Review

Pathophysiology and Management of Cardiovascular Manifestations in Marfan and Loeys–Dietz Syndromes

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Summary

Marfan syndrome (MFS) is an autosomal dominant heritable disorder of connective tissue that affects the cardiovascular, skeletal, ocular, pulmonary, and nervous systems and is usually caused by mutations in the *FBN1* gene, which encodes fibrillin-1. MFS is traditionally considered to result from the structural weakness of connective tissue. However, recent investigations on molecular mechanisms indicate that increased transforming growth factor-β (TGF-β) activity plays a crucial role in the pathogenesis of MFS and related disorders, such as Loeys–Dietz syndrome (LDS), which is caused by mutation in TGF-β signaling-related genes. In addition, recent studies show that angiotensin II type 1 receptor (AT1R) signaling enhances cardiovascular pathologies in MFS, and the angiotensin II receptor blocker losartan has the potential to inhibit aortic aneurysm formation. However, the relationship between TGF-β and AT1R signaling pathways remains poorly characterized. In this review, we discuss the recent studies on the molecular mechanisms underlying cardiovascular manifestations of MFS and LDS and the ensuing strategies for management. (Int Heart J 2016; 57: 271-277)

Key words: *FBN1*, TGF-β, Losartan, Cardiomyopathy, Pregnancy

Marfan syndrome (MFS) was first described by Antoine Bernard-Jean Marfan in a case of a 5-year-old girl with long limbs, digital and joint contractions, and kyphoscoliosis in 1896.[1)] Subsequently, features of ectopia lentis, mitral valve disease, aortic dilatation/dissection,[2,3)] and autosomal dominant inheritance have been added to the clinical spectrum of MFS. In 1991, mutations in the *FBN1* gene, which encodes the major component of extracellular matrix (ECM) microfibril fibrillin-1, were first reported to cause MFS.[4)] Accordingly, diagnoses of MFS are made using the criteria of Ghent nosology, which was established in 1996 and requires the evaluation of family history; *FBN1* mutations; and skeletal, ocular, cardiovascular, and pulmonary organ systems; skin; and dura.[5)] *FBN1* mutations are detectable in 60–90% of patients with firm diagnoses of MFS,[6)] whereas causative genes for MFS type II (MFS2), with prominent aortic/arterial phenotypes but without ectopia lentis, had not been identified until recently.

In 2004–2005, mutations in genes encoding TGF-β receptors 1 and 2 (*TGFBR1* and *TGFBR2*, respectively) were identified in a subset of patients with MFS2,[7,8)] which is currently referred to as Loeys–Dietz syndrome (LDS). Although LDS patients present several characteristics of MFS, LDS is characterized by rapidly progressive aortic/arterial tortuosity and aneurysmal disease that is known to result in ruptures at an early age and at smaller dimensions, and by widely spaced eyes (hypertelorism) and bifid uvula or cleft palate.[9-11)] Until recently, mutations in *TGFB2*,[12,13)] *TGFB3*,[14)] and *SMAD3*,[15,16)] which encode main members of the TGF-β/SMAD signal transduction pathway, were also reportedly associated with diseases that resemble MFS. Fibrillin-1 also regulates TGF-β bioavailability, and thus traditional definitions for the pathogenesis of MFS and related diseases have been dramatically revised. In particular, the dysregulation of TGF-β is considered the main contributor to the major extra-ocular features of MFS.[17)] Accordingly, the diagnostic criteria were revised in 2010 (revised Ghent nosology)[18)] to place more emphasis on genetic analyses, the presence of aortic root aneurysm/dissection, and ectopia lentis.

