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Targeting TGF-β and the Extracellular Matrix in Marfan's Syndrome

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Marfan's syndrome is a genetic disorder affecting connective tissues, and it can lead to death due to aortic defects if left untreated. β-blocker therapy has been used to slow the progression of this disease. Brooke et al. now report in this issue of *Developmental Cell* that combining angiotensin II receptor blockade by losartan with β-blocker treatment is an effective treatment combination therapy for this disorder.

Marfan's syndrome is an autosomal dominant systemic connective tissue disorder caused by mutations in the extracellular matrix (ECM) protein fibrillin-1 (Judge and Dietz, 2005). Cardiovascular, skeletal, and ocular systems are frequently involved along with mortality associated with proximal aortic aneurysm (dilation) and dissection (tearing of the wall) in as many as 40% of patients if left untreated. Four decades ago, Hugh Bentall introduced composite graft aortic root replacement in Marfan patients, offering the possibility of a normal life span.

It has long been thought that aortic root aneurysm in Marfan's syndrome is caused by deficiency in fibrillin, resulting in fragmentation of elastin and a weakened aorta, which is prone to rupture. β-blocker therapy has been the mainstay of medical treatment based on the hemodynamic consideration of reducing the rate of pressure change in the aortic root (Shores et al., 1994). However, rodent studies have indicated that angiotensin II receptor blockade therapy was more effective than β-blocker therapy in treating fibrillin-deficient mice with aneurysms (Habashi et al., 2006). Now, in an article in the *New England Journal of Medicine*, Brooke et al. (2008) present the first report where angiotensin II receptor blockade halts the progression of aortic root dilation in human children (aged 1 to 16 years), offering the promise of an additional medical therapy with significant effectiveness.

This exciting study constitutes direct clinical application of recent basic research on the molecular mechanism of the disease. Recent studies recognized that ECM proteins play a crucial role in the regulation of cytokine bioavailability in the vascular system—in particular, the release of vascular endothelial growth factor (VEGF) and latent transforming growth factor β (TGF-β) (Kalluri, 2003; ten Dijke and Arthur, 2007). The TGF-β family of proteins is composed of over 30 secreted cytokines in mammals, including three TGF-β isoforms, activins, and bone morphogenetic proteins, signaling through five type II receptors and seven type I receptors. The TGF-β family of proteins is involved in development as early as primitive streak formation, and plays an important role during hematopoiesis and organogenesis of the heart, kidney, bone, liver, GI tract, and vasculature. TGF-β family members continue to maintain tissue homeostasis in the adult, functioning through the autocrine, paracrine, and sometimes endocrine systems. Their dysregulation has been implicated in many human diseases such as cancer, fibrosis, autoimmune disease, and vascular disease (Zeisberg et al., 2003; ten Dijke and Arthur, 2007).

TGF-β isoforms are all synthesized as precursor proteins and mostly secreted as large latent complexes (LLCs). The LLCs are composed of large latent TGF-β-binding proteins (LTBP) covalently attached to the small latent complexes that are formed by latency-associated peptide noncovalently linked to the dimerized TGF-β (ten Dijke and Arthur, 2007). LTBP contains multiple epidermal-growth-factor-like repeats, which are also present in fibrillin-1. After secretion, the LLC binds to the ECM via binding of LTBP to fibrillin, which is required for effective TGF-β activation. TGF-β signaling requires release of the mature TGF-β embedded in the ECM and basement membranes by proteases or matrix metalloproteases in a tightly controlled manner to allow interaction with its receptor complexes, and initiation of downstream signaling cascades (ten Dijke and Arthur, 2007). A reduced amount of fibrillin-1 may result in deficiency of LLC sequestration and excessive activation of TGF-β signaling, as demonstrated in mice with deficiency of fibrillin-1, which exhibit features of Marfan's phenotype (Neptune et al., 2003). The aortic aneurysm in these mice can be prevented by either prenatal or postnatal administration of TGF-β neutralizing antibodies.

The angiotensin pathway provides another way to target TGF-β. Angiotensin II is a potent vasoconstrictor that signals through the angiotensin II type I (AT1) receptor and has long been known to upregulate TGF-β1 in animal experiments (Everett et al., 1994). In addition, angiotensin II activates thrombospondin-1 (Zhou et al., 2006), which is a potent activator of TGF-β signaling. Angiotensin II also signals through angiotensin II type II receptor, which antagonizes AT1 signaling.

