

Disorders of the Extracellular Matrix: Marfan Syndrome

- Marfan syndrome represents one of many inherited human disorders caused by defects in extracellular matrix proteins
- these disorders primarily affect connective tissue but some cause systemic problems
- Marfan syndrome is caused by mutations in the ECM protein, fibrillin-1
- the syndrome is manifested by defects in the skeletal, cardiovascular and ocular systems
- estimated incidence of 2-3 per 10,000 individuals
- surprisingly, 25% of the cases are caused by *de novo* mutations (no family history)
- some believe that Abraham Lincoln had Marfan syndrome

Skeletal system:

- disproportionate increase in linear bone growth that causes malformations of fingers, limbs and anterior chest wall, craniofacial defects, scoliosis (curvature of the spine) and joint hypermobility are also noted

Cardiovascular system:

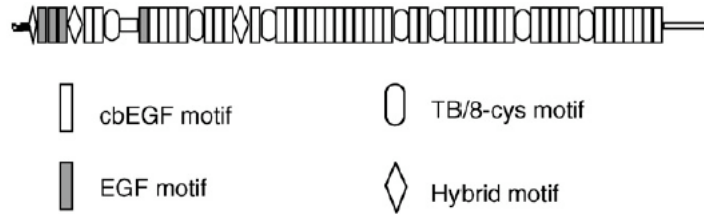
- progressive aortic root enlargement and thick valve leaflets, ascending aortic aneurysm can develop causing aortic regurgitation or rupture

Ocular system:

- early and severe myopia and dislocation of the lens

Fibrillin-1: large 350-kDa glycoprotein consisting of repeating calcium-binding EGF modules and 8-cysteine motifs that are unique to latent TGF- β binding proteins (LTBPs)

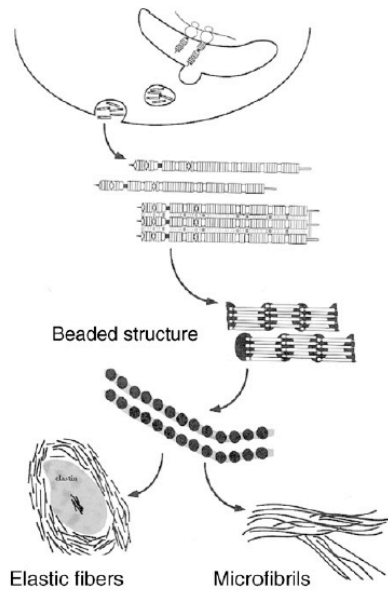
(a)



Fibrillin monomers polymerize into microfibrils that incorporate other proteins, in addition to associating with elastin in elastic fibers

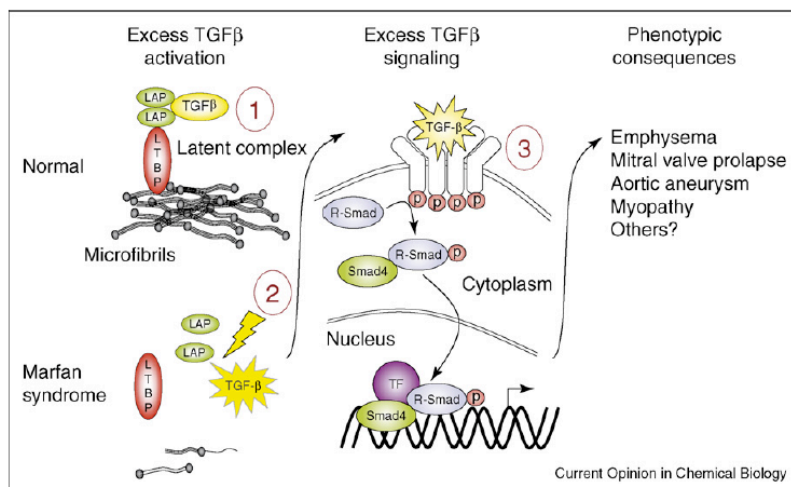
Microfibrils and elastic fibers fulfill the mechanical demands of individual organs and impart elasticity to the aortic wall

(b)



Fibrillin-1 Regulates TGF-beta Bioactivity

- mice homozygous for a partial deletion of fibrillin-1 were shown to have a loss of tissue integrity (similar to emphysema) in the lung that correlated with elevated TGF- β activity
- the lung phenotype could be rescued by systemic administration of anti-TGF- β neutralizing antibodies
- similar hyperactivity of TGF-beta was demonstrated in other organs such as the aortic wall and skeletal muscles



Marfan-related disorders

Loeys-Dietz syndrome: mutations in TGF-beta receptor 1 and 2 (TGFB1 and TGFB2); no lens dislocation

Congenital Contractural Arachnodactyly; mutations in fibrillin-2

Ehlers-Danlos syndrome: mutations in collagen proteins

Mitral valve prolapse

How is TGF- β signaling altered in Loeys-Dietz syndrome?

- even though the TGFB1 and 2 heterozygous mutations are present in conserved kinase domains and expected to result in attenuated TGF- β signaling, vessel walls from LD patients were found to have increased TGF- β signaling and could still respond to TGF- β ligand

possible mechanisms:

- 1) heterozygous mutations in receptor trigger unproductive compensatory events
- 2) mutations have gain-of-function properties

- high level TGF- β signaling might overwhelm half-normal receptor levels
- lower levels of the receptor might be more capable of handling subtle amounts of TGF- β associated with tissue homeostasis but this level might also predispose the cell to altered activity of other signal transducers
- Loeys-Dietz and Marfan might incorporate both excess and deficiency of signaling by multiple cytokines, depending on the extent and/or nature of the ECM changes

Treatments for Marfan Syndrome

- some therapeutic strategies for Marfan vascular disease include the use of beta-adrenergic blockers to slow aortic growth
 - drugs that block the activation of TGF- β are also of growing interest
- Losartan: approved by the FDA in 1995 acts as an angiotensin receptor blocker
- by blocking the action of angiotensin, losartan dilates blood vessels and reduces blood pressure
 - this drug is thought to rescue the Marfan phenotypes by either decreasing the expression of TGF-beta receptor or decreasing expression of TGF- β activators such as thrombospondin-1