Editorial

Stem Cell INVESTIGATION

Rescuing BMPR2-driven endothelial dysfunction in PAH: a novel treatment strategy for the future?

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Pulmonary arterial hypertension (PAH) may be idiopathic and corresponds to sporadic disease without any familial history or identified risk factors, or heritable when it occurs in the hereditary context; germline mutations in the *bone morphogenetic protein receptor type 2* (*BMPR2*) gene, are detected in 70% of heritable PAH cases (1). Even in sporadic cases, PAH is associated with impaired BMPRII signalling, occurring through small mothers against decapentaplegic (SMAD) proteins (2).

Several studies have used pulmonary arterial endothelial cells (PAECs) isolated from parenchyma of lung transplanted recipients with PAH. In their article recently published in Cell Stem Cell, Gu *et al*. have highlighted that the access to PAECs from familial PAH patients and unaffected mutation carriers is extremely limited (3). To overcome this impediment, Pollett *et al*. have developed a unique and innovative technique to isolate PAECs from the balloon of the Swan-Ganz catheter commonly used to perform right heart catheterization (4); however, the very low quantity of isolated cells remains a major concern. Consequently, it appears that inducing pluripotent stem cell-derived ECs (iPSC-ECs) is an elegant alternative to investigate *in vitro* the outcome of *BMPR2* mutation on the endothelial function, since according to Gu *et al*., the genetic *BMPR2* background is maintained (3). However, iPSC-ECs are originally circulating cells, which have never resided within the pulmonary vascular wall. Despite this minor limitation, iPSC-ECs are a valuable tool to further unravel the pathogenic consequence of *BMPR2* mutations, better understand the low penetrance of *BMPR2* mutations and develop novel therapeutic approaches.

Among *BMPR2* mutation carriers, only 20% will later develop PAH, indicating that a *BMPR2* mutation alone is not sufficient to cause PAH (5); accordingly, heterozygous *BMPR2*$^{+/-}$ deficient mice do not spontaneously develop PAH unless a second hit (inflammation, hypoxia) is applied (6). Besides, this may also suggest that unaffected *BMPR2* mutation carriers harbour protective pathways preventing them developing PAH, as hypothesised by Gu *et al*. (3). Therefore, by comparing iPSC-ECs isolated from unaffected *BMPR2* mutation carriers to those of PAH affected *BMPR2* mutation carriers, Gu *et al*. have identified protective BMPRII modifiers and differentially expressed genes, preserving adhesion, survival, migration and angiogenesis (3). More precisely, they demonstrated that the "protected" phenotype of unaffected *BMPR2* mutation carriers could be related to enhanced specific BMPRII activators including caveolin-1, low-density lipoprotein receptor-related protein 1 (LRP1), or to compromised BMPRII inhibitors such as Gremlin1 or FK506 binding protein 12 (FKBP1A). Interestingly, it seems that the only reduction in BMPRII protein expression, in idiopathic PAH as well as in familial PAH, is not responsible of impaired endothelial dysfunction in PAH. Although several authors

claimed a significant lower expression of BMPRII proteins in lung from idiopathic PAH and familial PAH patients (7) others appear much more nuanced (8). In addition to a decrease in BMPRII protein expression, *BMPR2* mutations result in defective cellular trafficking and misfolding of BMPRII protein in PAH (9, 10). This is in agreement with (I) the involvement of LRP1, which recycles the BMP ligand-receptor complex back to the cell surface (11) and (II) the role of caveolin-1 in regulating BMPRII localization and signaling in vascular smooth muscle cells (12). Moreover, the improved adhesion of iPSC-ECs from unaffected *BMPR2* mutation carriers to plastic or matrices could be attributed to p38 MAPK signalling consequently identified as a compensatory pathway. Among the 71 transcripts of the differentially expressed genes between iPSC-ECs from controls, unaffected *BMPR2* mutation carriers and FPAH patients and associated with endothelial function and PAH, baculoviral IAP repeat containing 3 (BIRC3) encoding a protein that maintains EC survival, was identified as a candidate able to preserve cell survival in iPSC-ECs from unaffected *BMPR2* mutation carriers. Noteworthy, the balance between activators and inhibitors of BMPRII appears crucial to preserve the p38MAPK signalling pathway; however, the impairment of this equilibrium can fulfil various aspects as illustrated by the difference between the 3 investigated families. This emphasizes the necessity of implementing individualized tailored therapeutic approaches; consequently, access to blood iPSCs provides a unique opportunity to determine the efficacy and safety of personalized drug-screening platform, as relevantly emphasised by Gu *et al*. in their discussion (3). In addition, the authors suggest that iPSCs could be used to identify drugs which could reproduce the gene expression profile of unaffected *BMPR2* mutation carriers or reverse that of FPAH patients by investigating their potential protective properties to restore normal pulmonary vascular function. In the top significantly dysregulated genes, they identified an upregulation of two alpha-adrenergic receptors (ADRA2C and ADRA1D) specifically in FPAH patients but not in unaffected *BMPR2* mutation carriers This ties in with the idea that beta blockers, especially those with alpha blocking activity, may alleviate endothelial dysfunction in some PAH patients (13).

Eventually, the *BMPR2* mutation has been corrected in iPSC-ECs from FPAH patients by using the CRISPR/Cas9 technology, resulting in improvement of cell adhesion and cell survival, together with a rescued p38MAPK signalling pathway, whereas the expression of the anti-apoptotic BIRC3 remained unchanged and still impaired angiogenesis and migration. It appears that a balance in the expression of protective activators and inhibitors of BMPRII combined with a corrected *BMPR2* mutation are required to fully normalize endothelial cell function in PAH.

The findings of Gu *et al.* (3) let glimpse new perspectives for the future treatment of PAH. It may become a reality to implement innovative therapeutic approaches combining gene therapy, cell therapy and oral therapy to definitely cure FPAH. Therefore, collecting iPSCs from patients with PAH, then correcting the *BMPR2* mutation or the defective BMPRII signalling pathway *in vitro* using the CRISPR/Cas9 technology and re-injecting the iPSCs with the corrected *BMPR2* mutation or BMPRII signalling pathway together with an oral treatment stimulating the activators or reducing the inhibitors of BMPRII, could be an option. Drugs such as tacrolimus, by activating BMPRII, can rescue endothelial dysfunction and reverse pulmonary hypertension in *BMPR2*$^{+/-}$ deficient mice and monocrotaline rats (14) and has been shown to seriously improve the condition of a limited number of patients with end-stage PAH (15). This novel combination might be an innovative and an alternative therapeutic approach to the current vasodilatory PAH drugs, which prevent progression of the disease without curing it.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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