Matrix modeling and remodeling: a biological interplay regulating tissue homeostasis and diseases

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Abstract

The overall structure and architecture of the extracellular matrix undergo dramatic alterations in composition, form, and functionality over time. The stochasticity begins during development, essential for maintaining organismal homeostasis and is heavily implicated in many pathobiological states including fibrosis and cancer. Modeling and remodeling of the matrix is driven by the local cellular milieu and secreted and cell-associated components in a framework of dynamic reciprocity. This collection of expertly-written reviews aims to relay state-of-the-art information concerning the mechanisms of matrix modeling and remodeling in physiological development and disease.

Concept of matrix modeling and remodeling

Proteoglycans are rapidly emerging as key effectors active in modeling and remodeling of both vascular and avascular tissues the stroma of most organs. Interacting with cell surface receptors [1–4], growth factors such as TGF-β [5,6], matrix remodeling enzymes [7–17], and matrix effectors imbue proteoglycans with unique and combinatorial biological properties and signaling cues [18–22], In this *Special Issue* on *Matrix Modeling and Remodeling*, novel roles of proteoglycans in orchestrating diverse biological activities are reviewed and summarized by internationally-recognized experts in the field. Possessing an array of functions, proteoglycans regulate not only structural aspects of the extracellular

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matrix (ECM) and tumor angiogenesis [23–28], but also cell signaling networks and behaviors governing normal and pathobiological states [29–34].

Reflecting the many biologically diverse systems in which proteoglycans operate [35,36], we will introduce the major overarching themes of this *Special Issue* such as senescence-driven ECM remodeling, proteolysis-mediated matrix remodeling, emerging roles in controlling tumorigenesis, and the mechanics of basement membranes in guiding development, tissue remodeling, wound re-epithelization, heart disease and myocardial infarction.

Cellular senescence drives ECM remodeling

The ECM is subjected to dynamic remodeling during development, inflammation, wound healing and diseases including cancer, atherosclerosis and osteoarthritis. Governed by cellular senescence, aging tissues display changes in both ECM function and organization. After undergoing a limited number of mitotic divisions, they enter into senescence and are unable to proliferate. This is caused by replicative senescence which is a gradual telomeric shortening that occurs every mitotic cycle. In addition, cells also experience "stress-induced premature senescence" upon exposure to certain stress factors including radiation and oxidative agents [37].

The ability of senescent cells to markedly modulate their phenotype and biosynthesis of matrix components affects tissue organization and functions as summarized by Mavrogonatou *et al.* found in this *Special Issue*. A key determinant of cellular senescence is the adaptation of senescence-associated secretory phenotype (SASP) by senescent cells that drives ECM remodeling and tissue behavior [38,39] (Fig. 1). They secrete numerous pro-inflammatory mediators including cytokines, growth factors and a plethora of proteolytic enzymes such as MMPs, plasminogen activators, and members from a class of intracellular cysteine proteases, the cathepsins [38–40], Further, senescent cells exhibit altered secretion of matrix molecules thereby establishing a provisional matrix that cooperates with the pro-inflammatory and catabolic milieu. This generates a favorable microenvironment that impairs tissue physiology, eventually leading to age-related disorders [37,39], Similarly, augmented expressions of cytokines and growth factors are implicated in wound healing [41] and in the progression of various age-related diseases including articular cartilage degeneration [42], atherosclerosis [43], and cancer development [39,44], Notably, cancer cells secrete various bioactive stimuli that induce stromal cell senescence, creating a provisional ECM to facilitate cancer cell growth and metastasis [39], Malignant cells benefit by senescent cells residing within the tumor stroma through the aberrant activation of multiple pro-growth and pro-survival pathways, driven primarily by SASP [45].

As reviewed by Mavrogonatou *et al.*, senescence-induced ECM remodeling is characterized by a reduced expression of important structural molecules including collagen, aggrecan, versican, decorin, and elastin—all essential matrix components for maintaining the proper biomechanical properties of tissues such as cartilage, skin, lungs and the vascular wall. The continuous presence of numerous proteolytic enzymes, inflammatory mediators and the expression of cross-linking enzymes such as lysyl oxidases (LOXs) increase matrix stiffness

and subsequently establishes a vicious feedback cycle of ECM remodeling that gradually diminishes the physiological and homeostatic properties of the afflicted tissue (Fig. 1).

