Structural and functional failure of fibrillin-1 in human diseases (Review)

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Abstract. Fibrillins (FBNs) are key relay molecules that form the backbone of microfibrils in elastic and non-elastic tissues. Interacting with other components of the extracellular matrix (ECM), these ubiquitous glycoproteins exert pivotal roles in tissue development, homeostasis and repair. In addition to mechanical support, FBN networks also exhibit regulatory activities on growth factor signalling, ECM formation, cell behaviour and the immune response. Consequently, mutations affecting the structure, assembly and stability of FBN microfibrils have been associated with impaired biomechanical tissue properties, altered cell-matrix interactions, uncontrolled growth factor or cytokine activation, and the development of fibrillinopathies and associated severe complications in multiple organs. Beyond a panoramic overview of structural cues of the FBN network, the present review will also describe the pathological implications of FBN disorders in the development of inflammatory and fibrotic conditions.

Contents

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1. Introduction

Fibrillin (FBN)-1 is a calcium-binding protein that assembles to form 10-12 nm microfibrils in the extracellular matrix (ECM) of elastic and non-elastic tissues. The human gene FBN-1 spans >230 kb (1) on chromosome 15q15-21.1 (2) and is highly fragmented into 65 exons. The primary protein structure reveals multi-domains (3), which primarily consist of epidermal growth factor (EGF)-like and certain other modules (4). Out of a total of 47 EGF domains (5), 43 modules contain the calcium binding (cbEGF) consensus sequence D/N-XD/N-E/Q-Xm-D/N-Xn-Y/F (6), which provides structural stabilization (7), a characteristic rigid rod-like shape (8-10) and protection against proteolysis (11), and allows the control of self- or FBN-2-interaction (12,13) and interactions with ECM components, including fibulin-2, heparin/heparan sulphate and microfibril-associated glycoprotein (MAGP)-1 (14-17). Disulphide bonds formed among the six cysteine residues in EGF and cbEGF, in a C1-C3, C2-C4 and C5-C6 pattern (9), contribute to further stabilize FBN-1. EGF-like domains are interspersed by seven transforming growth factor (TGF)-β binding protein (TB)-like modules and structurally related latent TGF-β-binding proteins (LTBPs) (18). Characterized by eight cysteine residues that form four disulphide bonds (C1-C3, C2-C6, C4-C7 and C5-C8 arrangement), TB domains occur seven times in FBN-1. Among them, the fourth TB module is of particular interest due to the presence of the cell binding site RGD (arginine-glycine-aspartic acid), which mediates interactions with integrins (19). Additionally, as with other FBNs, 'hybrid domains' are repeated twice in FBN-1 and are stabilized by four intradomain disulphide bonds in a C1-C3, C2-C5, C4-C6 and C7-C8 formation (20). The unique N- and C-terminal domains of FBN-1 include four and two cysteine residues, respectively, and contain the basic consensus sequence for processing by furin-type enzymes (21-23). A distinguishing feature of FBN-1 is the presence of a proline-rich domain close

to its N-terminus (4,24). A summary of the chromosomal location, domain organisation and primary functions of FBN-1 is presented in Fig. 1.

