4 Basic Components of Connective Tissues and Extracellular Matrix: Fibronectin, Fibrinogen, Laminin, Elastin, Fibrillins, Fibulins, Matrilins, Tenascins and Thrombospondins

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Abstract

Collagens are the most abundant components of the extracellular matrix (ECM) and many types of soft tissues. Elastin is another major component of certain soft tissues, such as arterial walls and ligaments. It is an insoluble polymer of the monomeric soluble precursor tropoelastin, and the main component of elastic fibers in matrix tissue where it provides elastic recoil and resilience to a variety of connective tissues, e.g., aorta and ligaments. Elastic fibers regulate activity of transforming growth factors β (TGFβ) through their association with fibrillin microfibrils. Elastin also plays a role in cell adhesion, cell migration, and has the ability to participate in cell signaling. Mutations in the elastin gene lead to cutis laxa. Many other molecules, though lower in quantity, function as essential, structural and/or functional components of the extracellular matrix in soft tissues. Some of these are reviewed in this chapter. Besides their basic structure, biochemistry and physiology, their roles in disorders of soft tissues are discussed only briefly as most chapters in this volume deal with relevant individual compounds. Fibronectin with its multidomain structure plays a role of "master organizer" in matrix assembly as it forms a bridge between cell surface receptors, e.g., integrins, and compounds such collagen, proteoglycans and other focal adhesion molecules. It also plays an essential role in the assembly of fibrillin-1 into a structured network. Though the primary role of fibrinogen is in clot formation, after conversion to fibrin by thrombin it also binds to a variety of compounds, particularly to various growth factors, and as such, fibrinogen is a player in cardiovascular and extracellular matrix physiology. Laminins contribute to the structure of the ECM and modulate cellular functions such as adhesion, differentiation, migration, stability of phenotype, and resistance towards apoptosis. Fibrillins represent the predominant core of microfibrils in elastic as well as non-elastic extracellular matrixes, and interact closely with tropoelastin and integrins. Not only do microfibrils provide structural integrity of specific organ systems, but they also provide basis for elastogenesis in elastic tissues. Fibrillin is important for the assembly of elastin into elastic fibers. Mutations in the fibrillin-1 gene are closely

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associated with Marfan syndrome. Latent TGFβ binding proteins (LTBPs) are included here as their structure is similar to fibrillins. Several categories of ECM components described after fibrillins are sub-classified as matricellular proteins, i.e., they are secreted into ECM, but do not provide structure. Rather they interact with cell membrane receptors, collagens, proteases, hormones and growth factors, communicating and directing cell-ECM traffic. Fibulins are tightly connected with basement membranes, elastic fibers and other components of extracellular matrix and participate in formation of elastic fibers. Matrilins have been emerging as a new group of supporting actors, and their role in connective tissue physiology and pathophysiology has not been fully characterized. Tenascins are ECM polymorphic glycoproteins found in many connective tissues in the body. Their expression is regulated by mechanical stress both during development and in adulthood. Tenascins mediate both inflammatory and fibrotic processes to enable effective tissue repair and play roles in pathogenesis of Ehlers-Danlos, heart disease, and regeneration and recovery of musculo-tendinous tissue. One of the roles of thrombospondin 1 is activation of TGFβ. Increased expression of thrombospondin and TGFβ activity was observed in fibrotic skin disorders such as keloids and scleroderma. Cartilage oligomeric matrix protein (COMP) or thrombospondin-5 is primarily present in the cartilage. High levels of COMP are present in fibrotic scars and systemic sclerosis of the skin, and in tendon, especially with physical activity, loading and post-injury. It plays a role in vascular wall remodeling and has been found in atherosclerotic plaques as well.

Keywords

Fibronectin · Fibrinogen · Laminin · Elastin · Fibrillins · LTBPs · Matricellular proteins · Fibulins · Matrilins · Tenascins · Thrombospondins

Abbreviations

ADAMTS	a-Disintegrin-and-etalloproteinase-with-thrombospondin motifs
cbEGF	Calcium-binding epidermal growth factor
CNS	Central nervous system
COMP	Cartilage oligomeric matrix protein
ECM	Extracellular matrix
EFEMP1	EGF-containing fibulin-like ECM protein 1
FGF	Fibroblast growth factor
FN	Fibronectin
LDL	Low-density lipoprotein
LE	Laminin-type epidermal growth factor-like
LOX	Lysyl oxidase
LTBPs	Latent TGFβ binding proteins
MMP	Matrix metalloproteinase
PDGF	Platelet-derived growth factor
SLRP	Small leucine rich proteoglycan
TGFβs	Transforming growth factors β
TIMP	Tissue inhibitor of metalloproteinase
TSP	Thrombospondin
VEGF	Vascular endothelial growth factor

The connective tissue in general is comprised of 3 groups of proteins: collagens, proteoglycans and a variety of different glycoproteins. In addition to the main weight-bearing structural proteins of connective tissue – the fibril forming collagens (discussed in Chap. 2) – as well as the often hydrophilic role of proteoglycan proteins (discussed in Chap. 6), growth factors (see Chap. 7), other proteins are also important for structure and signaling within the matrix tissue of the body. Many of these proteins are currently being identified as having important functions in the developmental phase of the tissue, where these molecules can act as mediators of signaling and/or structural changes in the matrix tissue. Further, many of the glycoproteins have been

demonstrated to play important roles in normal tissue physiology, including maintaining tissue homeostasis, and responding and adapting to perturbations such as mechanical loading/unloading, or tissue damage and subsequent regeneration. Furthermore, numerous, if not all, of these glycoproteins are important for pathological tissue response like in e.g. cancer, fibrosis or connective tissue anomalies. Of interest as far as the adaptation of these glycoproteins is that several of them – including collagens and proteoglycans – can be modulated in their level of expression and synthesis by the degree of mechanical loading that the specific tissue exposed to mechanical loading senses (Kjaer 2004). In the following pages some basic information about these glycoproteins is provided. However, as already mentioned above, because many of these glycoproteins are active participants in the pathogenesis of a variety of soft tissue diseases they will be discussed rather briefly in this chapter as they are also described in several chapters dealing with specific disorders of soft tissues.

4.1 Fibronectin

Fibronectin (FN) is a widely distributed multidomain glycoprotein present in most extracellular matrices. It has a molecular weight of 230–270 kD, and can, in addition to its presence in the ECM, be detected also at substantial concentrations in plasma. Fibronectin is composed of types I, II, and III repeating units or modules (FNI, FNII and FNIII) (Pérez-García et al. 2020). Two intramolecular disulfide bonds are formed within type I and type II modules to stabilize the folded structure. Type III modules are formed by seven-stranded β-barrel structures that lack disulfides (Leahy et al. 1996; Potts and Campbell 1994). The FN units or domains mediate self-assembly and ligand binding for collagen/gelatin, integrins, heparin, fibronectin, and other extracellular molecules (Sabatier et al. 2009). The 500-kDa FN dimer is formed through a pair of anti-parallel disulfide bonds at the C terminus. FN exists in multiple isoforms generated by alternative splicing. The single FN gene transcript encodes 12 isoforms in rodents and cows and 20 isoforms in humans. Alternative splicing occurs by exon skipping at EIIIA/EDA and EIIIB/EDB and by exon subdivision at the V region/IIICS. This gives fibronectin considerable diversity in module arrangement resulting in many isoforms (White and Muro 2011). Fibronectin is secreted in the form of soluble inactive dimers with disulfide bonds that must be activated by interaction with α5β1 and other integrins (Mao and Schwarzbauer 2005; Takahashi et al. 2007).

