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Marfan syndrome; a connective tissue disease at the crossroads of mechanotransduction, TGFβ signaling and cell stemness

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Abstract

Mutations in fibrillin-1 cause Marfan syndrome (MFS), the most common heritable disorder of connective tissue. Fibrillin-1 assemblies (microfibrils and elastic fibers) represent a unique dual-function component of the architectural matrix. The first role is structural for they endow tissues with tensile strength and elasticity, transmit forces across them and demarcate functionally discrete areas within them. The second role is instructive in that these macroaggregates modulate a large variety of sub-cellular processes by interacting with mechanosensors, and integrin and syndecan receptors, and by modulating the bioavailability of local TGFβ signals. The multifunctional, tissue-specific nature of fibrillin-1 assemblies is reflected in the variety of clinical manifestations and disease mechanisms associated with the MFS phenotype. Characterization of mice with ubiquitous or cell type-restricted fibrillin-1 deficiency has unraveled some pathophysiological mechanisms associated with the MFS phenotype, such as altered mechanotransduction in the heart, dysregulated TGFβ signaling in the ascending aorta and perturbed stem cell fate in the bone marrow. In each case, potential druggable targets have also be identified. However, the finding that distinct disease mechanisms underlie different organ abnormalities strongly argues for developing multi-drug strategies to mitigate or even prevent both life-threatening and morbid manifestations in pediatric and adult MFS patients.

Keywords

Cardiomyopathy; Fibrillin; Marfan syndrome; Mechanotransduction; Osteopenia; Stem cell niche; TGFβ; Thoracic aortic aneurysm

1. Introduction

Elastic assemblies (microfibrils and elastic fibers) are heterogeneous extracellular macroaggregates that, together with collagens, constitute the architectural scaffold of connective tissues [1]. Elastic assemblies are widely distributed in virtually every organ system where they support critical physiological functions, such as breathing and maintaining cardiovascular tone. Elastic fibers consist of insoluble elastin complexed with

non-collagenous microfibrils 10–12 nm in diameter, which can also exist as individual structures in both pericellular and interstitial matrices of elastic and non-elastic tissues. Microfibrils are predominantly made of fibrillin molecules associated with other extracellular matrix (ECM) proteins that modify microfibril biogenesis and function. Human mutations in different components of elastic assemblies give rise to clinically distinct syndromes [2]. This review focuses on recent advances in our understanding of how mutations in fibrillin-1 translate into organ-specific manifestations in Marfan syndrome (MFS), the most common among heritable disorders of elastic assemblies – in point of fact, the most common of all heritable disorders of connective tissue [3]. While other diseases of elastic assemblies are discussed in this same issue of Matrix Biology, the reader is referred to several excellent reviews for additional details about fibrillin biology and MFS pathophysiology [4–9].

2. MFS; clinical features

MFS is an autosomal-dominant inherited disease with an incidence of approximately 1 in 5,000 live births and cardinal manifestations in the cardiovascular, skeletal and ocular systems [3]. Additional abnormalities of variable penetrance can involve the lung, integument and skeletal muscle. In broad terms, the disease can have either an often-fatal cardiovascular presentation during neonatal life or a progressively severe cardiovascular morbidity during adolescence and adulthood. In spite of significant progress in characterizing key genetic and molecular aspects of the disease, MFS diagnosis remains strictly clinical and according to the criteria codified in the recently revised Ghent nosology [10].

2.1 Cardiovascular system

Major cardiovascular manifestations of MFS include thoracic aortic aneurysm (TAA), mitral valve prolapse (MVP) and cardiac dysfunction [4]. Progressive dilatation of the proximal ascending aorta is associated with alterations in smooth muscle cell (SMC) phenotype, localized inflammatory infiltrates and maladaptive matrix remodeling that, together, predispose the vessel wall to dissection and rupture [4]. Major histopathological findings include elastic lamellae fragmentation, disorganized aortic tissue architecture with excessive collagen and mucopolysaccharide accumulation, and significantly fewer SMCs than normal. Prevention of untimely death from TAA complications currently relies on early detection by routine imaging, chronic administration of anti-hypertensive drugs and prophylactic repair by surgical procedures [4].