2. FBN network assembly and elastogenesis

FBN-1 is synthesized as an ~350 kDa precursor molecule, profibrillin-1, which requires proteolytic processing by furin proteases into its biologically active form (~320 kDa) prior to incorporation into microfibrils (22,25). Accounting for all microfibril structural features, FBN alignment models predict the initial interactions between the N- and C-terminal sequences, which cause a head-to-tail alignment and an approximate one-third stagger that is stable as a 56 nm folded form (26-28). FBN bundles are stabilized by transglutaminase-derived cross-links (29). Microfibril assembly has been reported to be dependent and fine-tuned by a variety of FBN-associated proteins. When visualized by rotary electron microscopy (30), the extracted microfibrils exhibit a beaded string morphology with dark areas, which are termed 'bead' regions and appear in an average periodicity of 56 nm (31). Highlighting their important structural role, FBN microfibrils are essential for the process of elastogenesis, acting as a scaffold for the soluble precursor of elastin (tropoelastin) (32). Tropoelastin molecules are secreted and deposited extracellularly onto a preformed, organized FBN microfibril network, which gives rise to mature, elastic fibres that are subsequently processed by the lysyl oxidase enzyme for the formation of desmosine cross-links. The importance of FBN in the formation of elastic fibres is highlighted by the inability of FBN-1 knockout mice to form functioning elastic fibres, in addition to a disorganization of elastic fibres (33) and a reduction of tissue flexibility and extensibility, primarily in the arteries, lungs, skin and other dynamic connective tissues (17). Unlike cbEGF-cbEGF, EGF1-EGF2 and TB6-cbEGF32 are flexible domain interfaces (34,35).

3. Non-elastic components of the FBN network

FBN microfibrils interact with a large variety of ligands. The binding with ECM components involves the C-terminal regions of FBNs (36) and is essential for regulating protein assembly and functionality. Depending on the cell type, the FBN network (36-39) and MAGP (40-42) contribute to microfibril biogenesis. Additionally, fibulin-2 appears to colocalise with microfibrils in certain tissues at the interface between microfibrils and elastin (14). Fibulin-2 specifically binds to the N-terminal region of FBN-1, while it also interacts with fibronectin and exhibits a connecting role with other ECM molecules. As with fibulin-2, fibulin-1 localizes with elastin providing connective bridges to other ECM components and to cells through laminin, fibronectin, nidogen or fibrinogen (43). Contributing to elastic fibre assembly, fibulin-5 interacts with FBN and tropoelastin (44). According to experimental data, fibulin-5 null mice exhibit structural abnormalities due to disrupted elastogenesis (45,46). As they may be absent in tissues exerting strong tensional forces, such as tendons, fibulins are associated with elastic fibre assembly rather than the mechanical properties of microfibrils. Furthermore, studies have demonstrated that A disintegrin-like and metalloprotease (reprolysin-type) with thrombospondin type-1 motif (ADAMTS) and ADAMTS-like (ADAMTSL) proteins, including ADAMTSL4 (47), ADAMTSL6 (48) and ADAMTSL10 (49), bind to FBN and modulate microfibril assembly (49,50). If mutations occur in these genes, pathologies similar to fibrillinopathies are observed. Direct interaction of FBN with various proteoglycans are reported to be essential for network assembly and the maintenance of basement membranes (51,52). The proteoglycans decorin and biglycan are able to bind to tropoelastin, while only decorin directly interacts with FBN-1 (41,53). However, biglycan forms a ternary complex with tropoelastin and MAGP-1, indicating a potential role during elastogenesis (53). Notably, alterations in decorin expression have been observed in neonatal Marfan syndrome, which is connective tissue disorder (54,55). The heparan sulphate proteoglycan (HSPG) perlecan, also termed HSPG-2, colocalises with FBN and elastin (56), and binds to the central region of FBN-1 (57). Additionally, these HSPGs bind to cell surface molecules and growth factors (58), such as basic fibroblast growth factor, indicating an indirect involvement of FBN in the regulation of cell functions and stem cell niches (59,60). The chondroitin sulphate proteoglycan versican controls the genesis of elastic fibres (61,62) and acts as a key factor in inflammation by interacting with the adhesion molecules of activated leukocytes, including L-selectin, CD44 and chemokines, to recruit inflammatory cells (63,64). FBN-associated collagen with interrupted triple helices type XVI is associated with microfibrils in various tissues, including the upper papillary dermis (65) and dorsal root ganglia (66), indicating a potential association between FBN assembly and neuronal regeneration. LTBPs interact with FBN at the N-terminal region (16,67) while they are also anchored to other ECM components, such as fibronectin (68-70). These interactions are important in regulating the availability and the activation of TGF-β deposited in the ECM. LTBP 1, 3 and 4 covalently bind to the small latent TGF-β complex with their third TB domain and control the local TGF-β bioavailability (71). In addition to TGF-β via LTBPs, a number of bone morphogenetic proteins (BMPs), and growth and differentiation factors, directly bind to FBN at the N-terminal region (72-75). Furthermore, through the RGD binding site in the TB4 domain, FBN-1 interacts with different integrins that are responsible for cell-matrix communication.

