4

Deregulation of BMP Signaling in the Pathogenesis of Pulmonary Hypertension

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1. Introduction

Idiopathic pulmonary arterial hypertension (IPAH) is a rare disease that is defined by a sustained pulmonary arterial pressure of >25 mmHg at rest and a pulmonary capillary wedge pressure (PCWP) or left ventricular end-diastolic pressure (LVEDP) of no more than 15 mmHg. The disease is characterized by a constriction of the precapillary pulmonary arteries due to vascular remodeling. The excessive proliferation of endothelial cells and vascular smooth muscle cells gives rise to medial hypertrophy, plexiform lesions and narrowing of the vascular lumina due to the formation of a neointima (Figure 1) (Cool et al., 1999; Humbert et al., 2004). Patients develop right ventricular hypertrophy due to increased vascular resistance and are prone to heart failure (Farber & Loscalzo, 2004; Sastry, 2006).

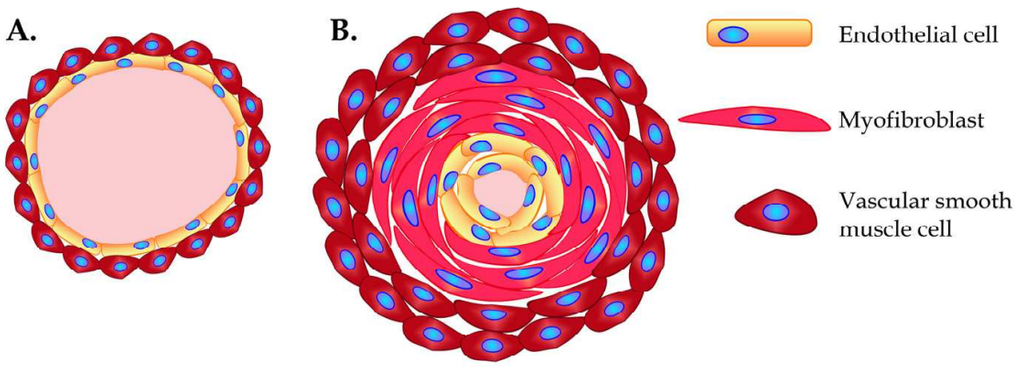

Fig. 1. Vascular remodeling in pulmonary arterial hypertension (PAH). A.) A healthy small pulmonary artery is lined by a single layer of endothelial cells (ECs) supported by vascular smooth muscle cells (VSMCs). B.) In PAH, excessive proliferation of ECs, myofibroblasts and VSMCs leads to a narrowing of the vascular lumen. (Adapted from ten Dijke & Arthur, 2007)

Most cases of idiopathic pulmonary arterial hypertension are sporadic, but in 6-10% of cases one or more family members are also affected thereby marking it as heritable pulmonary arterial hypertension (HPAH). The sporadic and heritable cases of PAH present with identical symptoms, yet HPAH occurs at a younger age and prognosis is worse (Sztrymf et

al., 2008). Interestingly, females have an increased risk of developing IPAH compared to males and the disease occurs mostly at 30-40 years of age, yet it can present at any age (Gaine & Rubin, 1998; Rich et al., 1987).

HPAH is inherited in an autosomal-dominant pattern, yet only 10-20% of family members develop overt pulmonary hypertension. This incomplete penetrance highlights the role of environmental factors and currently unknown genetic factors in the pathogenesis of PAH. However, in 70-80% of heritable cases heterozygous germ line mutations in the bone morphogenetic protein (BMP) receptor II gene (BMPRII) have been found. These mutations were also found to be the underlying cause of about 20% of IPAH cases (Machado et al., 2009). Also in patients suffering from non-hereditary forms of PAH a deregulation of BMP signaling has been observed in vascular beds of the lungs (Atkinson et al., 2002). These findings have driven researchers to investigate the role of BMPs and its family members in the pathogenesis of PAH.

In this chapter we will discuss the basic molecular biology and regulation of BMP signaling and the role of subverted BMP responses in vascular disease. In particular, we will focus on the pathogenesis of PAH and the effects of mutations in the BMP pathway in both murine models and PAH patients.

