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Category: Postdoc
Name: Mohammad Shadab
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Title: Spleen Tyrosine Kinase Mediates Endothelial Barrier Disruption in Acute Lung Injury via Phosphorylation of VE-cadherin
Abstract: Mohammad Shadab,1 Spencer Slavin,1 Michelle Millar,1 Rauf A. Najar,1 Zahra Mahamed,1 Antony Leonard,1 Anthony Pietropaoli,2 Fabeha Fazal,1 Arshad Rahman1 Departments of Pediatrics1 and Medicine,2 Lung Biology and Disease Program, Rochester, New York Increased endothelial cells (EC) permeability and inflammation are key pathogenic features of acute lung injury (ALI). We previously showed that Spleen Tyrosine Kinase (Syk), a non-receptor tyrosine kinase originally thought to be expressed only in cells of hematopoietic origin, plays an important role in EC inflammation. We now provide evidence that Syk is a critical determinant of endothelial barrier disruption and lung vascular leak in sepsis. Inhibition of Syk by pharmacological or genetic (siRNA-mediated knockdown or expression of kinase-defective mutant of Syk) approaches, each reduced thrombin-induced EC permeability. Inhibition of Syk also protected against EC barrier disruption caused by plasma from septic human patients, indicating the clinical relevance of Syk in sepsis-associated EC permeability. Mechanistic studies revealed that the barrier protective effect of Syk depletion/inhibition was associated with reduced phosphorylation (Tyr-658 and Tyr-685) and cleavage of VE-cadherin. Consistent with this, conditional deletion of Syk in the lung endothelium attenuated the loss of VE-cadherin in the lungs of mice with sepsis (induced by cecal ligation and puncture [CLP]). EC-specific deletion of Syk also reduced sepsis-induced lung vascular inflammation and injury. In view of these data showing a role of Syk in EC activation and the reported role of Syk in neutrophil (and other myeloid cells) activation, we examined the effect of targeting Syk in all these cell types (rather than in EC alone) on sepsis-induced lung injury and mortality. Inhibition of Syk by R788 (fostamatinib), which is currently in phase II clinical study for treatment of acute respiratory distress syndrome (ARDS) in COVID-19 patients, ameliorated lung inflammatory injury and improved survival in mice with sepsis. These data show that the barrier disrupting action of Syk derives, at least in part, from its ability to phosphorylate VE-cadherin and identify Syk as a viable therapeutic target to mitigate ALI in sepsis. Supported by: NIH (GM130463, HL148695)