The Sphingosine Kinase 1/Sphingosine-1-Phosphate Pathway in the Treatment of Pulmonary Arterial Hypertension


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Purpose: We aimed to examine whether SphKs and their product, S1P, play a role in the development of pulmonary arterial hypertension (PAH).

Background: Sphingosine kinases (SphKs) 1 and 2 regulate the synthesis of the bioactive sphingolipid sphingosine-1-phosphate (S1P), an important lipid mediator that promotes cell proliferation, migration, and angiogenesis.

Methods: SphK1−/−, SphK2−/−, and S1P lyase heterozygous (Sgpl1+/−) mice, a pharmacologic SphK inhibitor (SKI2), and a S1P receptor 2 (S1PR2) antagonist (JTE013) were used in rodent models of hypoxia-mediated pulmonary hypertension (HPH). S1P levels in lung tissues from patients with PAH and pulmonary arteries (PAs) from rodent models of HPH were measured.

Results: mRNA and protein levels of SphK1, but not SphK2, were significantly increased in the lungs and isolated PA smooth muscle cells (PASMCs) from patients with PAH, and in lungs of experimental rodent models of HPH. S1P levels were increased in lungs of patients with PAH and PAs from rodent models of HPH. Unlike SphK2−/− mice, SphK1−/− mice were more susceptible to HPH. Pharmacologic SphK1 and S1PR2 inhibition prevented the development of HPH in rodent models of HPH. Overexpression of SphK1 and stimulation with S1P potentially via ligation of S1PR2 promoted PASMC proliferation in vitro, whereas SphK1 deficiency inhibited PASMC proliferation.

Conclusion: The SphK1/S1P axis is a novel pathway in PAH that promotes PASMC proliferation, a major contributor to pulmonary vascular remodeling. Our results suggest that this pathway is a potential therapeutic target in PAH.