Fibronectin is widely expressed in embryos and adults, especially in regions of active morphogenesis, cell migration and inflammation. Tumor cells contain reduced levels of fibronectin, whereas fibronectin levels are high in tissues undergoing repair (i.e., wound healing) and/or fibrosis. In the process of matrix assembly, multivalent ECM proteins are induced to self-associate and to interact with other ECM proteins to form fibrillar networks. Matrix assembly is initiated usually by ECM glycoproteins binding to cell surface receptors, such as fibronectin dimers binding to α5β1 integrin. Receptor binding stimulates fibronectin self-association mediated by the N-terminal assembly domain and organizes the actin cytoskeleton to promote cell contractility. Fibronectin conformational changes expose additional binding sites that participate in fibril formation and in conversion of fibrils into a stabilized, insoluble form. Once assembled, the FN matrix impacts tissue organization by contributing to the assembly of other ECM proteins. Fibronectin plays an important role in fibrillogenesis in regard to initiation, progression and maturation of matrix assembly. The prominent role of fibronectin in matrix assembly lies in fibronectin ability, enabled by its multidomain structure, to bind simultaneously to cell surface receptors, e.g., integrins, and to collagen, proteoglycans and other focal adhesion molecules (Singh and Schwarzbauer 2012). This property also makes it possible to mediate the assembly of several ECM proteins, including type I and III collagen, thrombospondin-1 and microfibrils

(Sabatier et al. 2009). Fibronectin is also called a "master organizer" by some investigators (Sabatier et al. 2009; Dallas et al. 2006). Degradation of fibronectin by proteases activated during a variety of inflammatory processes, including infections leads to unmasking of binding sites within the fibronectin molecule. This triggers binding of fibronectin to different integrin receptors and toll like receptors, ultimately leading to activation of MAPK signaling pathway and transcription factors such as NF-κB, thus further stimulating progression of inflammation (Pérez-García et al. 2020). Perhaps more important in the context of this volume is to emphasize the role fibronectin plays in the assembly of fibrillin-1 into a structured network (see below).

4.2 Fibrinogen

Fibrinogen is a large, complex, fibrous glycoprotein with three pairs of polypeptide chains: Aα, Bβ and γ (Fish and Neerman-Arbez 2012). The chains are linked together by 29 disulfide bonds. Fibrinogen is 45 nm in length, with globular domains at each end and in the middle connected by α-helical coiled-coil rods and has M_r 340 kDa. The E-region consisting of N-terminal ends of the six chains and the D-regions consisting of the C-terminal ends of the Bβ and γ chains and a portion of the Aα chain are separated by a 3-stranded α-helical coiled-coil regions (Doolittle et al. 1978). Both strongly and weakly bound calcium ions are important for maintenance of fibrinogen structure and functions. Fibrinopeptides located in the central region of the molecule are cleaved by thrombin to convert soluble fibrinogen to insoluble fibrin polymer, via intermolecular interactions of the "knobs" exposed by fibrinopeptide removal with "holes" always exposed at the ends of the molecules. Fibrin monomers polymerize via these specific and tightly controlled binding interactions to make half-staggered oligomers that lengthen into protofibrils. The protofibrils aggregate laterally to make fibers, which then branch to yield a three-dimensional network-the fibrin clot-essential for hemostasis. X-ray crystallographic structures of portions of fibrinogen have provided some details on how these interactions occur. Finally, a transglutaminase, Factor XIIIa, covalently binds specific glutamine residues in one fibrin molecule to lysine residues in another fibrin molecule via isopeptide bonds, stabilizing the clot against mechanical, chemical, and proteolytic insults (Ariens et al. 2002). The gene regulation of fibrinogen synthesis and its assembly into multichain complexes proceed via a series of well-defined steps. Alternate splicing of two of the chains yields common variant molecular isoforms. The mechanical properties of clots, which can be quite variable, are essential to fibrin functions in hemostasis and wound healing (Cilia La Corte et al. 2011). The fibrinolytic system, with the zymogen plasminogen binding to fibrin together with tissue-type plasminogen activator to promote activation to the active enzyme plasmin, results in digestion of fibrin at specific lysine residues. Fibrin(ogen) also specifically binds a variety of other proteins, including fibronectin, albumin, thrombospondin, von Willebrand factor, fibulin, fibroblast growth factor-2 (FGF2), vascular endothelial growth factor (VEGF), and interleukin-1. Though its ability to bind to a variety of compounds, particularly to various growth factors makes fibrinogen a player in cardiovascular and extracellular matrix physiology (Fish and Neerman-Arbez 2012; Sahni and Francis 2000; Sahni et al. 1998; Clark et al. 1982; Donaldson et al. 1989), fibrinogen does not appear to play a specific role in pathogenesis of disorders discussed in this volume.

Studies of naturally occurring dysfibrinogenemias and variant molecules have increased our understanding of fibrinogen functions. Fibrinogen binds to activated αIIbβ3 integrin on the platelet surface, forming bridges responsible for platelet aggregation in hemostasis, and also has important adhesive and inflammatory functions through specific interactions with other cells (Armstrong and Peter 2012). Fibrinogen-like domains originated early in evolution, and it is likely that their specific and tightly controlled intermolecular

interactions are involved in other aspects of cellular function and developmental biology.

4.3 Laminins

Laminins are a family of large multidomain, heterotrimeric glycoproteins with molecular weights of 500–900 kDa, located in the basement membrane where they function as a bridge between cells and variety of ECM molecules (Chang and Chaudhuri 2019), more specifically, they interact with cellular receptors of cells of the basement membrane (Aumailley 2018). Sixteen trimeric isoforms have been described in mouse and human tissues and these isoforms vary in their cell and tissue specificity (Aumailley 2018). In general, each laminin isoform consists of three chains, α, β, and γ which each exist in five, four, and three genetically distinct forms, respectively (Aumailley et al. 2005; Miner and Yurchenco 2004; Domogatskaya et al. 2012). Most vertebrates have five α, three γ and three to six β genes (Domogatskaya et al. 2012). The large range in size is due to variability in the chain size: the α chains are the largest (M_r ~ 200–400 kDa), both the β and γ chains range in size from 120 to 200 kDa. In addition, all forms of these three chains are highly glycosylated, some have glycosaminoglycan chains attached (Aumailley et al. 2005; Domogatskaya et al. 2012). Homologous tandem repeats of structural motifs are incorporated in all laminins, with more similarities between β and γ chains. Laminins are cross or T-shaped molecules with 2 or 3 short arms and one long arm. The short arms consist of N-terminal parts of one of the three chains and they contain multiple laminin-type epidermal growth factor-like (LE) repeats (Domogatskaya et al. 2012; Hohenester 2019) The long arm contains portions of all 3 chains (Aumailley et al. 2005). Common to all laminins is a coiled-coil domain with about 80 heptad sequence repeats at or close to the C-terminal end. This coiled-coil domain bears homology to segments of β and γ chains and is responsible for proper assembly of the trimer (Domogatskaya et al. 2012; MacDonald et al. 2010). Assembly of the laminin molecule is also controlled to some extent by proteolytic processing prior to laminin binding to its receptors (Domogatskaya et al. 2012).

