Bone Morphogenetic Protein Receptor 2

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Bone Morphogenetic Protein Receptor 2 (BMPR2) are the most common genetic factor in hereditary forms of PAH, suggesting that the BMPR2 pathway is fundamentally important in the pathogenesis

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1. Introduction

Pulmonary Arterial Hypertension (PAH) is a cardio-pulmonary-vascular condition, where a progressive occlusion of the distal pulmonary vasculature leads to an increase in pulmonary vascular resistance and right ventricular (RV) afterload, resulting in RV failure and premature death [1][2]. Histopathological analysis suggests that dysfunction of key cellular components of the pulmonary vasculature, namely endothelial and smooth muscle cells, pericytes, inflammatory cells, and adventitial fibroblasts, induce pulmonary vascular remodeling [3][4]. This results in narrowing of the vessel lumen and formation of complex vascular lesions, which together raise pulmonary vascular resistance, increasing pulmonary arterial pressure as well as the afterload for the right ventricle.

Although PAH is a rare disease affecting only about 1–2 of every 1 million individuals annually, the mortality and morbidity rate is high and, if untreated, PAH quickly leads to right ventricle failure and death after 2–3 years [5][6]. PAH may be heritable (with a family history of PAH), idiopathic (without a family history, unknown cause), or associated (linked to interstitial lung disease, congenital heart disease, autoimmune disease, etc.) [7]. Whilst the exact cause of PAH is not known, genetic factors (mutations or epigenetic changes), environmental factors (e.g., hypoxia, viral infections, anorectic agents, stimulants, etc.) and immune or inflammatory triggers may contribute to the cause or progression of the disease [4]. Importantly, there is no cure for PAH. Existing drugs target pulmonary vasodilation, proliferation and endothelial function by increasing nitric oxide (NO), inhibiting endothelin and voltage-gated calcium channels and by augmenting prostacyclin signaling pathways [8]. However, these drugs only partially increase survival and improve quality of life, while the majority of patients ultimately become resistant to medication and succumb to the disease [9]. With current treatments, the 5-year survival of PAH patients has been improved from 34% to 60%, yet these drugs are not capable of reducing the extent and progression of vascular and cardiac remodeling, resulting in eventual clinical deterioration of PAH patients over time [10].

Thus, new, effective and disease modifying therapies are urgently needed [11], therapies that target the underlying molecular mechanisms responsible for pulmonary vascular remodeling, which is the hallmark of PAH. Over the past two decades, many cellular and molecular mechanisms have been described as playing key roles in the pathogenesis of disease in preclinical and clinical settings [4][12].

2. The BMPR2 Signaling Pathway

In 2000 two independent groups identified mutations in BMPR2 as causative for the familial form of PAH [13][14]. BMPR2 carriers with PAH have an earlier disease onset than idiopathic PAH patients [15]. Interestingly, male patients were more likely to possess a BMPR2 mutation than women and develop severe disease in presence of a BMPR2 mutation [16].

Meanwhile, researchers have identified mutations in over 16 genes in patient with hereditary PAH (HPAH) that may predispose to PAH, including BMPR2 of course, but also receptors that are part of or are interacting with the BMPR2 pathway such as activin A receptor type II-like 1 (ACVRL1), endoglin (ENG), caveolin-1 (CAV1), SMAD1, SMAD4, SMAD9, bone morphogenetic protein receptor type 1B (BMPR1B), eukaryotic translation initiation factor 2 α kinase 4 (EIF2AK4), and growth differentiation factor 2 (GDF2) [17]. While most identified gene mutations are relatively rare (1–3% cases), heterozygous loss-of-function mutations in the BMPR2 gene are the most common and occur in 53–86% of HPAH and 14%–35% of idiopathic PAH (IPAH) patients [18]. To date, more than 300 mutations, predominantly nonsense and frameshift types, have been identified in the BMPR2 gene in PAH patients. BMPR2, encoded by the *BMPR2* gene, is a

member of the serine/threonine kinase transmembrane proteins belonging to the TGFβ receptor superfamily. BMPR2 binds BMP ligands such as BMP2, BMP4, BMP6, BMP7 and BMP9. BMPs typically play a role in a wide range of signal pathways involved in cellular differentiation, growth, and apoptosis and in embryogenesis, development, and tissue homeostasis. In the canonical BMP signaling pathway, upon binding of BMP ligands, BMP type 2 receptors (e.g., BMPR2 (ActRIIA) and ActRIIB)) recruit, complex and phosphorylate BMP type 1 receptors (e.g., Activin receptor-like kinase 1(ALK1), BMPR-1A (ALK3), BMPR-1B (ALK6), and ActR-1A (ALK2)), which then phosphorylate receptor-regulated SMADs (R-SMADs). These R-SMADs form a complex with co-SMADs (e.g., SMAD4) and translocate to the nucleus where the complex binds to a BMP response element DNA sequence. As a result, the complex acts as transcriptional regulator of target gene expression including Inhibitor of DNA Binding 1, 2, and 3 (ID1, ID2, ID3) or cyclin-dependent kinase inhibitor 1A and 2B (CDKN1A and CDKN2B) by binding to the BMP responsive element (BRE), which plays a critical role in cell proliferation, apoptosis and migration. In addition to the canonical SMAD mediated signaling pathway, several non-canonical BMP signaling pathways are also activated by BMPR2, including p38 Mitogen-Activated Protein Kinase (MAPK), Extracellular Signal-Regulated Kinase (ERK), Phosphoinositide 3-kinase (PI3K)/Akt signaling, Peroxisome proliferator-activated receptor γ (PPAR γ)/Apolipoprotein E (ApoE)/ High –density lipoprotein cholesterol (HDLC), Wingless (Wnt), Caveolin, Rho-GTPases, Protein Kinase C (PKC) signaling and NOTCH signaling [19].