Marfan Syndrome

Fibrillin-1 and TGF-β signaling: In patients with MFS, cystic medial necrosis (CMN) is present in the medial layer of the aortic wall, and is characterized by fragmentation and disorganization of elastic fibers, fibrosis with collagen production, accumulation of amorphous matrix components, and loss of cell nuclei.[19)] In addition, inflammatory T lymphocytes and

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macrophages reportedly infiltrate aortic media and adventitia, and those numbers were negatively correlated with patient ages at referral for prophylactic surgical repair, suggesting that inflammation might affect disease progression.[20,21]

Dietz and his colleagues performed the most extensive mechanistic studies of these diseases, and identified *FBN1* as a causative gene in 1991,[4] with *FBN1* mutations accounting for > 60% of MFS patients. *FBN1* is a 230 kb gene with 65 exons, and the encoded microfibrillar protein fibrillin-1 contains 7 TGF-β binding protein-like (TB) domains and 47 epidermal growth factor (EGF)-like domains, which are characterized by 8 and 6 conserved cysteine residues that form 4 and 3 intramodule disulfide bonds, respectively. Of the 47 EGF domains, 43 contain a consensus sequence for calcium binding (cb-EGF), which plays a crucial role in microfibril stability and assembly.[22,23] Fibrillin-1 can limit TGF-β activation (Figure 1); TGF-β cytokines are secreted in large latent complexes (LLC) that contain latency-associated peptide (LAP) and latent TGF-β binding protein (LTBP) anchored to the extracellular matrix with fibrillin-1. Normally, inflammatory proteolytic enzymes such as elastase and/or certain physiological stimuli lead to microfibril degradation, which contributes to local TGF-β activation.[24] In contrast, mutated fibrillin-1 in MFS leads to failed sequestration of TGF-β, and the ensuing overactivity of TGF-β signaling cascades is considered crucial in the pathogenesis of MFS.[25]

Plasma total TGF-β1 levels were elevated in patients with MFS, and were lowered by treatment with the angiotensin II receptor blocker (ARB) losartan.[26] However, relationships between genotypes, changes in signals, and phenotypes remain incompletely characterized. In addition, more than 3,000 mutations have been identified in the *FBN1* gene, and these are mostly unique in families.[11,27] The revised nosology provides useful criteria for causative *FBN1* mutations,[18] emphasizing the significance of altered conserved residues of cysteine and EGF consensus sequences. Most mutations are considered to act in a dominant negative way exemplified by missense mutations, or through haploinsufficiency due to nonsense-mediated mRNA decay (NMD) mostly caused by splice-site, frameshift, and nonsense mutations. Although some studies suggest higher probabilities of ectopia lentis in patients with cysteine substitutions[27] and aortic events with truncating/splicing variants,[28] further studies are needed to confirm these relationships.

Mouse model of MFS: To elucidate the pathophysiological roles of fibrillin-1 *in vivo*, several genetically engineered *Fbn1* mice have been generated and analyzed. In 1997, mice lacking exons 19–24 were designed by replacement with a PGK-*neo* cassette. However, this gene targeting strategy produced a mutant allele (known as mgΔ) with 90% lower transcription than the normal *Fbn1* allele, reflecting transcriptional interference by the strong PGK promoter.[29] Moreover, the heterozygous mutants (mgΔ/+) were histologically indistinguishable from wild-type mice, possibly because the relative excess of the wild-type protein abolished the negative potential of the mgΔ product. In contrast, homozygous mice (mgΔ/mgΔ) died of cardiovascular complications such as aortic dissections before weaning, without skeletal manifestations.

Fbn1 hypomorphic mgR/mgR mice were reported in 1999 and are now widely used as an essential experimental tool. These mice were generated with an aberrant targeting strategy using the vector that was used to produce the mgΔ line.[30] The mgR protein is the same size as wild-type fibrillin-1, and homozygous mgR/mgR mice produced approximately 20% of the normal amount of fibrillin-1. These mgR/mgR mice rapidly developed ascending aortic aneurysms with macrophage infiltration, intimal hyperplasia, elastic fiber fragmentation, and calcified media.[30] In addition, they displayed MFS-like features in skeletal and pulmonary systems, such as severe kyphosis and overgrowth of the ribs, and air space dilatation with destructive changes and peribronchiolar inflammation. These mice die within the first 6–9 months of life because of aortic disorders, and the pulmonary insufficiencies associated with severe kyphosis.