4. FBN matrix: A dynamic deposit of growth factors

The FBN network is an important constituent of connective tissues that interacts with the cellular compartment. It controls the bioavailability and activity of the TGF-β superfamily, which activates specific cellular signalling pathways for preserving tissue homeostasis. The loss of cell matrix interactions is a factor implicated in the pathological manifestations observed in microfibrillinopathies (Fig. 2). By indirect interaction with FBN through LTBPs, as with TGF-β, or direct interaction, for example BMPs (76), growth factors regulate the cellular behaviour and control cell survival, differentiation and response to injury (77). TGF-β isoforms (TGF-β1, 2 and 3) are synthesized as precursor proteins that comprise a growth factor domain at the C-terminal end and a latency-associated peptide (LAP) at

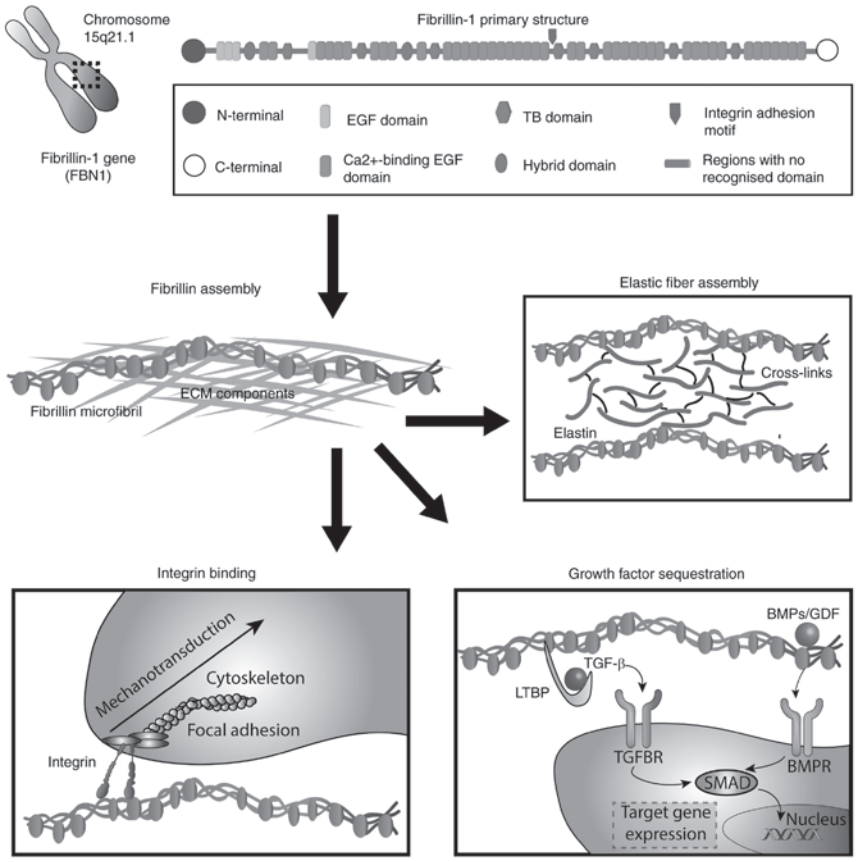

Figure 1. Schematic figure representing the chromosomal location, domain organization and primary functions of human fibrillin. EGF domain, epidermal growth factor-like domain; TGF, transforming growth factor; TB domain, TGF-β binding protein-like domain; ECM, extracellular matrix; LTBP, latent TGF-β-binding protein; BMPs, bone morphogenetic proteins; GDF, growth and differentiation factors; TGFBR, TGF-β receptor; BMPR, BMP receptor.

