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Review

TGF-β signalopathies as a paradigm for translational medicine

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ABSTRACT

This review focusses on impact of a better knowledge of pathogenic mechanisms of Marfan and related disorders on their treatment strategies. It was long believed that a structural impairment formed the basis of Marfan syndrome as deficiency in the structural extracellular matrix component, fibrillin-1 is the cause of Marfan syndrome. However, the study of Marfan mouse models has revealed the strong involvement of the transforming growth factor-β signalling pathway in the pathogenesis of Marfan. Similarly, this pathway was demonstrated to be key in the pathogenesis of Loeys-Dietz and Shprintzen-Goldberg syndrome. The elucidation of the underlying pathogenic mechanisms has led to new treatment strategies, targeting the overactive TGF-β pathway. Various clinical trials are currently investigating the potential new treatment options. A meta-analysis will contribute to a better understanding of the various trial results.

Contents

1. Introduction

In 1991, a major scientific breakthrough occurred with the discovery of the molecular basis of Marfan syndrome (MFS). Nearly a century after the first description of MFS the causal gene was identified, *FBN1*, encoding the extracellular matrix protein fibrillin-1 (Dietz et al., 1991). MFS is an autosomal dominant connective tissue disorder characterised by the pleiotropic involvement of several organ systems, including the cardiovascular (aortic aneurysms, mitral valve disease), ocular (ectopia lentis), skeletal (overgrowth, joint laxity) and cutaneous system. Subsequent development of MFS-mouse models has provided new insights into the pathogenesis. One paramount discovery in this respect was the demonstration of the involvement of transforming growth factor-beta (TGF-β) signalling dysregulation (Pereira et al., 1999; Neptune et al., 2003; Habashi et al., 2006). Within the aortic wall of MFS patients enhanced TGF-β signalling is observed, with both

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the canonical and non-canonical pathways playing a role in the formation of thoracic aortic aneurysms (TAA) (Neptune et al., 2003; Holm et al., 2011). The subsequent identification of the MFS-like condition, called Loeys-Dietz syndrome (LDS), and its molecular basis with mutations in transforming growth factor beta receptors 1 and 2 (*TGFBR1*, *TGFBR2*), transforming growth factor beta ligand 2 and 3 (*TGFB2*, *TGFB3)* and Smad family member 3 (*SMAD3*) contributing to the disease pathogenesis (Loeys et al., 2005; van de Laar et al., 2011; Lindsay et al., 2012; Bertoli-Avella et al., 2015), provided further proof of the involvement of the TGF-β pathway. In addition, mutations in v-ski avian sarcoma viral oncogene homolog (*SKI*), a known inhibitor of TGF-β signalling, cause Shprintzen-Goldberg syndrome (Doyle et al., 2012) (SGS). The discovery of the central role of the TGF-β signalling pathway provided new insights into the pathogenesis of these syndromes and new treatment strategies.

2. Transforming growth factor beta signalling paradox

With the discovery of fibrillin-1 being an important regulator of TGF-β homeostasis (Isogai et al., 2003; Chaudhry et al., 2007), it became clear that TGF-β signalling is involved in the pathogenesis of numerous connective tissue disorders. Fibrillin-1 is part of extracellular matrix (ECM) microfibrils, that interact with elastin, collagen and other ECM components. Besides its structural function, fibrillin-1 binds the latent transforming growth factor binding protein (LTBP), targeting the large latent complex (LLC) to the ECM. This interaction regulates the sequestration of TGF-β and thus the bioavailability of the TGF-β ligand. Mutations in the *FBN1* gene lead to fibrillin-1 deficiency and also affect the targeting of the large latent complexes. An uncontrolled release of TGF-β is observed in *FBN1* deficient mice (Neptune et al., 2003; Franken et al., 2013). Subsequently, an upregulation of the TGF-β pathway was confirmed in the aortic wall of Marfan patients. Under normal circumstances, TGF-β ligand is released from the LLC and will bind to the serine/threonine protein kinase receptors, TGFBRI and TGFBRII. First, active TGF-β binds to a TGFBRII dimer orchestrating the assembly and subsequent transphosphorylation of TGFBRI, resulting in the downstream canonical signalling cascade. Receptor-regulated SMADs (R-SMADs; SMAD2 or SMAD3) are recruited and phosphorylated, which in turn form a complex with SMAD4. After translocation of the SMAD4/R-SMAD complex to the nucleus, transcription of TGF-β target genes is initiated (Shi and Massague, 2003). SKI protein induces a negative feedback loop of the TGF-β pathway by binding to the SMAD4/R-SMAD complex, preventing nuclear translocation and TGF-β target gene transcription (Fig. 1).

