

Presenter: Mohammad Shadab

Authors: Mohammad Shadab, Spencer A. Slavin, Zahra Mahamed, Michelle W. Millar, Rauf A. Najar, Antony Leonard, Anthony Pietropaoli, David A. Dean, Fabeha Fazal, Arshad Rahman

Title: SPLEEN TYROSINE KINASE PHOSPHORYLATES VE-CADHERIN TO CAUSE ENDOTHELIAL BARRIER DISRUPTION IN ACUTE LUNG INJURY

Abstract:

Increased endothelial cells (EC) permeability is a cardinal feature of acute lung injury (ALI)/acute respiratory distress syndrome (ARDS). However, the molecular pathways that govern EC permeability in ALI are incompletely addressed. Here, we report that Spleen Tyrosine Kinase (Syk) is a key mediator of EC barrier disruption and lung vascular leak in sepsis. Using in vitro models, we show that Syk promotes EC permeability via its ability to associate with and phosphorylate VE-cadherin. To ascertain the in vivo relevance of Syk in sepsis-induced ALI, we used a novel, remarkably efficient and cost-effective approach that relies on gene transfer of Cre-expressing plasmids into the lung endothelium of Syk^{fl/fl} mice to generate EC-ablated Syk mice. These mice were protected against sepsis-induced loss of VE-cadherin and inflammatory lung injury. In view of these findings and the reported role of Syk in neutrophil (and other myeloid cells) activation, we examined if global targeting of Syk protects against ALI. Administration of Syk inhibitor R788 (fostamatinib), currently in phase II clinical trial for treatment of COVID-19, mitigated lung injury and improved survival in mice with sepsis. Together, these results identify Syk as a novel kinase for VE-cadherin and a druggable target against ALI in sepsis.