the N-terminus (78). Two precursor proteins homodimerize and, following cleavage by furin-like endoproteases, form a complex that is termed the small latent complex (SLC) (79), in which LAP is non-covalently bound to the active TGF-β dimer. The SLC binds covalently to the penultimate TB domain in LTBPs, which together form a complex termed the large latent complex (LLC). The C-terminal region of LTBP-1 and -4 exhibit non-covalent interactions with the N-terminus of FBN-1 within the core of beaded microfibrils, while the N-terminal regions bind to fibronectin. LTBP-3 localizes to microfibrils using a different mechanism (80). The LLC is biologically inactive and TGF-βs are accessible to its receptors following proteolytic degradation or conformational changes (81,82) induced by integrin binding or cell-mediated force transmission (79,83,84) The enzymatic activation followed by TGF-β release is reported to be mediated by matrix metalloprotease (MMP)-2 and -9 (85), the serine protease plasmin (85-88), thrombospondin-1 (89) and reactive oxygen species (90). Following cleavage and activation, TGF-β binds to its serine and threonine kinase receptors (TβRI and TβRII) on cell membranes, forming a receptor heterocomplex (77,91) that, through Smad signalling activation (92,93), promotes the expression of target genes (94,95), including collagen type 1 α1 chain, collagen type 3 α1 chain and TIMP metallopeptidase inhibitor 1, in addition to another 60 ECM-associated genes (96). The direct binding of FBN-1 to different BMPs, including BMP-2, -4, -5, -7 and -10, has been previously reported (73,75,97). In addition, there is increasing evidence that other growth factors are indirectly controlled through targeting to other FBN binding partners within the ECM, such as perlecan (57).

5. Cellular sensing of FBN signalling

As reported by Zeyer and Reinhardt (80) in 2015, FBN-containing microfibrils, which contain one RGD binding site within the fourth TB domain (98), represent key signal relay molecules for cell attachment, gene expression, spreading, migration and proliferation. *In vitro* studies on cells cultured on FBN-1 RGD-containing peptides have established the impact of this interaction on cell adhesion and gene expression (99). Cellular interactions have been reported to be mediated via integrins ($\alpha_5\beta_1$, $\alpha_5\beta_6$, $\alpha_v\beta_3$, $\alpha_v\beta_6$ and $\alpha_8\beta_1$) (19,99-103) and, potentially, by other cellular sensors, including angiotensin II type 1 receptor (AT1) and proteoglycans, such as syndecans (35,104-106). Mutations in regions close to the RGD binding site in FBN-1 lead to a condition that is termed stiff skin syndrome (SSS), a pathological condition that is characterized by excessive skin fibrosis and microfibril accumulation (107). *In vitro* and *in vivo* studies employing mice harbouring a mutation in this region reported disturbed cell contact with microfibrils and altered cell spreading. It is reported that AT1 is activated by mechanical stress in cardiac hypertrophy (108). Mice homozygous for a hypomorphic *FBN-1* allele (*FBN-1*$^{mgR/mgR}$) exhibited dilated cardiomyopathy (109). A heparin sulphate binding region upstream of the RGD motif