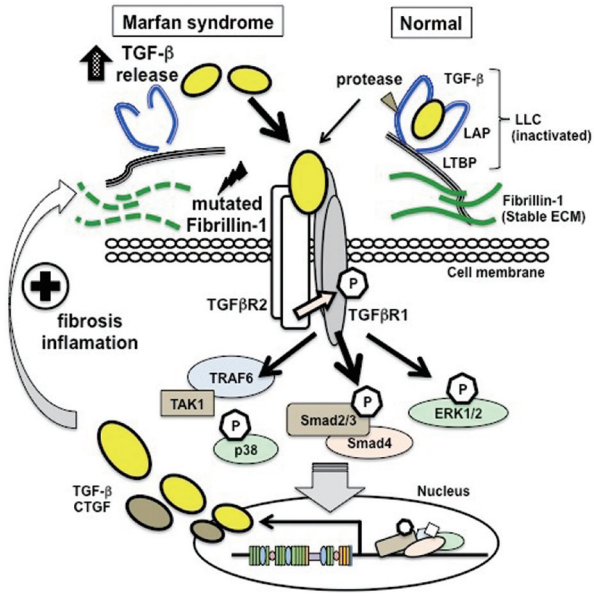

Figure 1. Dysregulation of TGF-β bioavailability in MFS caused by mutations in the FBN1 gene. Latent TGF-β is activated by physical and enzymatic stimuli under normal conditions (right side). Mutated fibrillin-1 in MFS leads to failed ECM sequestration of TGF-β and subsequent activation of TGF-β signaling cascades (left side), which play critical roles in the pathogenesis of MFS. CTGF indicates connective tissue growth factor; ECM, extracellular matrix; LLC, large latent complexes; LAP, latency-associated peptide; and LTBP, latent TGF-β binding protein.

The well-characterized mouse line *Fbn1*$^{C1039G/+}$ was generated by substitution of a cysteine with a glycine at amino acid 1039 in an EGF domain of fibrillin-1,[31-33] mimicking one of the most frequent mutations in human MFS. Homozygous knock-in mice (*Fbn1*$^{C1039G/C1039G}$) died from aortic dissections in the perinatal period, whereas heterozygous *Fbn1*$^{C1039G/+}$ mice had relatively good long-term survival of more than 90% at 8 months of age.[34] Moreover, after 2 months of age, *Fbn1*$^{C1039G/+}$ mice gradually recapitulated the skeletal, pulmonary, and cardiovascular characteristics of the human condition. In the aorta, elastic fiber fragmentation, disarray of proliferating smooth muscle cells (SMCs), and excessive collagen and proteoglycan deposition deteriorated progressively with occasional elastic fiber calcification, although the inflammatory cell infiltration and intimal hyperplasia seen in hypomorphic mgR/mgR mice were not markedly observed.

TGF-β signaling in mouse models: The most widely used models of MFS are *Fbn1*$^{C1039G/+}$ and mgR/mgR mice, and they

recapitulate the underlying mechanisms with dominant-negative effects and degradation of abnormal fibrillin-1, respectively. Accordingly, canonical TGF-β signaling was increased in affected tissues of these mice models, as indicated by increased accumulation of phosphorylated SMAD2 (pSMAD2) and target genes. Thus, systemic administration of TGF-β neutralizing antibody (NAb) could prevent some disease manifestations.[25,31,33] However, increasing experimental evidence shows the beneficial roles of TGF-β signaling during the early developmental period in MFS animal models. In particular, TGF-β NAb treatment from postnatal day 45 (P45) mitigated TAA formation, although early initiation from P16 exacerbated TAA formation in mgR/mgR mice.[35] In addition, *Tgfbr2* gene ablation in postnatal SMCs of *Fbn1*$^{C1039G/+}$ mice at 4 weeks of age inhibited TGF-β signaling in aortic media, and rapidly exacerbated aortic phenotypes.[36] Furthermore, when *Fbn1*$^{C1039G/+}$ mice were crossed with *Smad4* or *Tgfb2* heterozygous knockout mice to attenuate TGF-β signaling, *Fbn1*$^{C1039G/+}$;*Smad4*$^{+/-}$ mice died prematurely due to proximal aortic rupture,[34] and *Fbn1*$^{C1039G/+}$;*Tgfb2*$^{+/-}$ mice rapidly developed aortic root aneurysms.[13] These data suggest protective roles of TGF-β signaling during early development in the aorta, whereas excessive TGF-β signaling may be a therapeutic target after adolescence.

