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Extracellular matrix structure☆

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ABSTRACT

Extracellular matrix (ECM) is a non-cellular three-dimensional macromolecular network composed of collagens, proteoglycans/glycosaminoglycans, elastin, fibronectin, laminins, and several other glycoproteins. Matrix components bind each other as well as cell adhesion receptors forming a complex network into which cells reside in all tissues and organs. Cell surface receptors transduce signals into cells from ECM, which regulate diverse cellular functions, such as survival, growth, migration, and differentiation, and are vital for maintaining normal homeostasis. ECM is a highly dynamic structural network that continuously undergoes remodeling mediated by several matrix-degrading enzymes during normal and pathological conditions. Deregulation of ECM composition and structure is associated with the development and progression of several pathologic conditions. This article emphasizes in the complex ECM structure as to provide a better understanding of its dynamic structural and functional multipotency. Where relevant, the implication of the various families of ECM macromolecules in health and disease is also presented.

Contents

Abbreviations: ADAMs, a disintegrin and metalloproteases; ADAMTSs, ADAMs with thrombospondin motifs; BMPs, bone morphogenetic proteins; CSC, cancer stem cell; COMP, cartilage oligomeric matrix protein; CS, chondroitin sulfate; CSPG4, chondroitin sulfate proteoglycan 4; CNNs, cysteine-rich 61 connective tissue growth factor nephroblastoma overexpressed family proteins; DS, dermatan sulfate; DDRs, discoidin domain receptors; EMILIN-1, elastin microfibril interface located protein 1; ER, endoplasmic reticulum; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; EMT, epithelial-to-mesenchymal transition; ECMs, extracellular matrices; FACITs, fibril-associated collagens with interrupted triple helices; FGFs, fibroblast growth factors; FN, fibronectin; GAGs, glycosaminoglycans; GPI, glycosylphosphatidylinositol; Hh, Hedgehog; HS, heparan sulfate; HSPGs, heparan sulfate proteoglycans; Hep, heparin; HA, hyaluronan; HCC, hepatocellular cell carcinoma; HGF, hepatocyte growth factor; HASes, hyaluronan synthases; HYALs, hyaluronidases; HIF-1α, hypoxia inducible factor-1α; IGF-IR, insulin-like growth factor-I receptor; IFP, interstitial fluid pressure; KS, keratan sulfate; LG, laminin globular; LCC, laminin coiled-coil; LN, laminin N-terminal; LE, laminin-type epidermal growth factor-like repeats; LDL, low density lipoprotein; LRP-1, LDL-receptor related protein-1; LOX, lysyl oxidase; MMPs, matrix metalloproteases; MACITs, membrane-associated collagens with interrupted triple helices; MT1-MMP, membrane type 1-MMP; MAGPs, microfibril-associated glycoproteins; MULTIPLEXIN, multiple triple-helix domains and interruptions; N-CAM, neural cell-adhesion molecule; NC, non-collagenous; OPN, osteopontin; PEDF, pigment epithelium-derived factor; PAIs, plasminogen activator inhibitors; PDGF, platelet-derived growth factor; PDGFR, platelet-derived growth factor receptor; PRELP, proline/arginine-rich end leucine-rich repeat protein; Pyk2, proline-rich tyrosine kinase 2; PKCα, protein kinase Cα; PGs, proteoglycans; RPTPβ, receptor-type protein tyrosine phosphatase β; RECK, reversion-inducing cysteine-rich protein with Kazal motifs; SEA, sea urchin sperm protein, enterokinase, and agrin; SPARC, secreted protein acidic and rich in cysteine; SLRPs, small leucine-rich proteoglycans; STIM1, stromal interaction molecule 1; TNs, tenascins; TN-C, tenascin-C; TN-X, tenascin-X; TN-W, tenascin-W; TSP-1, thrombospondin-1; TIMP-3, tissue inhibitor of metalloproteases-3; tPA, tissue-type plasminogen activator; TLRs, Toll-like receptors; TGF-β, transforming growth factor-β; TGFRI, TGF receptor I; TNF-α, tumor necrosis factor α; uPA, urokinase plasminogen activator; uPAR, urokinase plasminogen activator receptor; VEGFA, vascular endothelial growth factor A; VEGFR2, vascular endothelial growth factor receptor 2; Wnt, wingless-related integration site.

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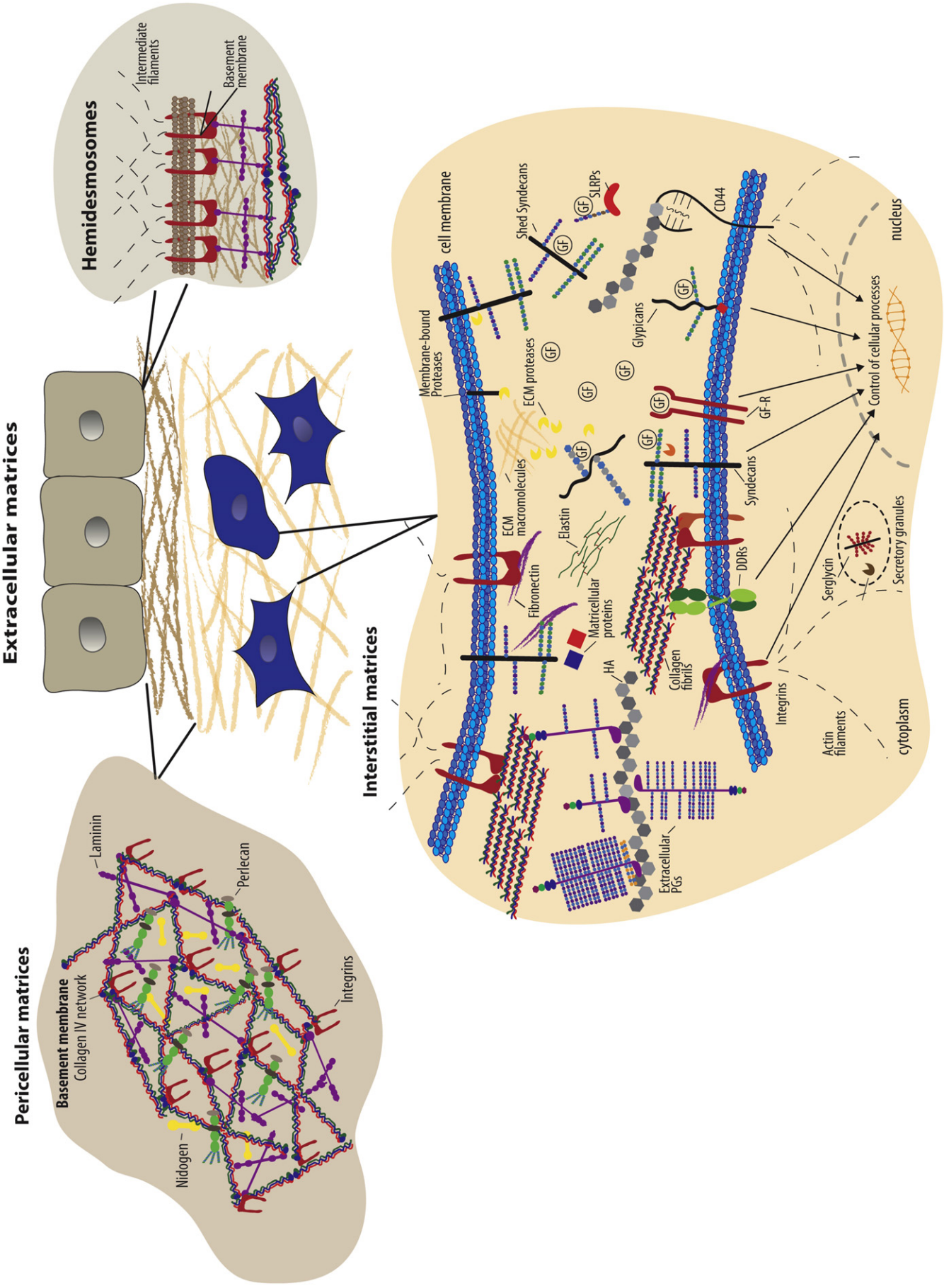
1. Types of extracellular matrices: structure and properties

All tissues and organs contain a mixture of cells and non-cellular components, which form well-organized networks called extracellular matrices (ECMs). The ECMs provide not only physical scaffolds into which cells are embedded but also regulate many cellular processes including growth, migration, differentiation, survival, homeostasis, and morphogenesis [1–3]. The ECMs consist of a large variety of matrix macromolecules whose precise composition and specific structures vary from tissue to tissue. The major constituents of ECMs are fibrous-forming proteins, such as collagens, elastin, fibronectin (FN), laminins, glycoproteins, proteoglycans (PGs), and glycosaminoglycans (GAGs), which are highly acidic and hydrated molecules. In most tissues, fibril-forming collagen type I and mainly in cartilage collagen type II are the major constituents of ECMs. They are associated with other collagens as well as ECM proteins and PGs to construct large fibrilar structures. These multi-molecular structures are interconnected with ECM molecules, which also associate with each other, building the complex three-dimensional matrix network (Fig. 1) [3].

ECMs can be classified into two major types that vary in composition and structure: the interstitial and pericellular matrices (Fig. 1). The interstitial matrices surround cells, whereas the pericellular matrices are in close contact with cells. For example, basement membrane, which is a type of pericellular matrix, is found in the interface between parenchyma and connective tissue providing an anchoring sheet-like layer for parenchymal cells in order to be held together preventing them from ripping apart. Basement membranes are composed of collagen type IV, laminins, nidogen 1 and 2, and PGs such as perlecan, agrin, collagen type XV, and collagen type XVIII [4]. Basement membranes consist of a laminin polymer that provides mainly epithelial cell adhesion sites and a collagen type IV network that stabilizes the overall structure. Both networks interact with other basement membrane components, which act as molecular linkers interconnecting the two networks [5]. For example, perlecan-containing aggregates are implicated in the tight connection of collagen type IV and laminin networks [6] but also influence the hydration and thus the biomechanical properties of basement membranes [5]. Although basement membranes show a symmetrical ultrastructure with a lamina densa placed between two lamina rarae structures, they present biochemical and mechanical asymmetry that allows the alternating arrangement of epithelium and connective tissue. For example, the laminin network is found at the epithelial side providing the substrate for binding of epithelial cells, whereas collagen type IV network is localized at the stromal side. Epithelial cells are anchored to basement membrane via specific structures named hemidesmosomes. They are formed when cell surface integrins interact with laminins at the extracellular level and intracellularly with intermediate filaments (Fig. 1) [7].

Cells embedded into ECMs interact with this macromolecular network through their surface receptors, such as integrins, discoidin domain receptors (DDRs), cell surface PGs, and the hyaluronan (HA) receptor CD44. In this respect, cells integrate signals from ECMs that dictate their functions and behavior (Fig. 1). All cell types (i.e. epithelial, fibroblasts, immune cells, endothelial cells) synthesize and secrete matrix macromolecules under the control of multiple signals thus participating in the formation of ECMs. Variations in the composition and structure of ECMs' components affect both the overall structure and biomechanical properties of the formed network, but also the signals transmitted to cells thus modulating their responses. Various growth factors, cytokines, and chemokines are deposited within ECMs through binding to specific ECM molecules and are able upon well-orchestrated procedures to be liberated and operate at developmentally and physiologically relevant time [8,9]. The ECMs are crucial for normal homeostasis, but also many syndromes and pathological/lethal conditions arise from abnormalities in ECMs components that emerge ECM molecules as potential targets for targeted pharmacological treatment [10].

ECM remodeling occurred during physiological conditions and as part of disease processes modulates the structure and properties of ECMs in multiple ways (Fig. 1). For example, the proteolytic degradation mediated by enzymes, such as matrix metalloproteases (MMPs), a disintegrin and metalloproteases (ADAMs), ADAMs with thrombospondin motifs (ADAMTSs), plasminogen activators, as well as degradation of heparan sulfate (HS) chains mediated by heparanase, liberate heparin (Hep)-binding growth factors that in turn activate angiogenesis and cell growth during tumorigenesis [11]. Especially, during tumorigenesis, marked alterations in the ECMs take place leading to the formation of fibrotic stroma with increased stiffness, excessive deposition of ECM components, and release of proteolytic enzymes that upon activation result in an abnormal ECM remodeling. Lysyl oxidase (LOX) activity is enhanced and promotes cross-linking of collagen fibers with ECM components resulting in matrix stiffness [12,13]. Various cell types within the tumor stroma, such as cancer-associated fibroblasts, endothelial cells, immune cells, pericytes, but also tumor cells themselves, participate in the formation