MVP associated with atrioventricular and semilunar valve elongation and myxomatous thickening is a frequent finding in MFS [4]. In contrast to adult patients, MVP in MFS neonates can often cause severe regurgitation and cardiac dysfunction leading to congestive heart failure. Although MVP can be surgically treated in adult patients, these individuals are at a greater risk of developing an acute TAA with dissection secondary to the rapid increase in cardiac output. Left ventricle (LV) dysfunction, including both systolic and diastolic function, has traditionally been considered a secondary phenomenon due to valvular insufficiency causing LV volume overload [4]. Increased arterial stiffness is also believed to

contribute to cardiomyopathy by altering hemodynamic load on the LV. However, occasional reports of MFS patients with cardiomyopathy out of proportion to valvular problems have suggested a primary defect in cardiac muscle function [4, 6].

2.2 Skeleton

The most striking and immediately evident abnormality in MFS patients is a dysregulated linear bone growth causing serious malformations of limbs, anterior chest wall and spine, which are often associated with severe chronic pain [4]. Substantial chest deformities, particularly pectus excavatum, can be problematic during surgical interventions to restore cardiovascular function. Joint laxity is another hallmark of the disease that can cause dislocation of the hip with severe pain and stiffness. Reduced bone mass (osteopenia) is a controversial finding in MFS, especially in pediatric patients, due to the inherent difficulty of assessing bone mineral density (BMD) in affected vs. healthy individuals. As a result, the contribution of osteopenia to increased long-term risk for fractures remains uncertain [4].

2.3 Eye and other organ systems

Displacement of the lens (ectopia lentis) usually occurs before the age of 20 and can cause nearsightedness and blurred vision [4]. MFS patients are also at a higher risk of developing early cataracts, retinal detachment and glaucoma. Additional abnormalities that can be associated with MFS include decreased skeletal muscle mass and tone, spontaneous pneumothorax, recurrent incisional hernia and stretch marks in areas of the skin subjected to flexural stress [4].

3. MFS; molecular pathophysiology

Fibrillin-1 assemblies represent a unique dual-function component of the architectural matrix [1]. The first role is “structural” in that they endow tissues with tensile strength and elasticity, transmit mechanical forces across them and demarcate functionally discrete areas of the matrix. The second role of fibrillin-1 assemblies is “instructive” for they regulate the activities of resident cells by interacting with mechanosensors\ and integrin and syndecan receptors, and by modulating endogenous (local) TGFβ activity. The latter function is exerted via fibrillin-1 interaction with latent TGFβ-binding proteins (LTBPs) that are part of large latent complexes (LLCs) containing bioactive TGFβ dimers non-covalently bound to the processed pro-peptides (aka, latency associated peptide or LAP) [11]. Intracellular association of TGFβ with LTBPs 1, 3 or 4 facilitates secretion and tethering of the LLC to the ECM from which the signaling molecule is released by proteolytic and/or non-proteolytic disruption of the LAP-TGFβ interaction. LLC incorporation into the ECM is believed to promote spatial distribution and proper concentration of TGFβ molecules for either immediate presentation to cells or subsequent release during tissue remodeling/repair [11].

Mutations in fibrillin-1 are therefore expected to negatively impact both ECM integrity and local TGFβ activity. Just one year before the discovery of the genetic lesion in MFS, Hollister et al. [12] made the seminal observation that tissues and cell cultures from MFS patients contained less immunoreactive fibrillin-1 than healthy specimens. This observation

implicitly predicted a loss-of-function phenotype at the tissue level -i.e., deficiency of fibrillin-1 microfibrils-irrespective of whether FBN1 mutations perturb ECM assembly and/or stability through haploinsufficient, dominant-negative or gain-of-function mechanisms. Characterization of mice with genetically engineered *Fbn1* mutations have corroborated this early prediction, in addition to yielding invaluable insights into molecular processes secondary to fibrillin-1 deficiency that are associated with onset and progression of cardiovascular and bone abnormalities.

