Mutations in Bone Morphogenetic Protein Receptor Genes in Pulmonary Arterial Hypertension Patients
– Possible Involvement of BMPRIB –

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Pulmonary arterial hypertension (PAH) is a progressive and substantially fatal disease characterized by sustained elevation of pulmonary artery pressure (mean >25 mmHg at rest). Pathophysiological features of PAH include vascular remodeling of precapillary resistance pulmonary arteries (ie, dysfunction of endothelial cells, activation and proliferation of smooth muscle cells, and fibrous infiltration into the arterial wall). These processes give rise to marked vasoconstriction and obstructive or plexiform changes of the small pulmonary arteries.¹

According to the updated clinical classification of pulmonary hypertension (Dana Point, 2008),² PAH is classified as: (1) idiopathic, (2) heritable, (3) drug- or toxin-induced, (4) associated with other diseases, and (5) persistent pulmonary hypertension of the newborn. Among these, genetic disorders of bone morphogenetic protein receptor type II (BMPRII), one of the TGF-β superfamily receptors, have been extensively studied and shown to be significant in the pathogenesis of PAH. Recent studies have clarified that mutations in BMPR2 have been identified in approximately 70% of the hereditable cases and in up to 40% of cases of idiopathic PAH.³

BMP signaling (Figure) in general regulates growth, differentiation, survival, and apoptosis in a variety of cells during embryogenesis, postnatal development, and maintenance of adult tissues.³⁻⁵ BMPRII is a constitutively active serine/threonine kinase and it initiates intracellular signaling in response to binding to the tissue specific BMP ligands. Upon binding to the ligands, BMPRII phosphorylates the glycine/serine-rich (GS-) domain on the proximal intracellular portion of associated type I receptors known as activin receptor-like kinase 1 (ALK1), BMPRIA (ALK3), or BMPRIB (ALK6). The activated type I receptors, in turn, phosphorylate downstream receptor-mediated signaling proteins (R-Smads) Smad1/5/8. After association with a common mediator Smad (Co-Smad) Smad4, the Smad1/5/8 complex translocates to the nucleus and regulates a variety of transcriptional responses in concert with nuclear cofactors and repressors. The Smad-mediated BMP signaling mainly executes pro-apoptotic properties to maintain the integrity of the vascular structure and function. In the normal small pulmonary arteries, BMPRII is highly expressed on the endothelial cell surface and, at a lower level, in smooth muscle cells and fibroblasts. In patients with PAH, the expression of BMPRII is markedly reduced in the pulmonary arterial wall, regardless of mutations, and the phosphorylation of Smad1/5/8 is reduced as well. These findings suggest that the downregulation of both BMPRII and Smad-mediated signaling may be important in the pathogenesis of PAH.⁴⁻⁵

On the other hand, several Smad-independent pathways and imbalance of vascular effectors have also been shown to play a role in the onset and progression of PAH.⁴⁻⁵ First, BMPRII directly or indirectly activates mitogen-activated protein kinases (MAPK) such as ERK1/2, JNK, p38MAPK. The exaggerated activation of p38MAPK is observed in the arterial wall of PAH, which leads to vascular smooth muscle cell proliferation⁶ and implies that the p38MAPK pathways are involved in the pathogenesis of PAH. Second, reduced penetrance in hereditable PAH and the wide range of the age distribution of the disease suggest that imbalance of multiple vascular effectors or “second hit” elements must be involved in the onset of the disease.⁷ To date, possible factors include serotonin (5HT), serotonin transporters (SHTT) and receptors, platelet-derived growth factor (PDGF), epidermal growth factor (EGF), endothelin-1 (ET-1), angioptetin-1 (Ang-1), Rho GTPases, [Ca²⁺] channels, matrix metalloproteinase (MMPs), elastase, thromboxan A2 (TXA2), inflammatory reactions, nitric oxide (NO), prostacyclin, [K⁺] channel, and PPARY, etc. The particular mechanisms of these factors in pulmonary vascular remodeling are now being extensively studied as possible therapeutic targets of PAH.

Mutations in a transforming growth factor (TGF)-β superfamily receptor activin-like kinase-1 (ALK1) and a co-receptor endoglin (ENG), which are predominantly associated with hereditary hemorrhagic telangiectasia (HHT), have also been recognized as uncommon genetic disorder of PAH. Considering that BMP-mediated signaling is crucial in the pathogenesis of PAH, it is likely that mutations other than BMPRII, ALK1, or ENG may also be involved in pathogenesis of PAH. To date, however, mutations in a Smad protein, Smad8, alone have been identified as a possible cause of heritable PAH.⁸

In this issue of the Journal, Chida et al⁹ report novel missense mutations in the BMP type I receptor protein BMPRIB (ALK6) gene in pediatric patients with PAH. Although BMPRII proteins are important partners and effectors of BMPRII and are likely to be involved in the pathogenesis of PAH, BMPRIB mutations have not been reported in PAH patients. The authors...
screened for mutation in Smad1-Smad7, BMPRIA/IB, and ENG genes in 43 PAH patients who had no mutations in BMPRII, ALK1 or Smad8. The authors identified 2 novel missense mutations of BMPRIB (ie, 479G>A and 1176C>A), which were not detected in 450 healthy controls. The mutations were located between the transmembrane- and GS-rich-domain, and in the serine/threonine kinase domain, respectively.

In addition to the detection of novel BMPRIB mutations in PAH, this study includes several interesting observations. The BMPRIB mutation in the kinase domain (1176C>A) strongly induced Smad8 phosphorylation and increased transcriptional activity in the presence of Smad8. As described earlier, BMPRII mutations in PAH diminish BMPRII protein expression and Smad1/5/8-mediated pro-apoptotic signaling of BMP. In contrast to the conventional hypothesis that the loss-of-signaling in BMPRII mutations may be a major cause of PAH, the authors propose a novel gain-of-signaling mechanism. This suggests that not only inhibition but also promotion of BMP signaling is likely to be associated with the pathogenesis of PAH. The precise molecular mechanisms remain uncertain. One report showed that the expression of BMPRIB is markedly increased in PAH smooth muscle cells not bearing BMPRII mutations and that this BMPRIB upregulation played a key role in the mitotic action of pulmonary artery smooth muscle cells in a sporadic case of primary pulmonary hypertension.

Another report also showed that experimental disruption of BMPRII leads to diminished signaling by BMP2 and BMP4 and augmented signaling by BMP6 and BMP7, suggesting gain-of-signaling mechanisms via the activation of other BMP receptor complexes. Mechanisms such as the enhancement of non-Smad-mediated ERK, JNK, p38MAPK, and LIM kinase-1 pathways, activation or inhibition of other BMP receptor complexes or TGF-β signaling, crosstalk with other signaling molecules, and direct or indirect modification of “second hit” vascular effector may also be involved in the underlying molecular mechanisms.

The functional roles and mechanisms by which the mutations in BMPRIB initiate and promote PAH remain uncertain. As the authors point out, further investigations, such as in vitro signaling assays using human pulmonary smooth muscle cells or in vitro study using a mouse model harboring the BMPRIB mutations, are necessary.

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References