Extracellular matrices
Hemidesmosomes
Intermediate filaments
Basement membrane
Pericellular matrices
Basement membrane
Collagen IV network
Laminin
Perlecan
Integrins
Nidogen
Interstitial matrices
cell membrane
Membrane-bound Proteases
Shed Syndecans
SLRPs
ECM proteases
Glypicans
CD44
ECM macromolecules
Elastin
Fibronectin
Matricellular proteins
HA
Collagen fibrils
Extracellular PGs
DDRs
Syndecans
GF-R
Integrins
Actin filaments
Serglycin
Secretory granules
Control of cellular processes
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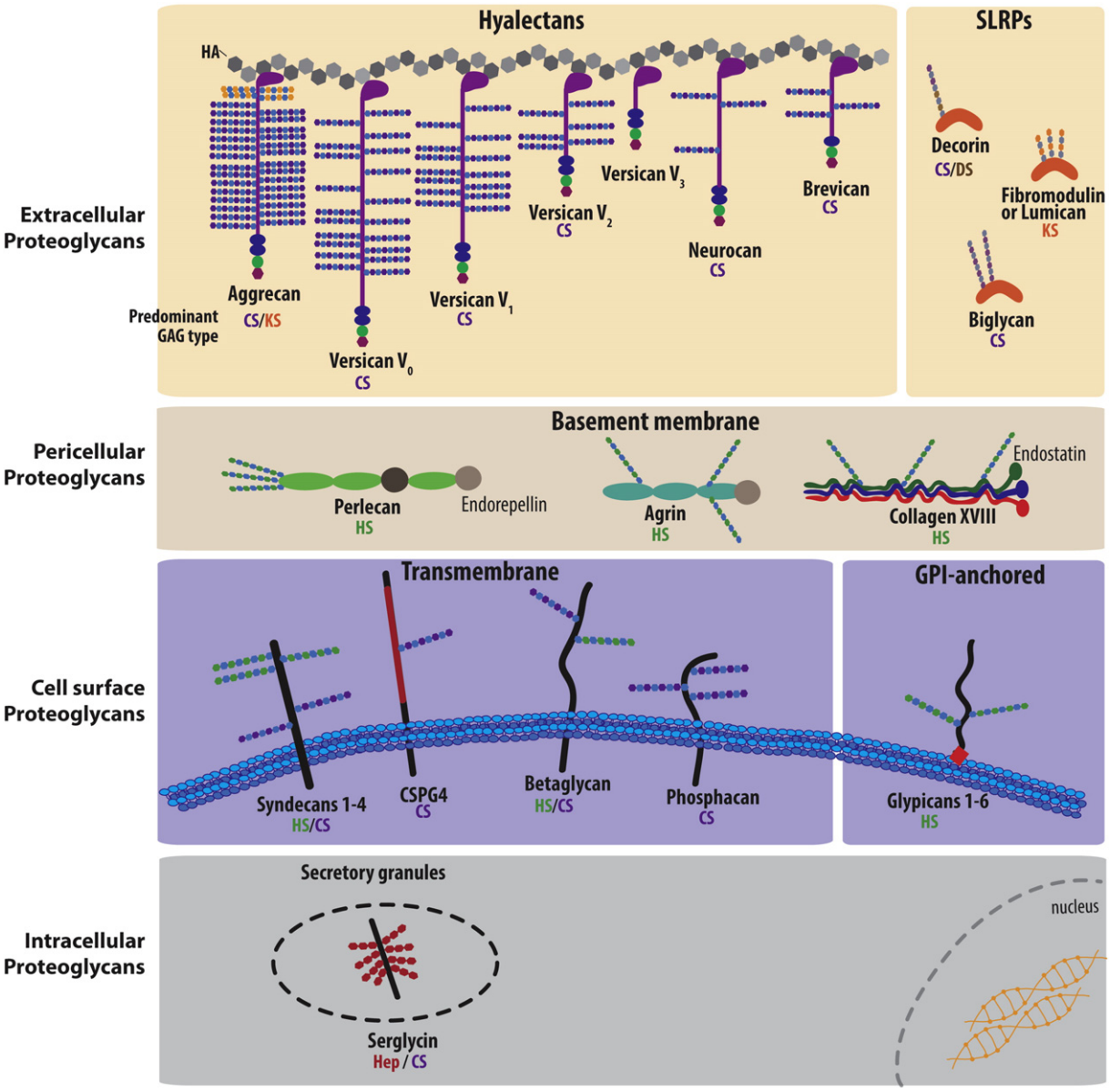

Fig. 2. *Classification and schematic representation of proteoglycans.* PGs are classified as extracellular, pericellular, cell surface, and intracellular according to their localization, homology at the protein and genomic levels, and the presence of unique protein modules. Extracellular PGs are divided into two subfamilies: the hyalectans, which interact with HA through their N-terminus and lectins via their C-terminus, and the SLRPs. Hyalectans consist of four members, aggrecan carrying CS/KS chains, versican, neurocan ,and brevican mainly bearing CS chains. Four splice variants of versican exist, the full-length variant V_0, and the three splice variants lacking GAGα (V_1), GAGβ (V_2), or both GAG attachment domains (V_3). SLRPs constitute a large subfamily of PGs containing eighteen members, which are divided into five classes. Decorin and biglycan belong to class I SLRPs and carry CS/DS chains, whereas fibromodulin and lumican are included in class II SLRPs containing KS chains. These SLRPs are among the most studied members of this subfamily that is characterized by the presence of a relatively small core protein (~36–42 kDa) that encompasses a central region constituted of leucine-rich repeats. SLRPs interact with various collagens and cell surface receptors participating in collagen fibrillogenesis and modulating cellular signaling. Pericellular PGs comprise perlecan, agrin, and collagens XV and XVIII, which are modular PGs containing HS chains. Perlecan and agrin contain at their C-terminus a processed domain called endorepellin that exhibits potent anti-angiogenic functions. Similarly, collagens XV and XVIII harbor at their C-terminus NC domain the anti-angiogenic endostatin and endostatin-like modules. Cell surface PGs comprise transmembrane type I PGs (syndecan-1 to -4), CSPG4, betaglycan, and phospacan bearing HS/CS chains, and GPI-anchored glypican-1 to -6, which carry HS chains. Serglycin is the only characterized member of intracellular PGs present in secretory granules and is substituted with Hep/CS chains.

Fig. 1. *Schematic overview of extracellular matrices, their major components, and cell surface receptors.* ECMs are classified into two major types, the interstitial and pericellular matrices. Basement membrane, a type of pericellular matrix, is found between epithelial cells and connective tissue. This layer is composed of a collagen IV network that associates with ECM components including nidogen, laminin, perlecan, and minor collagens like collagen XV and XVIII. Epithelial cells are anchored to basement membranes by hemidesmosomes formed via interactions of integrins with laminins. Interstitial matrices are composed of collagen fibrils, elastin, secreted PGs and HA, and matricellular proteins. They interact with each other creating a dynamic and complex three-dimensional network. Cells bind to ECM components by specific cell surface receptors, such as integrins; cell surface PGs; syndecans and glypicans; the HA receptor CD44; and DDRs. They transduce signals into cells that regulate various cellular functions. Growth factors (GF) are sequestered within ECM via binding to ECM components like PGs. They are liberated following ECM degradation bind to specific growth factor receptors (GF-R) and co-receptors (syndecans and glypicans) and activate various signaling pathways. Several proteolytic enzymes, such as MMPs, ADAMs, ADAMTs, cathepsins, and plasminogen activators, and GAG-degrading enzymes, such as heparanases and hyaluronidases degrade ECMs. Intracellular proteoglycan serglycin is also present in the cytoplasm into secretory granules in association with bioactive molecules, such as proteases and is secreted in ECM during inflammation and tissue remodeling. ECM degrading enzymes play critical roles in normal tissue remodeling and disease progression.

of deregulated and disorganized ECMs that favor and promote tumorigenesis [12].

2. ECM components: structure, interactions and functions

2.1. Proteoglycans and hyaluronan

PGs are among the most important structural and functional biomacromolecules in tissues. They consist of a core protein onto which one or more GAG chains of the same or different type are covalently attached. GAGs are long highly negatively charged heteropolysaccharides that contain repeating disaccharides composed mainly of *N*-acetylated hexosamines (*N*-acetyl-D-galactosamine or *N*-acetyl-D-glucosamine) and D-/L-hexuronic acid (D-glucuronic acid or L-iduronic acid). There are six types of glycosaminoglycans: the galactosaminoglycans chondroitin sulfate (CS) and dermatan sulfate (DS), and the glucosaminoglycans HS, Hep, keratan sulfate (KS) ,and HA. HA is the only GAG which is biosynthesized at the cell membrane and not at the Golgi apparatus and is present in a protein-free form. KS is another structurally unique GAG whose disaccharide unit contains D-galactose but not hexuronic acid [14]. GAGs are long polymers of variable molecular sizes depending on the type and tissue origin and are substituted with sulfate groups at various positions either in the hydroxyl groups of hexosamines, D-galactose, and hexuronic acid or in the amino-group of D-glucosamine (especially in Hep, a highly sulfated variant of HS, and in a lower extent in HS). HA is the only GAG which is not substituted with sulfate groups. Overall, each GAG chain is a mosaic of disaccharides of variable number and structure, the combination of which creates an extremely heterogeneous motif that may be unique for each individual chain [14,15].

PGs are found in intracellular compartments and at the cell surface but are also abundant in the ECMs (Fig. 2). They interact with numerous growth factors, cytokines and chemokines, cell surface receptors and ECM molecules either via their core proteins or, mainly, through their GAG side chains participating in several cell functional properties, such as cell signaling, proliferation, migration, differentiation, apoptosis, and adhesion [14,16–19]. Due to their ability to interact with other ECM molecules and cells, PGs are also important molecules for the organization of ECMs, thus contributing to the formation of ECM scaffold and cell embedding within it. PGs and GAGs play important roles in normal physiology and development of various diseases since their biosynthesis is markedly modified during ECM remodeling in all pathologies [14,16–19]. Recently, it has also been described that the epigenetic modifications play important roles in the synthesis of GAGs/PGs [20,21].

2.1.1. Hyaluronan

HA is a linear GAG containing repeating disaccharide units of D-glucuronic acid and *N*-acetyl-D-glucosamine. HA exists either as a free GAG or non-covalently attached to PGs in the ECMs of mammals [22,23], bacteria [24], as well as chlorella virus infected algae [25]. HA is a major constituent of the pericellular matrix of many cell types, where it binds either to its own synthases or to its cellular receptors affecting several cell functions [22,26]. Interestingly, HA has been also detected intracellularly as well as in the nucleus of normal and tumor cells [27,28]. Large HA polymers accumulation is a frequent feature of tissues that undergo reorganization, such as embryonic development, mainly because of HA's unique physicochemical properties and ability to imbibe large amounts of water molecules providing tissues with remarkable plasticity. However, in inflammation and tumor progression, HA is often observed in both high and low molecular mass forms in high amounts where they act as signaling molecules interacting with their receptors, such as CD44, RHAMM, and the HA-binding PG versican [29–31] (Fig. 2).

The size of HA depends on the relative activity of HA synthesizing and degrading enzymes [32]. In mammals, there are three hyaluronan synthase (HAS) isoforms (HAS1, 2, and 3) that mainly differ in their enzymatic ability to produce HA of different sizes [33,34]. On the other hand, hyaluronidases (HYALs; HYAL-1, -2, -3, -4, -P1, PH-20) degrade HA to low molecular weight fragments that possess size-dependent functions [35].

2.1.2. Proteoglycans

As recently proposed, PGs can be classified into four families: intracellular, cell surface, pericellular-basement membrane, and extracellular ones, according to their cellular and subcellular localization, protein sequence homology, and the presence of unique protein modules (Fig. 2) [17].

2.1.2.1. Extracellular proteoglycans. This is the largest class that encompasses two subfamilies: hyalectans and small leucine-rich proteoglycans (SLRPs) (Fig. 2).

2.1.2.1.1. Hyalectans. The subfamily of matrix PGs called hyalectans (HA- and lectin-binding PGs) contains aggrecan, versican, neurocan, and brevican, which share common structural features. Their N-terminal domain contains Ig-like repeat followed by link-protein-like modules (PG tandem repeats) that through disulfide-bonded Cys form globular domains (G1 globular domain for all hyalectans and an additional G2 globular domain only for aggrecan). Their central domain harbors variable number of potential GAG attachment sites, whereas the C-terminal domains contain the G3 globular domain. The G3 globular domain contains two epidermal growth factor (EGF)-like repeats (with the exception of brevican that contains only one EGF-like repeat), a C-type lectin domain, and a complement regulatory protein domain. The N-terminal domain evokes the binding of hyalectans to HA, whereas the C-terminal domain binds to lectins. A short description of hyalectan family members is given in the following sections.

2.1.2.1.1.1. Aggrecan. Aggrecan is the major PG in cartilage but is also expressed in intervertebral disc and brain, primarily in the perineuronal nets. Its G1 domain forms ternary complexes with link protein and HA that are very stable. These large aggregates create a densely packed, hydrated gel enmeshed in a network of reinforcing collagen fibrils and other PGs providing cartilage with unique biomechanical properties. The central part of aggrecan next to G2 globular domain presents a relatively small domain that can be substituted with KS chains, which is followed by a larger domain that can be substituted with more than 100 CS chains. The resulting densely negatively charged aggrecan molecules can hold large amounts of water in tissues, like cartilage, intervertebral disc, and brain [17]. G3 domain interacts with tenascins (TNs), fibulins, and sulfated glycolipids [36]. C-type lectin domain binds sugars in a calcium-dependent manner and may bind galactose present on collagen type II or other ECM and cell surface molecules. Thus, aggrecan may act as a bridging molecule connecting various ECM molecules but also connecting the matrix network with cell surface thereby providing a mechano-sensitive feedback to the chondrocytes [17].

2.1.2.1.1.2. Versican. Versican is expressed in various tissues with versatile functions. Its central domain consists of two large subdomains (GAGα and GAGβ), which can be alternatively spliced and carry CS/DS chains. Four splice variants of versican have been identified; V_0 represents the full versican molecule carrying both GAGα and GAGβ domains, V_1 and V_2 carry GAGβ and GAGα domains, respectively, and V_3 lacks both GAG attachment domains and is not glycanated. Versican isoforms are differentially expressed. V_0 and V_1 are the most ubiquitous isoforms in the developing heart and limbs, vessels, and several non-neuronal tissues, whereas V_2 is present in the brain [17,19,37]. Mutations in the versican gene results in autosomal dominant eye disorders, such as Wagner syndrome and erosive vitreo-retinopathy [38]. Recently, a novel V_4 variant that contains part of the GAGβ domain and is partially glycanated has been detected in human breast cancer tissues [39].

