parkin, a novel c-Abl substrate, as a critical mediator of endothelial dysfunction in ALI.

**Methods** ***In vitro*** Human pulmonary artery endothelial cells (EC) were transfected with siRNA for parkin and then challenged with LPS (1 μg/ml, 3 hrs). Inflammatory mediators were determined in cell lysates and supernatants by Western blotting and ELISA respectively.

***In vivo*** C57BL/6 (WT) and parkin deficient (PARK2 KO) male mice (8–12 wks, n=5–8) were subjected to LPS (intratracheally, 1 mg/kg) or PBS (controls), and allowed to recover prior to harvest 18 hrs later. Leakage of proteins into the alveolar space was assessed by measuring the protein levels in the bronchoalveolar lavage (BAL). To assess lung inflammation, neutrophil cell counts, myeloperoxidase (MPO) activity, and IL-6 levels were determined in BAL.

**Results** In human lung EC, down-regulation of parkin by siRNA reduces LPS-induced VCAM-1 expression (adhesion molecule involved in neutrophil adhesion to EC) (by 35%, $p<0.05$), IL-8 (neutrophil chemoattractant) (by 59%, $p<0.01$), and IL-6 (inflammatory cytokine) release (by 79%, $p<0.01$). PARK2 KO mice exhibit less ALI after LPS compared to WT. In PARK2 KO, BAL protein levels were reduced by 27% ($p=0.0024$) compared to WT mice. LPS-induced neutrophil recruitment into the alveoli of PARK2 KO was attenuated by 47% compared to WT ($p=0.0019$). BAL MPO activity (marker of neutrophil activation) and BAL IL-6 levels were also significantly lower in PARK2 KO by 52% ($p=0.03$) and 28% ($p=0.0061$) respectively.

**Conclusion** These results suggest that endothelial parkin mediates EC activation and neutrophil adhesion/migration after LPS, and therefore it may represent a new potential therapeutic target in ALI/ARDS.

## ID: 109 PARKIN MEDIATES ENDOTHELIAL PRO-INFLAMMATORY RESPONSES IN ACUTE LUNG INJURY

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**Introduction** Acute lung injury (ALI) and its more severe form, the Acute Respiratory Distress Syndrome (ARDS), are serious conditions resulting from direct or indirect lung injury that occur in critically ill patients and are associated with an unacceptable mortality of up to 40%. A key biological event in the pathogenesis of ALI/ARDS is the dysfunction of the lung endothelium (EC), which is triggered by a variety of inflammatory insults leading to damaged EC, vascular leak, and excessive inflammation. Recently, we demonstrated that an Abl family tyrosine kinase inhibitor, imatinib, protects against LPS-induced endothelial dysfunction by inhibiting c-Abl kinase through mechanisms that remain largely unknown. In the present study, we identified

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