UNIVERSITY HOSPITAL

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 is one of the most common cancers worldwide. Factors contributing to its development include smoking and specific genetic characteristics. Treatment options include surgical removal of the tumor, chemotherapy and radiotherapy, which have a low treatment success rate and result in a 5-year survival rate of only 15%. Current studies are focusing on immunotherapies as a new breakthrough treatment option in oncology. Effector and cytotoxic T cells play an indispensable role in ensuring a successful anti-tumor immune response.
In recent years, our group has been involved in the analysis of T cells present in the tumor microenvironment that influence the development and progression of lung carcinomas.
In most tumors, effector functions of tumor-infiltrating lymphocytes (TIL) are inhibited by various factors, such as accumulation of immunosuppressive cells or increased expression of inhibitory receptors, such as programmed cell death protein 1 (PD-1). PD-1 contributes to the functional impairment of T cell activation. Furthermore, inhibitory receptors are used by tumor cells to evade an immune response. For this reason, immunotherapies have been developed to reactivate effector immune cells by blocking so-called checkpoint receptors on immunoregulatory cells. In order to identify possible targets of immunotherapy, our group is investigating the influence of different genes and signaling pathways on tumorigenesis and development.
To this end, we are currently analyzing samples from more than 150 patients with non-small cell lung cancer (NSCLC) in collaboration with the Department of Thoracic Surgery. Tissue samples were taken from three different areas of the lung: the tumor region, the peri-tumoral region surrounding the tumor at a distance of 2 cm, and a control area free of tumor cells. Histological sections are generated from these tissue samples, RNA and proteins are extracted and various cell types are isolated. Further investigations are performed on peripheral blood mononuclear cells (PBMC). These procedures are necessary to understand specific tumor characteristics and to develop new therapeutic strategies.
Furthermore, using murine models of lung cancer by deleting different genes in specific cell types, we want to investigate what role these might play in the regulation of the immune response to lung cancer.
Current projects include the following:

- Role of STAT5 NSCLC
- Role of PU.1 in NSCLC
- Role of glucose in the initiation and development of NSCLC
- Role of Blimp-1 in NSCLC

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. Since 2020 we also conduct a new human study with healthy and asthmatic adults. In the AZCRA study they are invited to come to a baseline and a symptomatic visit comparable to AGENDAS. Here our focus lies on different chemokines and their receptors, as well as cytokines which are important in the immune response. In a third group we investigate the influence of the diet on the immune response. Here the asthmatic patients will change their diet into a healthy nutrition for 12 weeks in Cooperation with the hector center. 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. IL-3, NFATc1 or CCR3 deficient mice contribute to determine the role of these factors/mediators in allergic asthma. As a model antigen we use ovalbumin (OVA) and the human relevant allergen house dust mite (HDM) in these experiments. These studies should contribute to the development of new therapeutic approaches and prevention strategies for asthma.
Current projects include the following:

- Role of the transcription factor NFATc1 in allergic asthma
- Role of the chemokine Rantes and its receptors in allergic asthma
- Interferon type I and III immune responses to rhinovirus infections in asthma
- Role of vitamine D3 in asthma

Teaching

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

Selected publications

Sopel N, Kölle J, Dumendiak S, Koch S, Reichel M, Rhein C, Kornhuber J, Finotto S. Immunoregulatory role of acid sphingomyelinase in allergic asthma. Immunology. 2019 Apr;156(4):373-383

Kölle J, Haag P, Vuorinen T, Alexander K, Rauh M, Zimmermann T, Papadopoulos NG, Finotto S. Respiratory infections regulated blood cells IFN-β-PD-L1 pathway in pediatric asthma. Immun Inflamm Dis. 2020 Sep;8(3):310-319

Krug J, Kiefer A, Koelle J, Vuorinen T, Xepapadaki P, Stanic B, Chiriac M, Akdis M, Zimmermann T, Papadopoulos NG, Finotto S. TLR 7/8 regulates Type I and Type III Interferon Signalling in RV1b induced Allergic Asthma. Eur Respir J. 2020 Dec 10:2001562

Jakobi M, Kiefer A, Mirzakhani H, Rauh M, Zimmermann T, Xepapadaki P, Stanic B, Akdis M, Papadopoulos NG, Raby BA, Weiss ST, Finotto S. Role of nuclear factor of activated T cells 2 (NFATc2) in allergic asthma. Immun Inflamm Dis. 2020 Dec;8(4):704-712

Koch S, Knipfer L, Kölle J, Mirzakhani H, Graser A, Zimmermann T, Kiefer A, Melichar VO, Rascher W, Papadopoulos NG, Rieker RJ, Raby BA, Weiss ST, Wirtz S, Finotto S. Targeted deletion of NFAT-Interacting-Protein-(NIP) 45 resolves experimental asthma by inhibiting Innate Lymphoid Cells group 2

(ILC2). Sci Rep. 2019 Oct 30;9(1):15695

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 Łódz, Łódz: 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