Versican regulates cell adhesion, migration, and inflammation [40,41]. During inflammation, leukocytes encounter a provisional

matrix enriched in versican that in turn interacts with many cell receptors, such as CD44, selectins, and Toll-like receptors (TLRs) thus regulating their behavior [40,41]. Versican is accumulated in tumor stroma mainly as a result of fibroblasts' activation, although it is also expressed by some tumor cells and augments tumorigenesis [18,19]. Versican interacts with TLR2 present on bone marrow-derived macrophages activating TLR2/TLR6 complexes inducing tumor necrosis factor α (TNF-α) secretion and enhancing the formation of metastasis [42]. Furthermore, through its G3 domain and more specifically via EGF-like repeats, versican can activate epidermal growth factor receptor (EGFR) signaling promoting cancer cell growth, migration, invasion, and drug resistance [19,37].

2.1.2.1.1.3. Neurocan and brevican. Neurocan can carry up to seven CS chains and is expressed in the brain. It inhibits neurite outgrowth *in vitro* and is increased at the site of mechanical and ischemic injury [17,43,44].

Brevican is also expressed in the brain; more specifically, it is located at the outer surface of neurons and is enriched at perisynaptic sites. Brevican is implicated in nervous tissue injury and repair, Alzheimer's disease, and promotes growth and progression of gliomas [17,45,46].

2.1.2.1.2. Small leucine-rich proteoglycans. This is the largest family of PGs containing eighteen members that are grouped into five classes and are ubiquitously expressed in most ECMs. Classes I–III are canonical, whereas classes IV and V are non-canonical and do not carry GAG chains but share structural homology and several functional properties with the full-time PGs of this family. Class I consists of decorin, biglycan, asporin, ECM2, and ECMX; class II contains fibromodulin, lumican, proline/arginine-rich end leucine-rich repeat protein (PRELP), keratocan, and osteoadherin; whereas epiphycan, opticin, and osteoglycin belong to class III. Class IV consists of chondroadherin, nyctalopin, and Tsukushi, whereas class V comprises podocan and podocan-like 1 [17]. SLRPs share many biological functions, such as that they interact with various collagens regulating collagen fibrillogenesis, and they bind receptor tyrosine kinases and innate immune receptors thus modulating cell signaling in various signaling pathways [17,47–57].

2.1.2.1.2.1. Decorin. Decorin carries one GAG (CS or DS) chain. It is the prototype member of SLRPs awarded its eponym from its ability to decorate collagen fibrils. Decorin core protein binds non-covalently about every 67 nm (*D* period) on the surface of collagen fibrils. In addition, the GAG chain of decorin participates in collagen fibrillogenesis and alignment of collagen fibrils. Hence, decorin is important for the mechanical properties of various connective tissues and in maintaining corneal transparency [58,59]. Decorin gene mutations have been associated with congenital stromal corneal dystrophy syndrome [60,61].

Decorin directly binds transforming growth factor-β (TGF-β) and inhibits cell growth [62]. Notably, decorin is highly expressed in the tumor stroma acting as a tumor suppressor molecule. It has been well established that it activates EGFR by binding to a region of EGFR partially overlapping with EGF-binding epitope inducing growth arrest via expression of cyclin-dependent kinase inhibitor $p21^{WAF1}$ [51,63,64]. Moreover, decorin binding to EGFR promotes sustained down-regulation of EGFR *in vivo* due to its caveolar endocytosis and degradation thus controlling tumor cell growth [65,66]. Decorin binds with high affinity to hepatocyte growth factor (HGF) receptor (c-Met) and causes proteasomal degradation of Myc and β-catenin, stimulates the expression of anti-angiogenic molecules, such as thrombospondin 1 (TSP-1), tissue inhibitor of metalloproteinases-3 (TIMP-3), with concurrent inhibition of pro-angiogenic factors hypoxia inducible factor-1α (HIF-1α) and vascular endothelial growth factor A (VEGFA) [52,67–69]. Decorin also binds and suppresses both insulin-like growth factor-I receptor (IGF-IR) [53,70] and vascular endothelial growth factor receptor 2 (VEGFR2) [68] and evokes autophagy in endothelial cells through partial agonist activity of VEGFR2 and induction of Peg3 [71]. Overall, decorin has multiple inhibitory functions on cancer cell growth suppressing growth factor receptor signaling and angiogenesis [72] but also inducing a protracted and in this case deleterious, stromal cell autophagy [73].

2.1.2.1.2.2. Biglycan. Biglycan has two GAG attachment sites in its N-terminal region. It is ubiquitously expressed in tissues and plays a key role in postnatal skeletal growth [74]. Biglycan binds TGF-β and modulates its activity [75] but in contrast to decorin acts as pro-angiogenic stimulus by binding and regulating VEGFA expression [76]. Biglycan is also a pro-inflammatory molecule that activates TLRs [77,78]. Biglycan is highly expressed and secreted by circulating macrophages acting as a danger signaling molecule for the innate immunity receptors TLR2/4 [77] and by activating the inflammasome via TLR2/4 and the purinergic P2X receptors [78].

2.1.2.1.2.3. Fibromodulin and lumican. Fibromodulin is a KS-containing PG showing a wide distribution in connective tissues. It binds collagens and regulates collagen fibrillogenesis as well as the collagenous part of complement component C1q activating the classical pathway of complement [17,79]. In solid tumors, deposition of fibromodulin promotes the formation of a dense stroma and an elevated interstitial fluid pressure (IFP) that in turn decreases drug delivery and affects the response to chemotherapy [80]. Furthermore, fibromodulin may also augment tumor cell growth by promoting angiogenesis [81,82].

Lumican is another well-studied member of SLRPs carrying KS chains. It is localized primarily to mesenchymal tissues and tumor stroma [17]. It is important for maintaining the interfibrillar space of the corneal collagen architecture that is vital for corneal transparency. Lumican is highly expressed in breast cancer and melanomas [83–85]. Lumican blocks melanoma cell adhesion via interaction with β1-containing integrins [86] and also by modulating focal adhesion complexes [87]. It is also expressed in various other malignancies including osteosarcoma [88,89]. Notably, lumican via the modulation of TGF-β2 activity regulates osteosarcoma cell adhesion [90] and is also capable to inhibit membrane type 1-MMP (MT1-MMP) activity [91].

2.1.2.2. Pericellular-basement membrane proteoglycans. Pericellular membrane PGs carry mostly HS chains and are closely associated with the surface of many cell types anchored via cell surface receptors, such as integrins. They are also part of basement membranes. Perlecan, agrin, as well as collagen types XV and XVIII, which are discussed below, are members of this family (Fig. 2).

2.1.2.2.1. Perlecan. Perlecan is a modular proteoglycan that contains five discrete domains. The core protein shares homology with sea urchin sperm protein, enterokinase and agrin (SEA), neural cell-adhesion molecule (N-CAM), IgG, low density lipoprotein (LDL) receptor, and laminin and carries mostly three HS chains at the N-terminus. It is expressed by both vascular and avascular tissues and is located at the apical cell surface [14,17]. Perlecan affects various cellular functions. Via its ability to interact with numerous ligands and cell surface receptors, perlecan affects cell adhesion, growth, and survival. Notably, perlecan binds and sequesters Hep-binding ligands in the ECMs. It has been reported that perlecan displays dual functions in regulating angiogenesis. Cleavage of the HS chains by heparanase and its core protein by proteases releases various pro-angiogenic factors and presents them to their cognate receptors thus promoting angiogenesis. In contrast, the C-terminal processed form of perlecan domain V named endorepellin potently inhibits angiogenesis [92–94]. It is worth noticing that endorepellin induces autophagy in endothelial cells via VEGFR2 signaling suggesting a novel mechanism by which endorepellin inhibits angiogenesis [95].

2.1.2.2.2. Agrin. Agrin, similarly to perlecan, has a multimodular structure. Splicing of the N-terminus generates either a type II transmembrane form of agrin, highly expressed in nervous tissue, or an isoform containing the N-terminal agrin domain present in basement membranes. Starting from the N-terminus, a stretch of nine folistatin-like repeats exists. The last two of them are separated by two laminin-type epidermal growth factor-like repeats (LE). The last folistatin-like repeat is followed by two Ser/Thr-rich domains, which are separated

by a SEA module. The C-terminus contains three laminin globular (LG) domains separated by EGF-like modules exhibiting similarity to perlecan domain V / endorepellin [17]. HS chains of agrin are located at the central part of the core protein. Agrin through multiple protein modules and HS chains can bind multiple ECM components and cell surface receptors playing important biological roles, such as basement membrane organization and clustering of acetylcholine receptors [96]. Notably, recessive missense mutations in agrin cause congenital myasthenic syndromes associated with defective neuromuscular transmission [97,98].

2.1.2.3. Cell surface proteoglycans. Syndecans and glypicans are two main subfamilies of cell surface PGs and carry mostly HS chains. Other members of cell surface PGs are melanoma-associated chondroitin sulfate proteoglycan 4 (CSPG4), betaglycan, and phosphacan all containing CS chains (Fig. 2).

2.1.2.3.1. Syndecans. Syndecans are a family of transmembrane heparan sulfate proteoglycans (HSPGs) consisting of four members (syndecan-1/CD138, syndecan-2/fibroglycan, syndecan-3/N-syndecan, and syndecan-4/amphiglycan) in higher vertebrates [99]. Syndecans are expressed, either all four or at least one, by almost all cell types except of erythrocytes. In contrast to the other syndecans, which appear to be more widely expressed in many cell types and tissues, syndecan-3 is mainly found in neural tissue and, to a lesser extent, in the developing musculoskeletal system [100]. The expression and distribution pattern of syndecans dramatically change during normal development (involving morphological transitions and cell differentiation) as well as in a range of diseases, including cancer [101–104]. Structurally, syndecans consist of an ectodomain containing several GAG attachment sites, a single transmembrane domain, and a short cytoplasmic domain that harbors various binding motifs [105,106]. In contrast to their ectodomain variability, the transmembrane and cytoplasmic domains show high sequence homology [101]. Although HS is the main GAG moiety present in all four syndecans, syndecan-1 and -3 can also carry CS or DS side chains [107]. The HS chains are usually in proximity with the N-terminus and attach to the Ser-Gly attachment sites on the core protein of which there are at least three in each syndecan [108]. These chains are a significant feature of syndecans and may dominate their physicochemical properties, interactions, and functions.

Many ECM components have Hep-binding domains, which facilitate their interactions with syndecans. For example, FN (described in 2.4) has three Hep-binding sites, a low-affinity N-terminal site (HepI), a high-affinity site contained within type III repeats 13 and 14 (HepII), and a more cryptic domain contained within type III repeats 4 and 5 [100]. Considerable attention has focused on the interaction between the HS chains of syndecan-4 and the HepII domain of FN. Syndecan HS chains interact also with the laminin α chains. The Hep-binding sites are located at the LG-modules (LG4-5) of the C-terminal large globular domain [109]. Many collagens also contain Hep- and HS-binding domains; therefore, they can also bind to syndecans. Syndecan-1 appears to be a co-receptor for collagen with integrins, such as α2β1 [110]. This collaboration enhances the transcription of MMP-1 with implications for tissue remodeling. Hep-binding sites have been also identified in matricellular proteins, such as tenascin-C (TN-C) and TSPs (described in 2.6). A role for TN-C in regulating the interactions between syndecan-4 and FN has been suggested. TN-C can bind both HS and the heparin-binding FNIII repeat 13 of FN, and these interactions result in FN-mediated cessation of cell cycle progression [111]. Regarding TSP-1, there are two Hep-binding domains toward its N-terminus that compete, as in TN-C, with the HepII domain of FN for engagement of syndecan-4 HS chains. It is hypothesized that the N-terminal pro-angiogenic activity of TSP-1 correlates with its ability to interact with syndecan-4 during cell adhesion [112]. Moreover, syndecans can act as cellular receptors for growth factors, interleukins, morphogens, and chemokines since these molecules have also Hep/HS-binding properties. Hence, syndecans regulate secreted growth factors, like Hedgehog (Hh), wingless-related integration site (Wnt) and bone morphogenetic proteins (BMPs), concentration gradient formation, and their downstream signaling pathways [113].

Shedding of syndecans ectodomain is achieved by the action of various proteases and has been demonstrated to affect critical processes. For example, soluble syndecan-1 is elevated in many diseases and has a remarkable impact in tumor growth [19,114]. Shedding of syndecan-1 is enhanced by the action of heparanase thereby offering a novel mechanism that augments tumor growth and metastasis [115]. Heparanase is an endo-β-glucuronidase, which degrades HS between glucuronic acid and *N*-sulfo-glucosamine residues. The smaller HS fragments resulting from heparanase action have enhanced binding to specific ligands. Heparanase releases Hep-bound molecular effectors, such as growth factors, cytokines, and chemokines, which are stored in the ECMs, contributing to their dissemination and activity and enhancing cell migration and invasion. In addition, heparanase executes a variety of non-enzymatic functions that promote angiogenesis and tumorigenesis [11,116–118].

2.1.2.3.2. Glypicans. Glypicans are a family of glycosylphosphatidylinositol (GPI)-anchored PGs that consists of six members (glypican-1 to glypican-6) in mammals [119,120]. Common structural features of glypicans include the presence of fourteen cysteine residues as well as the GAG attachment sites close to their C-terminus, implying a role for these chains in the interaction of glypicans with other cell surface proteins [121].