Other signals and biomarkers: In addition to TGF-β signaling, other pivotal signals are evoked primarily and/or secondarily in affected tissues. In mgR/mgR mice, increased expression of cytokines such as interleukin-6 (IL-6), monocyte chemoattractant protein-1 (MCP-1/CCL2), and granulocyte/macrophage-colony stimulating factor (GM-CSF) were observed in aortic walls, and *IL-6* depletion ameliorated progressive aortic elastin degradation and aneurysm.[37] Moreover, in association with degradation of elastin and apoptotic cell death of the medial layer, activities of matrix metalloproteinases (MMP-2 and MMP-9) and proapoptotic factors (Bax and cleaved caspase-3, caspase-9) were increased in the aortic walls of mouse models.[32,38-40] Accordingly, systemic administration of the MMP inhibitor doxycycline and the pan-caspase inhibitor Q-V_D-OPh prevented aortopathy in these mice.[39] Recently, Merk, *et al* showed that increased miR-29b expression during early formation of aneurysms in *Fbn1C*$^{1039G/+}$ mice regulated a wide variety of targets with roles in ECM deposition and breakdown and apoptosis. Accordingly, treatment with a miR-29b oligonucleotide inhibitor prevented early formation of aneurysms.[41] Finally, plasma levels of TGF-β,[26] fibrillin-1 fragments,[42] macrophage colony stimulating factor (M-CSF),[21] and oxidative stress indicators[43] have been reported as useful biomarkers for disease progression in humans and animal models.

Noncanonical TGF-β signaling and angiotensin II receptor signaling: Numerous recent studies demonstrate the details of noncanonical (SMAD-independent) TGF-β signaling. Moreover, *Fbn1*$^{C1039G/+}$ mice showed significant increases in activation of extracellular signal-regulated kinase 1/2 (ERK1/2) and mitogen-activated protein kinase kinase 1 (MEK1), which is the upstream activator of ERK1/2. These signals were inhibited by systemic TGF-β NAb treatment, and the selective MEK1/2 inhibitor RDEA119 ameliorated aortic growth. Thus, noncanonical TGF-β signaling may be a prominent driving force in aortic disease in MFS mice, warranting investigation of ERK1/2 signaling as a potential therapeutic target.

Angiotensin II (AngII) type 1 receptor (AT1R) signals are enhanced in aortic aneurysmal walls and also leads to activation of ERK1/2 signaling independently. However, the relationships between TGF-β and AT1R signaling pathways in MFS remain elusive (Figure 2). The angiotensin-converting enzyme (ACE) inhibitor enalapril did not adequately inhibit ERK1/2 signals in *Fbn1*$^{C1039G/+}$ mice, whereas losartan inhibited ERK1/2 signals in *Fbn1*$^{C1039G/+}$ mice, but not in *Fbn1*$^{C1039G/+}$ mice lacking the *AT2* gene (*Fbn1*$^{C1039G/+}$;*AT2*$^{-/-}$).[44] These observations suggest that losartan activates or preserves AT2-receptor activated signal cascades, leading to reduced ERK1/2 activity and aortopathy.[44] Selective AT1-receptor blockade is considered an ideal therapeutic option for patients with MFS.

