Pathophysiology of Pulmonary Hypertension: Recognizing Triggers of the Disease

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It is unclear whether the various types of PAH share a common pathogenic mechanism. Although our understanding of the pathobiological changes underlying PAH has progressed rapidly over the past few years, it is still impossible to classify patients on a pathogenic basis and to define therapeutic approach accordingly. Three factors are considered to cause the increased pulmonary vascular resistance in PAH: vasoconstriction, remodeling of the pulmonary vessel wall, and thrombosis in situ. The latter two are easily evident with light microscopy, whereas vasoconstriction is best demonstrated by vasodilator testing. Most specialists now agree that pulmonary vascular proliferation and remodeling, and not vasoconstriction, is the hallmark of PAH pathogenesis.

Bone morphogenetic protein receptor 2 and related molecules

The recent identification of a pulmonary hypertension gene (bone morphogenetic protein receptor 2, *BMPR2*, a member of the transforming growth factor beta superfamily) provides the opportunity to develop a deeper understanding from a molecular biology perspective. Heterogeneous germline mutations in *BMPR2* occur in approximately 60%, 25%, and 10% of patients with familial, sporadic, and fenfluramine derivatives-associated PAH, respectively. In addition, germline mutations in the gene coding activin-like receptor kinase 1, another member of the transforming growth factor beta superfamily, have been identified in patients with hereditary hemorrhagic telangiectasia. These patients develop severe plexiform pulmonary (or idiopathic) hypertension, which is symptomatically indistinguishable from PPH. The relevance of the transforming growth factor beta superfamily in the etiology of PAH is further supported by a recent report of endoglin germline mutation in a patient who had hereditary hemorrhagic telangiectasia and dexfenfluramine-associated PAH. These observations support the hypothesis that mutations in the transforming growth factor beta superfamily may be a trigger for pulmonary vascular remodeling.

The transforming growth factor beta superfamily is diverse, comprising transforming growth factor beta isoforms, the bone morphogenetic proteins, activins, and growth and differentiation factors. A possible mechanism whereby such a mutation could trigger remodeling is emerging from studies on BMPR2. BMPR2 mediates its actions by binding ligand in conjunction with a type I receptor to form a heterodimer complex on the cell surface and subsequently propagate an intracellular signal via Smad molecules. As BMPR2 is involved in cell proliferation and apoptosis, the occurrence of a mutation in this protein could result in abnormal signaling in pulmonary artery smooth muscle cells, leading to loss of antiproliferative or apoptotic mechanisms. This theory is supported by the demonstration of dysregulated growth inhibition of pulmonary artery smooth muscle cells from patients with PPH exposed to bone morphogenic proteins and transforming growth factor beta. In fact, additional findings suggest that all forms of pulmonary hypertension may be linked to defects in the signaling pathways involved in angiogenesis, such as angiopoietin-1 and bone morphogenetic protein receptors. The possible involvement of the transforming growth factor beta superfamily in the pathophysiology of PAH may have identified a novel target for therapeutic intervention.

Modifier genes and environmental factors

As PAH develops in only 10% to 20% of individuals with *BMPR2* mutations, the contribution of other factors for the development of PAH is undeniable. The "multiple hit" hypothesis has been proposed whereby the combination of a number of factors may precipitate the disease. In such a scenario, a susceptible individual with a *BMPR2* mutation would require additional insults such as exposure to anorectic drug before manifesting PAH. Another theory is that of the role of modifier genes in the pathogenesis of PAH. As recently detailed by Runo and Loyd in their *Lancet* review, genes and gene products putatively implicated in the pathogenesis of PAH include prostacyclin synthase, nitric oxide synthase, serotonin transporter, serine elastases, matrix metalloproteinases, voltage-gated potassium channels, angiotensin-converting enzyme, vascular endothelial growth factor, carbamoyl phosphate synthase, plasminogen activator inhibitor type 1, and endothelins.

Endothelial dysfunction

Recent advances in the understanding of the molecular mechanisms involved in PAH suggest that endothelial dysfunction could correspond to downstream manifestations of the disease rather than a central pathogenic mechanism. There is now considerable evidence that endothelial dysfunction leading to exaggerated vasoconstriction, and impaired vasodilatation plays a key role in PAH. Interestingly, chronically impaired production of vasodilators such as nitric oxide and prostacyclin along with prolonged overexpression of vasoconstrictors such as endothelin-1 not only affect vascular tone, but also promote vascular remodeling and therefore represent a logical pharmacological target. ■