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Editorial Open Access

# Role of Bone Morphogenetic Protein Type II Receptor Signaling in Pulmonary Arterial Hypertension

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Pulmonary arterial hypertension (PAH) is a vascular remodeling disease with a relentless course toward heart failure and ultimately death [1-3]. Although existing therapies improve patients' quality of life and symptoms, none of the currently approved therapies can reverse the disease or significantly reduce mortality. The treatment is also extremely expensive and often associated with side effects. As such, furthering our understanding of the mechanisms and pathology of PAH is important to support more effective therapeutic target identification.

Bone morphogenetic proteins (BMPs) are members of the transforming growth factor-β (TGF-β) family that signal via type II and type I serine/threonine kinase receptors and intracellular transcription factors [4]. Genetic studies have demonstrated that 70% or more of patients with hereditary PAH [5-7], and 20% of patients with idiopathic PAH, are heterozygous for a mutation in BMP receptor type 2 (BMPR2). PAH patients carrying a BMPR2 mutation present the disease ~10 years earlier than non-carriers and are more hemodynamically compromised at diagnosis [8,9]. Mutations have been found in various regions of BMPR2 including the ligand-binding domain, the kinase domain, and the long cytoplasmic tail [4]. BMPR2 gene mutations confer a reduction in BMPR2 signaling activity. In addition, BMPR2 expression is also substantially reduced in patients with various forms of PAH [9]. Mutations can affect different functions of BMPR2, namely the ligand-binding domain, the signaling mechanism, and the interaction of the receptor with the cytoskeleton. BMPR2 is expressed ubiquitously and, in association with a co-receptor (usually BMPR1A), can signal through multiple signaling pathways including pSmad1/5, p-p38, pERK, JNK, Akt/PI3K, and downstream transcriptional factors such as PPARγ and Inhibitors of Differentiation 1 (ID1) [4,5].

The penetrance of PAH is low: only about 20% of individuals with a BMPR2 mutation develop PAH during their lifetime. This low penetrance suggests that certain genetic "hits" or environmental factors trigger a genetic predisposition attributable to BMPR2 mutations that accounts for the clinical manifestations of PAH.

The importance of BMPR2 in pulmonary hypertension has been supported by several animal studies. West et al. [10] have developed a smooth muscle-specific transgenic mouse in which a dominant negative BMPR2 receptor is expressed under the control of a tetracycline-responsive smooth muscle promoter cassette. When fed tetracycline, these mice spontaneously develop pulmonary hypertension. Mutations in BMPR2 have also been shown to synergize with environmental factors. Mice with the defective BMPR2 gene develop more severe pulmonary hypertension by mild hypoxia compared to wild-type mice. A separate experiment [11] shows that heterozygous BMPR2 knockout mice have the same life span, right ventricular systolic pressure, and lung histology as wild-type mice; however, they develop pulmonary hypertension in response to an inflammatory challenge mediated by intratracheal delivery of an adenoviral vector carrying the gene for lipoxygenase whereas the wild-type mice do not. The synergic effect of BMPR2 deficiency with environmental factors has also been demonstrated by a recent report showing that hyperoxia significantly worsens the PAH phenotype of elevated right ventricular systolic pressure, decreased cardiac output, and increased pulmonary vascular occlusion in BMPR2 mutant animals [12]. Another genetic animal model study shows that mice with endothelium-deficient BMPR2 are also predisposed to PAH. Hong et al. [13] have established a Cre/loxP system in which the BMPR2 gene has been deleted in pulmonary endothelial cells by using BMPR2 conditional knockout mice and an endothelial Cre transgenic mouse line. They show that a deficiency in BMPR2 signaling in pulmonary endothelial cells can induce an elevation of right ventricular systolic pressure and right ventricular hypertrophy in association with an increase in the number and wall thicknesses of muscularized distal pulmonary arteries. These experiments suggest that loss of BMPR2 function in either smooth muscle cells or endothelial cells is sufficient to produce PAH.