2. Transforming growth factor-β and bone morphogenetic protein signaling

BMPs are members of the transforming growth factor-β (TGF-β) superfamily of cytokines (Miyazono et al., 2010). Although the name BMP originates from its discovery as an inducer of bone formation (Wozney et al., 1988), it is currently well known to be important for many processes including the development (Wu & Hill, 2009) and homeostasis of the vascular system (David et al., 2009; Lowery & de Caestecker, 2010). The members of the TGF-β superfamily of signal transduction molecules are indispensible during both embryonic development and throughout adult life and are therefore well conserved through evolution. Disruptions in the various TGF-β family signaling pathways give rise to developmental disorders, fibrotic diseases, cancer and cardiovascular diseases among others (Bertolino et al., 2005; Goumans et al., 2009; Meulmeester & ten Dijke, 2011; Pardali et al., 2010) .

TGF-β family ligands are subject to intracellular cleavage by proteases before secretion as biologically active dimers. They signal through heterotetrameric complexes of type II and type I serine/threonine kinase transmembrane receptors (Heldin et al., 1997; Shi & Massague, 2003). Each TGF-β family ligand preferentially binds to a subset of the five type II receptors and seven type I receptors. BMPs signal via the type I receptors activin receptor-like kinase (ALK) 1/2/3/6 and the type II receptors BMPRII, activin receptor type IIA (ActIIA) and ActIIB. The signal can be enhanced by co-receptors such as betaglycan and endoglin. Type II receptors are constitutively active kinases that phosphorylate serine and threonine residues of type I receptors after ligand-induced oligomerization. This results in an activation of the kinase domain of the type I receptor and the recruitment of receptor-regulated Smads (R-Smads) to the receptor. R-Smads are subsequently phosphorylated and thereby activated. Type I TGF-β/Activin receptors activate Smad2 and Smad3, while type I BMP receptors activate Smad1, Smad5 and Smad8. These activated R-Smads form heteromeric complexes with the common Smad (co-Smad), Smad4. After translocation to the nucleus these complexes participate in the transcriptional control of target genes (Figure 2) (Feng & Derynck, 2005; Schmierer & Hill, 2007).

