Evidence for Inflammatory Signaling in Idiopathic Pulmonary Artery Hypertension

**TRPC6** and Nuclear Factor-κB

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Knowledge of molecular mechanisms underlying pulmonary arterial hypertension (PAH) continues to increase with the emerging theme that PAH is a heterogeneous disease involving multiple molecular abnormalities. Mutations in several genes have been identified in subsets of patients with PAH, and multiple signaling systems that influence vascular tone, function, and remodeling have been associated with PAH.1,2,3 In addition to mutations in BMPR2, serotonin (5-HT) and polymorphisms in its transporter (SERT) play a critical role in the pulmonary vascular smooth muscle hyperplasia and vascular remodeling found in PAH.4,5 Other genes and signals thought to contribute to the development of idiopathic pulmonary arterial hypertension (IPAH) include somatic mutations of BAX,6 upregulation of Angiopoietin 1,7 transforming growth factor β1 polymorphisms,8 ALK1 mutation,9 SMAD8 mutation,9 and increased hyaluronic acid content associated with increased Hyaluronan Synthase 1 and decreased Hyaluronoglucoaminidase 1 gene expression.10 A recent observation also suggests that the noncanonical Wnt pathway is activated in IPAH.11

Several transient receptor potential canonical (TRPC) family members are important in pulmonary arterial smooth muscle cell (PASMC) function and play a role in pathogenesis of familial PAH and IPAH. TRPC6 upregulation may play a role in PASMC proliferation. In IPAH-patient–derived PASMC, TRPC6 and TRPC3 expression is higher than in patients with secondary pulmonary hypertension.12,13 This not only implicates the TRPC family in IPAH but also suggests that its role is specific to the pulmonary vascular abnormality that occurs in primary form, rather than secondary to additional causes. Another TRPC family member, TRPC1, has also been shown to play a critical role in PASMC proliferation. TRPC proteins, a super family of canonical cation channels, are widely expressed in cardiac, pulmonary, and vascular tissues and partially regulate cellular Ca2+ flux either by acting as Ca2+ entry channels or by changing membrane potentials.14,15 TRPC channels are responsive to a wide variety of signals including but not limited to cellular and extra cellular messengers, temperature, and stress.

In this issue of Circulation, Yu et al provide further insight into the action of the TRPC6 gene in PASMC function in IPAH.16 Building on their earlier studies showing that TRCP6 expression is higher in IPAH-derived PASMC,17 they tested the hypothesis that upregulated TRPC6 gene transcription may promote the development of IPAH. To test this hypothesis, they sequenced TRPC6 regulatory regions of 268 IPAH patients and identified a single nucleotide polymorphism (SNP), -254(C-G) that associated with IPAH. They then explored the functional effects of this SNP. Their data convincingly show that the -254(C-G) SNP is statistically associated with IPAH, and the presence of this SNP results in gain of function in that it generates a nuclear factor κB (NF-κB) response element in the TRPC6 regulatory regions. They then showed that nuclear translocation of NF-κB upregulates TRPC6 expression and enhances agonist-induced Ca2+ influx in IPAH PASMCs with the -254G allele, and that the inhibition of nuclear translocation of NF-κB attenuates TRPC6 expression and function in these PASMCs.

These data directly link NF-κB and inflammation to TRPC6–associated PAH. This link is highly relevant because it has been hypothesized that some of the pathophysiology of PAH involves an inflammatory response. IPAH is associated with perivascular inflammation,18 and individuals with PAH have increased circulating inflammatory cytokines, including IL6 and MCP1.19,20 NF-κB is a ubiquitously expressed transcription factor that activates cellular responses to inflammation, oxidant stress, and responses to pathogens by enhancing other cell- and signal-specific transcription factors that control inflammatory and stress-response genes.21 NF-κB has been shown to be important in the rat model of PAH.22 Enhanced NF-κB activity has been observed in patients with pulmonary hypertension during bypass surgery.23

The data presented in the Yu article support the general hypothesis of IPAH pathogenesis that abnormalities in multiple pathways or genes can contribute to or lead to PAH. On the basis of their data, it is likely that TRPC6 SNPs/mutations represent only a small percentage of IPAH cases; however, these findings highlight the importance of this pathway and suggest that other genes involved in this pathway may be appropriate targets for future studies. These data also suggest that the SNP in the TRPC6 regulatory region is a modifying rather than a causative factor. That is, it primes the PASMC...
cells to an exaggerated response to NF-κB activation. Thus, any inflammatory triggers in the lungs of individuals carrying this SNP could increase their risk of developing PAH. No genetic evidence to date suggests that NF-κB activation itself is causative of human PAH. NF-κB response likely works in a synergistic manner with the associated molecular defect.

It remains to be determined what factors or stimuli could activate NF-κB in IPAH patients, what might terminate the NF-κB responses in PASMCs, and how the process is controlled. Answers to such questions will provide clues on how to modify the inflammatory response in IPAH and hopefully lead to new and different therapies for this difficult disease. The study by Yu et al is another important step in the path to discovery.  

**Disclosures**

None.

**References**


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