Laminins adhere to cells primarily via binding of the G domain of the α chains to integrins, dystroglycan, or sulfated glycolipids. The N-terminal globular domains of the α1 and α2 chains as well as the globular domains VI (LN) of the α5 chains can bind to several integrin isoforms (α1β1, α2β1, α3β1, and αVβ3). This process enables cell binding on both ends of laminins containing the three α chains. The laminin γ2 chain has been reported to bind α2β1 integrin. The N-terminal globular domains of some α-chains can also bind sulfatides. This type of binding may link the laminin molecules to the cell surface. Laminins contribute to the structure of ECM and influence associated cells in regards to adhesion, differentiation, migration, stability of phenotype, and resistance towards apoptosis. Laminin molecules interact not only with collagen type IV, integrins and dystroglycans but also with other components of the basal membrane matrix, and thus contribute to the overall structure. They also can interact with components in the underlying interstitial stroma. The cellular effects of laminins are mediated largely via ligand binding to cell membrane receptors, and this signaling can alter transcription levels of genes and even influence chromatin remodeling of gene promoters. The insoluble network formed by laminin and type IV collagen plays a structural and functional role in the basement membrane and cells associated with it. Though at this point we do not know to what extent, if any, laminins play a role in the pathogenesis of connective and soft tissue diseases it is clear that they contribute to normal function of tendons, blood vessels and other connective soft tissues. For example, this network participates in transmission of the contractile force from the skeletal muscle to the tendons (Grounds et al. 2005). A decrease in laminin content in the basement membrane covering the outermost aspect of the tendon was identified in type IV collagen deficient mice. This was accompanied by formation of spontaneous tendon adhesions (Taylor et al. 2011). That laminins are,

indeed, required for proper healing of tendons and other connective tissues, such as cornea, has been shown by Molloy et al. (Molloy et al. 2006) and Sato et al. (Sato et al. 1999), respectively. There is some evidence indicating increased expression of β2 chain of laminin in ascending aorta in patients with Marfan syndrome (Della Corte et al. 2006) .

Taken together laminins are not passive adhesion proteins, but rather, they actively modulate cell behavior; influence differentiation, migration, and phenotype stability. They also inhibit apoptosis by signaling via cell membrane receptors such as integrins and dystroglycan. However, the details of laminin signaling are still largely unexplored. Laminins constitute the first ECM component appearing in the developing early embryo, and embryonic laminins have found an important use as culture matrices for stem cells. Other laminins are crucial for normal function of numerous tissues and organs, e.g., nerve, epithelium, blood vessels, and kidney. The commercial unavailability of most laminin isoforms has hampered *in vitro* studies. However, many isoforms have been offered recently by several companies as recombinant proteins, which may enable deeper insight into functional properties. Laminins may find numerous new applications in cell biology and cell therapy research. The vast complexity of laminin effects cannot be explained solely by simple integrin binding and signaling (Domogatskaya et al. 2012).

4.4 Elastin

Elastin is an insoluble polymer of the monomeric soluble precursor tropoelastin. Elastin is the main component of elastic fibers in matrix tissue, and as such it is the main contributor to the elasticity of these fibers (Muiznieks et al. 2010; Mithieux et al. 2012). Tropoelastin is encoded by a single human gene and is secreted as an ~60 kDa unglycosylated protein by a variety of cells, including fibroblasts, endothelial and smooth muscle cells, chondrocytes and keratinocytes (Mithieux et al. 2012). The splicing of the primary tropoelastin transcript is tissue-specific and thus allows for conformational and functional adjustment for each location (Kielty 2006). The primary tropoelastin sequence is an arrangement of hydrophobic domains rich in valine, proline and glycine, providing elasticity to the final product, elastin. These hydrophobic domains alternate with hydrophilic domains which contain lysine residues whose role it is to stabilize elastin microfibrils by cross-linking (Csiszar 2001; Lee and Kim 2006; Kim et al. 2011). However, before this can occur tropoelastin units are initially assembled within the cells or at least on the cell surface (Kozel and Mecham 2019) before they are chaperoned to the extracellular surface (Hinek and Rabinovitch 1994) where they coacervate (Yeo et al. 2011) into protein-dense spherules (Kozel et al. 2006) which then undergo cross-linking and fibril assembly. Ninety per cent of the final product, i.e., of an elastic fiber, consists of a central amorphous core of elastin surrounded by a layer of microfibrils composed mostly of glycoprotein fibrillin, but also of many other proteins, among them fibulins, collagen VIII, and emilins with microfibrils as well (Kielty 2006; Berk et al. 2012; Nakamura 2018). Proteoglycans, including biglycan (Baccarani-Contri et al. 1990) and glycosaminoglycan heparan sulfate (Gheduzzi et al. 2005) have been detected within the elastic core. Moreover, it has been shown that the presence of sulfated proteoglycans within the ECM regulates elastin assembly (Kozel et al. 2004). In addition, water plays an important role not just in the three dimensional organization of elastin molecules but also in the final degree of hydration and elasticity (Gheduzzi et al. 2005). Elastic fibers form an interconnecting fenestrated network of lamellae in the arterial media. The lamellae are layers of elastic fibers surrounded by circumferentially oriented smooth muscle cells and collagen fibers (Wagenseil and Mecham 2012).

The high content of hydrophobic amino acids makes elastin one of the most chemically resistant and durable proteins in the entire body (Mithieux and Weiss 2005). It is distributed throughout the body in the form of tissue-specific elastic networks (Mithieux et al. 2012). Elastin containing fibers provide elastic recoil in tissues where repetitive distention and relaxation is a

requirement for their function, and is found typically in skin, lungs, ligaments, tendons and vascular tissues (Chung et al. 2006). The relative content of elastin can vary from around a few percentages in skin, to more than 70% in some ligament structures in the animal kingdom. Elastic fibers are essential for proper function of at least three areas. As a major structural component elastic fibers provide elastic recoil and resilience to a variety of connective tissues, e.g., aorta and ligaments. Elastic fibers regulate activity of TGFβs through their association with fibrillin microfibrils. In addition, elastin also plays a role in cell adhesion, cell migration, survival and differentiation, and can, to some extent, act as a chemotactic agent (Muiznieks et al. 2010; Kielty 2006). Elastin, and for that matter tropoelastin as well, is also a signaling molecule. Tropoelastin inhibits proliferation of arterial smooth muscle cells, induces the formation and organization of actin stress fibers and acts as a chemotactic agent (Karnik et al. 2003).

