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Category: Predoc
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Title: Endoplasmic Reticulum-Resident Protein Sigma1R Regulates Endothelial Inflammation and Permeability
Abstract: Acute lung injury (ALI) is a life-threatening condition which affects nearly 200,000 people annually in the United States and is associated with an ~ 40% mortality rate. ALI can be caused by direct insults such as pneumonia, viral infections such as COVID-19 or via indirect insults such as sepsis and multiple traumas, to the lungs. Key features of ALI include severe inflammation and disruption of capillary alveolar barriers. Understanding the mechanisms that lead to this functional disruption is critical to designing a therapeutic intervention that is safe and effective. Earlier studies in our lab have shown that the endoplasmic reticulum (ER)-resident protein BiP/GRP78 and mitochondrial-resident protein mortalin/GRP75 are critical players in regulating endothelial cell (EC) inflammation and permeability associated with ALI. In the present study we monitor the role of sigma-1 receptor (sigma1R), a ubiquitously expressed ER resident chaperone protein that has been shown to interact with BiP/GRP78 and IP3Rs (inositol 1,4,5-triphosphate receptors) and regulate Ca2+ signaling between the ER and the mitochondria. Sigma1R has been implicated in the regulation of neurodegenerative diseases, however, the role of sigma1R in acute inflammatory injury, particularly in the context of lung endothelium is poorly defined. Our data using human pulmonary artery endothelial cells (HPAEC) showed that siRNA-mediated knockdown of sigma1R potentiated lipopolysaccharide (LPS)-induced expression of proinflammatory molecules such as ICAM-1, VCAM-1 and IL-6. Consistent with this, sigma1R agonist (PRE084) blunted the above responses. In contrast, proinflammatory mediator thrombin-induced expression of adhesion molecules and cytokine was inhibited upon sigma1R knockdown, suggesting a stimulus-specific role of sigma1R in mediating endothelial inflammation. Our data also showed that sigma1R knockdown disrupted thrombin-induced Ca2+ release from the ER stores as well as Ca2+ entry from the extracellular medium. Together, these data implicate a novel role of sigma1R in endothelial inflammation and permeability.