Antagnism of GxxPG fragments ameliorates manifestations of aortic disease in Marfan syndrome mice
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Marfan Syndrome

- Autosomal dominant
- Prevalence ca. 1:5,000–1:10,000
- Tall stature and various skeletal anomalies
- Ectopia lentis
- Progressive dilatation of aortic root and aortic dissection
- Mutations in gene for fibrillin-1 (FBN1)
Molecular etiology of MFS still not well understood

- Some of then ideas (chronological listing):
  - Dominant negativ pathogenesis
  - Reduced homeostasis
  - Altered TGFβ-Signaling
  - Increased susceptibility of mutant fibrillin to proteolysis
  - Haploinsufficiency
  - Oxidative stress, impaired NO-mediated aortic relaxation
  - "Feedback" from Fibrillin/Elastin fragments: ↑ MMP aktivity
  - Chemotaxis/Inflammation Kiliç
Pathogenetic Mechanisms of TAAD in Marfan Syndrome

- Fibrillin-1 controls TGFβ bioavailability

Normal
- Few microfibrils or secondary proteolysis

Marfan syndrome
- Microfibrils

Excess TGF-β activation
- LAP, TGF-β, LTBP

Excess TGF-β signaling
- TGFBR2, TGFBR1, SMAD2/3, SMAD4

Phenotypic consequences
- Emphysema
- Mitral valve prolapse
- Aortic aneurysm
- Myopathy
- Others?

GxxPG fragments & Marfan syndrome, 4.10.2012
Our Hypothesis: Matrikines

- It was known that Matrix degradation products (Fibronectin and Aggrecan fragments) themselves possess catalytic activity in osteoarthritis and rheumatoid arthritis.

Matrikines in Marfan syndrome

- Mutant Fibrillin; susceptible to proteolysis. Booms et al. *Hum Genet* 2000
- RGD fragments of Fibrillin increase MMP production. Booms et al. *Hum Genet* 2005
- GxxPG fragments of Fibrillin increase MMP production. Booms et al *J Mol Cell Cardiol* 2006

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\[ xGxxPG: \text{Typ-VIII-\(\beta\) Turn} \]
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- 27x in Elastin
- 3x in Fibrillin-1
- Statistically significant increase in occurrences of GxxPG in matrix proteins in general
mgR/mgR aortic extracts induce macrophage chemotaxis


Experimental strategy

Marfan syndrome

- GxxPG fragments
- Neutralization of GxxPG by BA4 Ab
- Lactose shed EBP from cell surface

Elastin-laminin receptor

Signal transduction

Target cell

Upregulation of MMPs
Increased macrophage chemotaxis
Stimulation of cellular proliferation
others
Treatment with BA4 reduces elastin fragmentation and prevents macrophage infiltration in the aorta of mgR/mgR Marfan mice.
Treatment with BA4 reduces upregulation of MMP expression in the aorta of mgR/mgR Marfan mice.
Treatment with BA4 (3)

Immunofluorescence: F4/80 (Makrophages) and MMP-9 expression

MMP-9 expression from macrophages is reduced by BA4
Treatment with BA4 reduces upregulation of pSmad2 activity
⇒ In contrast to losartan, no effect on ppERK
Treatment with BA4 (5)

TGF-β1 and LTBP1-Expression in the Aorta

⇒ Health of matrix (fragmentation) and TGF-β metabolism are interconnected
Treatment with BA4 (6)

Treatment with BA4 reduces manifestations of pulmonary emphysema in mgR/mgR mice
Integrative model

Guo et al, under review.
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BA4 reaches tissues at relevant concentrations