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Title: MTOR MAINTAINS VASCULAR INTEGRITY IN THE LUNG

Abstract:

Acute lung injury (ALI) is a common cause of respiratory failure in critically ill patients, with a mortality rate of 30-40%. Acquisition of a proinflammatory phenotype and disruption of the vascular endothelial barrier leading to inflammatory cell infiltration and protein-rich edema formation are prominent pathogenic features of ALI and its more severe form acute respiratory distress syndrome (ARDS). Mechanistic (formerly mammalian) Target of Rapamycin (MTOR) has been shown by our lab to limit the endothelial cell (EC) inflammation. Our data show that MTOR is downregulated in injured lung, and to assess how its downregulation contributes to vascular dysfunction we determined the effect of knocking down MTOR in resting human pulmonary artery EC. This resulted in structural and functional changes in mitochondria, namely shape change and subcellular distribution of mitochondria, mitochondrial ROS generation, and increased mitochondrial fission via dynamin-related protein (Drp) 1 upregulation. Depletion of MTOR also caused impaired EC proliferation and migration, as well as disrupted barrier function. Consistent with this, VEGFR2 and VE-Cadherin levels were decreased in MTOR-depleted cells. Ongoing studies are investigating if Drp1/mitochondrial fission is causally linked to endothelial dysfunction, and preliminary evidence appears to support this possibility. To determine if the effect of MTOR depletion on EC dysfunction can be recapitulated in vivo in the lung, we used cationic liposome-mediated gene transfer to selectively target the lung endothelium for deletion or knockdown of MTOR (via transfer of Cre-recombinase or MTOR shRNA expressing plasmids in MTORf/f or WT mice, respectively) in mice. Loss of MTOR alone was sufficient to cause lung vascular inflammation and leakage, suggesting that the deleterious effects of ALI-causing agents may be mediated, at least in part, by MTOR depletion. Collectively, these data raise the exciting possibility that MTOR maintains vascular integrity in the lung, possibly via its ability to preserve mitochondrial function, and that restoring MTOR signaling in the lung endothelium may be an effective therapeutic approach against ALI.