3.1 Arterial disease

The pathophysiological mechanism responsible for TAA development in MFS mice remains unresolved due to conflicting results regarding TGFβ's role in this process. Early studies of MFS mice with non-dissecting TAA ($Fbn1^{C1039G/+}$ mice) concluded that aneurysm formation is principally the result of over-stimulation of TGFβ production and signaling by improper activity of the angiotensin II (AngII) type I receptor (AT1r), a disease-causing process further amplified by uncontrolled LLC release from the fibrillin-1-deficient matrix (Fig. 1A) [13]. This disease model is largely based on the finding that either AT1r antagonism (by losartan) or TGFβ inhibition (by a neutralizing antibody) prevented TAA formation in $Fbn1^{C1039G/+}$ mice. Losartan administration to MFS mice also normalized expression and activation of Mmp2 and Mmp9, downstream targets of TGFβ signals promoting media degeneration [14]. Additional genetic evidence correlated the scaffold protein β-arrestin2 in mediating AT1r stimulation of Mmp2 and Mmp9 through Erk activation independently of TGFβ [15]. As expected, the non-specific MMP inhibitor doxycycline mitigated TAA progression in MFS mice [16, 17]. Additional analyses of $Fbn1^{C1039G/+}$ mice suggested that TGFβ signaling through the Erk pathway is a prominent driver of TAA formation that is inhibited by AT2r-mediated AngII signaling (Fig. 1A) [18]. Losartan therapy therefore emerged as a promising new strategy that could blunt AT1r stimulation of non-canonical TGFβ signaling and downstream targets, while concomitantly inhibiting Erk activation by shunting AngII signaling through AT2r. However, losartan treatment of MFS patients was subsequently found to mitigate the rate of aneurysm growth to the same extent as the traditionally prescribed anti-hypertensive drug and without modifying clinical endpoints of the disease (i.e., aortic dissection, elective aortic surgery, cardiovascular death) [19]. While losartan dosage could have accounted for the disappointing outcome, an alternative explanation is that additional signaling pathways may contribute to arterial disease progression in MFS [19].

Several findings have corroborated and expanded the above postulate. The milder TAA phenotype of $Fbn1^{C1039G/+}$ mice indicates that aneurysm growth and media degeneration are not by themselves sufficient to precipitate dissection and rupture of the vessel wall [20]. Similarly, media degeneration throughout the entire aortic tree of $Fbn1^{mgR/mgR}$ mice implies that segment-specific factors (e.g., hemodynamic load and/or SMC's embryonic origin) are major contributors to the dilatation and subsequent dissection and rupture of a structurally compromised ascending aorta [21]. With regard to the TGFβ controversy, two research teams have independently reported that genetic disruption of TGFβ signaling in post-natal SMCs of $Fbn1^{C1039G/+}$ mice exacerbates (as opposed to mitigate) TAA pathology [22, 23]. The implication of these studies that TGFβ plays a protective role in TAA development

contrasts the earlier postulate of a prominent (AT1r-dependent) pathogenic role of TGFβ signaling [13, 18]. The reason of this discrepancy is unclear since all aforementioned studies have employed the same mouse model of MFS [13, 18, 22, 23].

Accelerated TAA progression was also the unexpected finding when MFS mice with dissecting (lethal) TAA (*Fbn1*$^{mgR/mgR}$ mice) were subjected to systemic TGFβ neutralization starting at post-natal day 16 (P16) [24]. By documenting an absolute requirement for basal TGFβ signaling in supporting post-natal vessel growth, these pharmacological studies independently supported the aforementioned genetic experiments excluding a prominent role of TGFβ in TAA onset. The additional finding of attenuated arterial disease in *Fbn1*$^{mgR/mgR}$ mice subjected to systemic TGFβ neutralization from P45 onward revealed a dimorphic, stage-specific role of TGFβ during TAA development [24]. Accordingly, it was argued that the primary consequence of fibrillin-1 deficiency is loss of TGFβ's protective activity on the growing vessel combined with persistent AT1r over-activation throughout postnatal life; and that the secondary consequence of the ECM defect is to promote TGFβ-driven maladaptive tissue remodeling/repair at later stages of TAA progression (Fig. 1B) [24]. Consistent with this new disease model, losartan administration from P16 onward combined with TGFβ neutralization from P45 onward prevented TAA formation and thus, premature death of *Fbn1*$^{mgR/mgR}$ mice from vascular complications [24]. Additional studies of MFS mice have further increased the molecular complexity of arterial disease by identifying several pro-inflammatory determinants of TAA pathology, including IL-6, NOS2 and COX-2 [25–27], in addition to documenting mitigation of aneurysm growth by mild aerobic exercise, statins or long-term miR29 suppression [28–30].