Glypicans display several sites for covalently bonding to GAGs (from two in glypican-3 to five in glypican-5). Most glypicans have been shown to carry HS chains. However, glypican-5 produced in transfected cells also display CS chains [122]. Moreover, CS chains have also been found in endogenous glypican-5 expressed by rhabdomyosarcoma cells [123]. Interestingly, the HS chains of glypican-3 and glypican-5 produced in mouse embryonal fibroblasts display a different degree of sulfation, indicating differences in the activity of the respective sulfotransferases [123]. Because the binding specificity of HS chains depends, at least in part, on their sulfation level, it is highly likely that this difference in the degree of sulfation of these chains in glypican-3 and glypican-5 has impact on their specific functions. Glypicans can bind and regulate the interaction of several growth factors (such as Wnts, Hhs, and others) with their cognate receptors thus modulating their

Fig. 3. *Classification, chain composition, distribution and structural features of vertebrate collagens.* Fibrillar collagens are organized when tropocollagen triple helices are self-assembled to form collagen microfibrils. The oxidation of lysine side chains by LOX and LOX-like enzymes and the formation of non-reducible covalent cross-links in the triple helix and in telopeptides stabilize the collagen fibrils. Collagen fibrils are packed together forming larger collagen fibers. Collagen type IV is the prototype of network forming collagens that contains interruptions in the triple helices. Collagen type IV forms dimers by head-to-head interactions of two trimeric NC1 domains and tetramers by interactions at N-terminus between four collagen IV molecules. Both interactions co-exist in the extended collagen network. FACITs are relatively short collagens with interruptions in their triple helices that interact with the surface of fibrillar collagens. MACITs are type II transmembrane proteins with a short cytoplasmic domain and a long C-ternimal collagenous domain with interrupted triple helices. Collagen type VII has a central collagenous domain containing a short interruption of triple helix and two NC domains at the C- and N-termini. Collagen type VII forms antiparallel dimers interacting by N-to-N interactions and aggregate laterally forming anchoring fibrils. Collagen VI forms dimers by antiparallel staggered alignment of the monomers, which then associate laterally to form tetramers. Disulfide bonds stabilize both dimers and tetramers. Collagen VI tetramers align end-to-end creating beaded filaments. Multiplexin class of collagens contains collagen types XV and XVIII that have a central triple helical collagen domain interrupted by several NC domains and carry CS (collagen XV) and HS (collagen XVIII) chains. Both contain an endostatin/endostatin-like module at their C-terminus.

Type
Composition
Distirbution
Microfibrils
Collagen fibrils
Collagen fibers
Network
Dimer
Tetramer
Monomer
Collagen type I fibrils (XII or XIV)
Collagen type II fibrils (IX)
cytoplasm
C-terminal
N-terminal NC
NC1
Antiparallel Dimer
Anchoring Fibril
NC2
Tetramer
Dimer
Beaded filament
N-terminal NC
Globular C-terminal
Endostatin
Fibrillar collagens
I α1 [I]2 α2 [I] Abundant and widespread: bone, dermis, tendon, ligament, cornea, etc
II α1 [II]3 Cartilage, vitreous
III α1 [III]3 Co-distribution with collagen I, skin, blood vessels, intestine
V α1 [V]3 α1 [V]2 α2 [V] α1 [V] α2 [V] α3 [V] Widespread: co-distribution with collagen I, bone, dermis, cornea, placenta
XI α1 [XI] α2 [XI] α3 [XI] Co-distribution with collagen II, cartilage, intervertebral disc
XXIV Bone, cornea
XXVII Cartilage
Network-forming collagens
IV α1 [IV]2 α2 [IV] α3 [IV] α4 [IV] α5 [IV] α5 [IV]2 α6 [IV] Basement membranes
VIII α1 [VIII]3 α2 [VIII]3 α1 [VIII]2 α2 [VIII] Widespread: dermis, brain, heart, kidney
X α1 [X]3 Cartilage
FACITs
IX α1 [IX] α2 [IX] α3 [IX] Co-distribution with collagen II, cartilage, vitreous, cornea
XII α1 [XII]3 Found with collagen I, dermis, tendon
XIV α1 [XIV]3 Widespread: found with collagen I, bone, dermis, cartilage
XVI Dermis, kidney
XIX Basement membrane
XX Cornea
XXI Stomach, kidney
XXII Tissue junctions
MACITs
XIII Neuromuscular junctions, skin, endothelial cells, eye, heart
XVII α1 [XVII]3 Hemidesmosomes in epithelia
XXIII Heart, retina
XXV Brain, heart, testis
Anchoring fibrils
VII α1 [VII]2 α2 [VII] Dermal-epidermal junction, bladder
Beaded-filaments-forming collagens
VI α1 [VI] α2 [VI] α3 [VI] α1 [VI] α2 [VI] α4 [VI] Widespread: bone, cartilage, cornea, dermis, muscle
XXVI Testis, ovary
XXVIII Dermis, sciatic nerve
MULTIPLEXIN
XV Basement membranes, eye, muscle, capillaries, testis, heart, kidney
XVIII Basement membranes, liver

downstream signaling pathways. For instance, glypicans have been shown to have both stimulatory and inhibitory functions in Hh signaling. Glypican-5 promotes Hh signaling in rhabdomyosarcoma cells by increasing the binding of Hh to its cellular receptor (Patched), while glypican-3 displays Hh-inhibitory activity by competing with the receptor for Hh binding [123–125].

2.1.2.3.3. CSPG4. CSPG4 is a single-pass type I transmembrane PG carrying one CS chain. Its large ectodomain is composed of three subdomains, which contain LG domains, CSPG repeats, and a juxtamembrane region all of which likely mediate binding to other ECM components and cell surface receptors. The intracellular domain harbors a proximal region with numerous Thr phospho-acceptor sites for protein kinase Cα (PKCα) and ERK1/2, and a distal region encompassing a PDZ-binding module [17]. It is highly expressed in various tumors and plays crucial roles in tumor progression. CSPG4 binds to collagen type VI in the tumor microenvironment and promotes cell survival and adhesion co-operating with integrins, is involved in the activation of pro-MMP-2 by MT3-MMP, and promotes tumor vascularization [18,126].

2.1.2.3.4. Betaglycan. Betaglycan, also known as TGF-β type III receptor, is a single-pass transmembrane PG that belongs to the TGF-β superfamily of co-receptors. The extracellular domain contains several potential GAG binding sites, whereas its short cytoplasmic domain contains numerous Ser/Thr residues that are candidates for PKC-mediated phosphorylation [17]. Furthermore, it harbors a PDZ-binding element similar to that observed in syndecans. Betaglycan is ubiquitously expressed and acts as a co-receptor for members of the TGF-β superfamily of growth factors. In triple-negative breast cancer cells, betaglycan promotes tumor growth [127] and the shedding of its ectodomain suppresses TGF-β signaling and breast cancer migration and invasion [128].

2.1.2.3.5. Phosphacan. Phosphacan corresponds to the soluble ectodomain of a receptor-type protein tyrosine phosphatase β (RPTPβ). RPTPβ is a single-pass type I membrane protein with a relatively large ectodomain that contains several potential GAG attachment sites. Phosphacan is substituted with CS chains, but it can also bear KS chains. Phosphacan interacts with neurons and neural cell-adhesion molecules and it has been proposed as an important ECM component of neural stem cell niche that supports neural stem cell self-renewal and maintenance [129].

2.1.2.4. Intracellular proteoglycans. Serglycin is the only characterized intracellular PG present in secretory compartments (Fig. 2) [130–132]. Serglycin has a short core protein with eight consecutive Ser-Gly repeats in human onto which up to eight GAG chains can be attached. It is the only PG that carries Hep in the granules of mast cells [130–132]. Serglycin is modified with CS/DS/HS chains with variable sulfation patterns depending on the cellular origin. Serglycin is crucial for the storage and packaging of bioactive molecules into granules in several hematopoietic cells and is released either constitutively or upon activation during inflammation [130]. More recently, serglycin has been found in numerous non-hematopoietic cells, including endothelial and smooth muscle cells, chondrocytes, fibroblasts, and tumor cells bearing mainly CS chains [132]. Notably, serglycin was found to be constitutively secreted by multiple myeloma and breast cancer cells [133–135]. Serglycin was also found to be located at the cell surface of myeloma cells and via binding to CD44 to promote adhesion to collagen type I and trigger the biosynthesis of MMPs [134,136]. Serglycin may play a key role in tumor progression since it augments the aggressiveness of tumor cells [133] and affects the release of angiogenic factors [134,137]. Serglycin also inhibits the classical and the lectin pathways of complement through direct binding to collagenous part of C1q and mannose binding lectin via its CS chains [138]. This may diminish pathological complement system activation during inflammation.

2.2. Collagens

Collagen is the most abundant fibrous protein within the interstitial ECMs in all animals but is also located in pericellular matrices like basement membranes (Fig. 3) [139]. Notably, the discovery of transmembrane collagens on the surface of various cell types and the fact that they contain bioactive peptides, which are liberated upon degradation and govern important cellular functions, have stimulated our interest on collagen biology [139]. Collagen constitutes up to 30% of the total proteins in humans and is synthesized and secreted in the ECMs mainly by fibroblasts. By exerting tension on the matrix, fibroblasts organize collagen fibrils into sheets and cables markedly influencing the alignment of collagen fibers [1].

Collagen superfamily is composed of twenty-eight different collagen types that are formed by at least forty-six distinct polypeptide chains (α chains) in vertebrates (Fig. 3). Collagen type I is the archetypal collagen showing widespread and abundant expression among tissues. It forms perfect heterotrimeric triple helices, which are self-assembled into fibrils. Collagen type I is a major structural element in tissues such as dermis, bone, and tendon [140]. Collagens differ with each other in respect to their structure and properties. For example, some collagen types have interruptions in the triple helix and do not self-assemble, whereas others, like transmembrane collagens, present long interruptions and play an important role in cell signaling and adhesion [139].

The characteristic feature of collagens is a structural motif in which three α chains display a polyproline II-type helical conformation and coil with each other with a one-residue stagger forming finally a right-handed triple helix [141]. In each α chain, a repeating Gly-X-Y triplet is occurred where X and Y positions are frequently occupied by proline and 4-hydroxyproline, respectively. α chains exhibit a tendency to form left-handed helices spontaneously due to the presence of high content of proline, 4-hydroxyproline, and glycine without any formation of intrachain hydrogen bonds. Finally, interchain hydrogen bonds hold together α chains. The small hydrogen atom side chain of glycine in every third residue within α chains allows them to pack tightly together in a triple helix with this residue in the interior of the helix and the rings of the proline and 4-hydroxyproline pointing outward [141]. Collagens have also non-collagenous (NC) non-triple helical domains at both C- and N-termini that are numbered from the C-terminus (NC1, NC2, NC3, etc) [139].

Several mutations have been identified in collagens that may affect trimerization, formation of collagen networks, and cleavage of propeptides. Mutations in collagens have been associated with various clinical pathologies, such as Ehlers–Danlos syndrome (collagen types I, III, V), osteogenesis imperfecta and osteoporosis (collagen type I), osteoarthrosis (collagen types II, IX, XI), chondrodysplasias (collagen types II, IX, X, XI), arterial aneurysms (collagen type III), Alport syndrome (collagen type IV), Bethlem myopathy and Ullrich muscular dystrophy (collagen type VI), epidermolysis bullosa acquisita (collagen type VII), generalized atrophic epidermolysis bullosa (collagen type XVII), Fuchs endothelia corneal dystrophy (collagen type VIII), and Knobloch syndrome (collagen type XVIII) [139,141].

Collagen biosynthesis and structure are markedly modified during remodeling of the ECM in several pathologies including tumorigenesis [13,142]. ECM stiffening, induced by increased collagen deposition and cross-linking, disrupts tissue morphogenesis and contributes to malignant progression. Increased collagen cross-linking is mediated by LOX and LOX-like enzymes and promotes signaling through collagen-binding cell surface receptors, such as integrins and DDRs, promoting tumor progression [13].

Collagens can be classified according to their common domain homology and functions into seven categories (Fig. 3). These contain fibrillar and network-forming collagens, FACITs (fibril-associated collagens with interrupted triple helices), MACITs (membrane-associated collagens with interrupted triple helices), anchoring fibrils, beaded-

filament-forming collagens, and MULTIPLEXIN (multiple triple-helix domains and interruptions) / endostatin-producing collagens [141], which are described below.

2.2.1. Fibrillar collagens

Fibrillar collagens include collagen types I, II, III,V, XI, XXIV, and XXVII. They are widely and abundantly expressed in tissues providing them with tensile strength. The triple helical collagen molecules are regularly staggered forming 67-nm *D*-periodic fibrils. The length of fibrils varies and the diameter ranges from 12 nm to more than 500 nm, depending on the stage of development [139]. Proper fibril formation is also affected by the presence and structure of other matrix macromolecules, such as decorin and biglycan [143]. They share a long uninterrupted collagenous Gly-X-Y domain that contains ~1000 residues, with the exception of collagen types XXIV and XXVII, flanked by N- and C-terminal propeptides [139]. α chains assemble in homo- and heterotrimeric helix with NC1 domains (short C-telopeptide with C-propeptide) providing correct alignment and guidance for the nucleation of the triple helix [144,145]. Collagen is extensively modified at post-translational level in the endoplasmic reticulum undergoing hydroxylation, glycosylation, formation of disulphide bridges etc, prior to triple helix formation [146]. α chains fold in a C- to N-terminal direction creating a procollagen triple helix that is cleaved in N-propeptides by ADAMTS and BMP-1 and in C-propeptides by proteinases identical to the BMP-1/tolloid proteinases and furin forming tropocollagen triple helix [139,147]. Tropocollagen triple helices undergo self-assembly and are packaged to form collagen microfibrils. LOX oxidizes the lysine side chains leading to the spontaneous formation of hydroxylysyl pyridinoline and lysyl pyridinoline cross-links occurred in the triple helix, and in telopeptides. Non-reducible covalently cross-links stabilize large collagen fibrils providing them with proper mechanical properties [141]. Although one collagen type usually predominates in fibers in a given tissue, other collagen types and matrix macromolecules are also found to associate and decorate collagen fibrils providing them with specific structural and functional properties. Apart from its function as the principal tensile element of tissues, collagen scaffolds provide signals to cells affecting various cellular functions including cell migration, adhesion, angiogenesis, tissue development, and repair [1,139].