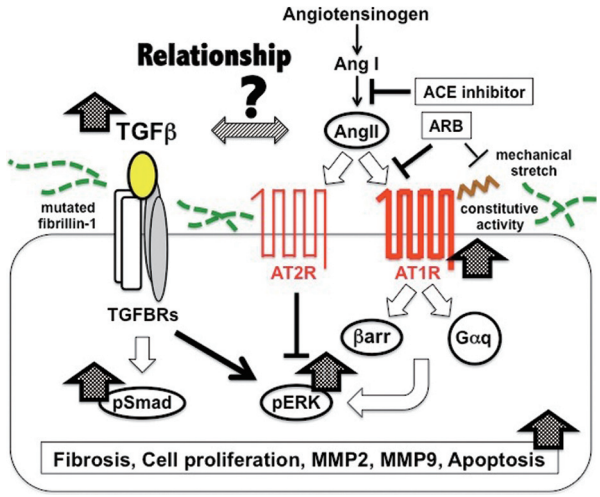

Figure 2. Involvement of non-canonical TGF-β signaling and angiotensin II receptor signaling in MFS. Multiple signals are activated in MFS (dotted arrows), and ERK signaling is activated by both TGFBR and AT1R signaling cascades. ARBs, such as losartan, can inhibit both angiotensin II-dependent and -independent AT1R activation and subsequent ERK activation, offering a promising drug for MFS. ACE indicates angiotensin-converting enzyme; Ang, angiotensin; ARB, Angiotensin II receptor blocker; AT1R, Angiotensin II type 1 receptor; AT2R, Angiotensin II type 2 receptor; βarr, β-arrestin; Gαq, a G-protein α-subunit; and MMP, matrix metalloproteinase.

AT1R signaling is activated by ligand dependent and independent (mechanical stress) mechanisms, and is mediated by Gαq-protein- and β-arrestin-dependent pathways. Multifunctional scaffolding protein β-arrestin 2 binds to phosphorylated G protein-coupled receptors (GPCRs) such as AT1R, and regulates numerous signaling pathways, including proproliferative and profibrotic signals in aortic SMCs. Accordingly, *Fbn1*$^{C1039G/+}$mice crossed with β-arrestin 2 knockout mice (*Fbn1*$^{C1039G/+}$; βarr2$^{-/-}$) displayed delayed aortic root dilatation, in which MMP-2 and MMP-9, and AT1R-mediated ERK1/2 activation were decreased.[45] These data warrant future investigation of AT1R/β-arrestin-biased ligands that might offer a new class of therapeutic agents for the treatment of MFS.

Loeys-Dietz Syndrome (LDS)

LDS is caused by mutations in TGF-β signal related genes, and is characterized by the diagnostic triad of rapidly progressive aortic aneurysms and generalized arterial tortuosity, hypertelorism, and bifid/broad uvula or cleft palate. LDS patients do not have ectopia lentis, but their blue or dusky scle-

ra can be a diagnostic clue. In initial reports, LDS patients with mutations in *TGFBR1* or *TGFBR2* were assigned to the type I category if craniofacial involvement comprising cleft palate, craniosynostosis, or hypertelorism was observed, or to the type II category following observation of cutaneous features associated with vascular Ehlers-Danlos syndrome, such as visceral rupture, easy bruising, wide and atrophic scars, joint laxity, and translucent skin, velvety skin, or both.[9] However, it is often difficult to distinguish one form from the other, and in a revised nosology for the diagnosis of LDS, patients are classified based on the presence of mutated genes encoding LDS 1 (*TGFBR1*), LDS 2 (*TGFBR2*), LDS 3 (*SMAD3*), and LDS 4 (*TGFB2*).[10] Moreover, mutations in *TGFB3* were recently associated with syndromic aortic aneurysms and dissections,[14] and mutations in these TGF-β signal-related genes were found in families with non-syndromic familial thoracic aortic aneurysm and dissection (FTAAD). Thus, further classification based on the molecular mechanisms of FTAADs might be required.

