PULMONARY ARTERIAL HYPERTENSION (PAH) is a rare and often fatal disease characterized by sustained and progressive elevation of mean pulmonary arterial pressure with pathological changes involving vasoconstriction, vascular remodeling, and inflammation, leading to right ventricular hypertrophy and heart failure (6). Endothelial dysfunction and subsequent excessive proliferation of smooth muscle cells give rise to medial hypertrophy, plexiform lesions, and obliteration of the vascular lumen (5, 6). Persistent hypoxemia with accompanying vasoconstriction plays an important role in the pathogenesis of pulmonary hypertension (PH). Indeed, the chronic hypoxia-induced PH rat model is among the most commonly used animal models of PAH. Many signaling pathways have been found to participate in the physiopathology of the disease (6). Among these, deregulated bone morphogenetic protein (BMP) signaling has been shown to contribute to the development and progression of PAH (3, 4). BMP ligands are secreted proteins, which form a subgroup of the TGF-β superfamily. Activation of BMP signaling is mediated by two types of receptors, known as type I (BMPRIa, BMPRIb, ActRIa) and type II (BMPRII, ActRIIa, and ActRIIb) receptors. Binding of BMP ligands to the type II receptor leads to phosphorylation of the type I receptor. Activated type I receptors initiate intracellular signaling through phosphorylation of regulatory Smad (R-Smad) proteins. Activated R-Smads then form a heteromeric complex with Co-Smads before translocating to the nucleus to regulate gene expression. In addition to the Smad-dependent signaling, and activation of ERK1/2 and p38 MAPK pathways. In direct connection with the present results, the same group, with an RNA interference approach, documented that BMP4-induced upregulation of TRPC expression, enhancement of calcium signaling, and activation of ERK1/2 and p38 MAPK pathways were BMPRII-independent in PASMC (10). Thus, the decrease in STAT3 axis along with the inhibition of TRPC1 and TRPC6, both known to be pro-proliferative actors in PAH (9), support a therapeutic value of NOGGIN at least in the hypoxic form of PH. Indeed, a role for NOGGIN/BMP4 axis in non-hypoxic forms of PH remains to be established. Interestingly, Wu and Paulson (7) revealed, in murine spleen, that hypoxia-inducible factor (HIF) activation upregulates BMP4 expression. The fact that HIFs are also activated in nonhypoxic models of PAH (1) might suggest a putative role of BMP4/NOGGIN in other forms of PAH. Moreover, effects of NOGGIN on TRPC1 and TRPC6 will likely decrease intracellular calcium levels. Elevated cytoplasmic Ca$^{2+}$ is a major trigger for pulmonary vasoconstriction and an important stimulus for PASMC proliferation. Increased Ca$^{2+}$ influx and STAT3 activation both stimulate nuclear translocation of the transcription factor NFATc2, the expression of which is directly associated with PAH (2).

In this issue of the journal, Yang and colleagues (8) present the results of their study on the in vitro effects of recombinant NOGGIN treatment on BMP4-induced pulmonary arterial smooth muscle cells (PASMC) proliferation and store-operated calcium entry (Fig. 1). The primary purpose of their study was to determine whether the expression levels of four BMP antagonists, namely Noggin, Follistatin, Gremlin, and Mgp, are altered in chronic hypoxia-exposed rat lungs and isolated PASMC. Among these, only expression of NOGGIN was found to be significantly diminished under hypoxia conditions, both in vivo and in vitro. Although PASMC exhibited clear reduction in NOGGIN expression under hypoxia, the mechanisms by which hypoxia downregulates its expression remain to be established. A secondary aim was to evaluate the potential benefits of NOGGIN supplementation on BMP4-treated or hypoxia-exposed PASMC. Treatment of PASMC with recombinant NOGGIN was shown to inhibit BMP4-induced phosphorylation of p38, ERK1/2, JAK2, and STAT3. Activation of the latter in PASMC was reported to suppress miR-204 expression and to activate KLF5, NFATc2, and PIM1, known to exert deleterious effects in promoting proliferation and apoptosis resistance in the pulmonary artery wall (6). More importantly, their study revealed that NOGGIN exposure attenuates hypoxia-induced store-operated calcium entry by reducing the expression of TRPC1 and TRPC6, the main calcium channels responsible for Ca$^{2+}$ influx and previously shown to be induced by p38 and ERK1/2 MAPK pathways. In direct connection with the present results, the same group, with an RNA interference approach, documented that BMP4-induced upregulation of TRPC expression, enhancement of calcium signaling, and activation of ERK1/2 and p38 MAPK pathways were BMPRII-independent in PASMC (10). Thus, the decrease in STAT3 axis along with the inhibition of TRPC1 and TRPC6, both known to be pro-proliferative actors in PAH (9), support a therapeutic value of NOGGIN at least in the hypoxic form of PH. Indeed, a role for NOGGIN/BMP4 axis in non-hypoxic forms of PH remains to be established. Interestingly, Wu and Paulson (7) revealed, in murine spleen, that hypoxia-inducible factor (HIF) activation upregulates BMP4 expression. The fact that HIFs are also activated in nonhypoxic models of PAH (1) might suggest a putative role of BMP4/NOGGIN in other forms of PAH. Moreover, effects of NOGGIN on TRPC1 and TRPC6 will likely decrease intracellular calcium levels. Elevated cytoplasmic Ca$^{2+}$ is a major trigger for pulmonary vasoconstriction and an important stimulus for PASMC proliferation. Increased Ca$^{2+}$ influx and STAT3 activation both stimulate nuclear translocation of the transcription factor NFATc2, the expression of which is directly associated with PAH (2).

Collectively, these findings suggest that strategies targeting Noggin restoration may be a useful way to attenuate the hypoxia-elevated proliferation of PASMC. Nevertheless, NOGGIN expression in human PH remains to be investigated and the...
therapeutic potential of this BMP antagonist in PH requires further in vivo studies.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

O.B. prepared the figure; O.B. drafted the manuscript; O.B. and S.B. edited and revised the manuscript; O.B. and S.B. approved the final version of the manuscript.

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