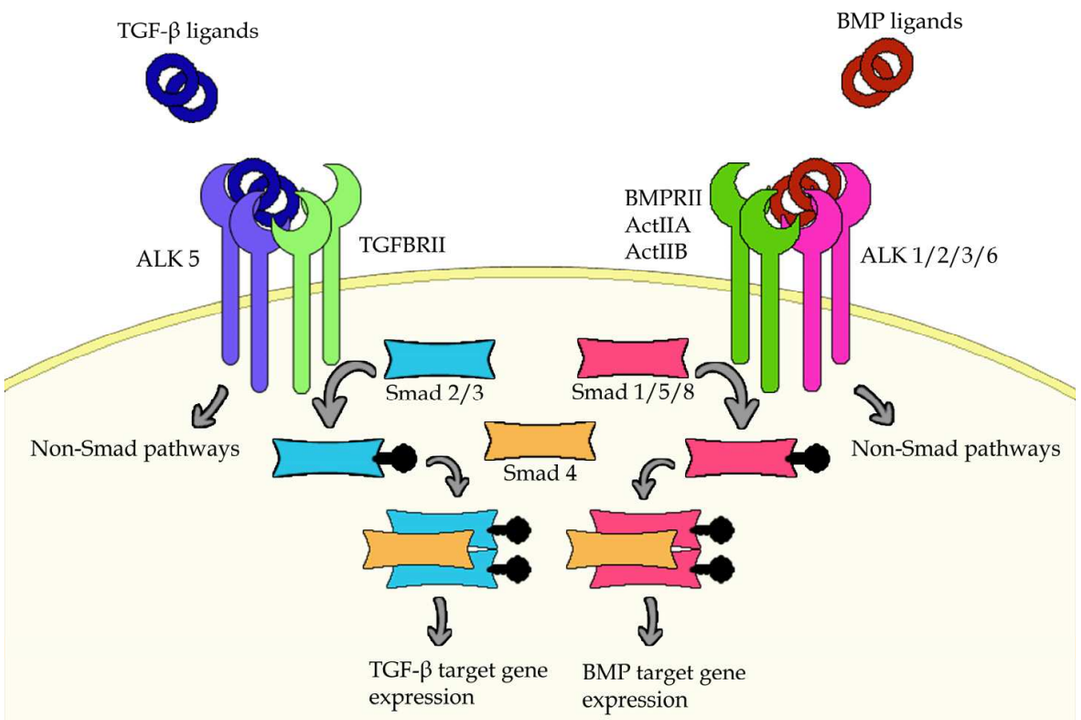

Fig. 2. Schematic overview of the TGF-β and BMP signaling pathways. Binding of ligand induces complex formation of type I and type II receptors. After activation by type II receptors, the type I receptors phosphorylate R-Smads. R-Smads form complexes with Smad4 and translocate to the nucleus to regulate target gene expression. Besides Smad-dependent signaling, also non-Smad pathways are involved.

TGF-β family members can also exert their effect via non-Smad pathways such as mitogen-activated protein kinase (MAPK) pathways, phosphatidylinositol-3-kinase/AKT pathways and Rho-like GTPase signaling pathways (Moustakas & Heldin, 2005; Zhang, 2009). TGF-β receptors directly activate components of these pathways. The cellular responses depend on the cell type and context and include proliferation, apoptosis, cytoskeletal rearrangements and modulation of Smad-dependent signaling. A well studied example of Smad-independent signaling is the activation of c-Jun N-terminal kinase (JNK) and p38 MAPK by TGF-β/BMPs. This pathway is mediated by TGF-β activated kinase 1 (TAK1), which is activated via BMP receptors (Shibuya et al., 1998). TAK1 not only activates MAP kinase pathways, but it also induces the phosphorylation of Smad1, Smad5 and Smad8, the BMP Smads, thereby linking the Smad-dependent and –independent pathways (Shim et al., 2009).

Because of the diverse effects BMPs have on cells, both the intensity and the duration of the signal are tightly regulated. First, the expression and maturation of ligands is a complex multi-step process that allows strict regulation prior to secretion (Saremba et al., 2008; von Einem et al., 2011). After secretion, BMPs are subjected to various extracellular regulatory mechanisms (ten Dijke & Arthur, 2007; Zakin & De Robertis, 2010). They can be sequestered by extracellular matrix molecules from which they can be released at the appropriate time (Nistala et al., 2010). They can also be bound by BMP antagonists such as chordin, noggin, twisted gastrulation, gremlin, DAN and cerberus, which inhibit the interaction of BMPs

with their receptors (Yanagita, 2005). Once BMPs reach the membrane of the target cell, they first interact with auxiliary receptors, such as those of the Dragon family (Corradini et al., 2009), which are expressed at higher levels but have lower BMP affinity than signaling BMP type I and type II receptors. Auxiliary receptors present BMP ligands to signaling receptors. Inhibitory decoy-receptors that inhibit BMP interaction with BMP type II/I receptor complexes have also been identified (Onichtchouk et al., 1999).

The BMP signal can be regulated intracellularly as well. Besides the R-Smads and Smad4, there are also inhibitory (I)-Smads, Smad6 and Smad7, which are induced by TGF-β and BMPs as a negative feedback mechanism. Smad6 acts as an inhibitor of BMP signaling, while Smad7 can inhibit signals of many members of the TGF-β family (Hariharan & Pillai, 2008; Itoh & ten Dijke, 2007). These I-Smads can compete with R-Smads for binding to type I receptors and can induce the dephosphorylation of the receptor by phosphatases. Smad6 has been found to compete with Smad1 for complex formation with Smad4, but it can also recruit transcriptional co-repressors in the nucleus (Lin et al., 2003). I-Smads can recruit E3 ubiquitin ligases such as Smurf1 to the receptors and thereby mediate ubiquitination and subsequent proteasomal degradation of the receptor complexes (Kavsak et al., 2000; Murakami et al., 2003).

Smurf1 also targets other components of BMP signaling for degradation, most importantly Smad1 (Zhu et al., 1999). Interestingly, activation of BMPRII leads to degradation of Smurf1, thereby stabilizing Smad1. BMPRII accomplishes this via the release of Tribbles-like protein 3 (Trb3) from its long carboxyl terminal tail domain upon activation by BMP. Trb3 subsequently induces the degradation of Smurf1 (Chan et al., 2007). Besides Trb3, the tail domain of BMPRII has been shown to interact with proteins such as c-Src, cGMP-dependent protein kinase I (Schwappacher et al., 2009), Tctex1 and LIM domain kinase 1 (LIMK1). The latter is a cofilin kinase and plays a role in the regulation of cell polarity and migration. LIMK1 is released from BMPRII and activated upon stimulation with BMP4 (Foletta et al., 2003). The importance of the tail domain of BMPRII is highlighted by the finding that mutations in it lead to PAH.

