Bone Morphogenetic Proteins

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Contributor: Ljuba Ponomarev

Bone morphogenetic proteins (BMPs) were originally identified as the active components in bone extracts that can induce ectopic bone formation. In recent decades, their key role has broadly expanded beyond bone physiology and pathology. Nowadays, the BMP pathway is considered an important player in vascular signaling. Indeed, mutations in genes encoding different components of the BMP pathway cause various severe vascular diseases. Their signaling contributes to the morphological, functional and molecular heterogeneity among endothelial cells in different vessel types such as arteries, veins, lymphatic vessels and capillaries within different organs. The BMP pathway is a remarkably fine-tuned pathway. As a result, its signaling output in the vessel wall critically depends on the cellular context, which includes flow hemodynamics, interplay with other vascular signaling cascades and the interaction of endothelial cells with peri-endothelial cells and the surrounding matrix.

Keywords: BMP ; BMP pathway fine-tuning ; lymphatic vessel biology ; mechano-transduction ; vascular malformations ; signaling cross-talk

1. Introduction

Dysfunction of endothelial cells lining the inner wall of the circulatory and lymphatic vasculature is a major cause and amplifier of vascular disease. Mutations in genes encoding different components of the bone morphogenetic protein (BMP) pathway cause rare but severe vascular diseases. Most of these diseases are due to loss of function of BMP signaling [1][2][3], but some vascular anomalies also result (indirectly) from a gain of function of BMP signaling [4]. Together, this underscores that the BMP signaling levels need to be well balanced in vascular development and physiology. Nowadays, the BMP pathway is an important therapeutic target for treatment of vascular diseases [3].

2. Fine-Tuning Mechanisms of BMP Signaling in the Vasculature

The shaping of BMP morphogen gradients or responses depends on the bioavailability of (tissue-specific) BMP ligand–receptor complexes, and intracellular effectors. In addition, the BMP signaling pathway is further fine-tuned by different extracellular and intracellular agonists and antagonists that bind and sequester BMPs or signaling components. In this respect, it is striking how target genes of BMP signaling often function as negative feedback regulators of BMP signaling themselves. Moreover, the BMP pathway cross-talks with mechanical cues in bone, a feature that is increasingly being recognized in the vessel wall as well [5]. However, also its interactions and cross-talk with other pathways contribute to the contextual status that regulates and fine-tunes the BMP pathway (**Figure 1**). Here, we provide the most relevant pathway tuning and interplay between BMP signaling and other vascular pathways. These have especially been documented in the blood vasculature and may inspire lymphatic studies of the future.