Mutations in *TGFBR1* and *TGFBR2* genes: TGFBR1 and TGFBR2 are transmembrane proteins with serine/threonine kinase motifs comprising 9 and 7 exons, respectively. Upon activation by TGF-β ligands, TGFBR2 (dimer) forms a stable receptor complex with TGFBR1 (dimer) and phosphorylates TGFBR1, leading to subsequent activation of SMAD2 and SMAD3 (SMAD-dependent pathway). In addition, TGFBR1 activates the SMAD-independent TRAF6/TAK1/p38 signaling pathway.[46] These TGF-β signaling pathways are crucially involved in the development and maintenance of various tissues, including vessels and craniofacial growth and patterning. Thus, mutations in *Tgfbr1* and *Tgfbr2* in mice caused craniofacial deformities such as cleft palate,[47,48] and craniofacial manifestations seen in LDS patients may reflect altered TGF-β signaling in neural crest derivatives.[49]

Most mutations of *TGFBR1* and *TGFBR2* genes are missense substitutions of evolutionarily conserved residues that encode serine/threonine kinases, and have been verified *in vitro* and/or predicted to be associated with loss-of-function (LOF).[50,51] However, chronic consequences of heterozygous mutations reportedly include increased accumulation of phosphorylated SMAD2 (pSMAD2) in the aortic wall,[8,9] suggesting TGF-β pathway over-activity *in vivo*. Moreover, in other types of LDS that are associated with mutations in *SMAD3*, *TGFB2*, and *TGFB3*, TGF-β activation is observed in aortic lesions, despite the presence of putative LOF mutations. The mechanisms of such paradoxical TGF-β vasculopathies have been examined.[52]

Gallo, *et al* showed that knock-in mouse strains with LDS mutations ($Tgfbr1^{M318R/+}$ and $Tgfbr2^{G357W/+}$) recapitulated vascular, craniofacial, and skeletal manifestations of LDS, whereas heterozygous knockout mice ($Tgfbr1^{+/-}$ and $Tgfbr2^{+/-}$) did not.[53] Analyses of TGF-β activities according to pSMAD2 levels and TGF-β target genes expression in these mice revealed apparently normal activation up to 8 weeks of age, and subsequent increases in aortic roots. Moreover, profuse infiltration of $CD45^+$ inflammatory cells was observed in thickened adventitia, and both medial and adventitial $CD45^+$ cells showed enhanced pSMAD2 expression, paralleling progression of aneurysm pathology and coinciding with increased *Tgfb1* expression. Losartan ameliorated the LDS mice vasculopathy, whereas propranolol did not. Next, Li, *et al* generated LDS-like mice by disrupting the *Tgfbr2* gene in smooth muscle cells postnatally ($Myh11\text{-}CreER^{T2}$;$Tgfbr2^{fl/fl}$), and showed that *Tgfbr2* mRNA expression was undetectable in the aortic media.[36] Subsequent analyses showed the development of TAAD and marked adventitial fibrosis without pSMAD2 elevation in these mice, whereas TGF-β ligand expression and MAPK activation (p-p38 and p-ERK1/2) were increased in the aortic wall. These data warranted speculation that TAAD was caused by a contractile apparatus perturbation of SMC and growth factor production (eg, IGF-1) from aortic wall cells including adventitia, which resulted in maladaptive paracrine signaling between vessel wall compartments. Collectively, these mutations may impair aortic wall homeostasis, which is not only attributed to altered medial smooth muscle cells function, but also modified and/or enhanced by activated adventitial fibroblasts and inflammatory cells. These secondary signals, including TGF-β signaling via the remaining wild-type allele, may also play active roles in the development of TGF-β vasculopathies.