3. The role of BMP signaling in vascular homeostasis

BMP signaling plays an important role in the development of the vascular system, demonstrated by the embryonic lethality caused by the loss of any one of several components of this pathway in mice (Goumans & Mummery, 2000). Also in several human vascular diseases the underlying causal mutations were identified to affect BMP signaling. BMP signaling is thought to be involved in the maintenance of homeostasis in adult vasculature (David et al., 2009; Lowery & de Caestecker, 2010). Disruptions of homeostasis by vascular injury, hypertension or atherosclerosis have been shown to affect the expression of BMPs, thereby suggesting a role of BMPs in vascular responses.

The role of BMPs in the pathogenesis of vascular diseases is complex. First, different BMPs may exert very different effects. BMP2 and BMP4 have partly overlapping effects, but can also oppose each other depending on the spatial and temporal context. Second, the cellular response to a specific BMP can vary enormously with changing concentrations of the ligand. Another consideration worth taking is the presence of antagonists that preferentially inhibit one BMP over the other. Finally, BMPs can be produced locally by neighbouring cells in the tissue or be released into the circulation.

Regarding the pathogenesis of pulmonary vascular disease, it is important to note that while much research has been done on BMPs and the systemic vasculature, the pulmonary vasculature responds very differently. BMP4 exerts pro-inflammatory and prohypertensive effects in the systemic circulation, whereas the pulmonary circulation responds differently in an *in vitro* setting (Csiszar et al., 2008). This could explain why a systemic loss of one functional BMPRII allele results in a pulmonary phenotype.

The main cell types involved in vascular homeostasis are endothelial cells (ECs) and vascular smooth muscle cells (VSMCs). Each cell type has its own expression pattern of BMP ligands, receptors, antagonists and intracellular signaling components. The response to BMPs also depends on temporal and spatial factors, for instance, there are differences between ECs in capillaries compared to the ECs of small arteries (Kiyono & Shibuya, 2006). *In vitro* studies in vascular cells have proven to be difficult to interpret, since contradicting results have been reported in for instance early versus late passage VSMCs (Frank et al., 2005). *In vitro* data also does not always match the *in vivo* observations (David et al., 2009; Lowery & de Caestecker, 2010).

In ECs, BMP2 was found to promote pulmonary arterial endothelial cell (PAEC) survival and proliferation *in vitro* (Teichert-Kuliszewska et al., 2006). BMP2 also induces the expression of endothelial nitric oxide synthase (eNOS), which is important for proper vascular function and vasodilation. Heterozygous null BMP2 mice show an increased susceptibility for hypoxic PAH. Conversely, heterozygous null BMP4 mice are protected from hypoxia-induced PAH (Anderson et al., 2010). BMP4 is expressed in lung epithelium and ECs and is upregulated by hypoxia. BMP2 and BMP4 are considered to be regulators of EC and VSMC proliferation and migration, therefore their deregulation may lead to vascular pathologies (Southwood et al., 2008; Yu et al., 2008).

BMP9 has been reported to be a circulating factor that inhibits angiogenesis (David et al., 2007). It is a ligand for ALK1, an endothelial specific type I receptor, and the type II receptors BMPRII and ActRII. BMP9 signaling via BMPRII induces transcription of target genes by activating Smad1 and Smad5 (David et al., 2007; Scharpfenecker et al., 2007). Signaling via ActRII also activates Smad2 (Upton et al., 2009). Interestingly, BMP9 stimulates the transcription of BMPRII and endoglin in pulmonary endothelial cells, thereby maintaining their expression (David et al., 2007). BMP9 was also shown to stimulate the production of endothelin-1 (ET-1) by ECs *in vitro* (Star et al., 2010). ET-1 is a vasoconstrictor and mitogen, which is possibly involved in the pathogenesis of PAH. BMP9 exerts its effects on endothelial cells while circulating in the blood. It is regarded as an important regulator of vascular quiescence (David et al., 2008), yet its precise role remains to be elucidated.

