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Knocking Out Smoking and Pulmonary Hypertension with a K^+

Although many patients with chronic obstructive pulmonary disease (COPD) develop mild pulmonary arterial hypertension (PAH), believed to result from hypoxia-induced pulmonary vasoconstriction, a small but significant fraction of patients with COPD develop more severe PAH, often without clinical evidence of hypoxemia or out of proportion to their degree of emphysema (1, 2). The mechanism for the development of pulmonary hypertension in these patients is not entirely clear, but pathologically, the pulmonary arterioles of these patients demonstrate endothelial cell dysfunction (3), smooth muscle cell hyperplasia, and arterial intimal fibrosis (4), features commonly observed in other forms of primary or group I PAH. As a consequence, these patients suffer significant morbidity and mortality, often independent of the severity of their obstructive airway disease (5). Why some patients with COPD develop significant PAH and the mechanisms that drive this process are not completely understood.

The harmful effects of cigarette smoke are well known to not only directly affect cells of the respiratory epithelium but also other cell types in the lung, including mesenchymal cells and vascular endothelial cells (6). Indeed, the ability of toxins from cigarette smoking to traverse the epithelial barrier and effect pulmonary and systemic vasculature is an oft-cited mechanism for how smoking contributes to cardiovascular disease, stroke, and other systemic diseases (7). Not surprisingly, tobacco smoking is also a risk factor for PAH (8).

Dynamic vasoconstriction and vasodilation are mediated by the contraction and relaxation of smooth muscle and mesenchymal cells of the vasculature, and like most muscle cells, they are mediated by the opening and closing of various ion channels. From the initial discovery of action potentials described by Hodgkin and Huxley in 1952, ion channel behavior is one of the oldest and most fundamental processes that has been studied in cell and molecular physiology. Patch clamp recordings, invented by Neher and Sakmann, provided a technique to study electrophysiology at the level of individual ion channels and cells. Today, we know the human genome codes for more than 300 different ion channels, whose function are not only limited to electrochemical homeostasis or neuronal communication but also to diverse functions including cell proliferation, differentiation, mitochondrial function, cellular metabolism, DNA repair, and cell–cell communication. Beyond muscle contraction, ion channels play a role in organ development, repair and regeneration, aging, and cellular senescence.

Potassium (K^+) channels themselves have been in eukaryotic, bacterial, and archaeal existence since before the evolution of neuronal signaling (9). They are found in nearly all organisms and cell types (10). In humans, they are often classified by their structure (for example, inward-rectifying K^+ channels have two transmembrane domains, whereas others have six) and gating mechanisms, where they may either remain constitutively open to help maintain resting membrane potential or open only in response to changes in voltage (often designated K_v) or calcium. Abnormalities

Supported by NHLBI grant HL127203.

Originally Published in Press as DOI: 10.1164/rccm.202011-4121ED on December 23, 2020

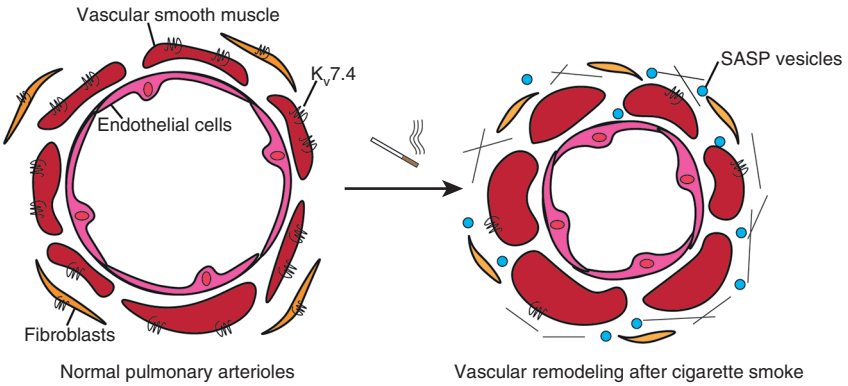

Figure 1. Schematic representation of the effects of cigarette smoking on K_v7.4 expression and vascular remodeling. SASP = senescence-associated secretory phenotype.

in K^+ channels have been implicated in PAH; indeed, PAH has been associated with genetic defects in *ABCC8* and *KCNK3* (11, 12). *KCNK3*, which is also called TASK1, belongs to a family of tandem-pore domain K^+ channels that maintain resting membrane potential and can be inhibited by local anesthetics, including lidocaine and bupivacaine. Endothelin-1 and serotonin, which are elevated in PAH, also inhibit *KCNK3* function (13). Loss of *KCNK3* function by these mediators contributes to PAH by promoting vasoconstriction and pulmonary artery smooth muscle proliferation (14). Dysfunction of voltage-gated K^+ channels, including K_v1.5 (*KCNA5*), has also been implicated in PAH. PAH is associated with single-nucleotide polymorphisms in *KCNA5* (15), and loss of K_v1.5 function in pulmonary artery smooth muscle cells contributes to increased cytosolic Ca^{2+} concentration and smooth muscle contraction.