Zilberberg et al. [31] have investigated a different aspect of TAA development by focusing on LTBP-3 contribution to arterial disease in mice with progressively severe MFS. The premise of the study was based on the investigators' prior demonstration that fibrillin-1 microfibrils dictate proper association of LTBP-3 and -4 (but not LTBP-1) with the vascular ECM [32]. Contrary to prior studies predicting that lowering TGFβ activity during post-natal vessel growth would lead to premature death [24], genetic disruption of LTBP-3 synthesis in *Fbn1*$^{mgR/mgR}$ mice prevented TAA development and death of the double mutant animals by normalizing the transcriptome of aortic cells, including transcription of genes associated with TGFβ hyperactivity [31]. To reconcile the apparent discrepancy between the pharmacological findings of Cook et al [24] and the genetic findings of Zilberberg et al. [31] it was argued that distinct TGFβ isotypes might subsume protective and pathological roles during TAA onset and progression, respectively, and that LTBP-3 binds the disease-driving isotype(s) [31]. As TGFβ-2 haploinsufficiency in *Fbn1*$^{C1039G/+}$ mice had previously been shown to exacerbate TAA pathology [33], it was further argued that selective association of LTBP-3 with TGFβ-1 and/or TGFβ-3 might specify the LLC complex driving degeneration of the fibrillin-1-deficient tunica media later in TAA progression [31]. In this view, disruption of spatiotemporally distinct interactions between LTBP and TGFβ molecules could represent another key determinant of TAA progression.

To gain additional mechanistic insights into medial degeneration in the MFS aorta, Granata et al. [34] have recently employed a clinically relevant cell-based approach that lends itself to more extensive biochemical analyses than studies in mice (Fig. 1C). MFS patient-derived

induced pluripotent stem cells (MFS-iPSCs) differentiated into vascular SMCs were found to phenocopy molecular and cellular abnormalities previously noted in aortic tissue and cells isolated from MFS patients, including TGFβ hyperactivity, MMP up-regulation, ECM degradation, increased SMC apoptosis, reduced muscle contractility and perturbed Ca^{2+} flux. TGFβ hyperactivity in MFS-iPSC cultures was associated with increased phosphorylation of Smad, Erk and p38 proteins, which were in turn correlated with regulating distinct cellular phenotypes at different stages of in vitro differentiation. For example, Erk1/2 activation augmented MMP-driven ECM degradation late in MFS-iPSC differentiation, but inhibited apoptosis and stimulated proliferation of SMCs throughout the entire process. The study also implicated p38-mediated TGFβ signaling in promoting MMP up-regulation and ECM degradation. Unlike p-Erk1/2, however, p38 activation remained abnormally high at more mature stages of cell differentiation. Furthermore, p38 activation antagonized p-Erk1/2 protective action on SMC survival by stimulating apoptosis and inhibiting proliferation. Cyclic stretch further increased p38 activation, conceivably through the action of β1 integrin, thus suggesting a potential connection with dysregulated mechanosignaling (Fig. 1C). This possibility is in line with recent reports indicating that the aortic wall of *Fbn1*$^{mgR/mgR}$ mice is mechanically compromised, as evidenced by the loss of elastic energy storage capability and mechanical degradation of the media [35, 36]. Hence, the emerging evidence-based hypothesis that progressive hemodynamic load on a structurally vulnerable aorta may represent the primary trigger and driver of TAA development in MFS [5, 9].

