

Department of Anesthesiology

Division of Molecular Pneumology

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Research focus

- Immunopathogenesis of lung tumor
- Immunopathogenesis of allergic asthma

Structure of the Division

Professorship: 1

Personnel: 13

- Scientists: 9 (thereof funded externally: 3)
- Graduate students: 8

Research

The Division of Molecular Pneumology studies the mechanisms underlying the immune responses in allergic asthma and lung tumors.

Immunopathogenesis of lung tumor

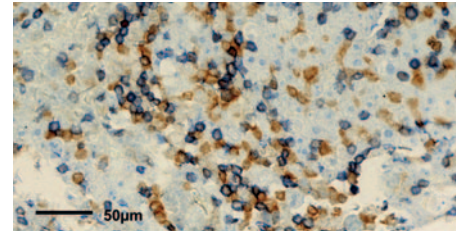
Lung cancer belongs to the cancer types with the highest mortality rate causing over a million deaths per year worldwide. Besides cigarette smoking, different other risk factors comprising gender and specific genetic traits are thought to contribute to lung cancer development. Treatment options include surgery, chemo- and radiotherapy which yield modest response and a 5-year survival rate of only 15 %. Present studies concentrate on immunotherapy as a new breakthrough treatment in oncology. Here, effector and cytotoxic T cells play an indispensable role for successful anti-tumoral immune responses. Over the past years our group has been focusing on the analysis of T cells present in the tumor microenvironment, including tumor infiltrating lymphocytes (TIL) as well as on a number of genes which play a role in the exhaustion of these cells. In most of the established tumors, effector functions of TIL are restricted by several environmental factors including the accumulation of immuno-suppressive cells and the increased expression of inhibitory

receptors like programmed cell death protein 1 (PD-1). These inhibitory receptors contribute to the functional impairment of T cell activation promoting T cell exhaustion and cancer immune evasion. Cancer immunotherapies have been developed that reactivate exhausted TILs by blocking inhibitory checkpoint receptors or other immunoregulatory cells.

In collaboration with the Division of Thoracic Surgery we analyzed lung samples from over 100 patients who were suffering from non-small cell lung cancer (NSCLC), underwent surgery, and gave their approval to be enrolled in our study. The diagnosis of lung cancer is based on pathological confirmation at the Institute of Pathology. The histological types of lung cancer are classified according to the classification of the World Health Organization (WHO) formulated in 2004. The staging of lung cancer is based on the Cancer TNM Staging Manual formulated by the International Association for the Study of Lung Cancer (IASLC) in 2010. Lung tissue samples were taken from the tumor area, representing the solid tumor tissue, the peri-tumoral area surrounding the tumor in a range of 2 cm, and the tumor-free control area. From these tissues, histological tissue arrays were generated, RNA and proteins were extracted, and we are able to isolate TILs. This whole procedure is substantial to identify specific biomarkers present in each patient which is a very important task to set up new therapeutical approaches. In fact, immunotherapy against immunosuppressive markers on TILs is a promising approach in the clinic and has been shown to partially reverse T cell exhaustion and to enhance anti-tumoral immunity in several cancer types including lung cancer. It should be noted, however, that clinical responses vary considerably and many patients do not or not completely respond to these antibody therapies. Thus we aim at identifying new TIL markers to be targeted in conjunction with common immunotherapeutic setting.

By using single gene-deficient mice in a murine model of lung carcinoma, we identified several not yet reported markers that might play a regulatory role in the immune responses to lung cancer and seem to be implicated in the reactivation of exhausted TILs. At the moment our studies focus on the following research topics:

- Role of NFATc1 in T cell-specific immune responses during the development of NSCLC
- Role of STAT1 in innate and adaptive immune responses during the development of NSCLC
- Role of Foxp3 and Tbet co-expressing Treg cells during the development of NSCLC



Co-localization of NFATc1 (brown) and CD3 (blue) in the tumoral lung region of early stage NSCLC patients

Immunopathogenesis of allergic asthma

Allergic asthma is an increasing chronic-inflammatory disease of the airways that affects millions of people worldwide. It is characterized by increased airway inflammation, hyperresponsiveness, and remodeling after allergen and rhinovirus challenge.

While the classical model of allergy-induced airway inflammation focuses on a Th2 driven immune-reaction, Th1 and T regulatory cells play instead a protective role in this disease. Th2 cytokines can also influence B cells which then develop into plasma cells producing IgE which activates mast cells via binding to the high affinity IgE receptor, resulting in the release of bronchoconstrictors, like histamine.