Matrix remodeling by proteolysis

Compounding the effects of SASP, various growth factors and cytokines induce epithelial to mesenchymal transition (EMT) as an important step towards local invasion and eventual systemic metastases. The composition of this "transformative" matrix is significantly enriched in adhesive proteins including fibronectin, laminin and matricellular proteins and catabolic enzymes such as matrix metalloproteinases (MMPs) that facilitate cancer cell migration and invasion. MMPs exhibit a variety of functions promoting EMT, signaling, migration and invasion [46], For example, MMP-1 and MMP-2 secreted by senescent fibroblasts trigger early EMT in keratinocytes, promoting the development of skin cancer [47], In another *in vivo* pre-clinical model, it was demonstrated that the beneficial effect of senescent fibroblasts on tumor development was alleviated by inhibiting the enzymatic activity of MMPs [48].

MMPs are key enzymes involved in ECM remodeling due to their ability to degrade various matrix components, cell surface receptors, cytokines and growth factors (Fig. 1). MMPs are zinc-dependent endopeptidases belonging to the metzincin superfamily of metalloproteinases that also includes their related families ADAMs and ADAMTs. MMPs are classified as collagenases, gelatinases, stromelysins, matrilysins, membrane type MMPs (MT-MMPs) and other MMPs according to their substrate specificity, homology, and domain organization [49].

MMPs are associated with disease development and progression including cancer, atherosclerosis, osteoarthritis and inflammation by affecting multiple signaling pathways. As reviewed by Hannocks *et al.* in this *Special Issue*, gelatinases MMP-2 and MMP-9 are key regulatory enzymes operative during neuroinflammation. It has been shown by *in vivo* and *in vitro* studies that both enzymes drive experimental autoimmune encephalopathy and subsume complementary functions in a murine model of the disease [50], Gelatinases MMP-2 and MMP-9 are secreted by immune and resident cells at the blood-brain barrier under the control of pro-inflammatory cytokines produced by recruited T-effector cells. Together, MMP-2 and MMP-9 promote the penetration of the outer parenchymal barrier by invading leukocytes. The elevated expression of MMP-2 and MMP-9 coordinates with pro-inflammatory cytokines to evoke the expression and modulate the activity of chemokines, thereby establishing a potent chemotactic gradient [51,52], MMPs also degrade ECM components and cell surface receptors such as β-dystroglycan from the astrocyte cell membrane, thus compromising parenchymal basement membrane attachment and reducing both their survival and the integrity of brain-blood barrier [50,51,53], Cleavage of cytokines and their receptors on the T-cell surface is postulated as a critical step for the prevalence of T-effector over T- ory cells for the inflammatory cascade.

The activity of MMPs is finely regulated by various mechanisms involving transcriptional regulation, activation by certain enzymes, inactivation by tissue inhibitors of MMPs (TIMPs) and α2-macroglobulin in serum and interactions with allosteric modulators [49], Initially, MMPs are synthesized as inactive proenzymes that are activated by proteolytic removal of

their N-terminal pro-peptide. The activation of MMPs is mediated by plasmin, other MMPs, ADAMs, ADAMTs as well as an autocatalytic activation extracellularly and furin intracellularly [49], This process is critical for the function of MMPs and is thereby tightly regulated by several matrix constituents.

Proteoglycans (PGs) and glycosaminoglycans (GAGs) are among these regulatory molecules that interact with MMPs to modify their activity [54] (Fig. 1). A prime example is the interaction of MMP-2 with syndecan-2 on the cell surface that ultimately inhibits activation of pro-MMP-2 [55], On the other hand, MMP-2 forms a complex with CSPG-4 and MT3-MMP on the melanoma cell surface for pro-MMP-2 activation via MT3-MMP to evoke tumor cell invasion in collagen l-enriched matrices. This mode of activation requires the CS chains on CSPG-4 [56], Similarly, MMP-9 interacts with glypicans on the cell surface promoting colon cancer cell motility [57], Intriguingly, MMP-9 further interacts with matrix- localized serglycin and versican forming large, multimeric complexes that modulate pro-MMP-9 activation and target substrate binding [58], Lumican, a small leucine rich proteoglycan (SLRP), binds directly to the catalytic domain of MMP-14 (MT1-MMP) to inhibit its enzymatic activity. This binding is mediated by specific fragments of the lumican core protein [59,60], Lumican affects endothelial cell migration by regulating the expression and activity of MMP-9 and MT1-MMP by integrins [61]. The delicate interplay between MT1-MMP and lumican and their ensuing biological effects on tumorigenesis are elegantly presented by Pietraszek-Gremplewicz *et al.* in this *Special Issue.*