3. Regulation of BMPR2 Signaling

A tight regulation of BMPR2 signaling is exerted by extracellular agonists and antagonists, such as the inhibitory molecule Noggin, Chordin and gremlin1 [20], which is upregulated by endothelin1 [21]. Intracellularly, a feedback loop controls BMPR2 signaling through the activity of inhibitory SMADs (iSMADs) SMAD6 and SMAD7, which inhibit the phosphorylation of SMAD2 and SMAD3, signaling molecules that function as counterparts to SMAD 1/5 signaling. SMAD1 degradation is initiated through SMURF1 and SMURF2 targeting, which downregulates further downstream gene expression [22]. BMPR2 downstream signaling is further regulated by FK binding protein 12 (FKBP12), which prevents the activation and phosphorylation of type 1 receptors in absence of a ligand [23] FKBP12 furthermore maintains the balance of rSMAD and iSMAD signaling, by regulating SMAD2/3 activity and recruiting SMAD7 [24].

The availability of BMPR2 receptors at the cell surface is provided by the balance of receptor expression and degradation, as well as receptor shuttling to the cell surface [25]. While upregulation of BMPR2 receptor expression has recently been explored as a therapeutic strategy in PAH [26], little is known about intracellular signaling molecules that target BMPR2 expression. We recently explored upstream modulators of BMPR2 expression and described two novel players in BMPR2 signaling that can increase BMPR2 expression, namely Fragile Histidine Triad (FHIT) and lymphocyte-specific protein tyrosine kinase (LCK) [27].

In contrast to the lack of data on the positive regulation of BMPR2 expression, the mechanisms of its downregulation are well-described, whereas regulation via micro RNAs (miRs) and receptor degradation play major roles. miR-20a and miR17 have both been connected to the downregulation of BMPR2 expression [28][29] whereas the miR17-92 cluster downregulated BMPR2 by engaging the inflammatory cytokine IL-6 via STAT3 [30]. Hypoxia downregulates BMPR2 signaling through miR-21 and miR-125a [31]. miR-302 targets BMPR2 signaling in PASMCs, thereby reducing their proliferation [32] miR21 is connected to a feedback inhibition of BMPR2 signaling, as its expression is induced by BMPR2 signaling on the one hand, but also reduces BMPR2 expression in PAECs. Therefore, the lack of its expression in vivo induces PH, while the use of miR-21 inhibitors in a rodent model of PH supports vascular regeneration in the hypoxia-remodeled pulmonary vasculature [33][34]. In addition to BMPR2 regulation by micro RNAs, it was recently described that 17-estradiol- induced binding of the estrogen receptor to the BMPR2 gene promotor, inhibited BMPR2 transcription, a finding that might explain the sex-based differences in PAH pathogenesis [35][36]. A reduction of BMPR2 receptor presence on the cell surface can be achieved by its premature degradation in connection to infection and inflammation. The inflammatory cytokine Tumor necrosis factor α (TNFalpha) activates metalloproteases that can cleave the receptor, and viral particles (i.e., Kaposi sarcoma-associated herpesvirus KSHV) can ubiquinate BMPR2, leading to its lysosomal degradation [37]. Furthermore, in the absence of BMPR2, SMAD signaling can shift from rSMAD-dominated signals of BMPR2 to the activation of the rSMADs SMAD2, SMAD3 and SMAD4, which are controlled by TGFβ [38] activating EC ITGB1 transcription, leading to EndMT, stress fiber production and actomyosin contractility.

Defective BMPR2 signaling caused by a mutational change in the BMPR2 gene can be rescued, as shown in unaffected BMPR2 mutant carriers through an effective feedback loop. When BMPR2 is functionally inactivated or reduced, the expression of receptor antagonists such as FKBP1A or Gremlin1 is reduced, while, similarly, cellular receptor activators are being upregulated [39].

4. BMPR2 Deficiency and Pulmonary Hypertension

Despite the high frequency of BMPR2 mutations in PAH patients, the disease penetrance rate is ~20% of the mutation carriers, suggesting that, in addition to BMPR2 mutations, other unidentified genetic, epigenetic, or environmental factors are involved in the development of the disease, potentially by decreasing BMPR2 expression and signaling activity below a specific threshold required to cause disease.

Furthermore, in PAH patients with and without BMPR2 mutations, BMPR2 expression and signaling activity is impaired in the pulmonary vasculature [40][41], suggesting that dysfunction of BMPR2 signaling is a key common feature in PAH patients.

Pulmonary endothelial-specific deletion of BMPR2 in mice recapitulates human PAH features [42]. PAH manifestations are also observed in mice expressing a dominant-negative BMPR2 gene in pulmonary smooth muscle cells [43][44]. Similarly, haplo-insufficient BMPR2 mutant rats developed severe dysfunction of the cardio-pulmonary-vascular system, such as distal vessel muscularization, loss of microvascular vessels, inflammation, RV and endothelial dysfunction as well as intrinsic cardiomyocyte dysfunction [45].

Impaired BMPR2 signaling is associated with aberrant vascular cell phenotypes, including pulmonary arterial endothelial cells (PAEC) apoptosis, hyperproliferation and apoptosis resistance of pulmonary arterial smooth muscle cells (PASMC), and inflammation [3][12]. These findings suggest that targeting and thereby increasing BMPR2 expression and signaling could be an effective therapeutic approach for treating PAH.

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