4. Deregulation of BMP signaling in pulmonary arterial hypertension

In the majority of HPAH cases and a subset of IPAH cases a mutation in the BMPRII gene is the likely cause of disease (Morrell, 2010). Over a hundred different mutations have been identified in HPAH families occurring in different regions of the gene (Cogan et al., 2005; Lane et al., 2000; Machado et al., 2006; Moller et al., 2010). Some mutations occur in the extracellular domain or the kinase domain of the receptor, yet others are present in the tail domain. Since the various mutations lead to the same phenotype it is generally believed that they cause a loss of function of the receptor leading to haploinsufficiency (Jiang et al., 2011; Machado et al., 2001). The expression of BMPRII by ECs and VSMCs is significantly reduced

in HPAH cases with a BMPRII mutation, but also in patients with secondary PAH the expression level of BMPRII is reduced (Atkinson et al., 2002; Du et al., 2003; Menon et al., 2011).

In PAH, excessive proliferation of ECs and VSMCs is an important part of the pathogenic process. Previously, and quite simplistically, it was thought that the reduction in BMP signaling through the BMPRII results in a loss of growth inhibitory signals. Yet the pathogenesis of PAH is more complex. It involves excessive proliferation, vascular inflammation, increased vasoconstriction and reduced dilation. The reduction in BMPRII was shown to not simply lead to a reduction in BMP signaling. As stated before, there are multiple BMP ligands and multiple type I and type II receptors. Yu et.al. have shown that the disruption of BMPRII in pulmonary arterial smooth muscle cells (PASMCs) leads to reduced signaling by BMP2 and BMP4, yet conversely signaling by BMP6 and BMP7 is enhanced (Yu et al., 2005). Also, a loss of BMP Smad signaling is accompanied by an activation of the p38 MAPK pathway causing aberrant PASMC proliferation (Dewachter et al., 2009; Rudarakanchana et al., 2002; Yang et al., 2005). PAEC dysfunction is also caused by a loss of BMP-induced eNOS expression and thereby increases pulmonary vasoconstriction (Anderson et al., 2010; Frank et al., 2008). Alterations in BMP signaling thereby lead to EC dysfunction and apoptosis, increased vasoconstriction, increased inflammation, excessive VSMC proliferation and the formation of plexiform lesions by apoptosis-resistant EC clones (Morrell, 2006).

Much attention is being paid to loss of BMP2 and BMP4 signaling through BMPRII, yet a mutation in ALK1 has also been found in PAH patients (Harrison et al., 2003). These patients suffer from hereditary hemorrhagic telangiectasia (HHT), a severe vascular disorder in which mucocutaneous telangiectasias and arteriovenous malformations develop in multiple organs (Shovlin, 2010). A subset of patients carrying an ALK1 mutation also develops PAH (Fujiwara et al., 2008; Harrison et al., 2003). ALK1 mediates both TGF-β and BMP9 signaling in endothelial cells. As described earlier, BMP9 induces the expression of BMPRII, therefore a loss of ALK1 signaling might result in a reduced expression of BMPRII (Upton et al., 2009). Also, a reduction of BMP9 signaling leads to reduced vascular quiescence, which may have pathogenic effects as well.

The role of TGF-β in PAH is also being investigated. BMP signaling through Smad1/5/8 is connected to TGF-β signaling through Smad2/3. Multiple mechanisms of crosstalk exist between the two pathways and it is thereby not surprising that TGF-β is involved in PAH next to BMPs. Abnormal TGF-β signaling has been observed in the pulmonary vasculature of PAH patients (Arcot et al., 1993; Morrell et al., 2001). TGF-β has various effects on vascular cells depending on context. The mechanisms by which TGF-β and BMP exert their pleiotropic effects in the adult vasculature are not yet understood. However, it is clear that they are interconnected and crucial for vascular homeostasis, making them both interesting therapeutic targets.