This signalling process is interrupted when loss-of-function mutations occur in different components of the TGFβ pathway. In LDS, mutations in the genes coding for the TGF-β ligands (TGFB2, TGFB3), receptors (TGFBR1, TGFBR2) or the intracellular downstream effector (SMAD3) are involved. Mutations in these genes were all shown to cause loss-of-function (Loeys et al., 2005; van de Laar et al., 2011; Boileau et al., 2012; Lindsay et al., 2012; Bertoli-Avella et al., 2015). Paradoxically, these genetic loss-of-function mutations result in an increase of TGF-β signalling, as demonstrated by elevated levels of phosphorylated SMAD2, ERK1/2, TGF-β target genes such as CTGF (Connective Tissue Growth Factor) and increased TGFβ1 levels in aortic wall tissue of patients (Loeys et al., 2005; Boileau et al., 2012; Lindsay et al., 2012; Bertoli-Avella et al., 2015). The *SKI* mutations in SGS specifically disrupt the SKI domain that interacts with the SMAD4/R-SMAD complex and affect the recruitment of transcriptional corepressors. As expected with the loss of an inhibitor, we observe enhancement of TGF-β signalling in fibroblasts from SGS patients (Doyle et al., 2012) (Fig. 1).

Several mechanisms have been proposed to explain the paradoxical increase in TGFβ signalling despite of the apparent loss-of-

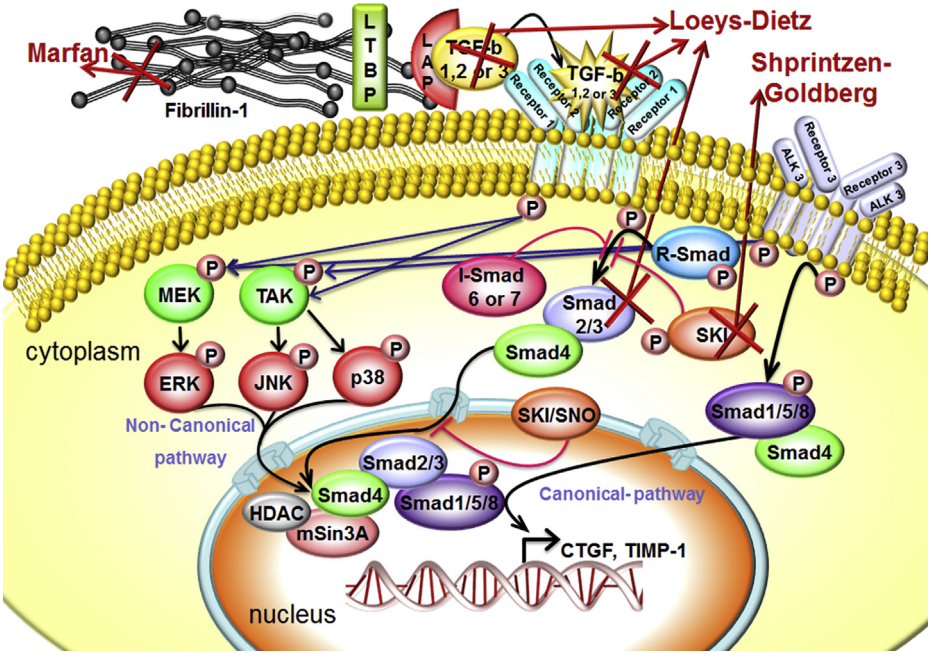

Fig. 1. TGF-β signalling via canonical and non-canonical pathways. The defective components of the pathway are indicated with a red cross and the corresponding diseases are specified with a red arrow. Deficiencies in the structural ECM component, fibrillin-1, lead to an uncontrolled release of the TGF-β ligands 1,2 or 3. Ultimately resulting in an upregulation of both the canonical and non-canonical pathway and thus an overexpression of the TGF-β target genes. In LDS, mutations occur at the level of the TGF-β ligands, receptors or effectors, resulting in a paradoxical increase of both downstream pathways. This enhancement is also observed in SGS, in which loss-of-function mutations occur in the proto-oncogene SKI. The proto-oncoproteins ski and sno normally induces a negative feedback loop of the pathway by interacting with the Smad2/3-Smad4 complex. CTGF: connective tissue growth factor; TIMP-1: tissue inhibitor of metalloproteinase 1. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)