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KCNK3: new gene target for pulmonary hypertension?

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EXPERT REVIEWS

Recently, *KCNK3* has been identified as a new predisposing gene for pulmonary arterial hypertension (PAH) by whole-exome sequencing. Mutation in *KCNK3* gene is responsible for the first channelopathy identified in PAH. PAH due to *KCNK3* mutations is an autosomal dominant disease with an incomplete penetrance as previously described in PAH due to *BMPR2* mutations. This discovery represents an important advance for genetic counselling, allowing identification of high risk relatives for PAH and possible screening for PAH in *KCNK3* mutation carriers.

In 1954, Dresdale and colleagues described the first cases of pulmonary arterial hypertension (PAH) occurring in a familial context, suggesting that the role of a heritable component in the development of this devastating pulmonary vascular disease be highlighted [1]. Since 2000, several PAH predisposing genes involved in the TGF-β pathway have been identified [2,3]. Recently, a new predisposing gene for PAH, namely, *KCNK3* or *TASK1*, has been described. The *KCNK3* gene encodes for a potassium channel subfamily K, member 3 [4].

In 2000, linkage analysis in affected families allowed researchers to demonstrate that germline mutations of the bone morphogenetic protein receptor type 2 (*BMPR2*) gene are a major cause of familial PAH [5,6]. The *BMPR2* gene encodes for the BMPR-II receptor, which belongs to the TGF-β superfamily. PAH due to *BMPR2* mutation is an autosomal dominant disease, with an incomplete penetrance estimated at 42% in females and 14% in males [7]. Mutations in this gene are identified in approximately 75% of PAH patients with a family history of the disease, and up to 25% of patients with sporadic PAH, making it the principal genetic risk factor for PAH. Occurrence of PAH in patients displaying hereditary hemorrhagic telangiectasia led to the identification of two additional PAH predisposing genes that belong to the TGF-β superfamily: *activin A receptor type II-like kinase 1*, and more rarely, *endoglin* [8,9]. Mutations have also been identified in genes encoding for cytoplasmic proteins of the TGF-β-signaling pathway: *Smad8* (two cases), *Smad5* (one case) and *Smad1* (one case) [10,11]. More recently, exome sequencing in a large PAH family identified *caveolin-1* (*CAV1*) as a predisposing gene for PAH [12]. Caveolae are critical for initiation of the cell signaling cascade and *CAV1* encodes a protein involved in their formation that are specialized microdomains rich in cell-surface receptors, such as BMPR-II. *CAV1* was sequenced in 260 other PAH patients (62 unrelated patients with familial PAH and 198 sporadic cases), leading to the identification of only one additional *CAV1* mutation carrier. Genetic abnormalities are currently identified in more than 80% of familial PAH and in about 15% of sporadic cases of PAH. In the last update from the French Pulmonary Hypertension referral center, we identified 70 different PAH families, and a mutation in a PAH predisposing gene was identified in 59 of them, leaving only 15% of PAH families without genetic explanation.

Recently, Ma and colleagues identified *KCNK3* as a new predisposing gene for PAH by whole-exome sequencing performed in one PAH family. *KCNK3* mutation was also identified in 2 out of 92 (3.2%) unrelated patients with familial PAH and in 3 out of 230 (1.3%) patients

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with sporadic PAH [4]. A mutation in the *KCNK3* gene is responsible for the first channelopathy identified in PAH. Channelopathies are well known to be involved in the development of other conditions, such as multiple sclerosis, type 1 diabetes, rheumatoid arthritis, neuromyelitis optica [13], cardiovascular diseases [14] and cystic fibrosis [15]. PAH due to *KCNK3* mutations is an autosomal dominant disease with an incomplete penetrance as previously described in PAH due to *BMPR2* mutations. Moreover, as observed in *BMPR2* mutation carriers, mutations in the *KCNK3* gene seem to be associated only with PAH. This discovery represents an important advance for genetic counseling, allowing identification of high-risk relatives for PAH and possible screening of PAH in *KCNK3* mutation carriers.