Independent of regulating collagen fibrillogenesis and mediating ECM organization, lumican exhibits potent anti-tumor effects by interfering with integrins and MT1-MMP at the cell membrane, inhibiting angiogenesis and tumor cell migration [59–62]. MT1-MMP localizes at lamellipodia forming complexes with CD44 and promoting tumor cell migration, invasion, and metastasis [63]. Co-localization of CD44 and MT1-MMP links both molecules to the actin cytoskeleton via the cytoplasmic tail of CD44, directing MT1-MMP to the migration front during cell migration [63]. MT1-MMP efficiently degrades a wide range of matrix components including collagens, fibronectin, laminins, proteoglycans, elastin and various cell surface receptors such as integrins, CD44, syndecan-1 and ICAM-1 [14]. Degradation of these targets are essential for pericellular remodeling and modulation of cell-matrix interactions [14].

MMPs play a central role in processing essential matrix components such as fibrillar collagens (Fig. 1). Collagen fibrils are widely distributed in all tissues providing unique mechanical properties and tensile strength. Their balanced synthesis and degradation is required for tissue homeostasis and imbalanced remodeling is recurrent in fibrosis, arthritis and cancer [64,65]. The tightly packed helical structure of collagen fibrils provide resistance against proteolytic degradation. The molecular pathways and enzymes involved in fibrillar collagen degradation are discussed by Sprangers and Everts in the corresponding review of this *Special Issue*. The ability of MMPs to degrade either intact or denatured collagen fibrils such as collagenases MMP-1, MMP-8, MMP-13, MT1-MMP, MT3-MMP and gelatinases MMP-2 and MMP-9 is presented. Extracellular degradation of collagen fibrils by MMPs is complemented with the action of other proteases including cathepsin K [66]. Apart from extracellular degradation, collagen fibrils are internalized by phagocytosis, a process

dependent on integrins and MT1-MMP, and stored in phagosomes [67,68]. Soluble collagen fragments processed in the ECM are internalized by macropinocytosis and endocytosis that mechanistically requires urokinase plasminogen activator receptor associated protein (uPARAP/Endo180) and clathrin-coated vesicles [69]. Internalized collagen fibrils and fragments within vesicles are directed to the endosomal/lysosomal compartment and subsequently degraded by cysteine proteases.

Cysteine cathepsins are the fundamental proteases of the endolysosomal system and are increasingly implicated as extracellular matrix remodeling enzymes involved in numerous diseases [70] (Fig. 1). For instance, there are 11 papain-like cysteine cathepsins in humans that show specific and differential tissue expressions to accomplish their requisite biological functions. They act as acid proteases and possess biological activity within the slightly acidic microenvironment prevalent in diseases such as cancer, osteoarthritis, and osteoporosis [71]. In addition, the interaction of cathepsins with GAGs evokes stabilization and autoactivation at a neutral pH [70,72], Cathepsin-mediated ECM remodeling is reviewed by Vizovisek *et al.* in this *Special Issue*. The authors describe the structural and functional roles of cathepsins with emphasis on ECM remodeling and its relevance to disease progression. Indeed, dysregulated cathepsin expression and extracellular activity has been implicated in several cancer types, inflammatory diseases, arthritis, cardiovascular, and skeletal disorders.

The implication of other non-classical matrix proteases such as granzyme B in pathologic matrix remodeling with a focus on skin inflammation and related diseases is discussed by Turner and colleagues. Granzyme B belongs to a family of five serine proteases called granzymes (granule-secreted enzymes) in humans. It is synthesized by immune cells and non-immune cells alike (chondrocytes and keratinocytes) and secreted in the presence or absence of perforin. It can be internalized by target cells for apoptotic initiation following the cleavage of various substrates. A portion of granzyme B that is not internalized, is biologically active in the extracellular milieu [73].