Heterozygous mutations in the *TGFBR1* gene have been shown to cause multiple self-healing squamous epithelioma (MSSE).[54-55] These tumors are characterized by the development of multiple squamous carcinoma-like locally invasive skin tumors that grow rapidly for a few weeks before spontaneously regressing. Most mutations in MSSE are extracellular ligand-binding domains or truncation mutations of the kinase domain, whereas most mutations in LDS are missense. However, differentiation of diseases on the basis of mutation domains and types may be more complicated. For example, a splice acceptor site mutation (c.806-2A>C) was found in a British family case of MSSE without LDS-like aortic features, and was predicted to result in skipping of exon 5.[56,55] However, in our institution, a Japanese family case of LDS without MSSE carried a splice donor site mutation, and omission of the same exon 5 was identified (T. Fujiwara and H. Hara, unpublished data). Thus, further studies are necessary to understand the pathophysiology of diseases associated with TGFBR mutations.

Mutations in *TGFB2*, *TGFB3*, and *SMAD3* genes: Mutations in genes encoding TGF-β ligands (*TGFB2* and *TGFB3*) may contribute to the phenotypic features of LDS, and are predicted to lead to LOF. However, aortic tissues from affected patients showed increased TGF-β signaling cascades, in which TGF-β ligand expression was instead normalized and/or upregulated.[12,14]

SMAD3 mutations were initially reported in patients with syndromic aortic aneurysms and dissections with early-onset osteoarthritis, referred to as aneurysms-osteoarthritis syndrome (AOS) patients,[15] however, some patients with *SMAD3* mutations do not have prominent osteoarthritis. SMAD3 mutations lead to increased aortic expression of several key players in the TGF-β pathway, including TGF-β1, pSMAD2, and SMAD3. Hence, these data may also support that TGF-β signals are secondarily activated in vascular development and homeostasis in LDS.

Marfan Cardiomyopathy

Cardiac dysfunction in MFS is usually considered in terms of underlying aortic and/or valvular diseases. However, subclinical cardiac dysfunction is present in a subgroup of MFS cases without significant valvular dysfunction. Accord-

ingly, mild but significant impairment of LV systolic and diastolic function have been reported in adult patients.[57-60] Moreover, Das, *et al* reported that children and young adult MFS patients were predisposed to prolonged mitral deceleration times (DT) and mitral E/A ratios in echocardiography, suggesting impaired LV relaxation (diastolic dysfunction).[61] In other studies, some patients developed dilated cardiomyopathy (DCM)-like features that were not consistent with aortopathy and valvulopathy,[62,63] but these patients could receive heart transplantation under careful monitoring.[63,64] It has been speculated that increased aortic wall stiffness may lead to increased LV afterload and associated LV dilatation,[65] and abnormal ECM may result in altered cardiac performance. However, no associated clinical and genetic factors have been described to date.

In 2014, Cook, *et al* showed that 3-month-old *Fbn1* hypomorphic mgR/mgR mice develop DCM-like cardiac dysfunction, but with severe mitral and aortic regurgitation. Subsequently, these investigators generated cardiomyocyte-specific *Fbn1*-deficient mice and showed substantial reductions of cardiac fibrillin-1 with characteristic cardiac dysfunction, suggesting that DCM is a primary MFS manifestation and reflects the presence of structurally abnormal myocardial matrixes.[66] Moreover, reduced passive mechanical tension of cardiac muscle and activated stretch-stimulated (AngII-independent) AT1R/β-arrestin 2 pathway were observed in mgR/mgR mice hearts, leading to decreased activation of focal adhesion kinase (FAK) and elevated ERK1/2 signaling. Importantly, cardiac dysfunction was restored by losartan treatment, which could partially block stretch-mediated β-arrestin-biased AT1R signaling,[67] but not by enalapril or propranolol. These observations indicate that fibrillin-1 plays a crucial role in the physiological adaptation of cardiac muscle to elevated workload, warranting further consideration of ARB such as losartan as drug therapies for cardiac dysfunction in patients with MFS.