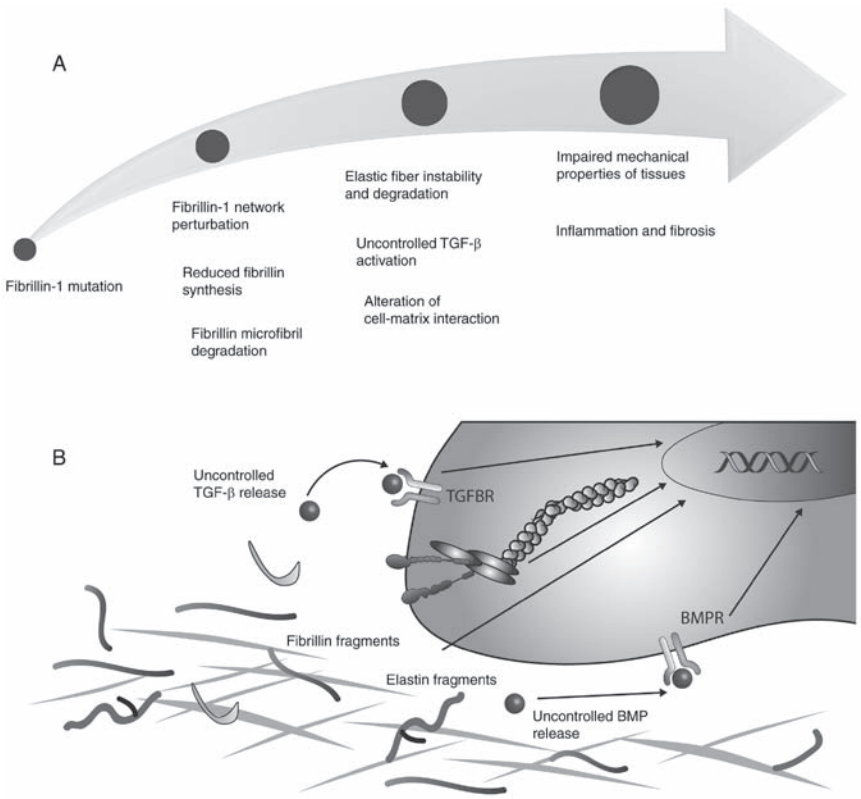

Figure 2. Schematic figure representing the structural and signalling effects of fibrillin mutations and the process of fibrillin network fragmentation. (A) Structural and signalling effects of fibrillin mutations. (B) Process of fibrillin network fragmentation caused by fibrillin mutations. TGF, transforming growth factor; TGFBR, TGF-β receptor; BMP, bone morphogenetic protein; BMPR, BMP receptor.

has been reported to be synergistically involved in integrin binding, while another downstream heparan sulphate binding site stimulates the formation of focal adhesion (103) through αvβ3-integrin (110). It has been demonstrated that, when heparin sulphate signalling is inhibited, the formation of the FBN network is disrupted (104).

6. FBN diseases in humans

Due to the number of functions that are controlled to a certain degree by FBN, it is clear that mutations in FBN genes lead to a number of diseases that affect multiple organs, which are collectively termed fibrillinopathies. Mutations in the FBN-1 gene have been demonstrated to cause Marfan syndrome, an autosomal dominant disorder of the connective tissue that is characterized by pleiotropic manifestations in ocular, skeletal and cardiovascular systems. Since the identification of the first mutation in 1991 (111), at present, >1,800 genetic abnormalities have been identified throughout the entire length of FBN-1 (112). Unfortunately, due to phenotypic variability and disease severity, a phenotype-genotype correlation remains to be established (113,114). Mutations in the central region of the FBN-1 gene, comprising exons 24-32, are commonly associated with severe myocardial dysfunctions, neonatal Marfan syndrome and mortality within the first two years of postnatal life (115-117). It is reported that approximately two-thirds of missense mutations involve cysteine residues and lead to ocular complications, while premature terminations are associated with severe skeletal and skin anomalies (115). A growing body of evidence indicates that not all mutations in FBN-1 result in Marfan syndrome; however, those that are not are associated with Marfan-like disorders (118), including MASS phenotype (119), familial thoracic aortic aneurysm (120,121), Shprintzen-Goldberg syndrome (122) and ectopia lentis (123). It has also been established that mutations in FBN-1 may lead to acromelic dysplasias, such as Weill-Marchesani syndrome (WMS), geleophysic dysplasia, acromicric dysplasia and Myhre syndrome (74,124,125). The patients affected by these syndromes generally exhibit short statue, short hands and feet, stiff joints and a hypermuscular build, which is unlike patients with Marfan syndrome, who present with a tall stature, arachnodactyly, hypermobile joints and a thin hypomuscular structure. By contrast to Marfan syndrome, the mutations in FBN-1 that cause acromelic dysplasias, such as WMS, are located in a hot spot within the FBN-1 gene (126) and are in-frame deletions of 24 nucleotides in exon 41 and 42, which encode the fifth TB (124,126,127). An in-frame deletion of exons 9-11, encoding the first TB domain, the proline rich region and the fourth EGF-like domain, have been identified in WMS (74). Notably, while FBN-1 mutations account for the dominant form of WMS, the recessive form is reported to be caused by mutations in ADAMTS10 (128). According to experimental evidence from mouse models expressing RGD sequence mutations and the ability of integrin-modulating therapy to prevent fibrosis and autoimmunity (129), the primary cause of SSS may be the loss of integrin binding sites. A mutation in the TB4 domain has also been reported in patients affected by this syndrome (107). A summary of the structural and signalling effects of mutations in FBN-1 is presented in Fig. 2.