2.2.2. Network-forming collagens

The class of network-forming collagens comprises collagen types IV, VIII, and X. Collagen type IV, which is the prototypical network-forming collagen, is found in basement membranes playing an important role in molecular filtration. On the other hand, collagen type VIII is located in Descemet's membrane and vascular sub-endothelial matrices, and collagen type X in the hypertrophic zone of growth plate cartilage [139]. They have many interruptions in their triple helical structures that make them flexible and capable of interacting with each other forming extensive networks. The folding of collagen type IV is initiated at the C-terminus and followed by triple helix propagation towards the N-terminus [148]. The NC1 domain also plays a crucial role in tail-to-tail association of two trimeric molecules resulting in the formation of a hexamer that is stabilized by covalent Met-Lys cross-links [149]. Finally, the N-to-N linkage of four collagen molecules leads to formation of a two-dimensional network [139]. Collagen types VIII and X form polygonal lattices retaining the NC1 domains, which are also critical for the initiation of the supramolecular assembly [150,151]. Furthermore, they can also interact with various ECM components creating multimolecular complexes [152].

2.2.3. FACITs

FACITs include collagen types IX, XII, XIV, XVI, XIX, XX, XXI, XXII [141]. They are relatively short collagens with NC domains that interrupt the triple helical collagenous domains providing these molecules with flexibility. FACITs interact with fibrillar collagens on their surface and link collagen fibers together and with other ECM molecules. For example, collagen type IX is covalently linked to the surface of collagen type II fibrils with collagenous domains 1 and 2, which are flanked between NC1 and NC3 domains [153]. NC4 domain projects into cartilage matrix and a CS chain is linked in NC3 hinge region [154]. Collagen type IX is crucial for the integrity of cartilage. Deficiency in *α1(IX)* gene in mice results in severe defects in the development of cartilage as well as in degenerative changes that exhibit similarities to those occurred in osteoarthritis [155]. Collagen type XII associates with collagen type I and II fibrils, whereas collagen type XIV co-localizes with collagen type I not directly but via binding to DS chains of decorin, which associates with collagen type I fibrils [156].

2.2.4. MACITs

MACITs are type II transmembrane proteins that have a long extracellular C-terminal domain composed of collagenous parts interrupted by NC domains and a short cytoplasmic N-terminal domain. They include collagen types XIII, XVII, XXIII, XXV, which are expressed by several cells, including malignant cells, and tissues. They act as cell surface receptors affecting cell adhesion, and upon proteolytic cleavage, they shed from the cell surface to the extracellular matrix generating soluble collagens. For example, the ectodomain of collagen type XVII can be cleaved by ADAMs modulating cells' motility [157].

2.2.5. Anchoring fibrils

Collagen type VII is the major component of anchoring fibrils beneath the lamina densa of basement membrane connecting it to underlying stroma [139]. This collagen type is formed by the homotrimerization of α1(VII) and has a central collagenous triple helical domain that is interrupted by a short NC domain and is flanked by N- and C-terminal NC domains. Two molecules of collagen type VII are dimerized and are further assembled to form anchoring fibrils.

2.2.6. Beaded-filament-forming collagens

Beaded-filament-forming collagens consist of collagen types VI, XXVI, and XXVIII. Collagen type VI is the most studied member of this category. It shows a widespread expression in tissues where it interacts with various ECM proteins, HA, PGs, as well as collagen type IV in basement membranes. Collagen type VI molecules form antiparallel dimers by staggered alignment of monomers. The dimers associate laterally generating tetramers, which are stabilized by the formation of disulfide bonds. The tetramers connect at the globular ends forming beaded filaments with 25 nm beads aligned in 100 nm intervals [156].

2.2.7. MULTIPLEXIN

Collagen types XV and XVIII belong to the category of MULTIPLEXINs/endostatin-producing collagens. Both collagen types XVIII and XV are ubiquitously expressed in all vascular and epithelial basement membranes of human tissues. Collagen type XV bridges adjacent collagen fibrils creating a variety of oligomeric assemblies promoting the adhesion of basement membranes to underlying connective tissue stroma [139]. Collagen types XV and XVIII have a central triple helical collagenous domain that is interrupted by several NC domains and carry CS and HS chains, respectively. Collagen XVIII is a homotrimer composed by three α1 chains. It contains ten interrupted collagenous domains, flanked by eleven NC domains at their respective N- and C-termini [17]. Collagen XVIII can carry three HS chains [17]. Both collagen types XVIII and XV contain a C-terminal NC domain harboring the anti-angiogenic endostatin and endostatin-like modules. Cleavage of part of the NC1 domain releases endostatin, which interacts with numerous receptors including integrins α5β1, αvβ3, and αvβ5 and VEGFR2. These interactions disrupt the actin cytoskeleton, evoke a signaling network that leads to down-regulation of the VEGF signaling cascade and, concurrently, to a stimulation of powerful angiostatic components, like TSPs, thus strongly inhibiting angiogenesis [14,17].

2.3. Elastin and elastin-associated proteins

Elastic fibers are large ECM structures that provide recoil to tissues, which undergo repeating stretching forces, such as large elastic blood vessels, lungs as well as heart, elastic ligaments, skin, bladder, and elastic cartilage. Elastic fibers, which are assembled in the early stages of the development, are very stable with very low or absent turnover. In adults, damaged elastic fibers are often repaired improperly and do not function normally [158]. Elastic fibers present within tissues as large network composed of two discrete components, elastin being the major constituent, and microfibrils. Elastin is a cross-linked polymer of the monomeric secreted precursor tropoelastin. Tropoelastin is a 60–70 kDa protein that contains intermittent hydrophobic and lysine-containing cross-linking domains. Tropoelastin has a unique composition and tendency to self-associate and little is known about the shape and mechanism of its assembly. It is suggested that tropoelastin molecules are self-assembled head-to-tail with domain 10 on the head of tropoelastin monomer to juxtapose domains 19 and 25 on the tail of the next monomer. Lysine residues are modified by LOX or LOX-like proteins to form cross-links that stabilize the polymer and make it insoluble [158,159]. The hydrophobic domains of elastin are responsible for the elastic properties of the network [159].

Microfibrils localize in the periphery of the fiber in adult tissues and are more complex in composition containing several proteins. It is suggested that microfibrils provide a scaffold that assists the alignment and cross-linking of the elastin molecules [158]. The major constituents of microfibrils are cysteine-rich glycoproteins of large size (~350 kDa), fibrillins (fibrillin-1, -2, and -3), and most likely perform structural roles in microfibril assembly, while other associated proteins might perform regulatory rather than structural roles [160]. Disruption of the fibrillin microfibril scaffold, due to mutations in *fibrillin-1* gene, causes Marfan syndrome, a connective tissue disorder with major phenotypic features in the cardiovascular, musculoskeletal, and ocular systems. *Fibrillin-2* gene mutations are found in congenital contractural arachnodactyly with primarily musculoskeletal manifestations, but also sharing with some features with Marfan syndrome (arachnodactyly, scoliosis) [160]. Fibrillin contains calcium-binding EGF-like domains that develop a rod-like structure [161], integrin-binding Arg-Gly-Asp (RGD) sequences [162,163], as well as heparin-binding domains, which are capable to bind cell surface HSPGs [164,165]. The presence of such structural motifs suggests that fibrillin may directly signal cells as well as assembly of fibrillin may require guidance from specific cell surface receptors.

Other components of microfibrils are microfibril-associated glycoproteins (MAGPs) (MAGP-1 and MAGP-2 proteins), which are localized to the beaded region of microfibrils. They are glycoproteins of relatively small size (~20 kDa) that bind to both tropoelastin and fibrillins and may play an important role as bridging molecules between them during the elastic fiber assembly [158,166].

Fibulins participate in the formation of elastic fibers. This family includes seven members. They are 50–200 kDa in size and consist of repeated calcium-binding EGF-like modules and a fibulin domain at the C-terminus. Short fibulins (fibulin-3, -4, and -5) play a central role in elastogenesis. It has been proposed that fibulin-4 and -5 are essential for the assembly of mature and proper elastic fibers. They interact with each other as well as with other components (tropoelastin, fibrillin-1, LOX, and LOX-like proteins) participating in elastogenesis [167].

Elastin microfibril interface located protein 1 (EMILIN-1) is another glycoprotein present at the interface between amorphous elastin and microfibrils. EMILIN-1 may regulate elastogenesis by stabilizing molecular interactions between elastic fiber components. EMILIN-1 interacts with α4/α9/β1 integrins and may connect cells to elastic fibers by providing them with specific cell adhesion properties [168,169].

A model for elastic fiber assembly has been proposed by Wagenseil and Mecham [158] and includes the following steps. Secreted tropoelastin is cross-linked and form aggregates at the cell surface by possibly interacting with cell surface PGs and LOX proteins. Fibulin-4 and -5 bound to such aggregates may promote cross-linking or control the size of the aggregates, while new elastin molecules are accumulated. Then, aggregates are relocated to preformed microfibrils in the ECM, which associate with the cell surface via binding to integrins. Fibulin-4 and -5, which both bind to microfibrilar proteins like fibrillin-1, may facilitate the relocation of the aggregates. Finally, the aggregates coalesce further creating larger structures, which are cross-linked by LOX proteins resulting in the formation of mature and functional elastic fibers [158].

Elastic fibers are degraded by various elastolytic enzymes, including aspartic proteases, cysteine proteases, serine proteases, and MMPs in pathological processes with consequent failure of the tissue/organ. Elastin degradation liberates elastin peptide fragments with significant biological activity. The pathobiologic importance of elastin fragments is especially significant in the organ systems with an abundance of elastin. For instance, overproduction of elastin in vascular walls contributes to the development of atherosclerosis. Val-Gly-Val-Ala-Pro-Gly (VGVAPG) is an elastin peptide fragment that is chemotactic for both monocytes and fibroblasts [170]. VGVAPG resulting in smooth muscle migration, leading to vascular intimal thickening and development of vascular disease and also has implications in cancer progression through several mechanisms [170].

2.4. Fibronectin

FN is ubiquitously expressed in the ECMs of a variety of cell types with critical functions in the development of vertebrates [171]. FN consists of two subunits with each one having an approximate size of 250 kDa that are covalently connected with disulfide bonds at their C-termini. These subunits are composed of three different types of modules: the type I, II, and III repeats [172,173]. These repeats have distinct structures. Although the conformations of type I and type II repeats are maintained by pairs of intramodule disulfide bridges, the type III repeat is a 7-stranded β-barrel structure that lacks disulfide bonds [174] and, therefore, can undergo conformational changes. Although FN is encoded by a single gene, it exists in form of multiple variants as a result of extended alternative splicing [175]. Based on its solubility, FN can be categorized into soluble plasma FN and cellular FN molecules, with the latter being a much more heterogeneous population due to cell type-specific as well as species-specific splicing.

The functional form of FN *in vivo* is in its fibrillar state. Thus, FN molecules must be assembled into supermolecular fibers that range in diameter from 10 nm to micrometers in size, with lengths of tens of micrometers. These fibers form an interconnected network that traverses long lengths, for example, encompassing developing tissues and even the entire developing embryo [176,177]. Cells can assemble soluble FN derived from FN in plasma into fibers [178]. Alternatively, cells can produce their own FN, which is secreted and formed into fibers. Finally, cells *in vitro* rapidly assemble FN that is adsorbed on surfaces, and hence used for cell attachment onto fibrils [179].

Sets of adjacent modules within FN molecules form binding domains for a variety of proteins and carbohydrates. The multidomain protein contains fibrin-, collagen/gelatin-, Hep-, and cell-binding domains. The interaction of FN with fibrin may be involved in adhesion and/or migration of cells into fibrin clots as well as in fibrin clearance from circulation in inflammatory conditions [175]. Moreover, FN interacts with denatured collagen (gelatin) much more effectively than to native collagen suggesting that unfolded regions of collagen triple helix are responsible for these interactions *in vivo* [180].

FN binds to cells primarily via integrin receptors [181]. FN-binding integrins have specificity for one of the two cell-binding sites within FN, either the RGD-dependent cell binding domain in III10 [182] or the CS1 segment of the alternatively spliced V region (IIICS) [183,184]. Some integrins require a synergy sequence in repeat III9 for maximal

interactions with FN [185,186]. Another family of cell surface receptors that bind to FN are the syndecans [99]. Syndecans use their GAG side chains to interact with FN at its C-terminal Hep-binding (HepII) domain [187,188], which binds to Hep, HS, and CS [189]. Syndecan binding to the HepII domain enhances integrin-mediated cell spreading and intracellular signaling, suggesting that syndecans operate as co-receptors with integrins in cell–FN binding [190,191].