3.2 Cardiac manifestations

Cardiac valve disease and stiffening of the dilating aortic wall have traditionally been thought to cause heart dysfunction in MFS by imposing volume overload on the LV [3, 6]. However, recent analyses of mice with tissue-specific *Fbn1* gene inactivation have refuted this notion by demonstrating that fibrillin-1 deficiency in the pericellular matrix of the myocardium is both necessary and sufficient to trigger dilated cardiomyopathy (DCM) [37]. Characterization of subclinical cardiomyopathy in *Fbn1*$^{C1039G/+}$ mice has independently reached the same conclusion [38]. These findings suggest that fibrillin-1 deficiency significantly weakens the physical properties of the myocardium and this in turn translates into abnormal myocyte mechanosignaling and impaired muscle contractility. In support of this argument, fibrillin-1 deficient cardiomyocytes display dysregulated activity of cardiac mechanosensors AT1r and β_1 integrin, as evidenced by increased β-arrestin2-mediated Erk1/2 signaling and abated FAK signaling respectively (Fig. 2A). Additional evidence suggests a probable cross talk between the two receptors stimulated by mechanical unloading of the entire fibrillin-1-deficient ECM (Fig. 2A) [37]. In contrast to TAA, TGFβ hyperactivity was not found to be a prominent determinant of DCM development. Consistent with these findings, losartan treatment prevented DCM formation in *Fbn1*$^{mgR/mgR}$ mice and mitigated ventricular dysfunction in a small cohort of MFS patients [37, 39].

MVP in *Fbn1*$^{C1039G/+}$ mice has been correlated with increased cellular proliferation and decreased apoptosis consistent with changes associated with myxomatous degeneration, as well as increased expression of TGFβ-induced stimulators of ECM remodeling [40]. Treatment of mutant mice with a TGFβ-neutralizing antibody normalized both the length

and thickness of MV leaflets, implying participation of TGFβ hyperactivity in valve disease [40]. It remains to be determined if also in this case, mechanical stress might be the primary trigger of MVP and TGFβ hyperactivity a secondary driver of maladaptive tissue remodeling/repair [41].

3.3 Osteopenia

Characterization of the natural history of progressive bone loss in MFS mice has revealed that fibrillin-1 is a structural component of the bone marrow niche that supports self-renewal and commitment of mesenchyme stem cells (MSCs), and lineage determination of progenitor cells [42]. While other ECM proteins have been associated with the structural microenvironment of a functional stem cell niche [42], fibrillin-1 is the first element of the architectural matrix to be implicated in regulating stemness. By advancing our primitive understating of ECM role in defining the niche microenvironment, this finding may also impact future development of more effective stem cell-based therapies in regenerative medicine.

Reduced BMD in $Fbn1^{mgR/mgR}$ mice was originally correlated with accelerated in vitro maturation of calvarial osteoblasts and increased osteoblast-dependent osteoclast activity [43]. Whereas TGFβ-dependent stimulation of RANKL expression by osteoblasts accounted for augmented osteoclastogenesis, accelerated osteoblast differentiation was associated with both TGFβ and BMP hyperactivity. Subsequent analyses of mice with restricted *Fbn1* inactivation in limb mesenchyme cells ($Fbn1^{Prx1-/-}$ mice) revealed that progressive bone loss is driven by constitutively enhanced bone resorption combined with premature depletion of MSCs and osteoprogenitor cells [44]. Fibrillin-1 deficiency also perturbed MSC commitment to adipogenesis resulting in osteopenic bones unusually depleted of marrow fat. All these cellular abnormalities were associated with improper over-activation of latent TGFβ complexes. By normalizing the number of MSCs, osteoprogenitor cells, osteoblasts, osteoclasts and adipocytes, systemic treatment of $Fbn1^{Pr1x-/-}$ mice with a TGFβ neutralizing antibody improved bone mass and trabecular microarchitecture, and restored marrow adipogenesis [44]. In contrast to cardiovascular manifestations, losartan treatment did not mitigate bone loss in MFS mice [43]. Consistent with these in vivo findings, Quarto et al. [45] have independently reported TGFβ-dependent inhibition of the osteoblastogenic potential of MFS-iPSC cultures. Both in vitro and in vivo findings therefore demonstrate that fibrillin-1 regulates MSC and progenitor cell fate by modulating TGFβ bioavailability within the functional microenvironment of marrow niches (Fig. 2B). With regard to enhanced bone resorption, dysregulated marrow hematopoiesis in $Fbn1^{Pr1x-/-}$ mice might also contribute to increasing the number of osteoclasts [46]. A decreased amount of proteolytic fragments of fibrillin-1 that normally restrict osteoclast differentiation through RANKL sequestration and NFATc inhibition might potentially be another stimulator of bone catabolism in $Fbn1^{Pr1x-/-}$ mice [47].