The *KCNK3* gene encodes for a pH-sensitive potassium channel characterized by the presence of four transmembrane domains and two pore domains per sub-unit [16]. The KCNK3 channel, a non-voltage-dependent outward rectifier potassium channel, participates in the regulation of plasma membrane resting potential [17–19] in several cell types including human pulmonary artery smooth muscle cells [20]. All mutations currently identified alter conserved residues, and electrophysiological studies demonstrated the loss of function of the potassium channel [4]. The decreased KCNK3 activities due to mutations probably cause depolarization of the resting membrane potential, which could lead to vasoconstriction and pulmonary artery remodeling. Interestingly, endothelin-1 has been shown to inhibit the KCNK3 channel in hPASMC via rho kinase phosphorylation [20,21].

Ma and colleagues expressed in Cos-7 cells each identified KCNK3 mutant and the patch-clamp recording revealed that in all mutants, the KCNK3 current was abolished compared to wild-type KCNK3 currents, suggesting a loss of function of these mutants [4]. They demonstrated that the function of the KCNK3 channel can be restored with the use of a phospholipase A2 inhibitor, indicating that this is not a total loss of function. Electrophysiological analysis showed that inversion potential of mutant channel current induced by a phospholipase A2 inhibitor was shifted in direction on positive potential, suggesting a change of ionic selectivity in mutant channels. T8K and E182K mutants are functional, but their ionic properties appear to be affected by mutation. On the other hand, G203D mutants are insensitive to the application of a phospholipase A2 inhibitor, suggesting a thorough loss of function of this mutant channel or a mislocalization of the channel into the intracellular organelle. The exciting discovery of *KCNK3* mutations in PAH patients' required additional experiments to decipher the pathophysiology of PAH induced by *KCNK3* mutations, and to determine the beneficial supply of the *KCNK3* activating pharmacological approach in non-mutated *KCNK3* PAH patients. In this context, *KCNK3*-knockout mice may be of interest. Incidentally, a model of the *KCNK3*-knockout mouse has already been used and showed a blunted ventilator response to hypoxia [22]. However, pulmonary artery pressure has not been studied yet in these mice. Currently, it is well known that *BMPR2* knockout mice die early during gastrulation, whereas heterozygous mice normally grow without developing PAH. The study of the *KCNK3*-knockout mouse provides new research tools in the field of PAH.

Even if the central role of the TGF-β pathway has been known since the early 2000s, mutation- or gene-specific PAH treatment has not been successfully developed yet [23,24]. A lesson can be learnt from research in other channelopathies such as cystic fibrosis where pharmacological therapies are directed to treat mutation-specific changes. Aminoglycosides and Ataluren (PTC124) are used in cystic fibrosis patient carriers of truncating mutations [25]. These molecules are able to complete translation of proteins containing a premature stop codon due to nonsense mutation and have beneficial effects in these patients. Lumacaftor increases the amount of protein expressed in the cytoplasmic membrane by correcting defective trafficking as observed with the mutation F508del [26]. Interestingly, it has been shown that phosphodiesterase type 5 inhibitors can improve channel activity of cystic fibrosis transmembrane conductance regulator with a F508del mutation by promoting its maturation and correcting its trafficking [27]. Similarly, the next step for PAH management may be the development of causal mutation-specific therapies. Frump and colleagues have demonstrated that it is possible to restore the TGF-β activity in cells carrying an in-frame deletion of exon 2 of the *BMPR2* gene by improving trafficking of the mutated protein using chemical chaperones [28]. These authors speculated that chemical chaperones could be beneficial for all carriers of a missense *BMPR2* mutation or an in-frame large rearrangement which affects the trafficking of the protein to the cell surface. Moreover, Drake and colleagues have described a beneficial effect of Ataluren (PTC124) to correct nonsense *BMPR2* mutations [29]. Finally, epigenetic modifications could represent potential future therapeutic targets, and preliminary studies have demonstrated the potential interest of targeting micro-RNAs which are key players of gene regulation [30].

In conclusion, better understanding of the pathophysiology of PAH resulting from the recognition of *KCNK3* and other genes as causes of heritable PAH opens new research directions for the diagnosis, prevention and treatment of this devastating disease.

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