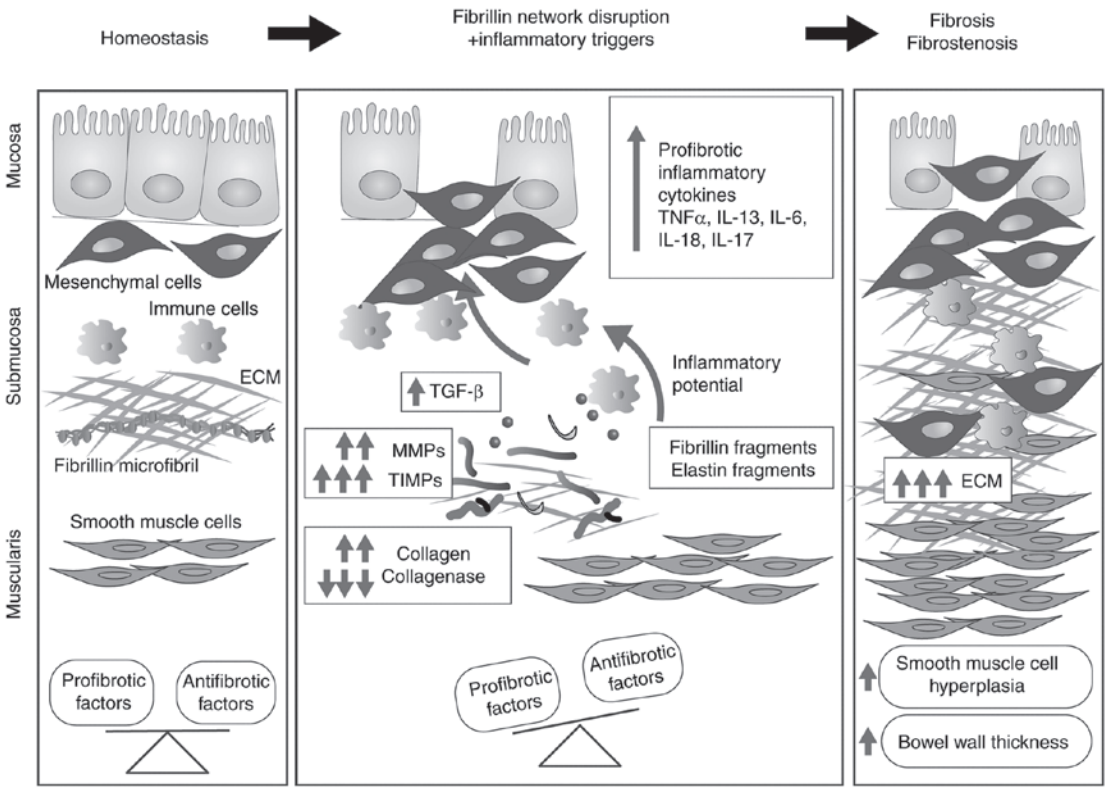

Figure 3. Schematic figure representing the development of gut fibrosis. TNF, tumour necrosis factor; IL, interleukin; ECM, extracellular matrix; TGF, transforming growth factor; MMPs, matrix metalloproteases; TIMPs, TIMP metallopeptidase inhibitors.