Elastin and collagen are the dominant components of the ECM in large elastic arteries, such as aorta (Wagenseil and Mecham 2012). The two compounds play different, but complementary roles in arterial physiology: reversible extensibility during cycling loading is provided by elastin (Wagenseil and Mecham 2012; Mecham 1998), whereas strength and the ability to withstand high pressure is the responsibility of collagen (Wagenseil and Mecham 2012; Fung 1993). The assembly of elastic fibers proceeds only during tissue development, and cedes with maturation so older tendons (and other tissues) contain less elastin than young tendons (Wagenseil and Mecham 2009; Kostrominova and Brooks 2013). In effect that means that with aging the stiffness of arterial wall increases due to degradation and fragmentation of elastic fibers (Wagenseil and Mecham 2012; Greenwald 2008). Matrix metalloproteinases (MMPs) are just some of the proteases participating in this destructive process (Wagenseil and Mecham 2012; Li et al. 1999). Increased levels of MMP-1 and MMP-9 have been detected in aortic aneurysms (Tamarina et al. 1999). Local inhibition of MMP activities in animal models either by tissue inhibitor of metalloproteinase 1 (TIMP-1) (Allaire et al. 1998), inhibition of MMP-2 by calpain-1 inhibition (Jiang et al. 2008), or by doxycycline, an inhibitor of MMPs (Castro et al. 2008) shows potential treatment venues. Whether they can be utilized for treatment or even prevention of complications of Marfan syndrome or related disorders remains to be seen. It is thought that production of collagen increases to compensate for the elastin deficit, however, this pushes the arterial wall towards increased stiffness (Wagenseil and Mecham 2012). Increased elastin production has been documented in some animal models of hypertension, but it is either not high enough (Wolinsky 1970) or the new elastin fibers are not assembled properly (Todorovich-Hunter et al. 1988).

Elastin gene mutations can be divided into two groups (Wagenseil and Mecham 2012). Autosomal dominant supravalvular aortic stenosis is a representative of the first group. Besides aortic valve stenosis, patients develop hypertension, increased arterial stiffness leading to congestive heart failure (Wagenseil and Mecham 2012). Hypertrophy and hyperplasia of smooth muscle cells in the media of the affected arteries is due to fragmentation of elastic lamellae and changes in ECM composition (O'Connor et al. 1985). This pathology is due to loss of function mutations in the elastin (*ELN*) gene (Urban et al. 2000). Consequently, the mutant elastin protein is nonfunctional and does not interfere with the production and assembly of normal, functional elastin in heterozygous individuals who are then less affected than homozygous people (Wagenseil and Mecham 2012).

An autosomal dominant form of cutis laxa belongs to the second group which encompasses disorders resulting from missense mutation, usually near the 3′ end of the transcript (Wagenseil and Mecham 2012; Rodriguez-Revenga et al. 2004; Tassabehji et al. 1998). Cutis laxa and related disorders are described in more detail in Chap. 13. The mutant elastin interferes with normal assembly, metabolism and function of elastic fibers (Tassabehji et al. 1998).

Lack of elastin in the body is fatal. Elastin knockout mice (*Eln−/−*) die shortly after birth

with subendothelial cell accumulation blocking blood flow and with markedly increased arterial stiffness (Wagenseil and Mecham 2012; Li et al. 1998). The presence of additional lamellar units in heterozygous *Eln+/−* mice indicates an attempt to compensate and to remodel in a response to increased hemodynamic stress during development (Faury et al. 2003). Fibrillin-1 hypomorphic mice (*mgR/mgR*) serve as a model of Marfan syndrome because of aneurysm formation in the ascending aorta and elastolysis in all segments of aorta (Schwill et al. 2013).

4.5 Fibrillins

Because of close association of mutated fibrillin-1 with Marfan syndrome which is being discussed in detail in Chap. 8, only a brief description of fibrillins is provided in this chapter. Fibrillins are a group of large extracellular glycoproteins (~350 kDa) (Kielty 2006) that consists of 3 isoforms, fibrillin-1, -2, and -3. Fibrillin molecules contain 40–80 amino acid residues, several calcium-binding epidermal growth factor (cbEGF)-domains interspersed with several eight-cysteine-containing motifs binding TGFβ (TB) (Sabatier et al. 2009; Kielty 2006; Kielty et al. 2005). No other extracellular proteins contain that much cysteine as fibrillins (Chung et al. 2006). Whereas fibrillin-2 and fibrillin-3 are mostly expressed in embryonic tissues with the exception of peripheral nerves and, to lesser degree, skin and tendon (Zhang et al. 1994; Charbonneau et al. 2003) fibrillin-1 is a protein appearing in both embryonic and adult tissues (Charbonneau et al. 2003; Cain et al. 2006; Robinson et al. 2006).

Fibrillins represent the predominant core of the microfibrils in elastic as well as non-elastic extracellular matrixes, and interact closely with tropoelastin and integrins, e.g., through direct binding. Not only do microfibrils provide structural integrity of specific organ systems, but they also provide a scaffold for elastogenesis in elastic tissues such as skin, lung, and vessels (Wagenseil and Mercham 2009). Thus, fibrillin is important for the assembly of elastin into elastic fibers. The precise arrangement of fibrillin within microfibrils is a matter of speculation; several working models have been suggested to explain the architecture of microfibrils (Kozel and Mecham 2019; Robinson et al. 2006). It is known that different mutations in different regions, including the propeptide sequence encoded by the C-terminal domain, of the fibrillin-1 gene lead to impaired assembly of microfibrils in individuals with Marfan syndrome (Robinson et al. 2006; Milewicz et al. 1995; Raghunath et al. 1999). Robinson et al. provide an excellent, more comprehensive review of these issues, including review of self-assembly of fibrillins and cross-link formation in fibrillin assembly (Robinson et al. 2006). Besides fibrillin and elastin, the two major components, many other proteins participate in the makeup of microfibrils. As noted above fibronectin in particular plays as an essential role in this process, more specifically, through binding of a C-terminal fibrillin-1 region with the fibronectin gelatin-binding region (Dallas et al. 2006). It is interesting to note that homocysteinylation of fibronectin in homocystinuria reduces fibronectin dimers to monomers, and, as a consequence, impairs assembly of fibrillin and microfibrils. Similar impairment is the result of homocysteinylation of fibrillin-1 (Hubmacher et al. 2011).

As already mentioned above, fibrillins contain several TGFβ-binding motifs, this feature makes their structure, and their function. Similar to that of latent-TGFβ-binding proteins (or LTBPs) (see below) (Robinson et al. 2006).