A variety of stimuli results in the production or up-regulation of FN matrix fibers. Continuous FN matrix production is needed in order to maintain the presence of pre-existing FN matrix [192,193]. FN matrix is produced at times of dynamic tissue remodeling, formation or repair, and is essential during embryonic development [171,194,195]. However, FN matrix is also dramatically up-regulated around tumor vasculature and appears to contribute to tumor progression [196–199].

2.5. Laminins

Laminins are large heterotrimeric cross-shaped glycoproteins, which are assembled along with collagen type IV, nidogens, agrin, and perlecan in basement membranes [200,201]. Each laminin heterotrimer consists of one α, one β, and one γ chain, each of which is encoded by individual genes [202]. Five α (*LAMA1-5*), three β (*LAMB1-3*), and three γ (*LAMC1-3*) chains have been identified in vertebrates. Moreover, a short α3A and a longer α3A isoform have been identified in the *LAMA3* gene [203] increasing the possible α chains to six. Although theoretically fifty-one different αβγ trimers could exist, only sixteen laminin trimers have been found *in vivo* due to limitations in the interaction potential of αβγ chains as well as their differential distribution within tissues [201,202].

Laminins names resemble the composition of their chains. Thus, the most widely studied laminin-111 is composed of α1, β1, and γ1 chains. All chains share common structural motifs, such as a large globular laminin N-terminal domain (LN domain) (with the exception of truncated α3A, α4, and γ2 chains lacking LN domain), a rod-like stretch of LE domain that contains one or two globular domains, one in β or γ chains (named L4 or LF, respectively), or two in α chains (L4a and L4b). β and γ chains end with a laminin coiled-coil (LCC) domain, which is involved in the trimerization with the exception of the α chains that additionally contain five LG domains (LG1–5) at the C-terminus [201]. Laminin molecules interact with each other as well as with other ECM components and resident cells participating in the organization of ECMs and cell adhesion. For example, laminins bind to each other through LN domains promoting self-assembly of laminin molecules into higher order networks or polymers found in basement membranes [204]. Although the functions of LE domains remain unclear, a particular LE domain in laminin γ1 chain (γ1LEb3) interacts with nidogen-1 and nidogen-2 with different affinities and may contribute in basement membrane assembly [205]. Most ECM molecules and cell surface receptors bind to LG domains in the α chain, whereas HSPG agrin binds to the central region of the coiled-coil domain. HSPG perlecan, fibulin-1, and sulfatides interact with LG domains participating in basement membrane assembly. The LG domains also interact with high affinity with cell surface receptors such as integrins, dystroglycan, and syndecans [201]. Various integrins can bind to laminins mostly to LG domains although some integrins also interact with αLN domains. Moreover, the C-terminus of β1, β2, γ1, and γ2 chains is also involved in integrin binding [206,207]. α-dystroglycan binds with high affinity the laminin α1 and α2 chains but presents lower affinity for other α chains. Syndecans bind laminins to LG domains, whereas Lutheran blood group glycoprotein binds only to laminins containing the α5 chains [200]. The potential of the α chain to interact is fine-tuned by the β and γ chains since the precise αβγ combination affects the binding affinities of the receptors for laminins [201].

Laminins play crucial roles in early embryonic development and organogenesis [200].

The distribution of laminin isoforms is tissue-specific, suggesting the involvement of particular laminins in tissue functions [208]. They influence cell differentiation, adhesion, and migration and are vital for the maintenance and survival of tissues. For example, laminins are up-regulated in wounded epithelium providing the substrate for the epithelial cells to adhere and move in order to cover the wounded area and therefore to re-establish the intact epithelium. They are also implicated in angiogenesis since they are important components of endothelial basement membranes contributing to blood vessel growth and maturation [201,208].

Numerous human congenital diseases are caused by mutations in laminin chains. Mutations in the laminin α2 chain result in congenital muscular dystrophy type 1A [209]. Pierson syndrome, which is associated with renal failure and loss of vision, is caused by mutations in the laminin β2 chain [210]. Junctional epidermolysis bullosa is a severe inherited disease, which is characterized by skin fragility and blistering in response to mild mechanical trauma due to the separation of the epidermis from the underlying dermis. Mutations in all chains of laminin 332 (α3, β3, and γ2) have been identified in patients with junctional epidermolysis bullosa [211–213]. Laryngo-onycho-cutaneous syndrome is a variant of junctional epidermolysis bullosa, which does not display blistering but exhibits increased granulation tissue production in exposed epithelia, and is associated with mutations in α3 chain that leads to production of a truncated form of α3 chain [203]. Laminins are also implicated in tumorigenesis. For example, laminin 332 interactions with other basement membrane components and cell surface receptors, such as integrins, syndecans, and EGFR, augment squamous cell carcinoma through PI-3K and RAC1 activation, promoting tumor cell invasion and survival [214,215].

2.6. Matricellular proteins: members, interactions, functions, and roles in cancer

Matricellular proteins have been characterized as non-structural extracellular modulators of cellular functions by facilitating cell–cell and cell–ECM interactions, and promote a transient cell adhesive mode necessary for cell migration [216–220]. Although matricellular proteins are structurally variable, they contain common ECM structural motifs and they exert similar functions [221–225]. Members of this family of proteins from different locations (extracellular, cell membrane, and intracellular) and their relevant functions are presented in Table 1. Matricellular proteins show a moderate expression in adult tissues that becomes strong in developing tissues as well as pathological

Table 1
Location, types, and main functions of matricellular proteins.

Location	Matricellular Protein(s)	Function(s)
Body fluids	TSPs, TNs, SPARC, OPN, CCNs, COMP, periostin, fibulin	Growth factor/growth factor receptors interactions [236, 250–252, 372, 373]; EMT [260, 262, 372, 374]; Hemostasis [226,228]; Innate immune functions [226, 228, 238, 246, 247]
ECMs	TSPs, COMP, fibulins, TNs, OPN, SPARC, hevin, PEDF	Collagen fibril/elastin/fibronectin organization [218, 220]; ECM calcification [221, 227, 246]; Proteoglycan interactions [112, 239–242]; Adhesion, migration, invasion [216, 217, 230, 237, 248, 249, 265, 266,3 73, 375]; Stem cell niche [238]
Inner plasma membrane	OPN	Adhesion, migration [256, 375]
ER	TSP-1, TSP-4, COMP, SPARC	ECM chaperone [257, 258]; ECM pre-assembly [376, 377]; Calcium regulation [254, 255]; ER function [253, 254]
Nucleus	SPARC	Unknown

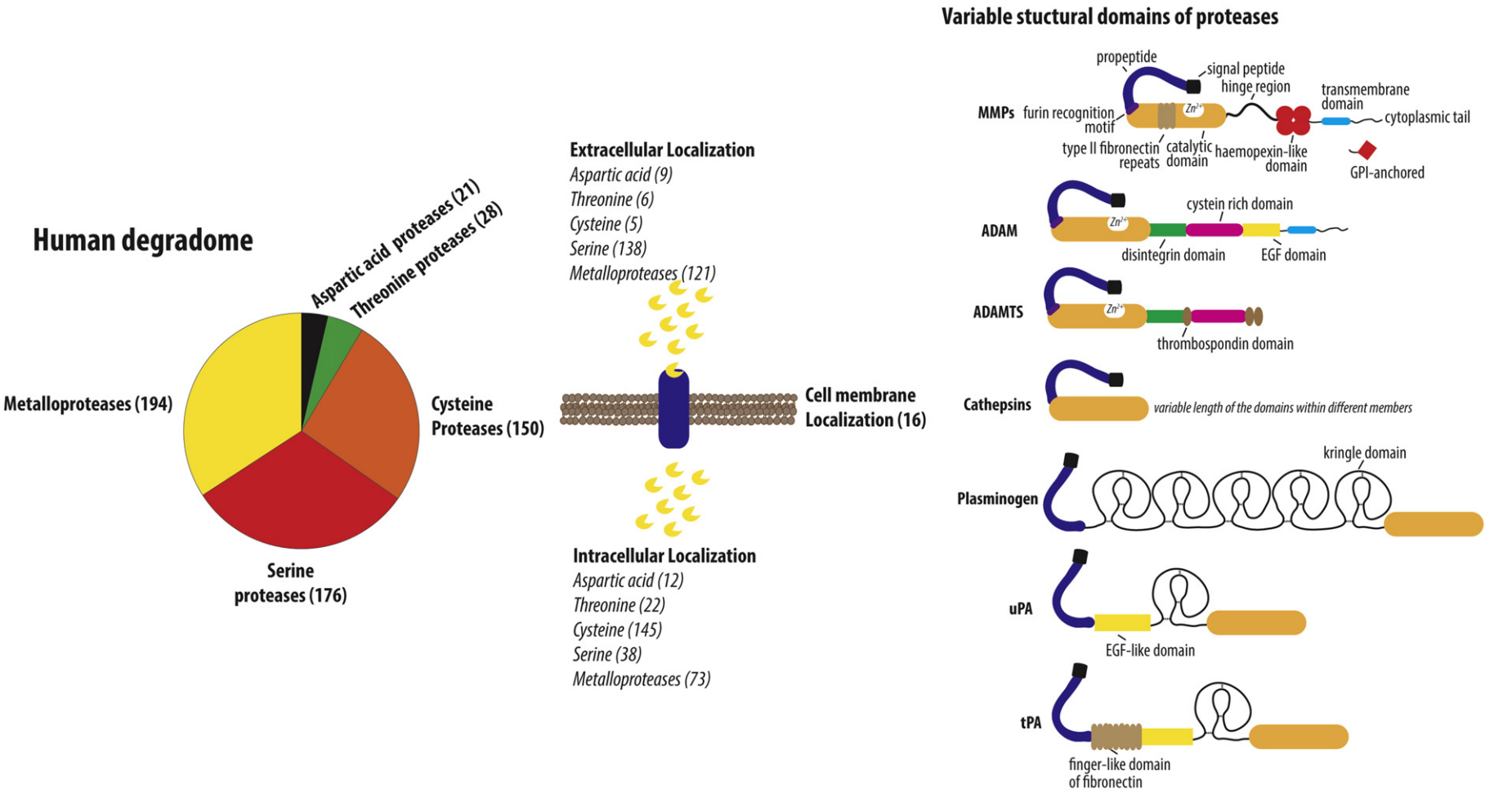

Fig. 4. *Human degradome and schematic representation of major extracellular matrix proteases*. The human degradome is represented by at least 569 proteases distributed intra- and extracellularly, as well as at the cell membrane and subdivided into five families: metalloproteases, serine proteases, cysteine proteases, aspartic acid proteases, and threonine proteases. In the right panel, a schematic representation of the variable structural protease domains is depicted. All proteases are basically expressed consisting of a signal sequence, a propeptide, that is cleaved upon activation, and a catalytic domain. However, several other structural domains distinguish the proteases families between each other, apart from the chemical moiety that participates in the hydrolysis, characterizing their localization and unique interactions.

conditions [217,226–228]. The expression of matricellular proteins is regulated at several levels by multiple mechanisms: from the transcriptional (alternative splicing of their mRNA) to the post-translational level (including glycosylation, phosphorylation) as well as from epigenetic (by microRNAs and DNA modifications) to internal timing mechanisms (involving circadian clock genes) [229–233]. Moreover, strong evidence support that cell contractility, shear forces, or mechanical stretch induce the expression of certain matricellular proteins (such as TSP-1, secreted protein acidic and rich in cysteine (SPARC), and TN-C), while others (such as osteopontin, OPN) are decreased revealing a role of specific matricellular protein members in fibrotic conditions [234–238].

Matricellular proteins are able to bind a large variety of cellular receptors (nicely reviewed in [220]). The existence of various structural motifs within matricellular proteins allows them to simultaneously interact with multiple receptors. Most matricellular proteins bind multiple integrins thereby activating relevant signaling pathways. For example, TSP-1, TSP-2, cartilage oligomeric matrix protein (COMP) / TSP-5, OPN, TN-C, TN-X, TN-W, CNN family proteins (CCN1 to CCN3), periostin, SPARC, and fibulin-5 bind to various integrins, while certain integrins (such as αvβ3) can be receptors for different matricellular proteins [220]. Various matricellular proteins (such as TSP-1, TSP-2, TN-C, CCN1, CCN2, and R-spondins) bind also to cell surface HSPGs (especially syndecan-4) [112,239–242]. In addition to integrins and HSPGs, some matricellular proteins, such as CCN2, and TSPs, interact with scavenger receptors (including LRP-6, CD36, and stabilin-1) [243–245]. The binding of matricellular proteins to scavenger receptors is considered to be a limiting mechanism for the availability and action of these proteins as well as their interacting effectors, as for example MMPs. Other receptors for matricellular proteins are the calcium channel gabapentin receptor (α2δ-1) for TSPs and TLR4 for TN-C indicating involvement of these proteins in immune responses [238,246,247]. In addition, OPN and TSP-4 bind to CD44 by competing each other and these interactions result in opposite cancer stem cell functions [248,249].