Together, MMPs, cathepsins, and granzyme B are capable of degrading a wide variety of ECM components, junctional proteins, and cell surface receptors culminating in authoritarian control of cell-cell, cell-matrix interactions and downstream signaling [46,49,73–75] (Fig. 1). The degradation of ECM components upon remodeling also results in the release of bioactive fragments [76], These matrikines [9] exert their activity by interacting with specific cell surface receptors in multiple cell types to guide matrix re-organization, tissue architecture, and function. The concept of producing bioactive fragments via certain proteases, their functional roles, and their potential applications as drugs and biomarkers is elegantly highlighted by Ricard-Blum and Vallet. For example, bioactive fragments such as endorepellin and endostatin produced by cleavage of perlecan and collagen XVIII, respectively, bind to integrins and VEGFR1, thereby inhibiting angiogenesis and evoking autophagy [77,78], In contrast, lumikine, a proteolytically-liberated peptide derived from lumican, binds to ALK5/TGFβR1 to activate signaling and promote wound healing [79].

Remodeling on the fly: the rise of exosomes in ECM modeling

Recently, extracellular vesicles (EVs) have emerged as integral components of ECM that play central roles in matrix remodeling. This concept is thoroughly reviewed by Rilla *et al.* and Sanderson *et al.* in this Special Issue. EVs are released by all cell types and found ubiquitously in body fluids. They are classified into three different categories according their size and mode of biogenesis. The smaller in diameter, named exosomes (30–150 nm), arise from the endocytic pathway with the subsequent formation of multivesicular bodies [80], They are transported to plasma membrane and fused to release exosomes to the ECM. Other larger extracellular vesicles such as microvesicles (100–1000 nm) and apoptotic bodies (1–5 μm) are derived from the direct budding of plasma membrane [80], EVs, especially exosomes, play fundamental roles in cell-cell communication as they transfer a plethora of chemical signals to neighboring cells that directly modulate their behavior [80], For example, nucleic acids (mRNAs, miRNAs, and non-coding RNAs), matrix proteins, growth factors, cytokines, enzymes and lipids are components of exosomes that affect cell differentiation, proliferation, migration, and matrix synthesis. The surface of exosomes contains numerous cell surface receptors including cell surface proteoglycans, integrins, and the specific enzymes that mediate their interaction with ECM molecules and cellular uptake [81], Exosomes are involved in ECM organization/re-organization that occurs under normal and pathological circumstances. A plethora of miRNAs influences the expression of matrix components involved in wound healing and matrix remodeling in various diseases [82], Exosomes derived from different cellular sources also regulate wound healing by promoting fibroblasts proliferation, migration, matrix biogenesis, and the release of inflammatory mediators. EVs transfer several matrix-degrading enzymes including MMPs and cathepsins that remodel the ECM [83,84], In addition, they induce the expression and release of proteolytic enzymes in target cells to induce matrix degradation. For instance, microvesicles enriched in EMMPRIN/CD147 are released by tumor cells to stimulate the expression of MMP-2 in stromal fibroblasts [85], Enzymes which are involved in matrix remodeling are also located on EV surfaces and are able to act directly on their matrix substrates. Lysyl oxidase-like 2 is enzymatically active on the vesicular surface and catalyzes the crosslink of collagen fibrils in the ECM [86], Increased tissue stiffness occurs in remodeled tissues in various diseases including cancer and is associated with disease progression [64], Also on vesicular surfaces, MT1-MMP degrades fibrillar collagens among other matrix components and is a potent regulator of cell migration and cancer cell invasion and metastasis [87,88], Glycosidases such as sialidase and heparanase are components of the exosomal surface and are involved in the removal of sialic acid from cell surface components and degradation of HS chains from HSPGs [89,90], Heparanase acts on various matrix and cell surface HSPGs to promote cell migration either via liberation of HS-sequestered growth factors and cytokines within the matrix or by modulating cell-matrix interactions [91], Notably, heparanase trimming of HS chains on syndecan stimulates exosome biogenesis by modulating the function of the syndecan-syntenin-ALIX complex [92], Heparanase up-regulation induced by chemotherapy treatment in multiple myeloma patients evokes exosome secretion, further supporting the role of the heparanase-syndecan axis on exosome biogenesis [89].

Proteoglycans as interior designers for the matrix

Basement membranes are chiefly composed of four requisite components: laminin [93], collagen IV [94], nidogen, and the heparan sulfate proteoglycan (HSPG) perlecan [95,96], The biology and contributions of collagen XVIII, a related basement HSPG implicated in tissue homeostasis and dysfunction, has been recently reviewed [97], Unbiased quantitative proteomic definitions of basement membrane compositions [98] and extracellular matrices [99,100] are leading an "-omics" revolution in understanding the functional contributions of basement membrane in associated diseases [101–103], development [104,105] and potentially as viable cell-based therapeutic modalities [106], Perlecan and related components [107] are critical for maintaining the structural integrity of cartilage and assembly of basement membrane [108], while maintaining sufficient plasticity for remodeling as the organism grows and develops over time. Indeed, embryo implantation triggers dynamic expression of the basement membrane toolkit [109].