Mutations in genes for fibrillin-1 and -2 lead to several disorders in people. Mutation in fibrillin-1, the most abundant fibrillin, and also the best characterized isoform can result in autosomal dominant Marfan and Weill-Marchesani syndromes (Thomson et al. 2019). It is expressed in embryonic and mature tissues (Ramirez and Sakai 2010). Its involvement in pathogenesis of Marfan syndrome is described in detail in Chap. 9. Above mentioned Weill-Marchesani syndrome leads to pathology of the musculoskeletal, cardiovascular and ocular system. Two forms of Weill-Marchesani syndrome have been identified: autosomal dominant type caused by a fibril-

lin-1 mutation, and somewhat heterogenous autosomal recessive form caused by mutations in genes for.

ADAMTS-10, ADAMTS-17 or LTBP-2 (Karoulias et al. 2019). Beals syndrome is characterized by congenital contractual arachnodactyly caused by mutation in fibrillin-2 (Sabatier et al. 2009; Robinson et al. 2006; Beals and Hecht 1971; Jaman and Al-Sayegh 2016). Not much is known about fibrillin-3 beyond its expression limited to embryonic extracellular microfibrils (Halper 2021).

4.6 Latent-TGFβ-Binding Proteins (LTBPs)

As described above, LTBPs 1–4 are structural proteins related to fibrillins. They bind to the latency associated peptide (LAP) non-covalently bound to TGFβ (Robertson et al. 2011). The entire complex is embedded in ECM, where it limits bioavailability of TGFβ (Thomson et al. 2019). Phenotypic changes resulting from mutations in individual *LTBP* genes point to the LTBP and TGFβ contribution to proper function of connective tissues. As mentioned above mutation in *LTBP2* leads to an autosomal recessive form of Weill-Marchesani syndrome, and can cause also ectopia lentis. It is deleted completely in a type of congenital glaucoma (Thomson et al. 2019). LTBP-4 together with fibulins -4 and -5 participates in elastogenesis. Persons with mutations and deletions in *LTBP4* and *LTBP3* may present with aortic dilatation and aneurysm (Thomson et al. 2019; Zilberberg et al. 2015). Other mutations in *LTBP4* are behind a form of autosomal recessive cutis laxa (Urban et al. 2009) as described in more detail in Chap. 13.

4.7 Fibulins

Fibulins are a group of eight glycoproteins that are expressed and secreted by many cell types and tissues, and that are tightly connected with basement membranes, elastic fibers and other components of ECM. Interactions with TGFβ and participation in elastic fiber assembly and stability are some of their important functions (Tsuda 2018). Fibulins serve not only as structural ECM components, but also as mediators of several cellular processes, such as cell growth, differentiation, angiogenesis and tumor growth. Thus they serve as modulators of cellular behavior and function (DeVega et al. 2009), and are classified by some investigators as matricellular proteins (Nakamura 2018). All fibulins share a C-terminal module which is preceded by variable number of cbEGF-like domains (Halper 2021). The members of the fibulin family are divided into class I and II, based on their length and domain structures (Yanagisawa and Davis 2010).

Class II consists of fibulins 3, 4, 5 and 7. They are called short because of their small size (M.W. ~60–70 kDa), and are discussed first because most of them (fibulins 3–5) contribute directly to assembly of elastic fibers, and thus mutations in genes encoding them lead to forms of cutis laxa and other disorders of connective tissues. Fibulins 3–5 bind to tropoelastin and are expressed during embryonic development, especially in skeletal and cardiovascular tissues (Yanagisawa and Davis 2010). This is facilitated by Ca^{2+} (Wachi et al. 2008). Fibulin-3 is predominantly found in mesenchyme that develops into heart, placenta, cartilage and bone among other organs (Giltay et al. 1999), fibulin-4 is markedly expressed in heart muscle, and fibulin-5 highly in vasculature. The molecules of short fibulins contain tandem repeats of six cbEGF domains that are connected by one amino acid in a pattern similar to the one found in fibrillin-1 (Hambleton et al. 2004). Human fibulin 3 is encoded by gene called *EFEMP1* (which stands for EGF-containing fibulin-like ECM protein 1). Mutations in this gene are numerous, some lead to autosomal dominant retinal disease (Nakamura 2018). Overexpression of *EFEMP1* is one of the genetic abnormalities identified in Werner syndrome, a form of progeria (Halper 2021; Sarbacher and Halper 2019).

Fibulin 5 contains an arginine-glycine-aspartic acid (RGD) motif which mediates binding to

integrin receptors on endothelial cells and vascular smooth muscle cells (Yanagisawa et al. 2009). This step is necessary for elastic fiber assembly (Yanagisawa and Davis 2010). Fibulin-5 also inhibits α5β1 and α4β1 integrin-mediated downstream signaling (Yanagisawa and Davis 2010). The C-terminal fibulin module contains an elastic-binding domain in fibulin-5 (Zheng et al. 2007). The same module in fibulin-5 also interacts with lysyl oxidase-like 1, 2 and 4 (Loxl 1, Loxl 2 and Lox 4), enzymes playing crucial role in cross-linking (Hirai et al. 2007; Liu et al. 2004) whereas it is the N-terminal domain responsible for binding to Lox in fibulin-4 (Horiguchi et al. 2009). Lysyl oxidases, including those binding to fibulin-5 and -4 mediate crosslinking of tropoelastin monomers into insoluble elastin polymer (Sato et al. 2007). The binding between the C-terminal module of fibulin-3 and tissue inhibitor of matrix metalloproteinase 3 is another example of close relationship between a short fibulin and connective tissue metabolism (Klenotic et al. 2004). The level of fibulin-5 is particularly high in the cardiovascular system and lung, though fibulin-4 is expressed in the outer layer of media of large blood vessels, and fibulin-3 appears in capillaries, skin and the basement membrane (Yanagisawa and Davis 2010). The participation of fibulin-5 in elastogenesis is solely due to its exclusive binding to tropoelastin but not to polymerized elastin *in vitro* (Zheng et al. 2007). Its role is inhibition of excessive tropoelastin coacervation into large aggregates, and consequently this allows for integration of microassembles of tropoelastin into the microfibril scaffolding (Yanagisawa and Davis 2010). Together with fibrillins-1 and -2 (see above under Elastin) fibulins are present in microfibrils of scaffolding for elastic fibers as well (Ramirez and Dietz 2007).

Mutations in genes for fibulin 4 and 5, *EFEMP2* and *EVEC*, respectively, are responsible for forms of cutis laxa (see Chap. 13). Fibulin-5 functions also as an inhibitor of angiogenesis (De Vega et al. 2016). Other mutations in gene for fibulin-5 lead to age-related macular degeneration (Tsuda 2018) and even vascular remodeling associated with arterial hypertension (Kartashova and Sarvilina 2019).

The last member of this group, fibulin-7 is not involved in elastic fiber formation. It is highly expressed in teeth, placenta, hair follicles, and cartilage where it functions as a cell adhesion molecule (De Vega et al. 2007). It regulates also calcium and phosphate metabolism in the kidney, and its dysfunction can lead to renal tubule calcification (Tsunezumi et al. 2018).