7. *In vitro* and *in vivo* studies of FBN assembly

Pathophysiological mechanisms accounting for the clinical manifestation of Marfan syndrome and similar disorders are associated with an altered FBN network. Early immunofluorescent studies using anti-FBN antibodies revealed qualitative and quantitative abnormalities of the dermal microfibrils, with a fragmented appearance in tissues extracted from patients with Marfan syndrome. Isolated dermal fibroblasts exhibited a reduced expression of FBN fibres and an abnormal morphology in immunofluorescent analyses (130,131). Differences in microfibril morphology have also been observed in neonatal Marfan syndrome fibroblast cultures (132). In contrast to the fragmented FBN networks observed in Marfan syndrome (130,133), the FBN network in WMS is abnormal for a different reason, as large FBN aggregate accumulations (74) have been reported in the skin of patients with SSS (107). Several *in vitro* and *in vivo* studies of FBN-1 disorders have been performed in the last two decades. The dominant negative model is supported by an *in vitro* study in which the wild-type protein function is disrupted by the mutant FBN, indicating that one FBN-1 mutant allele is sufficient to diminish microfibril assembly (131). Furthermore, data from this model are consistent with published data that reported that low levels of mutant FBN-1 expression in patients with Marfan syndrome is associated with a less severe phenotype (134). On the other hand, haplosufficient models have demonstrated that selected mutations, such as C1039G, lead to a disorganization of the microfibril network, while the C1663R FBN-1 mutation participates in productive microfibril assembly (135). Based on this body of evidence, it is clear that FBN-1 disorders are caused by mechanisms that are dependent on the position and type of mutation. *In vivo* studies of mutant FBN have indicated that abnormalities within the first hybrid domain do not affect microfibril stability (133), while mutations in cbEGF-like domains perturb microfibril assembly (136). Certain FBN-1 mutations also lead to a gene product that, although it may be assembled into microfibrils with a normal appearance, the mutation destabilizes the structure of FBN-1 and renders it more susceptible to proteolysis, leading to a gradual degradation (137,138). As reported by several studies, the regulation of MMPs is implicated in the pathogenesis of Marfan syndrome and other fibrillinopathies (139,140). In particular, MMP-1, -2, -3 and -9 appear to exert a pivotal role in FBN fragmentation, as demonstrated by the increased concentration of FBN fragments in the aortic specimens of patients with Marfan syndrome (140-142). Studies concerning connective tissue disorders caused by FBN-1 mutations have also revealed alterations in the targeting and activation of growth factors. In addition, an association between FBN-1 mutations and the altered release of TGF-β has been associated with the development of fibrillinopathies (143). In support of this hypothesis, the administration of TGF-β antagonists led to anti-apoptotic effects in the lungs of FBN-1-deficient mice (144). Additionally, neutralizing TGF-β antibodies successfully prevented the development of aortic aneurysm by normalizing the levels of TGF-β in Marfan syndrome mouse models (145). Furthermore, TGF-β antagonists have been reported to reduce the levels of circulating TGF-β in patients with Marfan syndrome (146). Notably, mutations in LTBPs or TGF-β receptors, as observed in Loyes-Dietz syndrome, may lead to the uncontrolled release of TGF-β. A perturbation of TGF-β signalling is also observed

in other fibrillinopathies, including SSS (107) and acromicric or geleophysic dysplasia (124).