The core regulatory mechanism is found in generating biomechanical forces that is sensed by and ultimately influences cell function, and *vice-versa* as discussed by Mrkonjic and colleagues in this *Special Issue*. The aggregate effect of basement membrane protein deposition (modeling) and degradation (remodeling) controls cellular and tissue stiffness as determined by atomic force microscopy, tissue plasticity [110], organ shape, and ligand retention by Ramos-Lewis *et al.* in this *Special Issue*. Reciprocal signaling, such as that mediated by DDR1 for collagen IV synthesis, is also necessary to maintain properties of the basement membranes [111,112], This functional paradigm for basement membrane synthesis, deposition, and remodeling is aptly and thoroughly demonstrated in the model organism *Drosophila melanogaster* and its step-wise assembly process is elegantly presented in the review of Ramos-Lewis and colleagues (Fig. 2). The subsequent examination of the wing disc basement membrane provides a microcosm for discerning the roles of cellular compression [113] processes and ligand retention for developing biological systems, which is especially applicable for stem and progenitor cell biology. The mechanisms gleaned from this invertebrate model organism is significantly advancing our knowledge regarding the subtle nuances of basement membrane intricacies and architecture and the roles that proteoglycans subsume.

The next major portion of articles deals with cutaneous wound healing which comprises three distinct phases of inflammation, re-epithelization, and tissue remodeling. The recurring theme of matrix remodeling is prevalent within all four continuous processes: hemostasis, inflammation, proliferation, and maturation [114], This theme is highlighted, largely in sequence, by recent advances in the role of CD44 in modulating inflammation, re-epithelialization, and thrombospondin-4 activity in tissue remodeling, all found within reviews by Govindaraju *et al.*, Rousselle *et al.*, and Stenina-Adognravi *et al.*, respectively (Fig. 2).

During wound healing, deposition of abundant of fibrillar cartilage maintains tissue and tendon biomechanics [23,25,26,115,116] while forming scar tissue, impairing normal tissue function and elastoplasticity. Dissecting the molecular and cellular processes governing this form of ECM deposition and remodeling are critical towards efforts to prevent fibrotic scarring. It has recently been demonstrated that CD44, the hyaluronan receptor, functions in

a heretofore unknown pathway for wound healing. As reviewed by Govindaraju *et al.*, mice lacking CD44 have increased levels of inflammatory markers with ablated fibrogenic responses during the initial injury response stage of wound healing. At later stages, as the wound is closing, proteolytic degradation of the deposited collagen is significantly diminished, resulting in increased retention times of the fibrillar collagen post closure, ultimately manifesting in a more severe scarring phenotype.

One of the most critical processes of mammalian wound healing is re-epithelization, which is considered the second step under proliferation, with defects resulting in chronic wounds and pressure ulcers [65]. Several ECM-derived factors are deposited, and the precise composition of this milieu is influenced by the local wound microenvironment, involving cytokines, growth factors, and MMPs [117]. Following wound injury, provisional matrix is deposited for proficient tissue repair at approximately 3 days to 1 week by granular fibroblasts and is characterized by the temporal synthesis of key effectors including fibronectin isoforms that incorporate the EDA and EDB domains, fibronectin species lacking these domains, and fibrillar and non-fibrillar collagens (I, V, VI, VII, XVIII) [118,119]. Recent studies, as discussed by Rousselle *et al.*, have determined precise functions for each of the EDA and EDB domains as critical for the recruitment of collagen I and an assortment of matricellular proteins, such thrombospondin (TSP), within the wound ECM (see below). As described above, a major constituent of basement membranes is the HSPG perlecan [120]. Structurally, perlecan augments cellular adhesion and co-localizes with laminins, specifically laminin 322, to further stabilize keratinocyte attachment. Primarily, perlecan functions as a repository for HS-binding growth factors whereupon degradation of the its HS chains or perlecan itself releases the pleiotropic growth factor progranulin [121,122] as well as other mitogens and trophic factors necessary for the reparative process. Supporting this concept, transgenic mice lacking these HS chains have delayed wound healing and decreased vascular density, despite maintaining wound closure rates [123].