Group I of so called long fibulins consists of fibulins -1 and -2, and hemicentins -1 and -2 (also known as fibulins -6 and -8) (Fujishima et al. 2017). Though their structure is well described, their functions are less characterized than that those of short fibulins. Fibulin-1 (molecular weight 90 kDa) was originally identified as an intracellular molecule linking cytoskeletal components to β integrins, but later it was shown that fibulin-1 was also present in fibril matrix secreted by fibroblasts in culture (Zhang et al. 1996), and in association with basement membranes and elastic fibers. It appears early in embryonic development, at sites of epithelial-mesenchymal transition (Tsuda 2018). It is expressed in adult blood vessels, lung and skin, i.e., tissues with high content of elastic fibers (Roark et al. 1995). Fibulin-1 participates in ADAMTS-1-induced processing of proteoglycans (Tsuda 2018).

Fibulin-2 is a homodimer of two 195 kDA monomers joined by two disulfide bridges (Sasaki et al. 1997) demonstrates some overlap with fibulin-1, but its expression is more prominent in the developing heart, both aortic and coronary vessels where it binds to tropoelastin and other ECM molecules, and thus contributes to formation of elastic fibers (Tsuda 2018; Tsuda et al. 2001; Timpl et al. 2003). Fibulin-2 null mice have only skin abnormalities, most likely due to compensation of fibulin-1 overexpression (Tsuda 2018). The last two fibulins (6 and 8) AKA hemiceptins -1 and -2 are the largest members of this family (M.W. 600 kDa), and the least characterized. They play roles in mesenchymal cell migration and skin development in zebra fish (Tsuda 2018).

4.8 Matrilins

This group of four matrilins has been included for completeness and future reference as the structural and functional roles of this family of four in musculoskeletal system and in connective tissues have been understood only incompletely. Whereas matrilins -1 and -3 are limited mostly to cartilage, matrilins -2 and -4 were identified in other types of ECM, including loose soft connective tissue (Paulsson and Matrilins 2018). In general, matrilins mediate interactions between collagens and other molecules, such as proteoglycans (aggrecan, small leucine rich proteoglycans (SLRPs)), and other ECM components. Matrilins are trimers or tetramers of units composed of von Willebrand module, EGF-like domain(s) and a C-terminal oligomerization domain. The von Willebrand module is required for protein-protein interactions (Whittaker and Hynes 2002).

Though skeletal disorders due to mutations in genes for matrilins -1 and -3 have been well documented (Paulsson and Matrilins 2018; Jackson et al. 2012; Anthony et al. 2015; Montanaro et al. 2006), so far no physiologically relevant mutations have been identified for matrilins -2 and -4.

4.9 Tenascins

Tenascins are matricellular ECM polymorphic glycoproteins with molecular weight between 150 and 380 kDa. They are a family of multimeric proteins labeled as tenascin-C, -R, -W, -X and -Y (Tucker et al. 2006; Tucker and Chiquet-Ehrismann 2009; Okamoto and Imanaka-Yoshida 2012). Tenascins are composed of identical subunits built from variable numbers of repeated domains, including heptad repeats, EGF-like repeats, fibronectin type III domains and a C-terminal globular domain similar to that seen in fibrinogens (Okamoto and Imanaka-Yoshida 2012). Polymerization of tenascins is facilitated by the heptad repeats. The pattern of arrangement of the domains renders tenascins highly interactive rather than structural proteins in the ECM because of and as such are considered matricellular proteins (Midwood et al. 2016). Whereas the presence of tenascin-R is predominantly limited to the central nervous system (CNS), and then mostly during CNS development, the other members of the tenascin family are found more widespread in connective and soft tissues in the body.

4.9.1 Tenascin-X

Tenascin-X is emerging as a significant player in physiological processes in many systems and in pathogenesis of classic-like type Ehlers-Danlos syndrome (cl-EDS) (Matsumoto and Aoki 2020). Its level rises gradually from undetectable in early embryos into measurable amount in post-natal life. Its presence is ubiquitous, but particularly prominent in skeletal muscle, heart, skin, and gastrointestinal and nervous tissue. It has close association with blood vessels as well (Matsumoto and Aoki 2020). Tenascin-X is less glycosylated than tenascin-C. Post-natal physical activity stimulates the expression of tenascin-X in skeletal muscle as a consequence of acute mechanical loading and is known to be present in tissues that are subjected to high stress (Flück et al. 2000; Chiquet et al. 2009). Tenascin-Y is an avian equivalent of tenascin-X, and it follows tenascin-X expression pattern (Tucker et al. 2006; Hagios et al. 1996).

Tenascin-X is localized in the perineurium and endoneurium of peripheral nerves (Geffrotin et al. 1995), and in leptomeninges of the central nervous system (Matsumoto et al. 2002). Though tenascins are classified as matricellular proteins, tenascin-X has structural function as well. It regulates fibrillogenesis of fibrillar (types I, III and V) and fibril-associated types XII and XIV collagens (Lethias et al. 2006; Veit et al. 2006). This is assisted by its binding to decorin (Elefteriou et al. 2001) and tropoelastin (Egging et al. 2007). These associations would explain how complete absence of tenascin-X due to homozygous or compound heterogenous mutations in both *TNXB* alleles leads to cl-EDS (Matsumoto and Aoki 2020). Patients with cl-EDS present with velvety, hyperextensible skin, joint hypermobility and

easy bruising. The diagnosis of this form of EDS can be confirm by the absence of serum form of tenascin-X, a protein of M.W. ~140 kDa which is a cleavage product of the nature 450 kDa form of tenascin-X (Schalkwijk et al. 2001). The deficiency of tenascin-X would extend to the nervous system and would explain chronic pain experienced by many sufferers of cl-EDS in their musculoskeletal and/or gastrointestinal systems (Matsumoto and Aoki 2020). See also Chap. 9 in this volume for more discussion on EDS.

The composition of tenascin-X, more specifically the presence of EGF–like and FNIII-like repeats in its molecule, makes it an angiogenic factor (Demidova-Rice et al. 2011). Interactions with VEGF-B contribute to its angiogenicity (Ikuta et al. 2000). Tenascin-X ability to activate latent TGFβ and TGFβ/Smad signaling pathway promotes epithelial-mesenchymal transition, and may contribute to its function as a matricellular protein (Valcourt et al. 2015).

