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# Commentary to: Single-Cell RNA Sequencing Reveals that BMPR2 Mutation Regulates Right Ventricular Function via ID Genes

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## COMMENTARY

Pulmonary hypertension is a progressive disease characterized by thickening and narrowing of pulmonary artery resulting in increased pulmonary vascular resistance and right ventricular hypertrophy, leading to right ventricular failure [1,2]. BMPR2 mutations have been found in PAH patients [3]. Whether ultimate heart failure in PAH patients is associated with primary myocardial abnormalities has not been clarified. The inhibitor of DNA binding protein (ID) is a helic-loop-helix (HLH) transcription factor, which is reported to be an important downstream target of the BMP receptor in cardiogenesis [4,5], but whether it has an important regulatory effect on heart at the occurrence of PAH has not been reported. The underlying mechanism of the intrinsic alteration of the right heart in PAH with BMPR2 mutations remains challenging. The aim of this study was to elucidate the role of IDs in PAH development and which cardiopulmonary lineages are the major responsive cell type[6,7]. For CHD-PAH, the authors hypothesized that CHD-PAH with BMPR2 mutations is one phenotype of BMPR2 mutations (and HPAH another phenotype but on the same "spectrum")? Findings: Among the BMPR2 mutations detected in CHD-PAH patients from China, nearly all were missense mutations. For H/IPAH, there were 5 types of BMPR2 mutations: nonsense, deletion, frame shift, splice site and missense. It is possible that CHD-PAH with BMPR2 mutation is a BMPR2 mutation phenotype.

Induced pluripotent stem cell binding single cell sequencing in congenital heart disease patients and corresponding myocardial cell knockout animal model were used to explain the role of BMP downstream ID gene in regulating myocardial cell differentiation and right heart function in CHD-PAH patients. IPSCs were reprogrammed from BMPR2 mutated CHD-PAH patients and were differentiated into cardiac muscle cells. It was found that BMPR2 mutated PAH iPSCs showed reduced id1/3 expression, reduced PAH IPSC-CM differentiation efficiency and reduced calcium transient ability. Further single-cell transcriptome sequencing analysis showed that ID knockout promoted the deviation of directed differentiation at the mesoderm stage and the loss of cell populations with low USP9X gene expression. Further studies on the regulation of ID on downstream gene expression showed that USP9X overexpression rescued the decreased expression of cardiogenesis related markers caused by ID1 and ID3 knockout. ID binding partners, such as E47, an E protein transcription factor, were then examined, containing basic DNA-binding regions juxtaposed with the HLH domain. E47 binding to the USP9X promoter was found to be increased in IDs KO cells. These results indicated that ID influenced downstream USP9X expression by binding with E47. By using a variety of methods, including iPSC generation and differentiation, CRISPR/Cas9-targeted hESC scRNA sequencing, and Ids cDKO mouse CM function determination, the authors found that BMPR2 signals through ID and USP9X could drive cardiac differentiation. Loss of ID1 and ID3 expression led to CM dysfunction in BMPR2 mutated CHD-PAH patients.

This study systematically studied the important role of ID1/ID3 downstream of BMPR2 in the development of pulmonary hypertension by influencing the development of cardiac myocytes and changing right heart function, providing a rational for the early genetic screening of patients with cardiopulmonary and vascular diseases. Improved prognosis in these patients requires genetic screening for suspect genes, including BMPR2, USP9X and other components in this signaling pathway. This study further strengthens the understanding of the effect of BMPR2 signaling in cardiac development and the pathogenesis of CHD, which will benefit the classification and diagnosis of patients with mutations, and the development of BMPR2 signalling pathway targeted therapy.

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In conclusion this is an interesting and meaningful paper contained many findings with an excellent series of experiments. This study identified that BMPRII signals through ID and USP9X regulates cardiac differentiation. The authors showed that loss of ID1 and ID3 expression contributes to cardiomyocyte dysfunction in CHD-PAH patients with a BMPRII mutation by using various sophisticated methodology. It is incremental in nature based on previous study. By using single cell sequencing, it provides further evidence regarding the potential downstream signaling of BMPRII in the dysfunction of cardiomyocytes derived from CHD-PAH patients. This paper is an accomplished work with profound implications for cardiopulmonary medicine.

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None

## CONFLICT OF INTEREST

Authors declare no conflict of interest

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