Give Me Some Room to Breathe! Can Targeting SPHK2 Reduce Airway Smooth Muscle Thickening in Asthma?

During the pathobiology of asthma, airway smooth muscle cells (ASMCs) play prominent roles in all aspects of the disease, including airway inflammation, hyperresponsiveness, and remodeling (1). Remodeling includes irreversible airway structural changes, leading to airway wall thickening, decreased airway luminal diameter, and fixed airway obstruction (2). Persistent airflow obstruction, which contributes to asthma severity, is associated with increased airway wall thickness and ASM area (3, 4). Furthermore, excessive airway narrowing is associated with airway hyperresponsiveness (AHR) in asthma (5). ASMC hyperplasia (6), hypertrophy (7), and migration (8) have all been implicated in human asthma as potential mechanisms of increased ASM mass. Studies of the beneficial effects of standard asthma therapies on airway wall thickening have yielded contradictory results (9–12), which may be related to corticosteroid resistance in subsets of patients and to reduction of airway inflammation rather than reversal of established airway remodeling. Thus, identification of pharmacological agents that can halt the progression of or even reverse ASMC accumulation in asthma is a key therapeutic goal.

S1P (sphingosine-1-phosphate) is a potent stimulator of ASMC proliferation, contraction, and airway hyperreactivity in the context of asthma and allergic airways disease (13–15). Sphingosine is a natural substrate of SPHK1 and SPHK2 (sphingosine kinases 1 and 2), which catalyze the intracellular formation of S1P. Transport of S1P outside of the cell renders it cell impermeant, and its signaling effects on cell activity are mediated by binding of S1P to several cell membrane G-protein–coupled receptors (S1P1–5) (16). Much research interest in recent years has focused on the ability of sphingosine analogs to abrogate disease progression through either receptor-mediated or -independent mechanisms. Prophylactic administration of the drug FTY720 (fingolimod), a synthetic sphingosine analog that has been approved for clinical treatment of multiple sclerosis, has been shown to reduce AHR and ASM mass in rodent models of allergic airways disease (17, 18). Thus, the sphingosine pathway represents a potential molecular target for development of new therapies to prevent airway remodeling in asthma.

In this issue of the *Journal*, Blais-Lecours and colleagues (pp. 35–42) define the mechanism of action of a synthetic sphingosine analog and SPHK2 substrate, AAL-R ([(R)-2-amino-4-(4-heptyloxyphenyl)-2-methylbutanol]), to inhibit ASMC proliferation (19). Previous work by this group demonstrated that intratracheal administration of AAL-R halted airway immune cell accumulation and AHR in a mouse model of allergic airway disease with established house dust mite allergen–induced airway inflammation (20). Building on those studies, the authors further showed that AAL-R reversed AHR and *in vivo* ASM thickening in a model of chronic house dust mite allergen challenge with established airway remodeling. Interestingly, *in vitro* studies of human ASMCs in complete media showed that at low concentrations (1 μM), AAL-R did not induce apoptosis but diminished cell proliferation and metabolic activity (21). The current well-designed study expands on these findings by delineating the mechanism whereby AAL-R inhibits ASMC growth. The authors show that AAL-R perturbed cellular metabolism such that oxygen use by the cells was reduced and metabolic activity was shifted to glycolysis. These metabolism-altering effects of AAL-R were associated with high levels of SPHK2 in Ki-67$^+$ (proliferating) ASMCs and in those cells after mitogenic stimuli. Other pulmonary stromal cells that express relatively lower levels of SPHK2, such as airway epithelial cells and arterial endothelial cells, were not as susceptible to the oxidoreductive effects of AAL-R as the ASMCs were. Finally, the authors show that SPHK2-induced phosphorylation was required for the AAL-R–mediated reduction of cellular metabolism in proliferating ASMCs, but S1P1 and S1P3 receptor signaling was not required for this effect.

Currently, the only approved therapy that effectively reduces ASM mass in asthma is bronchial thermoplasty, which is indicated for patients with severe asthma who have persistent symptoms that are refractive to other therapies (22). For the majority of patients with asthma, innovative pharmacological options are still needed to address airway wall thickening and hyperreactivity. Although Blais-Lecours and colleagues used normal ASMCs and stromal cell lines for most of their experiments, their results provide preliminary evidence that suggests that ASMCs derived from patients with asthma are susceptible to the metabolic perturbations induced by AAL-R. Much more work needs to be done to test the efficacy of sphingosine analogs and other therapies that modulate SPHK2 expression or activity to inhibit or reverse ASMC accumulation in asthmatic airways. Nevertheless, this work and other recent reports of pharmacology-mediated reductions of ASM mass in human asthma (23) reveal molecular pathways that may hold the key to alleviating airway remodeling in asthma. ■

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