In the course of the European asthma study PreDicta (Post-infectious immune reprogramming and its association with persistence and chronicity of respiratory allergic diseases; since 2011) with healthy and asthmatic pre-school children aged between 4 to 6 years, we have gained insight into important immunological processes during asthma development in general and in context to viral infections in particular. Since 2016, a local follow-up study (AGENDAS: Genetic, age, gender, and environmental factors that modify immuno-responses and the development of allergic asthma during the school age in childhood) has been recruiting healthy and asthmatic school children (6 to 10 years) during symptomatic or convalescent visit with the aim to substantiate and extend the results obtained in PreDicta. Especially the connection between rhinovirus infections and interferon type I and type III responses are a major research focus in our Division, but also T and B cell responses as well as innate lymphoid cells (ILC) are of interest to our group. Here we concentrate on cytokine patterns released by the different cell populations, e. g. IL-4 release from Th2 cells, and the expression of key transcription factors, such as T-bet in Th1 cells or Foxp3 in Tregs. To support our findings from the human studies, also mouse models of allergic

asthma are used. Here, mouse models lacking e. g. single transcription factors, cytokines or cytokine receptors, e. g. BATF, NIP45, NFATc1, contribute to determine the role of these factors/mediators in allergic asthma. As a model antigen we use ovalbumin (OVA), but we are currently also establishing a model with the human relevant allergen house dust mite (HDM). These studies should contribute to the development of new therapeutic approaches and prevention strategies for asthma. At the moment our studies focus on the following research topics:

- Role of the transcription factor NFATc1 and BATF in allergic asthma
- Role of Nip45 in allergic asthma
- Interferon type I and III immune responses to rhinovirus infections in asthma
- Role of ILC2s (innate lymphoid cells type 2) in experimental allergic asthma
- Role of vitamine D3 in asthma

Teaching

The Division of Molecular Pneumology supervises Bachelor's and Master's theses as well MD and PhD theses.

Selected publications

Vahl JM, Friedrich J, Mittler S, Trump S, Heim L, Kachler K, Balabko L, Fuhrich N, Geppert CI, Trufa DI, Sopol N, Rieker R, Sirbu H, Finotto S. Interleukin-10-regulated tumour tolerance in non-small cell lung cancer. *Br J Cancer*. 2017 Nov 21;117(11):1644-1655

Kachler K, Bailer M, Heim L, Schumacher F, Reichel M, Holzinger CD, Trump S, Mittler S, Monti J, Trufa DI, Rieker RJ, Hartmann A, Sirbu H, Kleuser B, Kornhuber J, Finotto S. Enhanced Acid Sphingomyelinase Activity Drives Immune Evasion and Tumor Growth in Non-Small Cell Lung Carcinoma. *Cancer Res*. 2017 Nov 1;77(21):5963-5976

Bergauer A et al. IFN- α /IFN- γ responses to respiratory viruses in paediatric asthma. *Eur Respir J*. 2017 Mar 29;49(3). pii: 1700006

Hentschke I, Graser A, Melichar VO, Kiefer A, Zimmermann T, Kroß B, Haag P, Xepapadaki P, Papadopoulos NG, Bogdan C, Finotto S. IL-33/ST2 immune responses to respiratory bacteria in pediatric asthma. *Sci Rep*. 2017 Mar 6;7:43426

Bielor C et al. Role of TGF- β in anti-rhinovirus immune responses in asthmatic patients. *J Allergy Clin Immunol*. 2017 Jul;140(1):283-286

Heim L, Friedrich J, Engelhardt M, Trufa DI, Geppert CI, Rieker RJ, Sirbu H, Finotto S. NFATc1 Promotes Antitumoral Effector Functions and Memory CD8⁺ T-cell Differentiation during Non-Small Cell Lung Cancer Development. *Cancer Res*. 2018 Jul 1;78(13):3619-3633

International cooperations

T. Vuorinen, Department of Virology, University of Turku, Turku: Finland

Prof. S.T. Weiss, Translational Genomics Core, Partners HealthCare, Cambridge, MA: USA

Prof. Dr. M.L. Kowalski, Department of Immunology, Rheumatology and Allergy, Medical University of Łódź, Łódź: Poland

Prof. T. Jartti, Department of Pediatrics and Adolescent Medicine, Turku University Hospital, Turku: Finland

Prof. N.G. Papadopoulos, Allergy and Clinical Immunology Unit, National and Kapodistrian University of Athens, Athens: Greece