ID: 114 AN ANTAGONIST OF LYSOPHOSPHATIDIC ACID RECEPTOR1, AM966, INCREASES PULMONARY ENDOTHELIAL PERMEABILITY THROUGH ACTIVATION OF VE-CADHERIN

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Background Maintenance of pulmonary endothelial barrier integrity is important for reducing severity of lung injury. VE-cadherin is a major component of cell–cell adherens junctions in endothelium. In response to inflammatory stimuli, VE-cadherin is tyrosine phosphorylated, resulting in dissociation with catenins, which links to f-actin. Lysophosphatidic acid (LPA) is a bioactive lysophospholipid, which regulates cell motility. LPA has been shown to increase lung epithelial barrier integrity, while it reduces endothelial barrier function. AM966 is an antagonist exhibiting an anti-fibrotic property. However, the effect of AM966 on pulmonary endothelial barrier integrity has not been well studied.

Methods and Results To investigate endothelial barrier integrity, electric cell-substrate sensing (ECIS) system was used to measure permeability in human lung microvascular endothelial cells (HLMVECs). Similar to the effect of LPA, AM966 increases permeability immediately in a dose dependent manner. To investigate the molecular mechanism by which regulates AM966-mediated reduction of endothelial barrier function, HLMVECs were treated with AM966, and then phosphorylation of myosin light chain (MLC) and VE-cadherin were determined by immunoblotting. AM966 increased phosphorylation of MLC and VE-cadherin. VE-cadherin and f-actin double immunostaining revealed that AM966 induces gap formation and f-actin stress fibers as well as dissociation between VE-cadherin and f-actin.

Conclusion This study reveals that AM966 induces lung endothelial barrier dysfunction, which is regulated by phosphorylation of VE-cadherin.

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