4. Concluding remarks and perspectives

Findings discussed in this review demonstrate that fibrillin-1 assemblies play a critical role in post-natal organ growth and homeostasis by integrating both structural and instructive

properties of connective tissue. As noted fifteen years ago in a Matrix Biology review [48], these architectural matrix components "*may function in the extracellular milieu in a manner similar to the way scaffold proteins act in the intracellular environment by focusing diverse molecules* (both structural and signaling molecules) *to promote their interactions*." The reviewers also argued that "*the unique organization of matrix in individual tissues* (may) *define which* (extrinsic signals and sub-cellular process) *will be modulated* (and how)." Characterization of cardiovascular and bone disease in MFS mice have validated these earlier predictions by causally linking disruption of fibrillin-1-centered networks of extracellular protein interactions with tissue-specific perturbations in mechanotransduction, TGFβ signaling and stem cell fate. An important corollary to these findings is the notion that multi-drug treatments will be required to manage both life-threatening and morbid manifestations of MFS.

In light of the above considerations, it is safe to predict that much research effort will be devoted in the future to develop unbiased study designs that can more effectively unravel the complex dynamics of fibrillin-1-centered regulatory networks associated with distinct MFS pathologies. For example, the progressive nature of skeletal complications constitutes a significant morbidity factor in MFS patients, particularly in older individuals and severely affected children. Unfortunately, effective treatment is hampered by the lack of an evidence-based mechanistic understanding of how a loss-of-function tissue defect (fibrillin-1 deficiency) translates into a gain-of-function organ phenotype (linear bone overgrowth). Resolving this fascinating scientific mystery will not only advance fundamental knowledge of molecular determinants of postnatal bone growth, but also improve the clinical management and life quality of MFS patients.

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Abbreviations used

AngII	Angiotensin II
AT1r	AngII type I receptor
BMD	Bone mineral density
DCM	Dilated cardiomyopathy
ECM	Extracellular matrix
	Human (FBN1) and mouse (Fbn1) fibrillin-1 genes
iPSC	Induced pluripotent stem cells
LAP	Latency-associated peptide

LTBP	Latent TGFβ-binding protein
LLC	Large latent complex
LV	Left ventricle
MFS	Marfan syndrome
MSC	Mesenchyme stem cell
MVP	Mitral valve prolapse
SMC	Smooth muscle cell
TAA	Thoracic aortic aneurysm

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Highlights

- Mutations in the architectural matrix component fibrillin-1 cause Marfan syndrome (MFS)
- Consistent with the multiple functions of fibrillin-1 assemblies, molecular abnormalities in MFS mice include dysregulated mechanotransduction, TGFβ signaling and stem cell fate.
- Association of organ-specific manifestations with distinct pathophysiological mechanisms argues for combinatorial drug treatments in MFS