Matricellular proteins can regulate cell functions either extracellularly or intracellularly (Table 1). At the extracellular level, matricellular proteins bind cells directly by interacting with their cellular receptors or indirectly by binding soluble growth factors (for example, VEGF, FGF-2, and latent TGF-β) which they present to their cognate receptors thereby modulating their activities. Moreover, they can modify the signaling of several growth factor receptors (such as EGFR/ErbB2, VEGFR-1, and TGF receptor I (TGFRI)) [250–252]. On the other hand, specific matricellular proteins modify cellular functions by being specifically localized within intracellular compartments (reviewed in [220]). For example, TSP-4 has been shown to participate in endoplasmic reticulum (ER) functions by binding to ATF6α in the ER [253]. TSPs bind also stromal interaction molecule 1 (STIM1) regulating STIM1 calcium sensing, which is important for several cellular functions (like platelet aggregation) [254,255]. OPN is located at the inner surface of cell membrane participating in CD44-ezrin/radixin/moesin complexes regulating cytoskeleton-related functions [256]. Interestingly, some matricellular proteins (SPARC, CCN5) have been shown to localize in nuclear compartments, however, with yet unknown roles [220]. Of particular interest is the putative role of matricellular proteins as chaperones for ECM components [257,258].

Aberrant up-regulation of matricellular proteins trigger protumorigenic interactions in the tumor microenvironment [259]. Notably, certain members of this protein family can induce epithelial-to-mesenchymal transition (EMT). For example, periostin, a secreted TGF-β inducible protein, promotes the invasiveness of 293 T cells through EMT induction [260]. TN-C has been also found to promote EMT in colorectal tumors by modulating the transcriptional activity of β-catenin [261]. In addition, SPARC overexpression in normal melanocytes as well as during melanoma development represses E-cadherin and promotes EMT by up-regulating Snail [262]. Paracrine interactions that occur within the tumor microenvironment also induce the expression of matricellular proteins, which in turn mediate the activity of growth factors released by cancer-associated fibroblasts to their neighboring tumor cell-associated signaling receptors [263]. Importantly, certain matricellular proteins have been shown to up-regulate specific proteinases expression and activity (such as MMP-2, MMP-12) in tumors leading to increased metastatic potential, but they can also be cleaved by MMPs generating protein fragments with tumor-promoting properties, as for example OPN fragments released by the action of MMP-9 in hepatocellular cell carcinoma cells [264–266].

3. Extracellular matrix proteases

Our view of proteases has come a long way since they were first introduced as generic destructive enzymes associated with protein catabolism and generation of peptides and amino acids during the early stages of protein evolution. The understanding that proteases constitute more than 2% of the total genes in the human genome highlights their contribution in physiological cellular functions as sharp selective scissors, regulating fate, localization, and activity of a variety of proteins, modulating protein-protein interactions and generating new bioactive molecules [267–271].

Proteases (alternatively termed proteinases, peptidases, and proteolytic enzymes) represent a large family of enzymes that catalyze the cleavage of proteins into peptides or amino acids through the hydrolysis of peptide bonds at their terminal ends (exopeptidases) or inside the peptide chain (endopeptidases) [272]. According to the MEROPS database, the human degradome contains at least 569 proteinases distributed intracellularly, at the cell surface and extracellularly, and comprises of five protease families known as (1) metalloproteases, (2) serine proteases, (3) cysteine proteases, (4) aspartic acid proteases, and (5) threonine proteases. This classification is based on the chemical moiety that participates in the hydrolysis (Fig. 4) [273].

3.1. Matrix metalloproteases

The metzincin family of metalloproteases, the largest class of proteases, is so named for the presence of a conserved zinc-binding motif (HEXXHXXGXXH) at the active site. The catalytic function and structural integrity of metzincins is dependent on the zinc ion usage during the enzymatic reaction [274]. MMPs, ADAMs [275], and ADAMTSs [276] represent some of the most investigated members of this family (Fig. 4).

MMPs are classified into six groups: collagenases, gelatinases, stromelysins, matrilysins, MT-MMPs, and other MMPs. This is based on common features like substrate specificity, sequence similarity, and domain organization [277]. Metalloproteases are multidomain enzymes that share common structural features. For example, their secretion or plasma membrane insertion occurs through N-terminal signal peptide, whereas the enzyme activation through cleavage by serine proteases and various MMPs of a propeptide that contains a highly conserved PRCGVPDV sequence. Apart from secreted MMPs, there are MT-MMPs that are cell surface anchored by a GPI anchor or contain a transmembrane domain followed by a short cytoplasmic tail. Furin convertases target also the furin recognition motif that lies between the pro-domain and the catalytic domain resulting to the release of functional proteins. Their catalytic domain, containing a motif of three histidine residues, chelates the zinc ion of the catalytic site. This domain is followed by a C-terminal hemopexin-like domain, which is responsible, except of MMP-7, for the substrate specificity and the non-proteolytic functions, such as interactions with the various MMPs and TIMPs [13,278,279] (Fig. 4).

A zinc-dependent family of proteases related to the MMPs is ADAMs. They include two subgroups the membrane-bound ADAMs and the secreted ADAMTSs that are characterized by cell de-adhesion/adhesion and fusion motifs. In the majority of type I transmembrane ADAMs, the MMP hemopexin domain is replaced by disintegrin, cysteine-rich,

and EGF domains. In the case of secreted ADAMTSs, however, the EGF and transmembrane domain are replaced by type I TSP motifs [280,281] (Fig. 4).

MMPs-mediated proteolysis is coordinated at the mRNA level, compartmentalization, transformation from proenzyme to the active enzyme, and last, the presence of specific inhibitors [170]. Additionally, the allosteric activation of metalloproteases is coordinated by their substrates or other binding partners like PGs either by their core protein or their GAGs side chains [13,282].

The biological significance of MMPs in normal and pathological conditions like cancer is well characterized throughout the literature highlighting their pharmacological targeting [13,170,283–285]. To start, metalloproteases produced by several cell types such as fibroblasts, epithelial, endothelial, inflammatory, and cancer cells are responsible for the catabolism of almost all ECM molecules [286], as well as non-ECM cell regulators [287,288]. The cells collaborate with each other in order to activate the proteolytic cascade upon stimuli; for instance, stromal cells provide tumor cells with inactive forms of MMPs that are activated by their membrane counterparts in cancer cells membrane [289]. Apart from their degrading ability, MMPs, along with ADAMs and ADAMTSs, dispose growth factors and cytokines to the ECM, whereas their actions on matrix molecules, including collagen, elastin, various PGs, cell membrane molecules such as integrins and receptors, generate bioactive molecules the so called matrikines [170] and modulate interactions between cells and the matrix [290–292]. In several cases, it is reported that the activation of cell surface receptors (EGFR, IGFR) or estrogen receptors signaling cascade alters the proteolytic balance (expression and proteolytic activity) of metalloproteases and in general of all proteases [293,294].

3.2. Plasminogen/plasmin system

The plasminogen/plasmin proteolytic enzymatic cascade is incriminated in various normal and pathological processes mainly due to its ability to concentrate potential proteolytic activity, associated with the regulation of fibrin degradation, the turnover of the matrix and the cell migration [295].

Apart from the basic structural features of other proteases like the signal domain, propeptide followed by the catalytic domain, the fibrinolytic proteases bear large functionally autonomous regions, common in ECM molecules, like kringle, growth factor-like or EGF-like and finger domains [296]. Such domains like kringle are responsible for substrate binding and interaction of plasminogen/plasmin with cell surface proteins, leading to its subsequent activation [297]. All enzymes of the plasminogen system are serine proteases and their active site amino acid sequence consists of serine, aspartic acid, and histidine [298] (Fig. 4). Urokinase plasminogen activator (uPA) and tissue-type plasminogen activator (tPA) are the serine proteases and act as the prime mediators of plasminogen activation, the zymogen form of the serine protease plasmin. uPA is synthesized by endothelial and epithelial cells, leukocytes, monocytes, fibroblasts, and cancer cells [299] triggering plasmin generation during cell migration and invasion under physiological and pathological conditions, whereas tPA is synthesized mainly by vascular endothelial cells, keratinocytes, melanocytes, and neurons [300] associated with the control of intravascular fibrin degradation. The peptide bond between Arg560 and Val561 constitutes a small disulfide-bridge loop in plasminogen, that when it is recognized and cleaved selectively by uPA and tPA, generates plasmin [298]. Binding of tPA to fibrin increases its activity, whereas binding of pro-uPA to its GPI-anchored receptor, urokinase plasminogen activator receptor (uPAR), increases its activation by several activators like MMPs, cathepsins, and restricts plasminogen activation to the cell membrane vicinity [298]. However, this enzymatic cascade is counteracted by the action of serpins plasminogen activator inhibitors (PAIs), which inhibit the protease activity irreversibly, as well as the plasmin's main physiological inhibitor α2-antiplasmin and the general protease inhibitor α2-macroglobulin [301].

The plasminogen/plasmin activator system participates actively to a dynamic interplay between other proteolytic networks, in particular with the MMPs, the coagulation, and complement system. Noteworthy, correlations of all components of the plasminogen activation system with cancer progression involving especially cell proliferation, migration invasion, apoptosis, and angiogenesis, are documented in the literature, introducing their prognostic value [298,302]. Activation of plasmin triggers a proteolysis cascade with a broad substrate specificity leading to degradation and modification of ECM proteins (FN, TSP, laminin), release of growth factors (TGF-β, FGF-2, VEGF) and stroma-derived cytokines, in addition to activation of several MMPs. Apart from its proteolytic activity, receptor bound uPA can influence intracellular signaling by interacting with vitronectin and integrins and in turn elicit functional properties, such as cell growth, adhesion, and migration, while the endothelial tPA with its receptor Annexin II regulates the intravascular deposition of fibrin [302,303].

3.3. Cathepsin proteases

The term “cathepsin” originated from the Greek word for “digestion.” Cathepsins are a large family of proteases from three different mechanistic classes: (1) cathepsins D and E (aspartic proteases), (2) cathepsins A and G (serine proteases), and (3) cathepsins B, C, F, H, L, K, O, S, V, X, and W (cysteine proteases) [273].

The principal and most studied members of the cathepsins' family are cysteine cathepsins with a conserved active site that is formed by cysteine and histidine residues (Fig. 4). The majority of cysteine cathepsins exhibit endopeptidase activity, cathepsins B, C, H, and X present exopeptidase activity, while cathepsin B possesses both enzymatic activities, resulting in potentially distinct substrate preferences for individual cathepsins. On the other hand, cathepsins also exhibit a unique expression profile depending on the tissue or cell types (cathepsins S, V, F, C, and W). However, cathepsins B, H, L, C, X, F, O, and V are expressed in human tissues ubiquitously [304,305]. All cathepsins are synthesized as inactive precursors. For optimal activity, conditions such as those in the lysosomes and endosomes, i.e. a reducing and slightly acidic environment are required [306,307]. Apart from their actions in the degradation of cellular proteins after cellular uptake, novel actions of cathepsins were introduced since they are also distributed to various cellular locations like secretory vesicles, cytosol, plasma membrane, and nuclei [308–312].

Endogenous inhibitors, such as cystatins (small protein inhibitors of approximately 10–13 kDa), tightly control cathepsin activity. Cystatins protect the accidental release of cathepsins present in lysosomes at the intracellular or extracellular space. It is also reported throughout the literature that the activation of cathepsins can be regulated by their interactions with GAGs and/or PGs, as well as by the action of other proteases [18].

The proteolytic specificity and functions of cysteine cathepsins are dependent on their localization on cell membranes, secreted and intracellular vehicles. They are implicated in processes like bone remodeling [313,314], production of hormones [315], as well as the presentation of antigens in the immune system [316]. Due to the acidic extracellular tumor microenvironment, cysteine cathepsins are able to function in proteolytic pathways that promote cancer progression. Among the potential extracellular roles for cysteine cathepsins are the cleavage of ECM proteins. Among them are laminin, collagen type IV, cell-adhesion proteins, matricellular proteins, and activation of pro-enzymes such as pro-uPA. In the intracellular milieu, cysteine cathepsins also degrade ECM proteins such as collagens, taken up into phagosomes via uPAR/pro-uPA complexes [317].

4. Extracellular matrix receptors

Apart from the cell surface PGs syndecans and glypicans described above, other ECM receptors include two major receptor families named integrins and DDRs, as well as the HA receptor CD44.

4.1. Integrins

Integrins mediate cell adhesion by linking the actin cytoskeleton with the ECMs. As well as acting to anchor cells, integrin adhesions provide sensory input via mechanotransduction and synergism with signaling pathways and provide the cells with the conditions necessary for differentiation in a permissive manner. This family of transmembrane receptors binds to ECMs through the interaction of two heterodimeric subunits. There are eighteen α subunits and eight β subunits present in mammals that can combine to form twenty-four different integrin dimers, each with different tissue and matrix-binding specificity. Most integrins bind to RGD-containing proteins (such as FN, fibrinogen, and vitronectin), and binding specificity is promoted by specific residues close to the RGD motif [318]. Integrins can signal information from the ECMs to the cell interior by coordinating with other intracellular linkage molecules, such as FAK and Src tyrosine kinases (outside-in signaling). In addition, integrin activation can occur in an inside-out fashion by binding of β subunits to intracellular activators (i.e. talin), whereby intracellular signals are transmitted to the outside of the cell by influencing integrin affinity for ECM ligands affecting ECM assembly, cell migration, and adhesion processes. The structure and function of integrin binding and activation is comprehensively reviewed elsewhere [181].

Integrin binding to collagens is mediated by α1β1, α2β1, α10β1, and α11β1 integrins [319]. Fibrillar collagens are bound preferentially by the α2β1 and the α11β1 integrins, whereas α1β1 and α10β1 bind non-fibrillar collagens such as collagen IV. The binding sequences for integrins in collagens involve the coordination of a metal ion-dependent adhesion site (MIDAS) along with GFOCER sequences of collagens [320]. Binding exerts complex conformational changes within integrin molecules, which ultimately result in signaling across the cell membrane. However, the exact mechanisms of how integrins differentiate between fibrillar and non-fibrillar collagens are yet to be elucidated [320,321].