SMAD1 is one of the canonical signal transducers of the BMPR2 pathway, and its reduced activity has been shown to be associated with PAH. Han et al. [14] have investigated a cell-type specific role of SMAD1 in PAH pathogenesis by conditionally deleting the Smad1 gene in either endothelial cells or in smooth muscle cells using an L1Cre or Taglin-Cre line and demonstrating that SMAD1 is indeed a critical downstream molecule of the BMPR2 pathway in PAH. Smad1 deletion in either cell type can predispose mice to PAH. Their study also shows that the BMPR2-deficient endothelial cells demonstrate the presence of an opposing balance between TGF-β1 and BMP4 signaling in endothelial cells, suggesting that not only diminished SMAD1 signaling but also enhanced TGF-β signaling may contribute to PAH development. This observation is in line with their finding showing that mice having a BMPR2 deficiency in endothelial cells develop PAH with a much higher frequency than mice with a BMPR2 deficiency in smooth muscle cells. Importantly, in the human lung, BMPR2 is predominantly expressed in the endothelium [15].

A number of studies have been undertaken to rescue the defective BMPR2 signaling in PAH. Reynolds et al. [15] have developed adenoviral vectors containing the intact BMPR2 gene and determined the impact of vector administration on the development of pulmonary hypertension and vascular remodeling. Transfection of cells in vitro results in upregulation of SMAD signaling and reduced cell proliferation. Targeted delivery of the vector to the pulmonary vascular endothelium of rats substantially reduces the pulmonary hypertensive response to chronic hypoxia, as reflected by reductions in pulmonary

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artery and right ventricular pressures, right ventricular hypertrophy, and muscularization of distal pulmonary arterioles.

The activation of defective BMPR2 signaling can also be achieved by increasing BMPR2 trafficking within the cells. The substitution of cysteine trafficking in the ligand-binding domain of BMPR2 prevents receptor trafficking to the cell membrane [16]. A panel of chemical chaperones is able to rescue cell-surface expression of mutant BMPR2 and restore BMPR2 signaling in association with enhanced Smad1/5 phosphorylation in response to BMPs, suggesting that enhancement of cell-surface trafficking of mutant BMPR2 may have therapeutic potential in PAH [17].

Recently, an active compound for the treatment of PAH related to defective BMPR2 signaling has been developed [18]. A transcriptional high-throughput luciferase report assay was performed to screen over three thousand FDA-approved drugs and bioactive compounds for induction of BMPR2 signaling. The best response compound FK506, like BMP4, induces ID1 and pSMAD1/5 in pulmonary arterial endothelial cells from patients with idiopathic PAH. The molecular mechanism underlying FK506-induced BMPR2 signaling is that FK506 restores normal signaling through the dual action of removing FKBP12 from the type I receptor and inhibiting calcineurin when BMPR2 is mutated or dysfunctional. Next, they used three animal models (hypoxia-induced PAH in mice, monocrotalin-induced PAH in rats, and SUGEN plus hypoxia-induced PAH in rats) to determine the functional role of FK506 on PAH. They chose mice with a deletion of BMPR2 in endothelial cells to determine whether a low-dose of FK506 could prevent hypoxia-induced PAH in the absence of endothelial BMPR2 and found that FK506 was effective in both the BMPR2-deficient and wild-type genotype. Low-dose FK506 is also able to reverse monocrotaline-induced PAH in rats. In severe established PAH and neointima formation in the SUGEN5416/hypoxia rat model, FK506 reverses the elevation in right ventricular systolic pressure and right ventricular hypertrophy resulting in values not significantly different from those of controls. In addition, FK506 preferentially restores the number of arteries so that the ratio of arteries versus alveoli is increased.

Taken together, a deficiency in BMPR2 signaling is implicated in the pathogenesis of PAH, and genetic and environmental factors that regulate expression and function of BMPR2 play an important role in the development of PAH. The ongoing development of molecule activators targeting insufficient BMP signaling will provide new opportunities for manipulating BMP signaling in therapeutic strategies.

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