Pulmonary Cell Research

Michael Roth

Department of Biomedicine
Pulmonary Cell Research
University of Basel

Michael Tamm

Department of Biomedicine
Pulmonary Cell Research
University of Basel

Group Members

Dr. Eleni Papakonstantinou*
(Postdoc)

Sabrina Blumer
Frederick Bright
Basil Wicki
Liang Zhou
(PhD Students)

Dr. Junling Li*
Cui Zhu*
(MD Students)

Dorotej Alexander Sasha Jovanovic
Ly Chu Phuong*
(Undergraduate Students)

Dr. Lucas Boeck
Dr. Lei Fang
PD Dr. med. Katrin Hostettler
Dr. Petra Khan-Seidel
(Research Associates)

Dr. Wei-Chih Chen*
Dr. Tao Zhang*
Dr. Ming Zhang*
(External Collaborators)

Guendalina Gherardini
Andreas Wüst
(Intern)

*left during report period

Causes and control of tissue remodelling in chronic inflammatory lung diseases

Chronic inflammatory lung diseases (CILD) include asthma, chronic obstructive pulmonary disease (smokers lung), and fibrotic disorders of the lung. The prevalence of all CILD is increasing worldwide since several decades. All CILD have an increase susceptibility to bacterial or viral infections, which cause exacerbations of the disease. Together, they incurred the fourth highest health care costs and significantly reduced education and productivity of the patients. None of the CILD can be cured with available therapies, only the symptoms can be controlled. The American Thoracic Society suggested in 2017 that a cure for CILD would only be found when we understand the cause and role of tissue remodelling, which occurs in all such diseases. Recent studies implied that the pathogenesis of CILD results from a disturbed response of the lung to environmental factors such as allergens, dust, ashes, or microorganisms, as well as humidity, temperature, exercise or stress. Each of these factors alone, or together, trigger epigenetic events that become persistent. Today, it is assumed that the first epigenetic event has to occur during late embryogenesis and early childhood, followed by a second event later in life. However, the nature of these epigenetic events seem to be disease specific and remain largely unknown.

Asthma affects 300 million people worldwide and is characterised by chronic airway inflammation and airway wall remodelling. Today, none of the available drugs can reverse airway wall remodelling, while inflammation can be well controlled. This supports the idea that both pathologies are largely independent. The only therapy that has been shown to reduce airway wall remodelling is bronchial thermoplasty, but the mechanism is largely unknown. In our latest studies, we have proven that the expression of an important epigenetic regulator, protein methyl arginine transferase 1(PRMT1), is constitutively expressed in mesenchymal cells of asthma patients. This is due to the over-expression of C/EBP-β, which suppresses miR-19a, and thereby stimulates the expression of a proliferative signalling pathway. PRMT1 is a major methyl donor for histones, which control the accessibility of pro-inflammatory genes and mitochondria regulating factors. Our research revealed that many well-known asthma triggers, such as TGF-β, PDGF-BB, IL-4, and IL-1β, stimulate the expression of PRMT1 by upregulating C/EBP-β. Thus, we found a mechanism that merges the action of different asthma stimulating factors. Furthermore, bronchial epithelial cells from asthma patients secrete heat shock protein-60 (HSP60), which stimulates the expression of PRMT1 in sub-epithelial mesenchymal cells. Thereby, HSP60 drives remodelling and mitochondria activity in asthma. Bronchial thermoplasty reduced the secretion of HSP60 in asthma patients, and thereby interrupted the remodelling driving signalling cascade of PRMT1. Independent from PRMT1, we showed that non-immune IgE stimulates an autologous signalling loop through inhibition of PTEN by increased synthesis of miR-21. This study indicates that the increased IgE found in many asthma patients contributes to remodelling, even in the absence of an allergen.

Connection to Clinical Practice

Prof. Dr. Michael Tamm
Prof. Dr. Daiana Stolz
Department of Internal Medicine, Pneumology,
University Hospital Basel

Translational medicine studies in chronic inflammatory lung diseases

Our studies are focused on chronic inflammatory lung diseases. We link basic and clinical research to find novel bio-markers and therapeutic targets for asthma, COPD, ACOS, and idiopathic fibrosis. None of these diseases is easy to diagnose, and despite symptom control, curative therapies are not available. All studies are based on large patient cohorts, diagnosed according to international guidelines. We preform risk factor analysis and validate new biomarkers, as predictors for exacerbation and survival of patients.

The clinical studies are enabled by a close collaboration of pulmonologists, thoracic surgeons, haematologists, pathologists, and basic researchers. This translational approach benefits from the close co-location of the Clinic of Pneumology and the research laboratory (DBM). Using human lung samples of patients we are able to isolate primary diseased human epithelial cells, fibroblasts and bronchial smooth muscle cells and provide them to our collaborators in other countries. The cells are analysed for disease specific expression and regulation patterns of biomarkers and inflammatory mediators. This also allows us to identify novel disease specific pathophysiological pathways and test new medications on the cellular level. Components of tissue remodelling are studied under the influence of allergic and non-allergic stimuli. In addition to this translational research projects numerous investigator driven non-commercial randomised studies are performed to optimise patient's safety during bronchoscopy in COPD patients. Our clinic leads collaborative studies with groups in Germany, Italy, Spain, France, the Netherlands, Belgium, UK, Serbia and Greece.

Selected Publications

Sun Q, Liu L, Wang H, Mandal J, Khan P, Hostettler KE, Stolz D, Tamm M, Molino A, Lardinois D, Lu S and Roth M (2017). Constitutive high expression of protein arginine methyltransferase 1 in asthmatic airway smooth muscle cells is caused by reduced microRNA-19a expression and leads to enhanced remodeling. J Allergy Clin Immunol. 140 510–524.e3.

Benmerzoug S, Rose S, Bounab B, Gosset D, Duneau L, Chenuet P, Mollet L, Le Bert M, Lambers C, Geleff S, Roth M, Fauconnier L, Sedda D, Carvalho C, Perche O, Laurenceau D, Ryffel B, Apetoh L, Kiziltunc A, Uslu H, Albez FS, Akgun M, Togbe D and Quesniaux VFJ (2018). STING-dependent sensing of self-DNA drives silica-induced lung inflammation. Nat Commun. 9 5226.

Papakonstantinou E, Bonovolias I, Roth M, Tamm M, Baty F, Louis R, Milenkovic B, Boersma W, Kostikas K, Blasi F, Aerts J, Rohde G, Lacoma A, Torres A, Welte T and Stolz D (2019). Serum levels of hyaluronic acid are associated with COPD severity and predict survival. Eur. Respir .J. 2019pii: 1801183.

Sun Q, Fang L, Lu S, Tamm M, Stolz D and Roth M (2019). TGF-β upregulated mitochondria mass through SMAD2/3-C/EBPβ-PRMT1 signal pathway in primary human airway wall fibroblasts. J Immunology 202 37–47.

Sun Q, Fang L, Roth M, Tang X, Papakonstantinou E, Zhai W, Louis R, Heinen V, Schleich FN, Lu S, Savic S, Tamm M and Stolz D (2019). Bronchial thermoplasty decreases airway remodelling by blocking epithelium-derived heat shock protein-60 secretion and protein arginine methyltransferase-1 in fibroblasts. Eur Respir J. 54 1900300.