The bidirectional signaling of integrins is crucial for cancer onset and progression. Several studies have identified certain integrins with tumor-promoting functions. For example, the high expression and signaling of αvβ3, αvβ5, α5β1, α6β4, α4β1, and αvβ6 integrins by tumor cells is correlated with disease progression in various tumor types, such as breast tumors [322].

4.2. Discoidin domain receptors

Two forms of the DDRs (DDR1 and DDR2) are expressed as products of two distinct genes [323]. DDR1 is generally found in epithelial cell types, whereas DDR2 is largely confined to mesenchymal cells. DDR1 and DDR2 are receptor tyrosine kinases that are activated by their interaction with collagens [324]. Structurally, both DDRs consist of an extracellular discoidin homology domain, a second globular domain, a transmembrane domain, a large juxtamembrane domain, and a C-terminal tyrosine kinase domain. DDRs are involved in organogenesis, remodeling of ECMs, cancer, and atherosclerosis [325,326]. The binding site for collagens is located within the discoidin domain and binding requires a native triple-helical collagen conformation. The two DDRs have different preferences for collagen types; DDR1 binds to collagen I and IV, and DDR2 binds to collagen I, II, and X, but not to collagen IV. Collagen binding to DDRs is accompanied by only minor structural changes in the discoidin homology domain, and it is likely that changes within the DDR dimer, or aggregation of DDR dimers, are involved in signal transduction. Tyrosine phosphorylation of the DDR cytoplasmic domain results in the creation of docking sites for adaptor proteins, which include ShcA, Nck2, and other molecules containing phosphotyrosine-binding domains [324,327].

The fact that both the integrin and the DDR families of collagen receptors are capable of sensing ECM and transmit ECM signals within cells indicates that these two collagen receptors engage in cross-talk of signaling pathways. Depending on cellular context, both stimulatory and inhibitory cross-talk between integrins and DDRs have been described so far. The former was evident in pancreatic cancer cells, where it was determined that collagen I can signal simultaneously via the β1-integrin and DDR1 receptors utilizing common downstream effectors [328]. The signals from both the β1-integrin-induced FAK activation and the DDR1-induced proline-rich tyrosine kinase 2 (Pyk2) activation were necessary for the induction of EMT process. The inhibitory cross-talk between these collagen receptors was shown in Madin–Darby canine kidney cells, where collagen binding to α2β1 integrin stimulated cell spreading by activating Cdc42, a GTPase that regulates actin cytoskeleton, while the opposite occurred upon collagen-dependent DDR1 activation [329]. Similarly, collagen-induced DDR1 activation was associated with inhibition of α2β1-intergrin-mediated phosphorylation of STAT1/3 leading to decreased cell migration [330]. The overexpression of DDRs in many human cancers, such as ovarian cancer and non-small-cell lung carcinoma [331], is a common finding and thus DDR1 has been touted as a marker of disease association.

4.3. CD44

CD44 is a transmembrane glycoprotein lacking intrinsic enzymatic activity that functions as a cell surface receptor mainly for HA, but also for other ligands, such as OPN, FN, collagen, growth factors, MMPs, and others. CD44 molecules are characterized by high heterogeneity because of alternative splicing of a single pre-mRNA as well as post-translational modifications, such as N- and O-glycosylations [332]. Structurally, CD44 consists of an ectodomain, which is variable among CD44 proteins due to exon insertions (v1–v10), as well as a transmembrane domain and a short cytoplasmic domain that are common to all CD44 molecules [333]. CD44 can also exist as a part-time PG containing HS and/or CS chains at its ectodomain close to the cell surface, and this structural feature is responsible for the binding of growth factors, such as VEGF and HGF, to CD44 variant isoforms [334,335]. On the other hand, the cytoplasmic domain of CD44 contains several binding motifs enabling CD44 to bind various intracellular proteins that critically regulate cellular functions [336,337]. Several studies have demonstrated a structure–function relationship for CD44 in cancer, since the structure of CD44 in normal cells is distinct from that of cancer cells. It has been suggested that tumor microenvironment promotes post-transcriptional as well as post-translational modifications of CD44 proteins that result in the predominance of CD44 variant isoforms leading to increased tumorigenicity [338–346]. Importantly, the prominent role of CD44 in multiple signaling pathways that affect cancer cell behavior together with the fact that CD44 is a major cancer stem cell (CSC) marker for multiple types of tumors [347] suggests a functional role for CD44 in the tumor-initiating potential of these cells (CSCs).

5. Extracellular matrix targeting: Novel therapeutic approaches

ECM is markedly modified in all pathologies, such as atherosclerosis, autoimmune and inflammatory diseases, and cancer. Nowadays, the microenvironment, in which diseases progress, is thought as equally important as cell populations implicated in the development of the pathologic conditions. For example, healthy microenvironment prevents the cancerous outgrowth of epithelial cells, whereas perturbation of homeostasis enables the initiation and progression of malignancy as well as the emergence of resistance [348–351]. Although much attention has been focused on therapies targeting directly tumor cells, the

interest on targeting ECM has been rapidly increased in the last decades. ECM molecules may be direct targets for tumor treatment due to their key roles in tumor cell biology [352]. ECM, due to its ability to regulate drug transport and delivery, is also a useful target for treatment in order to improve drug delivery and efficacy [351]. ECM components, such as heparanase, PGs like CSPG4 and glypicans, proteolytic enzymes, and many other matrix components have been proposed as possible direct targets for disease treatment and the development of ECM-based therapies is in progress. For example, the administration of autologous T cells bearing chimeric antigen receptor that can specifically recognize glypican-3 is tested in phase I clinical trials (NCT02395250) in patients with relapsed or refractory HCC. Another study (phase I) is performed to determine the safety and tolerability of escalating doses of heparanase inhibitor SST0001 in the treatment of advanced refractory multiple myeloma (NCT01764880). CSPG4 is another attractive target for treatment due to its high expression in tumor and CSCs and its restricted distribution in normal tissues. In addition, the outcome of using therapeutic antibodies against CSPG4 in animal models is promising [19]. Moreover, an interference with the HA/CD44 signaling pathway or the use of CD44/HA as targeting strategies for cytotoxic drugs have been the subject of numerous therapeutic targeting approaches (including HA conjugated drugs, HA conjugated nano-carriers, anti-CD44 antibodies, tissue-specific deletion of CD44 variant signaling) [57,333].

In addition to directly affecting tumor cell behavior, ECM molecules promote recurrence by preventing effective transport of therapeutic agents. In order to reach all tumor cells, anti-cancer drugs have to be dispersed uniformly by means of tumor vasculature and to cross vessel walls before traversing through the tumor interstitial space to gain access to the tumor cell membrane [353]. Transport of drug molecules through interstitial tissue is dependent on convection and diffusion [354]. Tumorigenesis is associated with the development of abnormal blood vessels. Tumor vasculature comprises irregular, dilated, and leaky with chaotic branching patterns including shunts and loops. Tumor vessels provide tumor tissue with low and heterogeneous blood flow due to mechanical forces applied on them. Inefficient blood flow in tumors results in the establishment of hypoxic and acidic conditions that further benefit tumor cells [355]. Mechanical forces arising from tumor cell growth, abnormal ECM deposition, and elevated IFP compress vessels, reducing or partially blocking the flow. IFP is increased in solid tumors due to increased vessel permeability and hyperperfusion, poor lymphatic drainage, hyperplasia, and abnormal deposition of ECM molecules. Elevated IFP inhibits convection-mediated transport and markedly hinders extravasation and movement of drugs towards tumor parenchyma [351,353].

Vascular normalization is one strategy to improve adequate and homogeneous distribution of anti-cancer drugs. Vascular normalization is achieved through the correction of rapid angiogenic signaling by using anti-angiogenic treatment that slows down the fast and abnormal development of tumor vessels. This results in the formation of tumor vessels that resemble normal ones in phenotype and functions reducing leakiness and establishing increased blood flow. Targeting potent angiogenic factors, such as VEGF and PDGF, which are overexpressed in tumors, is vital for vascular normalization and lowering of IFP [356,357]. The combination of VEGFR inhibitor PTK/ZK with platelet-derived growth factor receptor (PDGFR) inhibitor STI571 exhibited additive effect on the lowering of the IFP of KAT-4 tumors that was accompanied by vascular remodeling and decreased vascular leakiness [358]. Furthermore, peptides derived from various ECM molecules such as FN, collagen type IV, collagen type XVIII (endostatin), laminins, TSP etc., with proven anti-angiogenic properties have been suggested as possible agents for vascular normalization and improved tumor therapy [359]. Targeting heparanase by using the heparanase inhibitor SST0001 combined with other conventional drugs is a promising strategy to overcome abnormal angiogenesis and poor drug delivery. These agents showed synergistic effects on anti-angiogenesis and tumor growth inhibition [360].

Drug delivery within tumor stroma mainly depends on diffusion, and both tumor cell mass and ECM components represent barriers that impede transport through the interstitial matrix. Notably, specific parameters that regulate diffusion such as diffusion distance, available volume fraction of pores, tortuosity of pathway, hydrodynamic resistance, and affinity for the deliverable molecule are all affected by ECM remodeling occurred in tumor stroma [351]. For example, the development of fibrotic tumor stroma, which is characterized by deregulated accumulation of various types of collagen networks with modified orientation and stiffness, as well as deposition of other ECM components result in decreased available volume fraction of pores and increased tortuosity of the void space, and thus reduced rate of drug diffusion [351]. In addition, accumulation of PGs and HA increase ECM viscosity and consequently the hydrodynamic resistance affecting drug diffusion. Furthermore, they can also reduce the available volume fraction of pores and/or cause local sequestration of the drug through electrostatic repulsive or attractive forces, respectively [351].

Equally important to normalize tumor vasculature is to normalize ECM in order to improve drug penetration and efficacy, especially in highly desmoplastic tumors [355]. Collagen degrading enzymes, such as collagenase and MMPs, markedly improved the penetration and efficacy of administrated therapeutic agents in tumors [355]. Inhibition of LOX activity by using specific inhibitors such AB0023 may prevent ECM stiffening and thus facilitate the penetration of administrated drugs [361]. In this study, the inhibition of LOXL2 markedly reduced TGF-β pathway signaling and activated fibroblasts [361]. Blocking TGF-β signaling can normalize both blood vessels and ECM within tumor stroma and enhance the treatment outcome of liposomal doxorubicin in experimental models [362,363]. The use of other anti-fibrotic agents such as relaxin, angiotensin II receptor blockers (losartan), and angiotensin-converting enzyme inhibitors, that either re-organize collagen matrices or reduce collagen production, increases the penetration and efficacy of anti-tumor drugs [355]. Accordingly, the use of modified recombinant human PH-20 induced HA degradation and efficient penetration of chemotherapeutic agents, doxorubicin, and gemcitabine markedly increasing their efficacy in a mouse model of pancreatic cancer [364].

Numerous synthetic or naturally derived biomaterial matrices such as collagen, gelatin, fibrin, alginate, HA, polylactide, polyglycolide, polyethyleneglycol, and others have been explored as delivery carriers to improve controlled delivery and efficacy of pharmaceutical agents. Biomaterials are recognized for their biocompatibility, biofunctionality, and bioresorsability *in vivo* [365,366]. Incorporation of ECM molecules into biomaterials improved the delivery and efficacy of therapeutic agents and cells for the treatment of degenerated intervertebral discs [365] and bone regeneration [366]. For example, covalently incorporated Hep or Hep mimetic molecules into biomaterials sequester Hep-binding growth factors and control their release [366]. In another paradigm, an engineered FN fragment containing an integin- and a growth factor-binding domain was incorporated into biomaterial. Notably, co-delivery of multifunctional FN fragment with PDGF-BB and BMP-2 induces bone regeneration by promoting synergistic signaling between the integrin $\alpha_5\beta_1$ and growth factor receptors [367]. Intact laminins or laminin-derived peptides have been also used for the development of therapeutic applications. Incorporation of laminin-332 on polytetrafluoroethylene scaffolds increased tissue vascularization and accelerated neo-vascularization on subcutaneous implantation [368,369]. Conjunction of laminin-derived bioactive peptides to polymers such as chitin or chitosan have been tested for wound repair and re-epithelialization [370,371].

6. Conclusion

ECM is a complex and dynamic structure that provides the scaffold wherein cells are located. Matrix components encompass multiple, independently folded domains as well as specific glycosylation that provide

them with specific sites for interaction. ECM components, such as collagens, PGs, GAGs, elastin, laminin, FN, and matricellular proteins contain various interacting sites with different specificities to matrix components and cell surface receptors, which make them capable to bind with each other forming a complex three-dimensional network associated with resident cells (Fig. 1). ECM provides signals to cells regulating their behavior and can trigger multiple biological activities that are essential for normal organ development and tissue homeostasis (Fig. 1). Loss-of-function mutations and modifications in ECM molecules are associated with various pathologies. ECM undergoes an enduring and controlled remodeling normally by several matrix proteases and other degrading enzymes, such as heparanase. Although this fine-tuned process is normally under control, it progresses unrestrained in pathological conditions resulting in the formation of a favorable microenvironment for disease development and progression (Fig. 1). All recent evidence supports the notion that abnormalities in ECM structure and composition and establishment of a modified cross-talk between abnormal ECM and cells are crucial for the development and progression of diseases. The deeper understanding of diverse biological activities and properties of the ECM components will help us to develop novel targeted therapeutic interventions for disease treatment.

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