Intriguingly, both collagen XVIII and perlecan harbor proteolytically sensitive C-termini, [124] in the form of endostatin [125] and endorepellin [126–133], respectively, that acts to fine-tune angiogenesis [77]. Recently, both anti-angiogenic fragments have been implicated in coordinating the evolutionarily-conversed catabolic process of autophagy [78,134,135]. Intriguingly, there appears to be a fundamental antithetical correlation between autophagic activation and angiogenesis insofar as pro-autophagic molecules possess anti-angiogenic properties [95,136,137] and vice versa. This concept is further underscored by transgenic mice expressing HS-less perlecan; perlecan no longer exhibits angiogenic bivalency (pro- and anti-angiogenic cues embedded within the same molecule) and only contains anti-angiogenic signals via C-terminal endorepellin. The form of perlecan sans the HS chains results in a less favorable angiogenic wound healing environment characterized by decreased granularity and vascularization. Therefore, proteoglycans, such as collagen XVIII and perlecan, may exert their roles in wound healing by controlling autophagy as an under-appreciated contributor to wound healing.

In contrast to the anti-angiogenic modalities inherent to the basement membrane HSPGs, collagen XVIII and perlecan, as well as to other thrombospondin family members, TSP-4 promotes angiogenesis. Expressed throughout embryonic development and within the adult

organism in the osteogenic mesenchyme, tendons, skeletal and nervous tissues as well as the eye and cardiovascular tissue, TSP-4 performs several other key roles in opposition to TSP-1 and TSP-2. Specifically, TSP-4 reduces fibrosis and collagen production. As an evolutionarily conserved multi-modular molecule, TSP4 subsumes a critical role as an organizational factor for the ECM and provides structural support. Being a proangiogenic factor, TSP-4 has been implicated in cancer due to high levels of expression and its subsequent association to cancer progression, particularly facilitating progression and invasion as described by Stenina-Adognravi *et al.* However, the precise role of TSP-4 is uncertain as studies have demonstrated both tumor-promoting and tumor-inhibiting properties, depending on the tissue of origin.

The role of proteoglycans in remodeling the cardiovascular system has long been underappreciated; however, this emerging field is spotlighted within this *Special Issue* in two elegantly written reviews by Nielson *et al.* and Christensen *et al.* in this *Special Issue*. Cardiovascular diseases are primarily characterized by extensive (and aberrant) ECM remodeling over decades of life, leading to fibrotic scarring and inevitable heart failure. Importantly, SLRPs, including decorin, biglycan, and lumican, have surfaced as vital regulators of this process as well as membrane-localized proteoglycans including glypican and syndecans. In this context, they function as receptors to regulate cardiac fibroblast signaling and may represent therapeutic targets or biomarkers. In the same vein, ECM components are considered as biomarkers for myocardial infarction of the left ventricle to predict patient outcome (Fig. 2).

Proteoglycans also exert major roles as key molecular determinants throughout tumorigenesis and angiogenesis as comprehensively reviewed by Theocharis and Karamanos in this *Special Issue*. Proteoglycans are able to remodel the tumor stroma in a cell- and context-specific manner that can generate a provisional matrix for tumorigenic growth and drug resistance. Recently, it was discovered that decorin, the prototypical member of the SLRP family, evokes endothelial autophagy and tumor cell mitophagy, as reviewed by Buraschi *et al.* in this Special Issue (Fig. 2). We found that decorin evokes excessive flux through this conserved catabolic process under nutrient-rich conditions downstream of receptor tyrosine kinase activity, chiefly VEGFR2 and Met for endothelial cells and breast carcinoma, respectively. Under these specific circumstances, autophagic regulation is considered "non-canonical". Engagement of the autophagic or mitophagic machinery relied on two novel effectors, Peg3 or mitostatin, respectively. These proteins represent a novel, matrix-regulated nexus for augmenting cellular catabolism and organelle clearance. The resultant effects of pro-autophagic/pro-mitophagic process underlies the molecular versatility of decorin as an anti-tumorigenic and angiostatic factor.