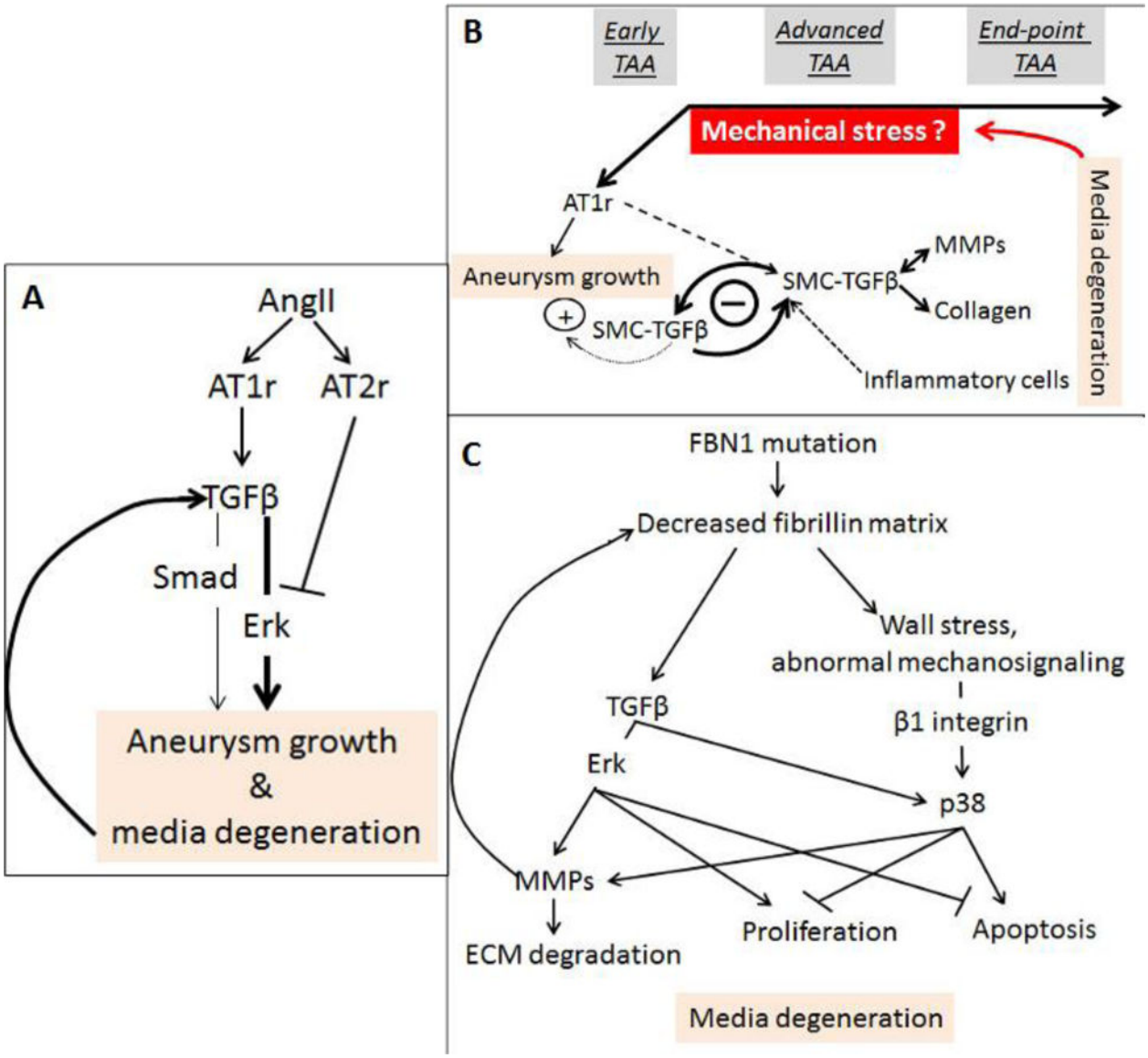

Figure 1.

(**A**) Original disease model of a linear relationship between AT1r activation and TGFβ signaling derived from the characterization of TAA in *Fbn1*$^{C1039G/+}$ mice (modified from Habashi et al, 2006 and Holm et al, 2011). (**B**) Revised model of TAA progression derived from studies of *Fbn1*$^{mgR/mgR}$ mice (modified from Cook et al, 2015). (**C**) Model of medial degeneration during TAA progression derived from the analysis of MFS-iPSCs differentiated into vascular SMCs (modified from Granata et al, 2017).