In this issue of the *Journal*, Sevilla-Montero and colleagues (pp. 1290–1305) examine the role of K_v7.4 (*KCNQ4*) in cigarette-smoking–induced pulmonary vascular remodeling (16). Members of the K_v7 family are also highly expressed in vascular smooth muscle, and K_v7.4 has been implicated in systemic hypertension (17). Sevilla-Montero and colleagues show that cigarette smoking contributes to pulmonary arterial remodeling via induction of arterial smooth muscle and adventitial fibroblast senescence. They then show that cigarette smoking contributes to loss of K_v7.4 expression, and this leads to impaired vasodilation (Figure 1). They also interestingly observed impaired vasoactive constriction as well in response to serotonin. Cigarette-induced impairment in vasoactivity and loss of K_v7.4 were later confirmed in animal models and finally in human tissue of patients with COPD.

Although these studies provide a comprehensive and elegant analysis of how loss of K_v7.4 might contribute to cigarette-induced pulmonary vascular remodeling and PAH, many questions remain. Voltage-gated K^+ channels like K_v7.4 allow cells to repolarize and are thus critical for smooth muscle relaxation; loss of K_v7.4 would thus be expected to contribute to PAH through impaired vasodilation. However, cigarette smoke was also shown by the authors to impair vascular responsiveness to vasoconstricting agents as well, and whether this may be due to loss of K_v7.4 is unclear. It is increasingly recognized that PAH is characterized by not just impairment in vascular relaxation but also in defects of overall vascular responsiveness to both vasodilating and vasoconstricting agents. How might loss of K_v7.4 cause impairment in vasoconstriction? Could cigarette smoking induce gain (or loss) of function of other ion channels that results in impaired vascular responsiveness?

In the study by Sevilla-Montero and colleagues, cigarette smoke exposure was also observed to contribute to arterial smooth muscle and fibroblast senescence (16), but how it does so and whether it is dependent on loss of K_v7.4 is not known. The effect of K^+ channel opening is best thought to result in cellular repolarization, and K^+ ions themselves are not often considered second messengers in signaling. However, the importance of K^+ channels in diverse cellular processes suggests that their actions likely induce a variety of downstream signaling effects, only some of which have been explored. K^+ channels, including K_v7.4, are known to locate not just on plasma membrane but also in organelles including mitochondria (18), affecting cellular metabolism, aging, and survival. Different classes of K^+ channels, many of which are expressed simultaneously in a given cell, also offer different gating thresholds and electrochemical properties; how they integrate in a systems-based fashion to regulate diverse processes such as cell proliferation, differentiation, senescence, and metabolism remain a mystery.

The function of K^+ channels has historically been focused on neurons, cardiac muscle, and systemic vasculature, but accumulating evidence has shown alterations in K^+ channel biology to be important in asthma, COPD, and pulmonary fibrosis (19, 20). Specificity of different K^+ channels and their expression on cell surfaces lend themselves to easy therapeutic targeting by agonists and antagonists. The work by Sevilla-Montero and colleagues leads to a long line of accumulating evidence of the importance of K^+ channels in not just PAH but also a variety of lung diseases and offers unique opportunities for targeting specific K^+ channels as a novel line of therapeutics. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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Time to Trust Transbronchial Cryobiopsy in Identification of Usual Interstitial Pneumonia Pattern?

Usual interstitial pneumonia (UIP) refers to a morphologic pattern characterized by a combination of *1*) patchy interstitial fibrosis sharply demarcated from areas of normal lung ("patchy fibrosis"), *2*) temporal heterogeneity of fibrosis characterized by scattered fibroblastic foci in a background of dense acellular collagen, and *3*) architectural derangement mainly represented by cysts covered by cells that usually express bronchiolar stem cells markers (honeycombing) (1, 2). The patchy interstitial process often emanates from the subpleural zones and septa or, occasionally, from one edge of an airway. Therefore, the distribution of the lesion is better described as periacinar instead of perilobular (1) (Figure 1). UIP pattern is the histopathologic background of idiopathic pulmonary fibrosis (IPF) but it may be observed in biopsies obtained from subjects affected by a variety of other entities (collagen vascular diseases, chronic hypersensitivity pneumonitis, etc.). Ancillary

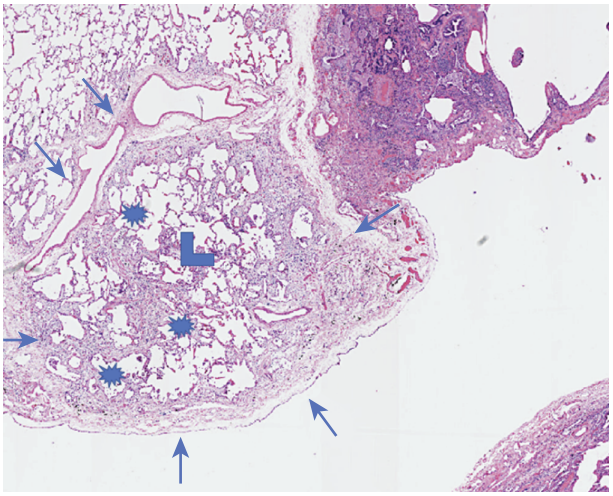

Figure 1. Usual interstitial pneumonia pattern. The boundaries of a secondary pulmonary lobule (marked by arrows) with fibrosis beneath the pleura and along the interlobular septa are shown. Tongues of fibrosis, however, also run along the periphery of an acinus (stars) surrounding a small bronchiole (arrowhead). An adjacent lobule is occupied by honeycombing (hematoxylin and eosin, low power).

Originally Published in Press as DOI: 10.1164/rccm.202012-4382ED on January 27, 2021