CHINESE-AMERICAN LUNG ASSOCIATION

2020 CALA Happy Friday Seminar

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Time: EST 10:30 am; PST: 7:30 am; Beijing time: 10:30 pm

Role of Sphingolipid Pathways in the Pathobiology of Pulmonary Arterial Hypertension

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Sphingosine kinase 1 (SphK1) regulates the synthesis of the bioactive sphingolipid sphingosine 1-phosphate (S1P), an important lipid mediator that promotes endothelial cell proliferation, migration and angiogenesis. Serum S1P activates YAP1 signaling pathways and YAP1 activation promotes cell proliferation. We first reported that SphK1 mRNA and protein levels were significantly up-regulated in pulmonary artery smooth muscle cells (PASMCs) isolated from patients with pulmonary arterial hypertension (PAH). Later we further investigated whether smooth muscle cell conditional SphK1 deficient (SM22αCre+SphK1f/f) mice are protected from experimental models of pulmonary hypertension (PH) and whether YAP1 plays a role in SphK1-mediated PH development. We demonstrated that SM22αCre+SphK1f/f mice are protected against hypoxia or hypoxia plus sugen mediated pulmonary hypertension. S1P or hypoxia activate YAP1 signaling by enhancing its translocation to the nucleus. YAP1 translocation is dependent on SphK1 enzymatic activity. We also showed that a YAP1 specific inhibitor, verteporfin, blocks S1P mediated proliferation in human PASMCs and attenuates hypoxia-mediated PH and pulmonary vascular remodeling in mice or hypoxia Sugen mediated severe PH in rats. We conclude that smooth muscle cell specific SphK1 plays an essential role in PH via YAP1 signaling. YAP1 inhibition may have a therapeutic effect for PH.