Agents that can block the angiotensin receptor, such as losartan (an AT1 receptor antagonist; see Figure 1), were initially developed to reduce blood pressure. In the years since their introduction into the clinic, numerous studies have convincingly established the molecular

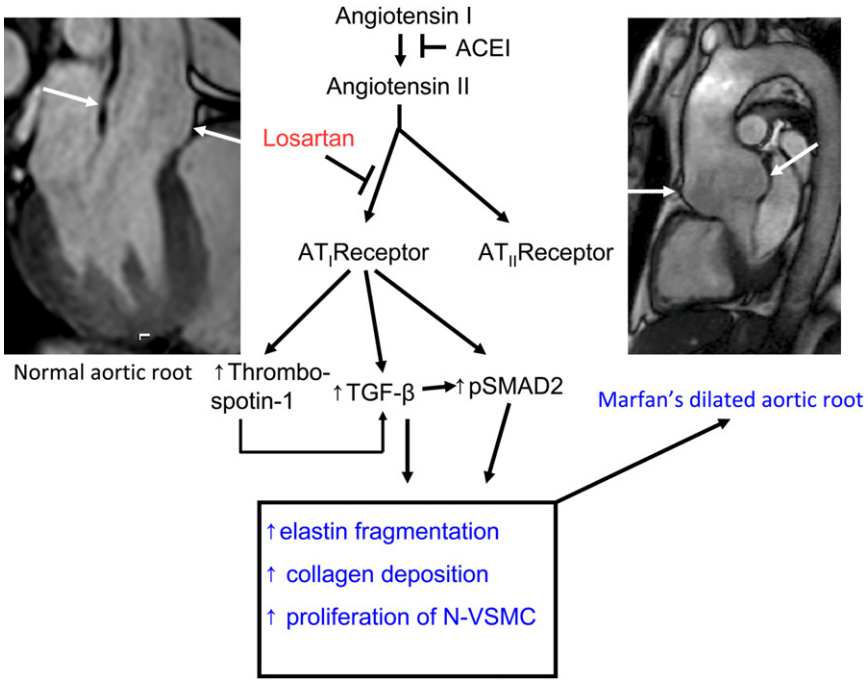

Figure 1. Magnetic Resonance Images of a Normal and a Marfan's Dilated Aortic Root
Brooke et al. (2008) suggest that specific AT1 inhibition by losartan blocks TGF-β signaling, preventing deleterious effects that ultimately result in aortic root dilation. The magnetic resonance images were provided by the BIDMC Division of Cardiology.

connection between angiotensin II action and TGF-β-induced matrix production. Subsequent studies demonstrated the efficacy of losartan in decreasing TGF-β signaling. The study by Brooke and colleagues extends this research to evaluate the efficacy of losartan in targeting TGF-β activity via ECM manipulation in children with Marfan's syndrome.

Brooke et al. report that children on β-blocker therapy alone showed a mean aortic root diameter increase of 3.54 ± 2.87 mm/year as compared with 0.46 ± 0.62 mm/year in children receiving a combination of losartan and β-blocker therapy. This trend continued over several years during which the children were followed. Thus, losartan was effective in counteracting the increase in TGF-β signaling in Marfan patients. This study highlights the importance of cytokine activation by ECM manipulation and opens up exciting treatment possibilities for other conditions in which TGF-β is abnormally expressed, such as Duchenne muscular dystrophy, organ fibrosis, cancer progression, and many others.

The study of rare genetic diseases often leads to a better molecular understanding and novel treatments of more common diseases. Aortic aneurysm and dissection is the fifteenth leading cause of death in the U.S. and accounts for 0.7% of total deaths. The usual risk factors include smoking, male gender, atherosclerosis, and hypertension. β-blockers have been the only treatment modality, in combination with reducing underlying risk factors. In a recent report using a mouse model of thoracic aortic aneurysm, TGF-β signaling alterations were convincingly demonstrated. Perhaps inhibition of TGF-β signaling may prove to be fruitful in treating these patients.

While the prospect of targeting TGF-β signaling may lead to future therapies against many diseases, we must also recognize that normal TGF-β signaling is critical for development, adult tissue homeostasis, and immune function. In particular we must be cautious when considering TGF-β-related therapies in children. Brooke et al. found a drop in the linear growth of body height in treated children. Therefore, losartan may not be a viable long-term treatment option for very young children. The authors report insignificant change in renal function after 3 months of therapy, but the deleterious effect of AT1 inhibition on renal development is well-established in rodents. The balance between the need for TGF-β in normal development and suppression of its activity in the treatment of disease must be carefully considered and evaluated. Future work should focus on identifying novel ways to target TGF-β specifically at the arterial wall interface.

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