5. Evidence from animal models of PAH

In order to study the pathogenesis of PAH and to test potential treatments, we need reliable animal models of PAH. Since a heterozygous germ line mutation in the BMPRII is found in a large percentage of HPAH cases, various transgenic and knockout mouse models have been

developed trying to mimic the pathogenesis seen in patients. A homozygous null mutation in BMPRII is lethal early during embryogenesis (Beppu et al., 2000). A RNAi germline 90% knockdown of BMPRII gives rise to a severe vascular phenotype including mucosal hemorrhage, vascular dysmorphogenesis and dysplasia (Liu et al., 2007). Heterozygous null mice initially show no phenotype, yet after challenge with serotonin (Long et al., 2006), chronic hypoxia (Frank et al., 2008), or inflammatory stress (Song et al., 2005) they are more susceptible to PAH. These findings support the idea that the development of PAH requires a second insult besides BMPRII mutation. The phenotype does not show the vascular remodeling seen in patients, which is a limitation to the use of this model.

An inducible transgenic mouse model that overexpresses a dominant-negative BMPRII specifically in smooth muscle cells develops PAH spontaneously (West et al., 2004). These mice show muscularization of small pulmonary arteries and an increase in medial thickness due to SMC proliferation. The loss of BMPRII signaling in VSMCs was sufficient to induce PAH, yet it does not reconstitute the complexity of human PAH (West et al., 2004). Mice with an inducible SMC specific expression of BMPRII with a truncating mutation in the tail domain (R899X) also show vascular abnormalities. About one third of the animals develop PAH. Interestingly this mutation does not lead to a loss of Smad signaling, yet it increases MAPK signaling (West et al., 2008).

Heterozygous or homozygous deletion of BMPRII in pulmonary ECs predisposes mice to PAH. A subset of animals develop PAH spontaneously, including right ventricular hypertrophy, vascular inflammation and histopathological changes (Hong et al., 2008; Majka et al., 2011). Disruptions in BMPRII signaling in either ECs or VSMCs lead to phenotypes resembling aspects of human PAH. Therefore, in patients both cell types most likely play a role in the complex pathogenesis of this disease.

A mutation in Smad8 has been identified as the cause in one IPAH case (Shintani et al., 2009). Smad8 is highly expressed in the pulmonary vasculature. Loss of Smad8 function in mice does not cause developmental problems. These mice do however show abnormal vascular remodeling, increased vascular inflammation and pulmonary tumors (Huang et al., 2009). Since other mouse models of PAH often do not present with the excessive vascular remodeling seen in patients, this Smad8 mutant is interesting in the way it recapitulates an important aspect of PAH.

Two commonly used rat models are the chronic hypoxia model and the monocrotaline (MCT)-induced PAH model (Altiere et al., 1986). Both models develop PAH and right ventricular hypertrophy within only a few weeks. A disruption of BMP signaling via the BMPRII has been documented in the pulmonary arteries of these animals (Long et al., 2009; Morty et al., 2007; Ramos et al., 2008). Murakami et al. have shown an increase in Smurf1 and I-Smad expression in the arteries of rats after MCT treatment or chronic hypoxia. The BMPRII is downregulated and BMP-Smad signaling is inhibited. This potentiates MAPK pathways and could be responsible for the observed proliferation and remodeling of the pulmonary vasculature (Murakami et al., 2010).

6. Implications for the treatment of PAH

This review has focussed on the pathogenesis of primary forms of PAH, IPAH and HPAH. PAH can arise as a secondary disease, which means the underlying medical condition

should be taken into account when deciding on the course of treatment. Since right heart failure develops as a consequence of PAH, patients are treated with anticoagulants, diuretics and oxygen. Furthermore, patients can be treated with calcium channel blockers, prostanoids, endothelin antagonists or phosphodiesterase inhibitors (Badesch et al., 2007; Sastry, 2006). In severe cases, patients need a lung or heart/lung transplant.

Because of the role of BMPs in the pathogenesis of PAH and the crosstalk between BMP and TGF-β signaling, both pathways are regarded as potential drug targets. However, it is crucial to realize that the TGF-β family signaling pathways are tightly regulated and important for all tissues. Inhibition of TGF-β signaling as a potential treatment for PAH is currently under investigation. In rats with monocrotaline-induced PAH, anti-TGF-β treatment has prevented the development of PAH, right ventricular hypertrophy, vascular remodeling and reduced the loss in exercise capacity (Long et al., 2009; Megalou et al., 2010; Zaiman et al., 2008). Specific BMP agonists or TGF-β antagonists might prove to be valuable in fighting both BMPRII mutation positive and negative PAH. However, it is uncertain whether a reversal of the pathogenic processes is possible. It remains crucial to diagnose and start treatment early.