Management of Aortic Aneurysm

β-Blockers are the current gold standard for prevention and treatment of all MFS patients, including children, but require titration to achieve a heart rate after submaximum exercise of < 100 beats/minute in patients aged > 5 years. Recently, losartan was shown to prevent and possibly reverse aortic root dilation in humans,[68-70] whereas calcium channel blockers may require cautious use.[71] The timing of ARB initiation and dose escalation, especially in children with MFS, remains to be fully elucidated, and other drugs that may inhibit TGF-β signaling are currently under consideration as additional therapeutic options. Interestingly, the HMG-CoA reductase inhibitor (statin) pravastatin attenuated elastin loss and aortic root dilation in *Fbn1*$^{C1039G/+}$ mice,[72] presumably reflecting cholesterol-independent pleiotropic anti-inflammatory effects.

Surgical replacement of the aorta is recommended when the aortic diameter is ≥ 45 mm or shows rapid change (5 mm/year) or there are concerns regarding heart or valve function. Moreover, patients with LDS show more widespread and/or aggressive vascular disease, and thus surgical repair of the aortic root should be considered earlier, potentially at a diameter of ≥ 40 mm.[10] Finally, aortic root replacement with preservation of the patient's aortic valve could eliminate the need for lifetime anti-coagulation therapy and may provide good long-term prognosis.[73]

Cardiovascular Problems During Pregnancy

Pregnancy in patients with MFS is associated with increased risk of aortic dissection[74,75] by 1% and 10% when aortic root diameters are less and more than 4.0 cm, respectively.[76] These risks likely follow hemodynamic changes, hormone-mediated fragmentation of reticular fibers, decreases in acid mucopolysaccharide levels, and loss of normal corrugation of elastic fibers in the aortic wall during pregnancy,[77] although the pathophysiological details remain unclear. Selective β1-blockers, such as metoprolol, have been considered as treatments for MFS during pregnancy, and cesarean delivery is recommended in patients with aortic dilatation (≥ 4.0 cm), rapid growth during pregnancy, or previous history of aortic dissection or repair.[74] In contrast, pregnancies in LDS patients should be considered a higher risk. Accordingly, an initial report described a high incidence of pregnancy-related complications in 6 of 12 women (21 pregnancies), including aortic dissections in 4 and uterine rupture in 2.[9] In agreement, we describe our experience of a pregnant woman with LDS presenting serious aortic, cervical, and intracranial arterial dissections after her first and second deliveries.[78] However, this case was the only one of 12 LDS women (20 pregnancies) with *TGFBR1* or *TGFBR2* mutations who experienced complications at our institute (N. Takeda, unpublished data). Moreover, only 1 of 31 women with LDS (93 pregnancies) developed a pregnancy-related vascular complication in another report.[79] Although marked differences in the incidence of pregnancy-related complications in LDS are present, evaluations of cervical and intracranial vessels and genetic testing for LDS in patients with suspected MFS may contribute to the detection of high-risk subgroups that require improved risk-stratification and management.[78]

Future Perspective

Improvements of medical and surgical management for MFS have led to increases in the average life expectancy from about 32 years in 1972[80] to more than 70 years currently. In addition, aortic valve-sparing operations that eliminate the need for lifetime anti-coagulation therapy significantly improve quality of life[73] and are particularly appealing for young women who are expecting later pregnancies. In contrast, MFS patients after middle age may require more multi-disciplinary care and management. Accordingly, even after successful aortic root replacement, other aortic segments remain a source of late aortic aneurysm/dissection formation,[73] and a previous report documented a high prevalence of ventricular arrhythmias, often with left ventricular dilatation.[81] In addition, lifestyle-related diseases including hypertension, dyslipidemia (hyperlipidemia), and diabetes likely trigger more serious cardiovascular disease. Accordingly, *Fbn1*$^{C1039G/+}$mice crossed with atherosclerosis-prone *ApoE* deficient mice (*ApoE*$^{-/-}$;*Fbn1*$^{C1039G/+}$) died suddenly following plaque rupture and dilated aneurysm in the ascending aorta more frequently than *ApoE*$^{-/-}$ mice.[82] Furthermore, skeletal manifestations such as kyphoscoliosis may develop or become more pronounced with age.[83] Thus, clinical guidelines for the management of such middle-aged to elderly patients are needed.

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