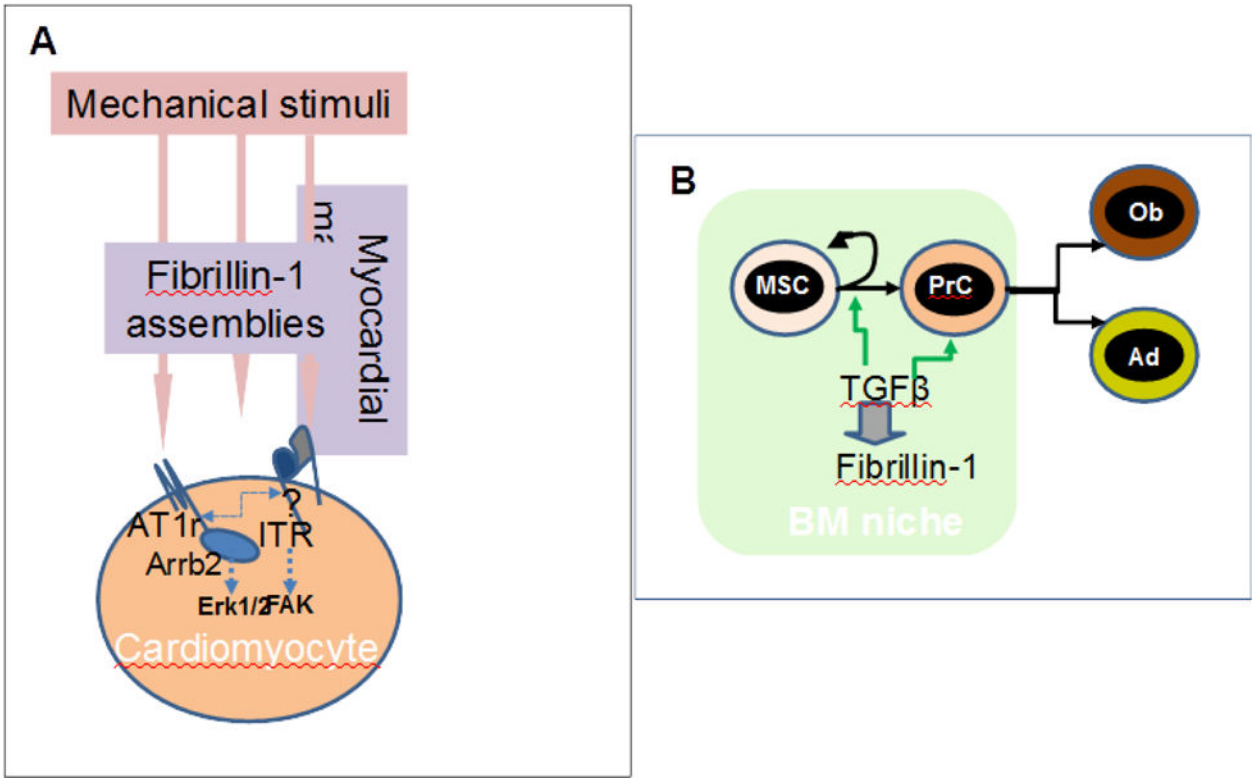

Figure 2.

(**A**) Schematic representation of the mechanotransducing role of fibrillin-1 assemblies in the myocardium as inferred from DMC characterization in *Fbn1*$^{mgR/mgR}$ mice. In this model, fibrillin-1 assemblies influence cross talk between AT1r and integrin by participating in ECM loading on the mechanosensors (**B**) Proposed role of fibrillin-1 in stem cell fate regulation by modulating TGFβ bioavailability within the bone marrow niche, as implied from the characterization of progressive bone loss in *Fbn1*$^{Prx-/-}$ mice. Arrows points to cellular processes of self-renewal, commitment and differentiation, while abbreviations signify mesenchyme stem cell (MSC), progenitor cell (PrC), osteoblast (Ob) and adipocyte (Ad).