European Respiratory Society
Annual Congress 2013

Abstract Number: 1561
Publication Number: 1506

Abstract Group: 3.1. Molecular Pathology and Functional Genomics
Keyword 1: COPD - mechanism **Keyword 2:** Chronic disease **Keyword 3:** Molecular pathology

Title: Implication of microRNA-148b in chronic obstructive lung disease of βENaC-overexpressing mice

Dr. Raman 16593 Agrawal Raman.Agrawal@med.uni-heidelberg.de [1], Dr. Mirco 16594 Castoldi mirco.castoldi@med.uni-duesseldorf.de [2], Dr. Sandro 16595 Altamura Sandro.Altamura@med.uni-heidelberg.de [2], Dr. Michael 16596 Meister Michael.Meister@thoraxklinik-heidelberg.de [3], Dr. Thomas 16597 Muley Thomas.Muley@thoraxklinik-heidelberg.de [3], Dr. Catherine 16598 Greene CMGreene@rcsi.ie [4], Prof. Martina 16599 Muckenthaler Martina.Muckenthaler@med.uni-heidelberg.de [2] and Prof. Dr Marcus 16600 Mall Marcus.Mall@med.uni-heidelberg.de [1]. [1] Department of Translational Pulmonology, Translational Lung Research Center, Member of the German Center for Lung Research, University of Heidelberg, Heidelberg, Germany ; [2] Department of Paediatric Oncology, Haematology and Immunology, University of Heidelberg, Heidelberg, Germany ; [3] Translational Research Unit, Thoraxklinik, Translational Lung Research Center, Member of the German Center for Lung Research, University of Heidelberg, Heidelberg, Germany and [4] Respiratory Research Division, Department of Medicine, Royal College of Surgeons in Ireland, Beaumont Hospital, Dublin, Ireland .

Body: MicroRNAs are involved in diverse biological and pathological processes. Here, we studied the potential role of miRNAs in the in vivo pathogenesis of chronic obstructive pulmonary disease (COPD) using βENaC-overexpressing (βENaC-Tg) mouse model. We performed miRNA array analysis in lung tissue of βENaC-Tg and wild-type (WT) mice. Differentially expressed miRNAs were validated by qRT-PCR and their functional importance was determined by bioinformatics analysis and in luciferase reporter assays. Tissue specific localization was performed by in situ hybridization using locked nucleic acid-modified DNA probe. Direct functional studies were performed by knockdown of miRNA expression in the lungs of βENaC-Tg mice using antagomirs. The effects of knockdown were studied by lung histology, pulmonary function testing using flexiVent system and analysis of inflammatory cells in bronchoalveolar lavage. We demonstrate that miR-148b is upregulated in the lungs of βENaC-Tg mice and predominantly localized in the conducting airways. Luciferase reporter assay in Hela cells suggests Mig-6 (mitogen inducible gene-6), a protein previously shown in normal lung development, as a potential target of miR-148b. Knockdown of miR-148b in the lung of βENaC-Tg mice results in reduced emphysema and decreased numbers of neutrophils compared to WT mice. Moreover, we observed upregulation of miR-148b in bronchial brushing of cystic fibrosis and COPD lung tissue from human. Taken together, these results indicate that dysregulation of miR-148b expression may play an important role in the pathogenesis of COPD and may serve as a novel therapeutic target. Supported by BMBF (82DZL00401).