4.9.2 Tenascin-C

Tenascin-C was the first described tenascin. It is a large molecule of M_r ~300 kDa, assembled into a hexamer. As other tenascins, the molecule consists of an N-teminal domain, EGF-like repeats, several fibronectin type II domains and a C-teminal fibrinogen-like globular domain. The structure of several repeats of the same domain or module enables binding of numerous ligands (Okamoto and Imanaka-Yoshida 2012). Tenascin-C is expressed transiently in the mesenchyme around developing organs such as kidney, teeth and mammary glands. Its expression is associated with epithelial-mesenchymal transition, branching morphogenesis and vascular development (Imanaka-Yoshida et al. 2014; Akbareian et al. 2013). It is present in the periostium, ligaments, tendons, myo-tendinous junctions, smooth muscle and perichondrium both during embryonic development and in adult tissues. However, expression of tenascin-C in the adult tissue is generally low, only to be transiently elevated upon tissue injury (and likely associated with stem cell proliferation) and often down-regulated again after tissue repair is complete (Midwood et al. 2016). Although tenascin-C shares structural relationship to fibronectin, it differs in its adhesive function. Where fibronectin is adhesive in nature, tenascin-C is only weakly adhesive – if at all – for most cells, and it does in fact limit the fibronectin-mediated cell spreading when the two proteins interact in cell cultures (Chiquet-Ehrismann et al. 1988). Tenascin-C interferes with cell spreading by inhibiting binding of fibronectin to its co-receptor syndecan-4, and integrin α5β1 signaling to FAK and RhoA is also impaired whereby focal adhesions are diminished (Huang et al. 2001; Midwood and Schwarzbauer 2002; Chiquet-Ehrismann and Chiquet 2003; Jones and Jones 2000).

As mentioned above, the expression of tenascin-C is regulated by mechanical stress both during development and in adulthood, and its expression is predominantly present in tissues experiencing high tensile stress, such as ligaments, tendons and smooth muscle (Kreja et al. 2012). Mechanical loading of muscle induces tenascin-C mRNA and protein in endomysial fibroblasts of the affected holding muscle (Järvinen et al. 2003). Tenascin-C was found to be over-expressed in hypertensive rat arterial smooth muscle (Mackie et al. 1992) and in the periosteum of rat ulnae loaded in vivo, but tenascin-C expression was low in the osteotendinous interphase of immobilized rat legs (Järvinen et al. 2003). Interestingly, elevated levels of tenascin-C were found in the blood of patients with rheumatoid arthritis (Page et al. 2012), and in synovial fluid after injury to the human and canine knee (Chockalingam et al. 2013).

In relation to ECM tissue damage, tenascin-C has been demonstrated to play different roles that can mediate both inflammatory and fibrotic processes to enable effective tissue repair. For example, tenascin-C makes a prominent appearance in pathological heart conditions. Though barely expressed in the normal adult heart its level increases in the heart after myocardial infarction, during myocarditis, hypertensive heart disease, to name just a few examples (Okamoto and

Imanaka-Yoshida 2012). According to the current hypothesis tenascin-C is directly involved in ventricular remodeling through releasing cardiomyocytes from the adherence to the extracellular matrix and through upregulation of matrix metalloproteinases (Okamoto and Imanaka-Yoshida 2012; Imanaka-Yoshida 2012). A high level of expression of tenascin-C in cardiac tissues correlates with poor patient prognosis (Midwood et al. 2011) Interestingly, tenascin-C was found in calcified aortic valves together with matrix metalloproteinase-12 where they likely contribute to the fragmentation of elastic fibers (Perrotta et al. 2011). Tenascin-C is involved in development of atherosclerosis, and possibly of aortic dissection, though whether its effect stimulating or inhibiting is unclear (Matsumoto and Aoki 2020).

TGFβ and platelet-derived growth factor (PDGF) induce expression of tenascin-C (Midwood et al. 2016). Tenascin-C binding to PDGF receptor or endothelin receptors modulates its inhibition of fibronectin adhesive effect (Midwood et al. 2016).

Similar to tenascin-C, tenascin–W has been identified in a variety of developing tissues, and a large interest has been invested in these tenascins in relation to tumor development and growth, where they play important roles.

In summary tenascin proteins are found to be dysregulated in many pathological conditions like cancer, heart- and vessel disease, as well as in connective tissue diseases with manifestations in skin, tendon and muscle like e.g. special forms of Ehlers-Danlos syndrome (more discussed in Chap. 9) and Dupuytren disease (Berndt et al. 1994). Further, tenascins have been shown to be important in regeneration and recovery of musculo-tendinous tissue, in that they possess a de-adhesive effect whereby they potentially can contribute to a coordinated tissue reorganization and build-up (Mackey et al. 2011). It has been suggested that they "orchestrate" muscle build up after injury (Flück et al. 2008). Thus, it is likely that tenascins are important for ensuring mechanical properties of weight bearing ECM as well as ensuring an optimal recovery of ECM after mechanical injury.

4.10 Thrombospondins

Thrombospondins (TSPs) form the last matricellular group. There are five modular glycoproteins, each one of them encoded by a separate gene (Murphy-Ullrich and Iozzo 2012; Adams and Lawler 2004; Adams and Lawler 2011). Group A consists of TSP-1 and TSP-2, and TSPs 3–5 are in group B. Their binding to various components of the ECM, such as heparan sulfate proteoglycans, and to numerous cell membrane receptors enables TSPs to modulate cell functions in a variety of tissues (Murphy-Ullrich and Iozzo 2012). They are considered to be "adhesion-modulating" components of the ECM (Mosher and Adams 2012).

In particular, we will discuss TSP-1 and TSP-5 in more detail as their involvement in metabolism of the ECM is pertinent to issues discussed in this volume. The activation of latent TGFβ by TSP-1 plays an important role in wound healing, and also in pathogenesis of fibrotic processes in kidney and heart in diabetes (Lu et al. 2011; Belmadani et al. 2007). Increased expression of TSP-1 (accompanied by increased TGFβ activity) was observed in fibrotic skin disorders such as keloids (Chipev et al. 2000) and scleroderma (Mimura et al. 2005).

TSP-1 is released from platelet α-granules where it is stored so it can participate in tissue repair (Sweetwyne and Murphy-Ullrich 2012). It is a homotrimer of three 150 kDa subunits. Each unit is composed of N-terminal laminin G-like domain, and in the last 650 amino acids, of several EGF-like domains, 13 calcium-binding repeats and a globular L-type lectin-like domain. These regions in the last 650 amino acids are usually referred to as the C-terminal or "signature" region (Mosher and Adams 2012). With glycosylation the size of TSP-1 balloons to staggering M_r ~ 450 kDa (Rogers et al. 2012). Its expression in adult organism is minimal (except for storage pool in platelets) and is upregulated only as a result of injury (Agah et al. 2002) and/or chronic disease (Rogers et al. 2012; Hohenstein et al. 2008). TSP-1 binds to many cell membrane receptors, including CD47 (Rogers et al. 2012), integrins (Chandrasekaran et al. 1999), also