Acknowledgments

Abbreviations

ECM	extracellular matrix
EMT	epithelial to mesenchymal transition
EV	extracellular vesicle
HSPG	heparan sulfate proteoglycan
LOX	lysyl oxidase
MMP	matrix metalloprotease
MT-MMP	membrane type MMP
SASP	senescence-associated secretory phenotype
SLRP	small leucine rich proteoglycan
TGF-β	transforming growth factor β
TSP	thrombospondin

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Highlights

- During development and organ pathology, the extracellular matrix undergoes a dramatic restructuring in composition, form and functionality.

- Modeling and remodeling of the matrix are driven by the local cellular milieu and secreted components via a framework of dynamic reciprocity.

- We will critically address key concepts related to the role of extracellular matrix modeling and remodeling in various disease processes.
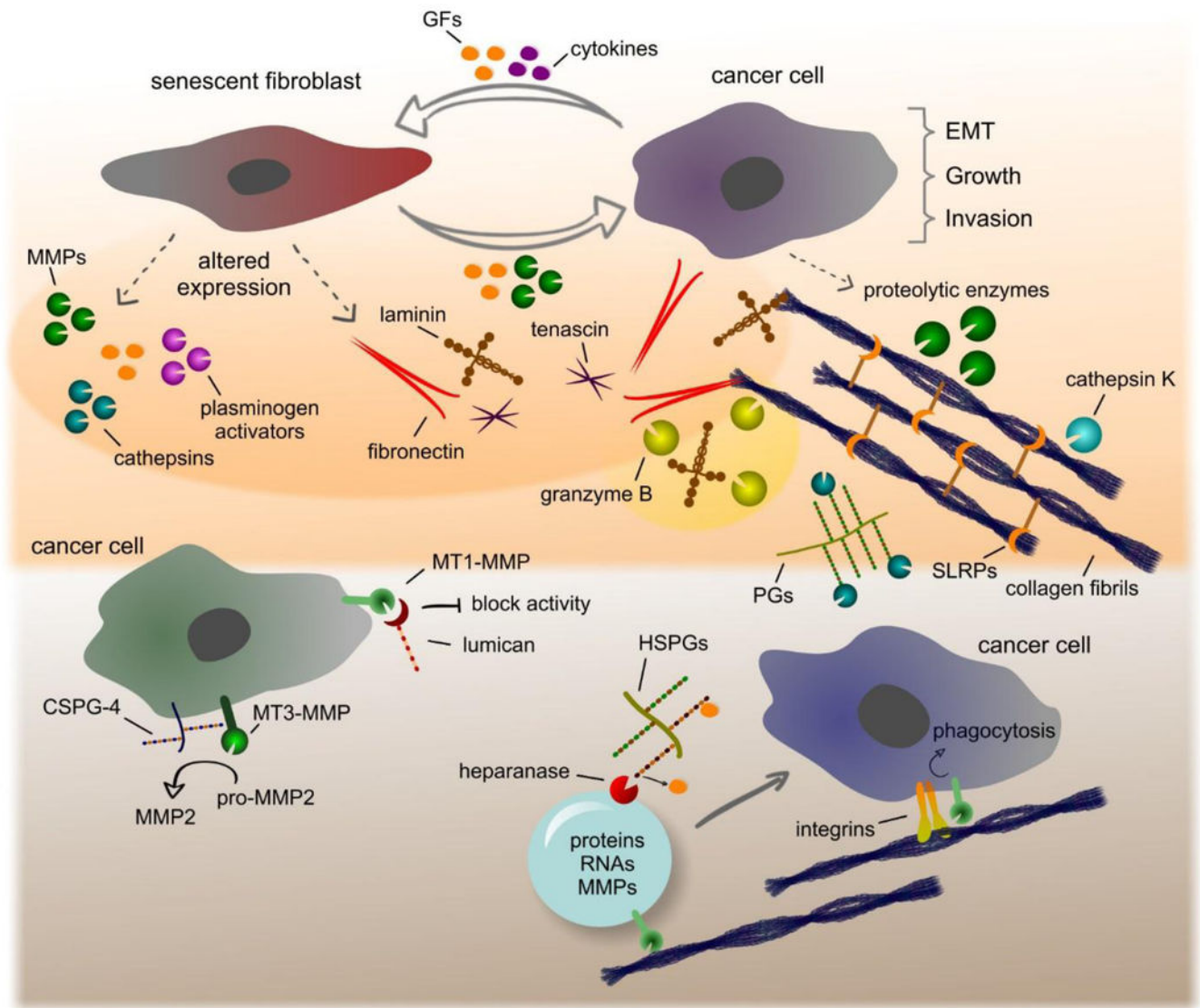
Fig. 1.
Schematic depiction of matrix modeling and remodeling driven by SASP and various proteolytic effectors including MMPs and cathepsins. Please consult the text for additional information.
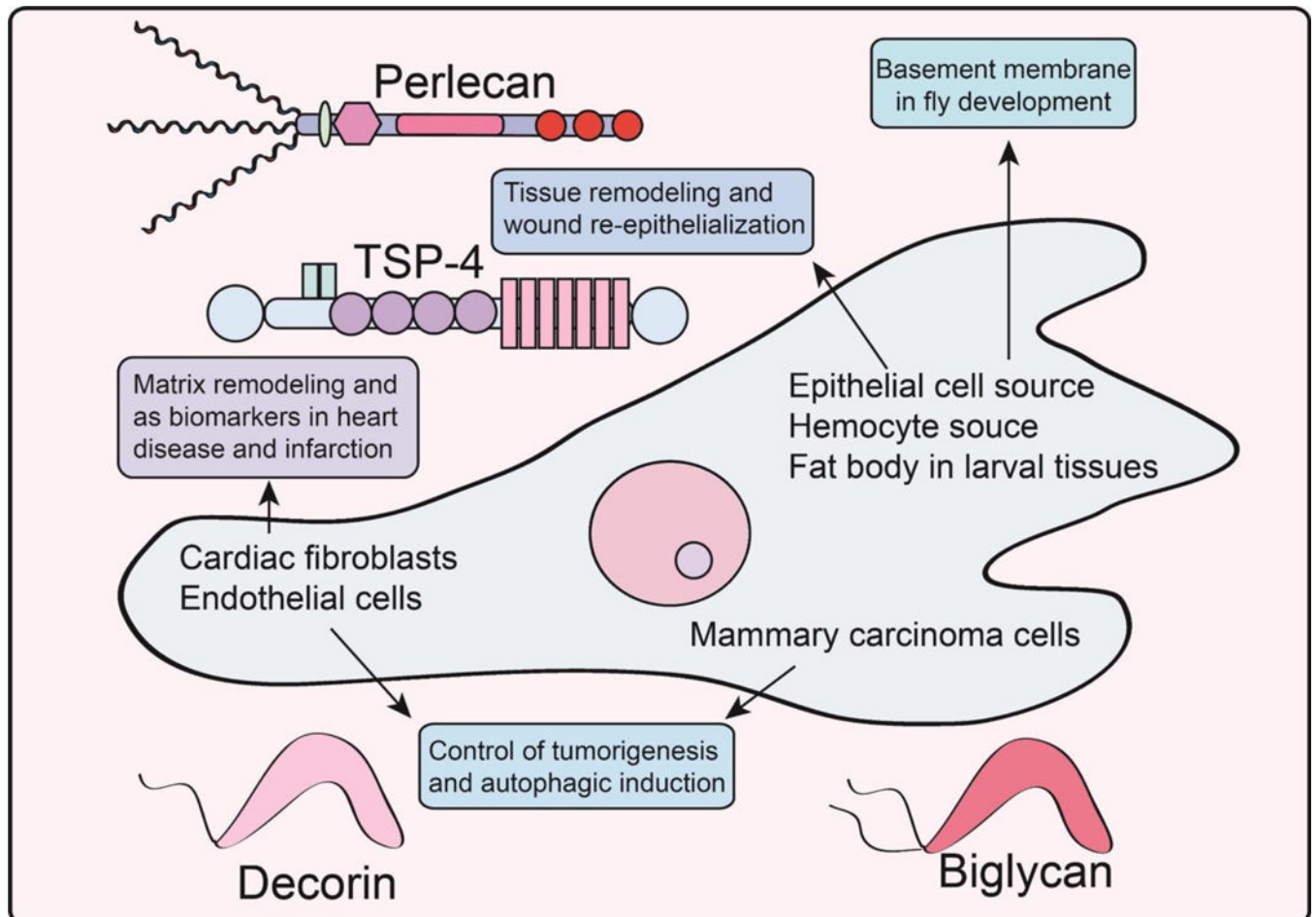
Fig. 2.
Schematic representation of various roles discovered for proteoglycans in regulating development, as biomarkers in adverse cardiac events, and in controlling tumorigenesis and catabolism. Please refer to the text for additional information.