Aortic Aneurysms in Loeys-Dietz Syndrome - A Tale of Two Pathways?

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Aortic aneurysms in Loeys-Dietz syndrome —
a tale of two pathways?

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Loeys-Dietz syndrome (LDS) is a connective tissue disorder that is characterized by skeletal abnormalities, craniofacial malformations, and a high predisposition for aortic aneurysm. In this issue of the JCI, Gallo et al. developed transgenic mouse strains harboring missense mutations in the genes encoding type I or II TGF-β receptors. These mice exhibited several LDS-associated phenotypes. Despite being functionally defective, the mutated receptors enhanced TGF-β signaling in vivo, inferred by detection of increased levels of phosphorylated Smad2. Aortic aneurysms in these LDS mice were ablated by treatment with the AT1 type 1 (AT1) receptor antagonist losartan. The results from this study will foster further interest into the potential therapeutic implications of AT1 receptor antagonists.

TGF-β and Ang II pathways in thoracic aortic aneurysm formation

Aneurysms that present in the thoracic aorta have a wide range of syndromic and nonsyndromic associations (1). Marfan syndrome is one of the most researched syndromic associations (1). Marfan syndrome is one of the most researched syndromic associations (1). Marfan syndrome (6). Although these studies shed light on the interactions between TGF-β and AT1R signaling in TAA development, the specific mechanism of these interactions has not been elucidated (7).

TGF-β was further implicated in the development of aortic aneurysms following the discovery of mutations in the genes encoding TGF-β receptors in individuals afflicted with a clinical syndrome that has similarities to Marfan syndrome. This condition was subsequently termed Loeys-Dietz syndrome (LDS). Patients afflicted with LDS have a more aggressive form of ascending aortic dilation compared with those with Marfan syndrome (8). Dilation of the aortic root is detected very early, with documented aortic dissections occurring in patients with LDS as young as 3 months of age (9). Unlike Marfan syndrome, the vascular pathologies associated with LDS are more diffuse in location, as these aneurysms occur in other aortic regions and several vascular beds (10). The genetic basis of LDS is the presence of mutations in the genes encoding either type I or type II TGF-β receptors (11). TGF-β receptors function as multimers of both subtypes; therefore, clinical presentations are similar when defects are present in either receptor subtype. Although the TGF-β receptor mutations result in impaired function, detection of enhanced Smad2 or Smad3 phosphorylation in surgical samples implies that TGF-β signaling is actually increased in patients with LDS (11). The involvement of TGF-β signaling in LDS development parallels the mechanisms of TAA in Marfan syndrome. Unlike Marfan syndrome, there is a paucity of information on a role for Ang II in LDS.

TGF-β receptor mutations promote aortic aneurysms in LDS mouse models

In this issue of the JCI, Gallo et al. (12) generated an array of mouse models with TGF-β receptor dysfunction. These mouse models included mice with haploinsufficiency of either TGF-β receptor (Tgfb1−/− or Tgfb2−/− mice), knockin of LDS-associated alleles (Tgfb1M318R or Tgfb2G357W mice), and transgenic overexpression of the Tgfb2G357W mutant. Haploinsufficiency of either receptor subtype did not produce vascular pathologies; however, heterogenous knockin of Tgfb1M318R or Tgfb2G357W mutations or transgenic overexpression of mutated Tgfb2G357W led to severe aortic pathologies. These included...
Mechanism of TGF-β and Ang II interactions in TAA development

The authors conclude that aortic pathologies are generated by Ang II augmentation of TGF-β signaling (Figure 1). Indeed, Ang II stimulates TGF-β signaling by promoting secretion of TGF-β isoforms from vascular smooth muscle cells (15). Conversely, TGF-β signaling in vascular smooth muscle cells downregulates AT1R expression (16). The specific mechanisms by which defective TGF-β receptors lead to augmented AT1R stimulation and generation of aortic pathologies in LDS is still a quandary. This issue is further complicated by evidence that suggests that TGF-β promotes ascending aortic dilation through a combination of AT1R-dependent and -independent pathways (17). Clearly, additional studies are warranted to further elucidate the pathways that promote aortic aneurysm.

Therapeutic implications

Overall, the findings of Gallo et al. (12) provide important insight into the pathogenesis of aortic aneurysms in LDS. The authors demonstrated that a missense mutation in a single allele within either of the genes encoding TGF-β receptor type 1 or 2 is sufficient to recapitulate LDS phenotypes in mice. In addition, these studies provide rationale for considering the potential issue is the promiscuity of Smad2 phosphorylation, which is not exclusively a result of TGF-β signaling. Therefore, the use of Smad2 phosphorylation as an indicator of TGF-β pathway activation could compromise data interpretation (13). Another intriguing aspect of the Gallo et al. study was that administration of a TGF-β-neutralizing antibody failed to prevent aortic root dilation, unlike the efficacy of this antibody treatment that has been demonstrated in the Marfan mouse (3).

In contrast to TGF-β neutralization, Gallo et al. (12) provided convincing evidence that losartan administration ablated aortic pathology and expansion. Similar to the Marfan mouse, the decreased pathology was not mimicked by administration of a β-adrenoceptor antagonist (3). While losartan is primarily defined as an AT1R antagonist, its metabolites do have a potential range of other activities (14). Therefore, evaluation of other ARBs would assist in determining whether losartan-associated effects are due specifically to AT1R antagonism.
application of AT1R antagonism as a therapy for patients with LDS. There is both retrospective and evolving prospective evidence that AT1R antagonism may be beneficial to patients with Marfan syndrome (6, 18, 19). Together, the findings in patients with Marfan syndrome and the results from the Gallo et al. study (12) indicate that patients with LMS may potentially benefit from AT1R antagonism. Losartan has been the ARB of choice in most ongoing trials; however, the use of an ARB with a more favorable pharmacokinetic profile and longer half-life may enhance the protective effects against TAAs. The availability of the LMS mouse described by Gallo et al. (12) provides a model to determine the relative efficacies of this class of drugs before application to humans.

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Toward postnatal reversal of ocular congenital malformations
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Aniridia is a panocular disorder that severely affects vision in early life. Most cases are caused by dominantly inherited mutations or deletions of the PAX6 gene, which encodes a transcription factor that is essential for the development of the eye and the central nervous system. In this issue of the JCI, Gregory-Evans and colleagues demonstrate that early postnatal topical administration of an ataluren-based formulation reverses congenital malformations in the postnatal mouse eye, providing evidence that manipulation of PAX6 after birth may lead to corrective tissue remodeling. These findings offer hope that ataluren administration could be a therapeutic paradigm applicable to some major congenital eye defects.

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Conflict of interest: José-Alain Sahel is a founder of and consultant for GenSight and Puxim Vision and a consultant for Sanofi and Genesis Signal.

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Mutations that inactivate gene function by promoting premature translational termination cause a large number of human diseases. It is thought that at least one-third of all genetic diseases and many types of cancer are the result of such mutations (1, 2). These mutations are referred to as nonsense mutations, premature stop mutations, or premature termination codons (PTCs). Given that PTCs often result in a complete loss of protein function, the associated diseases usually manifest as severe phenotypes. Examples of PTC-associated diseases include CF, Duchenne muscular dystrophy (DMD), and aniridia, among others.

Aniridia, a panocular disorder
Aniridia is a rare eye disease with an estimated prevalence of approximately 1 in 40,000 to 1 in 100,000 individuals. It is present at birth and characterized by a total

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