to heparan sulfate and low-density lipoprotein (LDL) (Chen et al. 1996). TSP-1 binds not only to latent TGFβ through thrombospondin repeats, but it also activates this growth factor (Murphy-Ullrich and Poczatek 2000). It is thought that TSP-1 facilitates presentation of TGFβ to the TGFβ receptor (Sweetwyne and Murphy-Ullrich 2012). TSP-1 was shown to upregulate type I collagen expression through its N- and C-terminal domains which may explain the sometimes opposing cellular responses stimulated by TSP-1 (Sweetwyne and Murphy-Ullrich 2012; Elzie and Murphy-Ullrich 2004). TGFβ activity induced by TSP-1 is a normal process during early tissue repair, however, if TSP-1 expression persists in later stages of wound healing fibrosis may prevail (Sweetwyne and Murphy-Ullrich 2012). In addition, TSP-1 regulates activity of several other growth factors, most notably, VEGF, EGF and PDGF. In particular, TSP-1 plays an important role in transactivation of EGF receptors in epithelial and endothelial cells, and thus can disrupt endothelial barrier (Goldblum et al. 1999). TSP-1 is an endogenous inhibitor of angiogenesis conferred by type I repeat domain found only in TSP-1 and TSP-2 (which is also anti-angiogenic – see below) (Bornstein 2009). Though TSP-1 has hypertensive effect on cardiovascular system and is known to play a role in pathogenesis of atherosclerosis and peripheral vascular disease (Robert et al. 2012), the activity is mediated through control of nitric oxide synthesis (and thus increasing arterial resistance), rather than through an impact on or binding to a structural component of the blood vessel wall (Robert et al. 2012). TSP-2 is involved in collagen fibril assembly and is capable of inhibition of angiogenesis and protease activity, but unlike TSP-1 it does not activate TGFβ (Okamoto and Imanaka-Yoshida 2012).

There is at least one syndrome where a mutation in a gene encoding an enzyme responsible for proper TSP-1 function leads to structural changes which form the basis of the so called Peters Plus syndrome. This syndrome is an autosomal recessive disorder phenotypically characterized by eye defects, short stature, developmental delay and cleft lip due to a mutation of a gene encoding a β1,3-glucosyltransferase which adds a glucose to *O*-linked fucose (and producing a rare glucose-β 1,3-fucose disaccharide) and which is responsible for glycosylation of thrombospondin type 1 repeats (Hess et al. 2008; Heinonen and Maki 2009). Beside TSP-1, properdin, F-spondin, some members of a-disintegrin-and-metalloproteinase-with--thrombospondin-like-motifs family (ADAMTS-13 and ADAMTSL-1) carry the same disaccharide (Hess et al. 2008; Heinonen and Maki 2009). Heart defects, such as hypoplastic left heart syndrome (Shimizu et al. 2010), patent ductus arteriosus, and atrial septal defect are present is some variants (Hanna et al. 2010). Though the eye involvement is usually characterized by anterior eye chamber defects leading to glaucoma (Hess et al. 2008; Hanna et al. 2010), corneal pathology has been recognized in some cases as well, and then it consists of intracorneal fibrosis (Eberwein et al. 2010) and keratolenticular adhesions (Hess et al. 2008; Hanna et al. 2010).

4.10.1 Cartilage Oligomeric Matrix Protein (COMP) or Thrombospondin-5

COMP or thrombospondin-5 belongs to the family of five extracellular calcium- and glycosaminoglycan-binding proteins that play a role predominantly during development, angiogenesis and wound healing. It consists of 5 identical subunits that are linked together at their N-terminal pentamerization end to result in an almost "star-like" structure and has M_r ~ 524 kDa (Oldberg et al. 1992). COMP shares a conserved multidomain architecture in its C-terminal region with TSP-1 (Mosher and Adams 2012). It also contains eight calmodulin units, four EGF-like repeats, and a globular C-terminal domain (Oldberg et al. 1992; Rock et al. 2010), and the 5 "arms" have on their C-terminal end high affinity binding sites for type I, II and IX collagen (Holden et al. 2001; Rosenberg et al. 1998), and for fibronectin (Di Cesare et al. 1994). Thrombospondin-5/COMP is present primarily in cartilage, and has been suggested to be impor-

tant in relation to cartilage turnover and pathogenesis of osteoarthritis (Heinegård 2009). It is also expressed in other connective tissues like tendon, especially if the tissue has undergone strenuous mechanical loading, but also in cardiac cells and activated platelets (Smith et al. 1997; Södersten et al. 2013; Posey et al. 2018). The exact role of COMP in the fibril formation and assembly in the ECM is becoming better understood, and it is thought that COMP facilitates the joining of collagen molecules during formation of fibril structures (Södersten et al. 2013; Halasz et al. 2007). It has been shown that high levels of COMP are present in fibrotic scars and systemic sclerosis of the skin (Smith et al. 1997; Hesselstrand et al. 2008). It has been suggested that a very high concentration of COMP can in fact inhibit collagen fibril formation (115).

COMP is expressed in normal tendon where its mRNA is confined to tenocytes and the protein itself is located in the normally aligned fiber structures together with type I collagen. Virtually no COMP (and no type I collagen), but only type III collagen was found in the normal endotenon (Södersten et al. 2013). Physical activity leads to increased expression of COMP, at least in the equine tendon (Smith et al. 1997), as do pathological processes. High levels of COMP were identified in the synovial fluid obtained from the sheaths of the equine superficial digital flexor tendons diagnosed with synovitis (Smith et al. 2011). Likewise, injury to superficial digital flexor tendons leads to increased expression of COMP, and type I and III collagens in the endotenon and high levels of all three molecules can be visualized in the injured and granulation tissue (Södersten et al. 2013). Rock et al. have shown that COMP promotes attachment of ligament cells and chondrocytes to components of the ECM using two mechanisms which involves CD47 and integrins. Such data indicate an important role for COMP in formation of structural scaffolding, an essential step in cell attachment to the ECM and in matrix-cell signaling (Rock et al. 2010).

In addition, new data indicate that COMP, and its degradation by ADAMTS-7, plays an important role in vascular remodeling (Wang et al. 2010). COMP has been found in atherosclerotic plaques and lesions forming in arteries undergoing re-stenosis (Riessen et al. 2001), together with SLRPs, such as decorin (Riessen et al. 1994). It has been suggested that COMP promotes differentiation of vascular smooth muscle cells and that binding and degradation of COMP by ADAMTS-7 in injured arteries enables migration of vascular smooth muscle cells and neointima formation. The hope is that ADAMTS-7 may be a suitable therapeutic agent in combating restenosis of atherosclerotic blood vessels after angioplasties and related procedures (Wang et al. 2010). More recent study from the same laboratory shows that COMP inhibits vascular smooth muscle calcification by interacting with bone morphogenetic protein 2 (BMP2) and that the COMP in atherosclerotic arteries story is a little bit more complicated than initially thought (Du et al. 2011).

Though COMP has been involved in metabolism of multiple tissues, including cartilage, tendons and blood vessels the only mutations in the COMP gene known to be responsible for pathological conditions identified so far, are those affecting the skeleton, such as pseudoachondroplasia and multiple epiphyseal dysplasia (Rock et al. 2010; Posey and Hecht 2008). COMP is a good biomarker of cartilage turnover and was found to be elevated in osteoarthritis and rheumatoid arthritis (Posey et al. 2018).

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