Understanding the Low Penetrance of Bone Morphogenetic Protein Receptor 2 Gene Mutations

Another Needle in the Haystack

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Pulmonary arterial hypertension (PAH) is a progressive disease of the pulmonary circulation in which thrombosis, inflammation, and unbridled cellular proliferation obliterate the arterial lumen, causing progressive right heart failure and death. The pathogenesis remains enigmatic, and current therapeutic strategies are limited. In 1951, Dresdale published the first report of a family in which 3 first-degree relatives had what was then called primary pulmonary hypertension. Subsequently, the initial, prospective National Institutes of Health (NIH)-sponsored North American primary pulmonary hypertension registry included 11 patients who had a relevant family history (6%). Several features of the gene transmission were apparent by the 1980s: vertical transmission indicated a single dominant gene, transmission to offspring of either sex argued against X- or Y-linkage, and multiple skip generations highlighted an incomplete penetrance.

The race to identify the causative gene was ultimately won simultaneously by 2 groups working in parallel. Nichols et al used a microsatellite marker strategy to identify the locus within families on chromosome 2q32. Then groups at Columbia Presbyterian in New York and an International Consortium, including Vanderbilt, simultaneously identified mutations in a receptor for the transforming growth factor β family, the bone morphogenetic protein receptor 2 (BMPR-2), as the cause of most cases of what is now classified as heritable pulmonary arterial hypertension (HPAH). BMPR-2 mutations have subsequently been found in between 5% and 25% of patients who have idiopathic PAH without any relevant family history. Mutations in other transforming growth factor β family proteins, activin-like kinase-1 and endoglin, are unusual causes for HPAH. Although numerous BMPR-2 mutations have been found, in most cases (~70%) the mutation leads to a haploinsufficient state in which cellular BMPR-2 levels are reduced by ~50%, usually because the mutated transcript is subject to nonsense-mediated decay.

Signaling in the lung vasculature downstream from BMPR-2 receptor activation has been studied intensely, and we now know that pulmonary vascular smooth muscle cells isolated from patients who were transplanted to treat PAH demonstrate proliferation in response to bone morphogenetic protein (BMP) 2, 4, and 7; in contrast, cells from control lungs are quiescent after stimulation. For endothelial cells, the opposite is true: healthy pulmonary endothelial cells require BMP signaling to avoid apoptosis, and reductions in BMPR-2 signaling increase the susceptibility to apoptosis. It is thought that exaggerated pulmonary endothelial apoptosis (eg, in response to injury) and excess vascular smooth muscle proliferation both contribute to the pathogenesis of PAH.

Thus, a reduced level of BMPR-2 signaling in the lung vasculature probably contributes to 2 of the many pathophysiologic processes that collectively result in PAH. Indeed, reduced BMPR-2 protein has been identified in many different forms of experimental and human PAH, even when BMPR-2 gene mutations were not identified.

In summary, a variety of lines of investigation have demonstrated that germline mutations in the BMPR-2 gene result in HPAH. The disease is transmitted in an autosomal dominant fashion, and BMPR-2 signaling is associated with a healthy pulmonary vasculature in that BMPR-2 and its associated signaling are reduced in PAH tissues without BMPR-2 mutation. Moreover, patients with the gene mutation appear to have a particularly severe clinical course compared to idiopathic patients without the mutation. Because of the abundant evidence that BMPR-2 signaling plays such a critical role in the lung vasculature, it has been particularly vexing that so many mutation carriers have no apparent phenotype (for a representative family, see Austin et al). This incomplete penetrance (only ~20% of carriers develop disease) has been an enormous source of frustration for all members of the afflicted families and the clinicians who take care of them. It has made genetic counseling difficult, and it has made large-scale attempts to screen family members for early signs of disease prohibitively costly.

With 13 years having elapsed since identifying BMPR-2 receptor mutations as causative for HPAH, research to explain the incomplete penetrance has been much like looking for a needle in the haystack. Large-scale single nucleotide polymorphism studies exploring other disease-modifying genes have been generally negative. However, at a cellular level, a number of plausible mechanisms have emerged that could contribute to disease penetrance by altering BMPR-2
expression. For example, the BMPR-2 transcript is a target for several micro-RNAs, including miR-17/92 which is regulated by interleukin-6. In addition, BMPR-2 protein is metabolized at the cell surface by E3 ubiquitin ligase. These pathways could reduce the expression of BMPR-2 in response to inflammation, which could further impair BMPR-2 signaling on the genetic background of haploinsufficient mutation. In patients, studies have examined variations in disease penetrance among BMPR-2 carriers. Austin et al demonstrated that female gene carriers are more likely to manifest disease than male carriers, and furthermore that among the female carriers those with a more active cytochrome P450 isoform 1B1 (CYP1B1) were more likely to manifest disease. They corroborated the genetic CYP1B1 testing by measuring urinary metabolites in a small cohort and found that 2-hydroxyestrogen was less abundant than 16-$\alpha$-hydroxyestrone in afflicted carriers. Although important in understanding both the female predominance of HPAH disease and in explaining why some female carriers might be more likely to manifest disease than others, this finding only scratched the surface of the penetrance problem. Hamid et al subsequently reported that the level of expression for the wild-type (normal) allele among mutation carriers with 4 different haploinsufficient mutations correlated with disease expression. Carriers with relatively lower expression of the wild-type BMPR-2 allele were more likely to be afflicted. This observation suggested that there was a threshold effect and that genetic variation, which reduced the BMPR-2 expression from the normal wild-type allele, would determine the disease expression. Of course, this observation correlated with the published data showing reduced levels of BMPR-2 protein in lung tissue from idiopathic PAH patients without BMPR-2 mutations. Despite these important pieces of data, the authors concede, it remains unclear whether the alteration in isoform expression is fixed or can be acquired. It would be straightforward to test this in cultured cells, for example, in response to inflammation, or in animals with similar isoform expression. The authors argue that observations in lymphocytes suggest that these differences are primarily genetic, but the bone marrow has recently been shown to be markedly abnormal in patients with idiopathic PAH, and so the cultured lymphocyte functional changes could be secondary to the disease itself. The impact of the isoform expression on canonical Smad signaling should also be evaluated. Nevertheless, the present data offer a new and testable hypothesis: that alternative splicing can change BMPR-2-mediated signaling and the development of the HPAH phenotype. The authors point out that at least one splice repressor (hnRNPA1) may have been higher in the patients as compared with the healthy carriers, and their detailed description of splice-modifying sequences in exon 12 opens the door for additional research.

Indeed, although identifying the gene responsible for most HPAH was a remarkable accomplishment, the task of understanding such low disease penetrance has been much like finding a needle in the haystack. A number of recent advances have been made that increase our understanding of how mutations can contribute to disease pathobiology. These include the importance of cellular specificity in BMP signaling and the identification of a wider role for BMPR-2 in inflammation and metabolism. The contribution by Cogan et al has implications for predicting whether a gene carrier is or is not likely to develop disease and simultaneously offers a novel target
for intervention. Both of these aspects require additional research and corroboration, and a more thorough understanding of disease penetrance remains a top priority within the field. Not only would this information be powerful for the patients as they plan their lives (especially for the majority who are unlikely to develop disease), it would also allow us to target a group of people for critical research toward understanding the earliest mechanisms of disease pathogenesis. Accurate prediction of which carriers will eventually manifest disease would also facilitate development of therapies that either directly augment the BMPR-2 receptor expression/function or rescue the aberrant downstream signaling.23

Disclosures

None.

References


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