European Respiratory Society
Annual Congress 2013

Abstract Number: 597

Publication Number: 1814

Abstract Group: 3.3. Mechanisms of Lung Injury and Repair

Keyword 1: ARDS (Acute Respiratory Distress Syndrome) **Keyword 2:** Airway smooth muscle **Keyword 3:** Anti-inflammatory

Title: Smooth muscle cells as immunological relay in acute pulmonary inflammation by ADAM17-mediated ErB receptor transactivation

Dr. Daniela 6128 Dreymueller daniela.dreymueller@rwth-aachen.de [1], Dr. Christian 6129 Martin chmartin@ukaachen.de [1], Julian 6130 Schumacher jschumacher@ukaachen.de [1], Esther 6131 Groth egroth@ukaachen.de [1], Julia Katharina 6132 Boehm julia.boehm@rwth-aachen.de [1], Dr. Kathleen 6133 Reiss kreiss@ukaachen.de [1], Prof. Dr Stefan 6134 Uhlig suhlig@ukaachen.de [1] and Prof. Dr Andreas 6135 Ludwig aludwig@ukaachen.de [1]. [1] Institute of Pharmacology and Toxicology, RWTH Aachen University Hospital, Aachen, NRW, Germany, 52074 .

Body: Acute respiratory distress syndrome (ARDS) can develop from acute pulmonary inflammation caused by pathogen infection or acid aspiration. Danger signals of the stimulated epithelium have to be relayed to vascular responses at the endothelial layer, eventually by smooth muscle cell mediator release. This release may be regulated by the action of the disintegrin and metalloproteinase (ADAM) 17. In vivo, we compared Adam17+/+ and Tagln-Adam17-/- (deficient for SMC-ADAM17) for LPS- or acid-aspiration-induced pulmonary inflammation. In vitro, primary murine and human tracheal SMC were analyzed for cytokine release and the mediating signaling pathways targeting ADAM17 and pathway members by pharmacological and transcriptional inhibition. The in vivo-conditions were mimicked by either LPS stimulation or treatment with acid-treated epithelial cell (BEAS-2B) supernatant. The importance of these ADAM17-dependent signaling pathways in vivo was demonstrated by instillation of TNFα, CXCL1, or coinstillation of LPS and TGFα into the lungs. SMC-ADAM17 acts proinflammatory in both in vivo-models, demonstrated by the reduction of cytokine and neutrophil attracting chemokine release, leukocyte recruitment, and edema formation in Tagln-Adam17-/- in comparison to Adam17+/+ mice. Endotoxin-induced inflammation is mediated by ADAM17-dependent ErbB1 transactivation via TGFα and release of TNFα and CXCL1 by SMC, whereas acid-induced inflammation is relayed by ErbB4 activation via neuregulins. Thus, local targeting of ADAM17 and/or the transactivation pathways in SMC may be an option for the development of an efficient therapy for acute pulmonary inflammation.