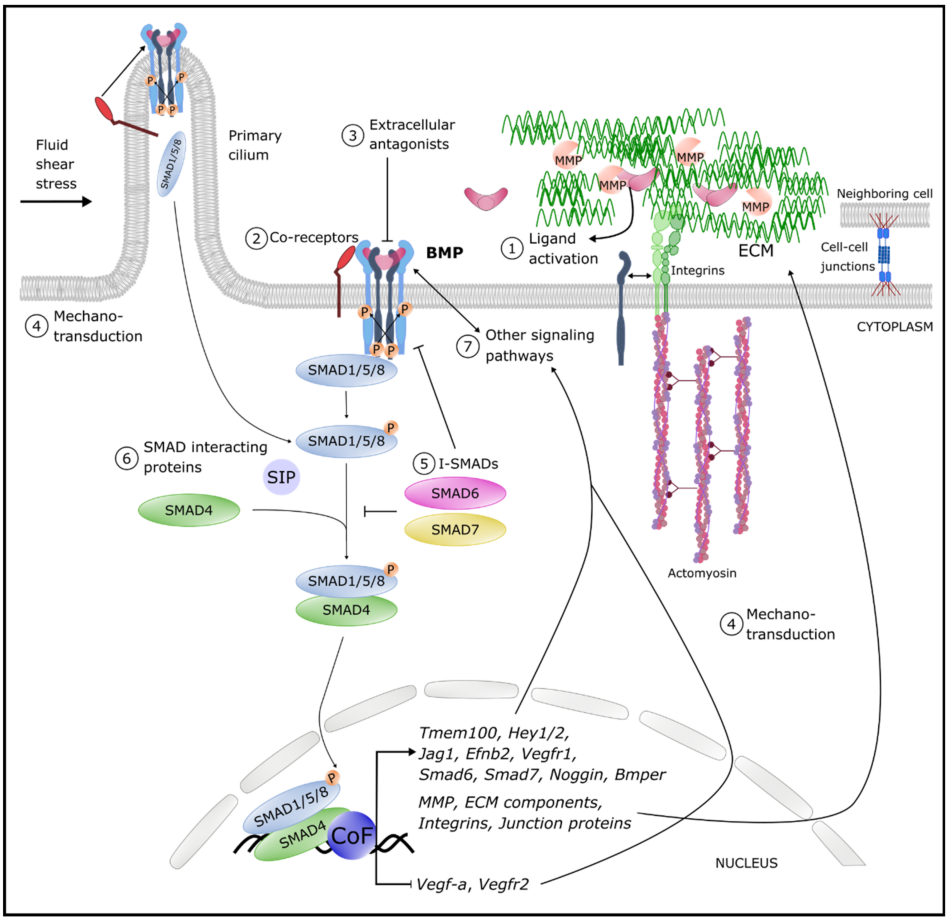

Figure 1. Overview of the different levels of BMP pathway fine-tuning. Circled numbers denote examples of levels of regulation of the signaling output. Cell–cell junctions are tight, adherence and gap junctions (details are provided in the text). Abbreviations: BMP: bone morphogenetic protein BMPER: BMP endothelial cell precursor-derived regulator; CoF: co-factors; P: Phosphorylation; ECM: extracellular matrix; Ephb2: Ephrin B2; Hey: hairy/enhancer-of-split related with YRPW motif protein; Jag: Jagged; MMP: Matrix metalloproteinases; SIP: SMAD interacting proteins; Tmem100: transmembrane protein 100; Vegf: vascular endothelial growth factor; Vegfr: VEGF receptor.

3. BMP-Linked Vascular Pathologies

Blood vasculature—The germline deletion of all vascular BMP genes, except for BMP9 (*Gdf2*), and BMP receptor genes in mice causes embryonic lethality, with most prominent defects in mesoderm formation and cardiovascular development. This illustrates that this pathway exerts critical functions during embryogenesis [1][2][6]. Additionally, mutations in genes encoding BMP pathway components, ranging from ligands, type I and type II receptors, co-receptors and intracellular effectors, have been associated with cardiovascular disease [1][2][3][4] (**Figure 2**). Indeed, human studies have shown that impaired BMP signaling causes hereditary hemorrhagic telangiectasia (HHT), pulmonary arterial hypertension (PAH), cerebral cavernous malformation (CCM), bicuspid aortic valve with thoracic aorta aneurysm (BAC/TAA) and aortic valve stenosis (AOVD2), atherosclerosis combined with vascular calcifications and fibrodysplasia ossificans progressiva (FOP). Some of these diseases, i.e., HHT, PAH, BAC and AOVD2, result from reduced BMP signaling (loss of function), whereas others such as CCM and FOP reflect a gain of function. This illustrates, again, the critical dosage of signaling of this family of morphogens.

