Aberrant TGF-β signaling underlies the pathogenesis of aortic aneurysm in Shprintzen-Goldberg syndrome

References


Mutations in the TGF-β repressor SKI cause Shprintzen-Goldberg syndrome with aortic aneurysm Doyle et al. (2012)
Nature Genetics 44(11):1249–54

Aberrant transforming growth factor-beta (TGF-β) activation has been associated with the presentation of aortic aneurysm in disparate connective tissue disorders including Marfan syndrome (MFS) (1), Loey-Dietz syndrome and Shprintzen-Goldberg syndrome (SGS). TGF-β signaling pathway plays a central role in the regulation of diverse arrays of cellular processes, both during development as well as in adult organism, including cell proliferation, differentiation, angiogenesis, apoptosis and maintenance of homeostasis. The signaling cascade involves the binding of TGF-β ligands to TGF-β receptor II with subsequent recruitment and phosphorylation of TGF-β receptor I. This triggers the phosphorylation of receptor-regulated SMADs (R-SMADs) which, after binding to SMAD4, are translocated to nucleus as R-SMAD/SMAD4 complex and regulate the expression of target genes (Fig. 2).

In a recent study, Doyle et al. elegantly demonstrate the important role of increased TGF-β signaling in the pathogenesis of aortic aneurysm in SGS patients. Using whole-exome sequencing and mutation analysis, the authors identified de novo substitution or deletion mutations in the Sloan-Kettering Institute (SKI) protein in the affected individuals. The SKI family of proteins is an important part of the negative feedback loop in TGF-β signaling pathway (Fig. 2). Interestingly, a substantial number of substitution mutations in SKI were localized in the N-terminal region (residues 17–45) of the protein which is known to be the R-SMAD-binding domain. The authors postulated that the inherent nature of the identified mutations disrupts the molecular interactions of SKI with R-SMAD and impedes the
recruitment of transcriptional corepressors resulting in elevated TGF-β signaling. Confirming this, the authors found enhanced SMAD-2/3 phosphorylation, as well as increased expression of many TGF-β responsive genes (COL1A1, COL3A1, FN1, VIM and CDKN1A) in the fibroblasts derived from SGS patients. Furthermore, specific silencing of mammalian SKI paralogs (skia and skib) in zebrafish embryos leads to malformations in the cardiac outflow tract and other cardinal features of SGS including craniofacial defects, microcephaly and spinal malformations, thus supporting a critical role of SKI in regulating TGF-β activation during cardiac development. The findings by Doyle et al. suggest that the regional and temporal differences in SKI expression in vessel wall, cellular distribution and proper function are the underlying mechanism for the distinctive aneurysm phenotype in SGS. This also raises the exciting possibility that regulating the SKI function in vessel wall may ameliorate vessel wall defects in SGS and potentially other disorders characterized by abnormal TGF-β signaling.

Therapeutic targeting of components in TGF-β signaling pathway represents an attractive area of research for the treatment of not only vascular malformations but also skeletal muscle diseases such as Duchenne’s muscular dystrophy. In fact, Losartan – an angiotensin (AT1) receptor antagonist, has been shown to reduce TGF-β activation in muscles and reduce fibrosis in dystrophin-deficient mice (2), and improve aortic function in a mouse model of MFS (3). Given a critical role of the extracellular matrix components (ECM) in regulating TGF-β levels and activity, it would not be surprising that more mutations in ECM components will eventually be discovered in association with inherited vascular diseases in relation to the aberrant activation of TGF-β signaling. In conclusion, given the complex regulation of TGF-β signaling pathway during development and tissue homeostasis, derangements in the form of over or under activity can lead to common phenotypes in clinical disorders of diverse etiologies. In addition, it also underlines the need for assessing potential therapies targeting TGF-β signaling in the context of specific cellular responses.

A Jan

Centre for Molecular Medicine and Therapeutic, University of British Columbia, Vancouver, BC V5Z 4H4, Canada.
e-mail: ajan@cmmt.ubc.ca