POLYCYSTIC KIDNEY DISEASE

TGF- β signalling and vascular complications in ADPKD

Dysregulation of TGF- β signalling might have a role in the development of aortic aneurysms in patients with autosomal dominant polycystic kidney disease (ADPKD), according to new data from Terry Watnick and colleagues. Such dysregulation was previously implicated in the pathogenesis of vascular complications in Marfan syndrome. “Based on phenotypic overlap between ADPKD and Marfan syndrome, we speculated that there might be a relationship between these two disorders,” explains Watnick.

Marfan syndrome is caused by mutations in the *FBN-1* gene, whereas ADPKD is caused by mutations in *PKD1* or *PKD2*. To investigate a potential genetic interaction between these disorders, Watnick and colleagues crossed mice that had one *Pkd1* knockout allele (*Pkd1*^{KO/+}) with mice that were heterozygous for a *Fbn1* mutation (*Fbn1*^{C1039G/+}). They found that double heterozygous offspring with mutations in both *Pkd1* and *Fbn1* had more-severe aortic pathology than did their *Fbn1*^{C1039G/+} littermates.

“A series of seminal papers by our colleague Hal Dietz had recently shown that mutations in *Fbn1* result in upregulation of the canonical TGF- β signalling pathway, and that this was of primary importance in several manifestations of Marfan syndrome, including aortic aneurysms,” says Watnick. “We speculated that the genetic interaction between *Fbn1* and *Pkd1* might be based on further upregulation of TGF- β activity in the context of a *Pkd1* mutation.”

Consistent with this hypothesis, TGF- β activity in the aortic wall was increased in the double heterozygotes compared with *Pkd1*^{KO/+} or *Fbn1*^{C1039G/+} mice. Moreover, vascular smooth muscle cells from *Pkd1*^{KO/+} mice showed

Magnetic resonance angiogram showing an ascending aortic aneurysm (arrow) in a patient with ADPKD. Image courtesy of Terry Watnick, Division of Nephrology, University of Maryland School of Medicine, Baltimore, MD, USA.

an increased response to TGF- β compared with wild-type controls. The researchers also report evidence of increased TGF- β signalling in aortic tissue sections from a patient with ADPKD who had an ascending aortic aneurysm at the age of 19 years.

Watnick believes that these data might have implications for the treatment of vascular complications in patients with ADPKD. She suggests that if ADPKD follows the Marfan's paradigm, angiotensin receptor blockers, which decrease both canonical and noncanonical TGF- β signalling, might be more effective than angiotensin-converting-enzyme inhibitors, which decrease canonical TGF- β signalling only, in improving aortic pathology in these patients. The researchers plan to continue to pursue this hypothesis in mouse models of ADPKD.

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