



2011 Abstracts



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BMP9-Mediated Regulation of Endothelin-1 Expression in Vascular Endothelial Cells

Pulmonary arterial hypertension (PAH) is a highly morbid condition characterized by abnormal pulmonary vasoreactivity and pulmonary angiopathy leading to progressively increased pulmonary resistance, and frequently culminating in right heart failure and death. The molecular basis of PAH has yet to be fully elucidated, although dysregulated bone morphogenetic protein (BMP) signaling due to loss-of-function mutations in *BMPR2*, encoding the BMP type II (BMPRII) receptor, have been implicated in several forms of PAH. Recent reports also indicate that BMP9, a BMPRII ligand, regulates transcription of the potent vasoconstrictor endothelin-1 (ET-1), an important mediator of PAH. BMP9 appears to function as a circulating vascular quiescence factor that promotes endothelial survival while inhibiting angiogenesis. We found that BMP9 activates both canonical BMP and TGF- β pathways via their respective effector molecules, SMAD1/5/8 and SMAD2/3. Blocking either BMP or TGF- β signaling pathways using small molecule receptor kinase inhibitors or recombinant receptor ectodomains prevents the induction of ET-1 by BMP9, suggesting a requirement for the coordinated activity of these two pathways. Preliminary ET-1 promoter analysis revealed distinct *cis*-regulatory elements involved in BMP9- and TGF- β -mediated activation of ET-1 transcription, suggesting a novel BMP-responsive regulatory element as well as cooperativity between BMP9 and TGF- β pathways. We previously found that ablation of BMPRII does not disrupt BMP signaling in vascular cells, but instead augments signaling for some BMP ligands, and attenuates signaling of other BMP ligands via transduction by Activin type II receptor (ActRIIa).



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Thus, the loss of BMPRII function has the potential to either disrupt or augment BMP9-induced regulation of ET-1, with potential consequences for pulmonary vascular tone in PAH associated with *BMPR2* mutations. In this proposal we investigate the molecular mechanisms by which BMP9 and BMPRII contribute to the regulation of ET-1 in endothelial cells, using a combination of small molecule, recombinant protein, and molecular genetic approaches. We test the hypothesis that impaired BMPRII function dysregulates BMP9-induced ET-1 expression and may thereby contribute to abnormalities in vascular tone and/or remodeling in PAH.