGs for example CS-4 with cathepsin K renders cathepsin capable to unfold and further digest the triple-helical collagen. In coordination, HS and KS chains also enhance cathepsin K activity, while HS and DS inhibit it (*top-right panel*). Heparin, a highly sulfated glycosaminoglycan, enhanced the autolytic activation of proMMP-2 and proMMP-7. Heparin, along with HS chains, protects cathepsin B action from alkaline pH, whereas members of serpin family bind to heparin and this significantly enhances the inhibition of cathepsin L-like proteolytic activity (*top-right / middle panel*).

Table 1

PGs / GAGs as binding partners for matrix proteinases

Proteinase	Domain	Interacting PG/GAGs	Biological roles [Ref]
MMP-2	Pro-form and active form	Syndecan-2 (HS)	Inhibits activation of pro-MMP-2 [191]
MMP-2	Hemopexin	CSPG4 (CS-4)	Activation of MMP-2, increased cell migration and invasion [160]
MMP-7	?	HSPGs/heparin	Increase activity [184]
MMP-7	Pro-form (higher affinity) and active form (less affinity)	Heparin/CS-E/DS	Autocatalytic activation and increase activity [185, 186, 218]
MMP-7	Pro-form	Syndecan-2 (core protein)	Activation and cell migration [37, 187]
MMP-9	?	HSPGs	Cell migration and invasion [188]
MMP-9	Pro-form (hemopexin / fibronectin-like module)	Serglycin / Versican (core proteins	Modulates the activation of proMMP-9 and the binding to substrates [194, 195]
MMP-13	hemopexin	Syndecan-4, serglycin, decorin (core proteins)	Unknown [198]
MT3-MMP	?	CSPG4 (CS-4)	Cell invasion [160, 161]
ADAMTS-4	?	Syndecan-1 (HS/CS)	Cell surface localization and activation [189]
ADAMTS-5	?	Syndecan-4	Activation and MMP-3 expression [190]
ADAM-12	Pro-form and catalytic form	HSPGs (HS)	Inhibition or activation against specific substrates [192]
Cathepsin K	GAG binding sites	HS / DS	Inhibit the activity [206]
Cathepsin K	GAG binding sites	CS-4 / KS	Enhance activity [206]
Cathepsins V and K	GAG binding sites	CS-4 / CS-6 / DS / heparin	Inhibit elastolytic activity [213]
Cathepsin S	GAG binding sites	CS-4	Inhibits activity [209]
Cathepsin B	GAG binding sites	Heparin / HS	Enhance activity and stability [210]
Cathepsin X	GAG binding sites	Heparin / HS / HSPGs	Enhance activity, cell surface localization [212]
Pro cathepsin D	GAG binding sites	Heparin / HS / CS-E	Enhance activity [214]

Proteinase	Domain	Interacting PG/GAGs	Biological roles [Ref]
	(catalytic / pro-form)		