7. Conclusion

Transforming growth factor (TGF)-β family members are cytokines which are crucial for embryonic development and adult tissue homeostasis. This large family includes TGF-β isoforms, activins and bone morphogenetic proteins (BMPs), which act on cells via their type I and II serine/threonine kinase receptors and a specific subset of Smad transcription factors.

BMP signaling has been shown to be involved in vascular development and angiogenesis and deregulation gives rise to vascular disease. Mutations in the BMP receptor II gene are responsible for 80% of heritable pulmonary arterial hypertension cases, yet also in non-hereditary forms of PAH deregulation of BMP signaling occurs. PAH is characterised by an increase in blood pressure due to the constriction of small pulmonary arteries. Aberrant BMP signaling has been shown to be involved in the proliferation and dysfunction of ECs and VSMCs and vascular remodeling leading to PAH. In rat models of PAH, induced by hypoxia or monocrotaline, a disruption in BMP signaling has been found. Additionally, mouse models in which BMP signaling is disturbed in either ECs or VSMCs show a predisposition to develop PAH.

It is clear that BMP and TGF-β signaling play an important role in the pathogenesis of PAH. However, the exact roles of various signaling components and cell types remain unclear due to the complexity of these pathways. By studying different animal models of PAH we have learned much about the underlying processes and we can use these models to test whether BMP and TGF-β signaling can be targeted for treatment.

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9. List of abbreviations

ActIIA/B	Activin receptor type IIA/B
ALK	Activin receptor-like kinase
BMP	Bone morphogenetic protein
BMPRII	Bone morphogenetic protein receptor II
EC	Endothelial cell
eNOS	Endothelial nitric oxide synthase
ET-1	Endothelin-1
HHT	Hereditary hemorrhagic telangiectasia
HPAH	Heritable pulmonary arterial hypertension
IPAH	Idiopathic pulmonary arterial hypertension
I-Smad	Inhibitory Smad
JNK	c-Jun N-terminal kinase
LIMK	LIM domain kinase 1
MAPK	Mitogen-activated protein kinase
MCT	Monocrotaline
PAEC	Pulmonary arterial endothelial cell
PAH	Pulmonary arterial hypertension
PASMC	Pulmonary arterial smooth muscle cell
R-Smad	Receptor-regulated Smad
Smad	Sma and Mad related protein
TAK1	TGF-β activated kinase 1
TGF-β	Transforming growth factor-β
Trb3	Tribbles-like protein 3
VSMC	Vascular smooth muscle cell

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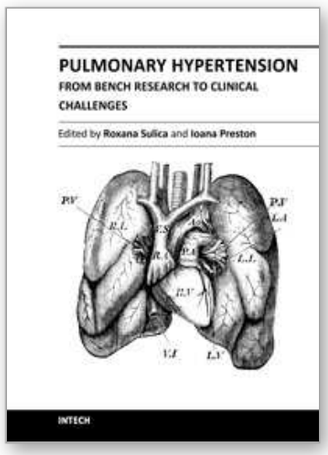

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The textbook "Pulmonary Hypertension - From Bench Research to Clinical Challenges" addresses the following topics: structure and function of the normal pulmonary vasculature; disregulated cellular pathways seen in experimental and human pulmonary hypertension; clinical aspects of pulmonary hypertension in general; presentation of several specific forms of pulmonary hypertension, and management of pulmonary hypertension in special circumstances. The textbook is unique in that it combines pulmonary and cardiac physiology and pathophysiology with clinical aspects of the disease. First two sections are reserved for the basic knowledge and the recent discoveries related to structure and cellular function of the pulmonary vasculature. The chapters also describe disregulated pathways known to be affected in pulmonary hypertension. A special section deals with the effects of hypoxia on the pulmonary vasculature and the myocardium. Other three sections introduce the methods of evaluating pulmonary hypertension to the reader. The chapters present several forms of pulmonary hypertension which are particularly challenging in clinical practice (such as pulmonary arterial hypertension associated with systemic sclerosis), and lastly, they address special considerations regarding management of pulmonary hypertension in certain clinical scenarios such as pulmonary hypertension in the critically ill.

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