8. Involvement of FBN-1 in inflammatory disorders

Scleroderma is a heterogeneous connective tissue disease that is characterized by excessive cutaneous and visceral fibrosis, Raynaud's phenomenon, vascular lesions and gastrointestinal manifestations (147). A widely used mouse model of systemic sclerosis is the tight skin (Tsk) mouse, which exhibits an in-frame tandem duplication of FBN-1 (148). While homozygotes suffer embryonic lethality at day 7-8 of gestation, heterozygotes (Tsk/+) have a normal life span but manifest myocardial, skeletal, and pulmonary abnormalities. Furthermore, heterozygotes also present with abnormal/altered fibrotic, inflammatory and autoimmune function. Comparable levels of normal and mutant FBN-1 transcripts in Tsk/+ tissues, and the presence of abundant tissue microfibrils, indicates that the mutant FBN-1 is regularly synthesized and assembled (148). Mutant FBN copolymerizes with wild-type FBN-1, which leads to an unstable structure (149) that is more sensitive to proteolysis (150). Briefly, Tsk/+ mice synthesize two types of microfibrils that present with a normal morphology and a well-organized periodicity, or diffuse interbeads, a longer periodicity and a tendency to aggregate (151). The instability of Tsk microfibrils leads to a disorganization and fragmentation of elastic fibres, subsequently leading to reduced ECM integrity (152,153) and increased cellular processing, followed by an autoimmune response and the development of autoantibodies (154). The autoimmune phenotype, however, is not required for the development of dermal thickening observed in Tsk/+ mice, and the Tsk phenotype appears to be independent of the immune system, as this phenotype has also been reported in mice lacking mature T and B cells (155,156). A potential mechanism involved in the promotion of the fibrotic phenotype may be driven by altered TGF-β signalling (157).

9. Gut-FBN axis

Inflammatory bowel disease (IBD) comprises a group of gut immunopathological conditions that are a result of genetic, environmental and cellular cues (158). ECM components have important immunoregulatory roles, and the composition and ultrastructure of the ECM are involved in intestinal immune responses, pathological signalling, and chronic inflammation (159). Uncontrolled alterations in ECM composition are reported in IBD and involve collagen I (160), collagen III (161,162), collagen V (163), collagen XVI (164), laminin (165,166), hyaluronan (167) and, recently, FBN-1 (164). FBN and elastic fibre networks have important structural and biomechanical roles within the intestinal tract as they are essential for the peristaltic movement of the gastrointestinal tract. Notably, in up to 90% of patients with SSS (168), FBN network perturbations are reported to lead to excessive fibrosis, inflammation and vascular dysfunction (169-175). Reinforcing the hypothesis that the FBN network is involved in intestinal homeostasis, a previous study reported the downregulation of FBN in the lamina propria of patients with IBD compared with healthy donors (164). The development of gut fibrosis (176) involves multiple cell types and a large number of soluble factors (Fig. 3). Among soluble factors, TGF-β1, which is generally considered to be the key mediator of fibrosis (177), is overexpressed in IBD (178), while under physiological conditions TGF-β1 regulates the immune homeostasis by preventing abnormal proinflammatory responses, as demonstrated by the development of severe and lethal systematic inflammation in TGF-β1 knockout mice (179) or animals expressing T cells that do not respond to TGF-β1 (180). As observed in other organs, FBN and elastin fragments deriving from unstable networks lead to the upregulated expression of MMPs, including MMP-1, -2, -3, -7, -9, -10, -12 and -13 (181-183), which results in disturbed ECM turnover and subsequent fibrosis (184,185).

10. Conclusions and perspectives

FBN-1 is an important ECM component that integrates the biological network of structural and instructive information for the modulation of cell-cell and cell-matrix interactions. Acting as a key relay molecule for the transmission of extracellular information into cellular signalling and function, FBN-1 contributes to the accumulation of latent forms of growth factors, such as TGF-β and BMPs, and regulates their bioavailability and activity. Regulating the expression of MMPs, fragmented microfibrils are associated with the development of multiorgan inflammation and fibrosis. At present, the characterization of FBN-1 dysfunction has improved the characterization of the pathological pattern of connective tissue diseases and the identification of novel therapeutic biological approaches for the treatment of inflammation-associated states.

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