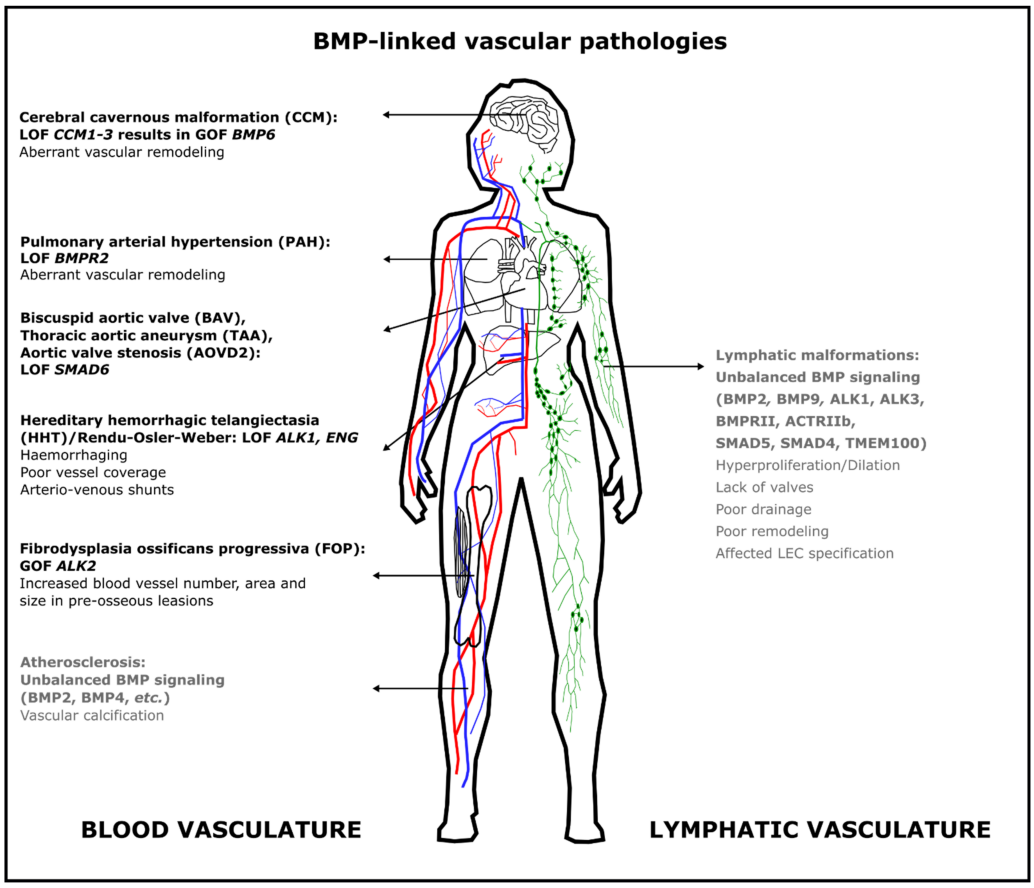

Figure 2. Aberrant BMP signaling in the blood vasculature causes different severe but rare diseases in humans. Some pathologies are due to loss of function of BMP signaling, whereas others result from gain of function of BMP signaling. The most frequent mutations are indicated here; additional mutations are discussed in the text. Text in gray indicates that this role for BMP signaling has only been demonstrated in animal models. Abbreviations: ACTRII: activin type II receptor; ALK: activin receptor-like kinase; AOVD2: aortic valve stenosis; BAV: bicuspid aortic valve; BMP: bone morphogenetic protein; BMPR2: BMP Type 2 receptor; CCM: cerebral cavernous malformation; ENG: endoglin; FOP: fibrodysplasia ossificans progressiva; HHT: hereditary hemorrhagic telangiectasia; GOF: gain of function; LEC: lymphatic endothelial cell; LOF: loss of function; PAH: pulmonary arterial hypertension; TAA: thoracic aortic aneurysm; TMEM100: transmembrane protein 100.

4. Conclusions

The growing wealth of single-cell transcriptome data and protein–protein interaction databases, also in lymphatic vascular cells from different niches, will progressively reveal putative additional functions of BMPs in lymphatic endothelium specification and functions. Ligand–receptor pairing between lymphatic vascular cells and cell types in their environment and analysis of target genes of BMPs will facilitate inferring the intercellular communication and BMP-sensitive niche-specific specialization of the lymphatic endothelium. In any case, it will be important to consider the context-dependent regulation of this pathway, which contributes to the subtle variations in functions of the BMP signaling components in different lymphatic endothelial cell types.

The first data on human lymphatic malformations and BMPs, together with the reported studies in zebrafish and mice, suggest a potential role for BMP signaling in human lymphatic vessel development and/or maturation. The many examples that are provided in this review on very specific BMP functions and tuning of this pathway in the vascular endothelium and the emerging picture of a cross-talk between BMP signaling and mechanobiology and VEGF, Notch and WNT signaling in the (lymphatic) vasculature can inspire the lymphatic vessel field. Moreover, the recent finding that BMP6 regulates TAZ-Hippo signaling and neo-vessel formation in the vasculature [7], as well as the growing link between BMP and vascular inflammation [8][9][10][11][12], and BMP signaling and hypoxia [13][14][15], is promising and may also plug into lymphatic vessel studies. The striking set of severe rare vascular diseases upon alterations of the BMP pathway provided in this review is likely to fuel the future exploration of this important pathway in lymphatic vessel development, physiology and pathology.

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