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
Professorships: 1
Personnel: 13
• Scientists: 6 (thereof funded externally: 2)
• Graduate students: 3

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 has the highest death-rate of all cancers in the world. Besides cigarette smoking, different other risk factors comprising gender and specific genetic traits are thought to contribute to lung cancer. Our group has been focusing in the last ten years in the analysis of T cells present in the tumor microenvironment, including tumor infiltrating lymphocytes (TIL), and focuses 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 immunosuppressive cells and the increased expression of inhibitory receptors, e.g. PD1 or CTLA4. These inhibitory receptors contribute to the functional impairment of T cell activation and promote T cell exhaustion. Cancer immunotherapies have been developed that reawaken exhausted TIL by blocking inhibitory checkpoint receptors or other immunoregulatory cells.

During the last five years we analyzed in collaboration with the Division of Thoracic Surgery lung samples of at least 90 patients who were suffering from non-small cell lung cancer (NSCLC), underwent surgery and gave their approval to being enrolled in this study. The diagnosis of lung cancer was based on pathological confirmation at the Institute of Pathology. The histological types of lung cancer were classified according to the classification of the World Health Organization (WHO), formulated in 2004. The staging of lung cancer was based on the Cancer TNM Staging Manual, formulated by the International Association for the Study of Lung Cancer (IASLC) in 2010.

Tissue samples were taken from the tumor area (TU: solid tumor tissue) as well as from the tumor free control area (CTR: at least 5cm away from the solid tumor) of the surgically removed lung material. From these tissues histological tissue arrays were generated, RNA and proteins were extracted and we are able to isolate TIL by fluorescence activated cell sorting (FACS). This whole procedure is substantial to understand the precise biomarkers trait present in each patient which is a very important task to set up new therapeutic approaches. In fact, although surgery is the elected therapy for this kind of tumor, in the last period immunotherapy against immunosuppressive genes has been successfully used to cure at least partially lung cancer. By using single gene deficient mice in a murine model of lung carcinoma, we identified several proteins that play a protective role in the immune-regulation of lung cancer development. Some examples for those proteins are described below:

• The role of NFATc1 in T cell specific immune responses during the development of NSCLC. NFATc1 is a member of the family of Nuclear Factor of Activated T cells (NFAT) controlled by Ca2+ signaling. In peripheral T cells, NFATc1 contributes to effector functions by regulating the expression of e.g. IL-2 and IFNγ and controls cell cycle regulation and apoptosis. As NFATc1 is important for T cell signaling and effector functions, we asked whether this transcription factor could be important for the activation of TIL to turn against established NSCLC tumors. This will be analyzed in samples from patients with NSCLC as well as in NFATc1-CD4 mice in a murine model of lung carcinoma.
• The role of Tbet+Fop3+CD4+ T cells in NSCLC anti-tumoral immune responses require the function of T helper 1 (Th1) and cytotoxic T cells (Tc1) which are both characterized by the expression of the hallmark transcription factor T-box expressed in T cells (Tbet, Tbx21). Tbet controls the differentiation of Th1 cells and promotes the production of cytolytic effector molecules by Tc1 cells. By contrast, regulatory T cells (Treg) are known to suppress pro-inflammatory immune responses, including Tbet-mediated effects. Therefore, Treg are regarded as one of the major obstacles for efficient anti-tumor immunity. A characteristic feature of Treg cells is the expression of the transcription factor forkhead box protein 3 (Foxp3) that controls the development and function of these cells. Despite the opposite roles of Tbet and Foxp3 in the immune system as well as in tumor biology, there is evidence for the existence of CD4+ T cells, expressing both transcription factors. The biological function of these Tbet+Fop3+CD4+ T cells, especially in the context of tumor diseases, is unknown. Our aim is therefore to investigate if Tbet and Foxp3 co-expressing CD4+ T cells could be involved in the immune-pathogenesis of lung cancer. For this purpose, we analyze Tbet/Foxp3+CD4+ T cells in human lung samples from patients with NSCLC.

• The role of Interleukin (IL)-9 in NSCLC
The type of immune reaction that is being induced at the tumor site can be influenced by a variety of factors. For instance, anti-tumoral responses can be increased or suppressed depending on the composition of the cytokine milieu. In this context, we investigate the influence of interleukin 9 (IL-9) on lung tumor growth. It has been shown before that IL-9 can be secreted by CD4+ Th9 cells. This T cell subtype develops in the presence of interleukin 4 (IL-4) as well as the immunosuppressive cytokine transforming growth factor β (TGFβ). Previous studies have shown that adoptive transfer of Th9 cells can enhance the anti-tumor immune response in a murine model of melanoma. In order to investigate the role of IL-9 in lung tumor as well as the effects of IL-9 on anti-tumoral immune responses, we analyze IL-9 deficient mice in an experimental model of lung carcinoma. Also in this project we have the possibility to reinforce our data from the murine model by the analysis of human lung carcinoma samples.
• The role of Interleukin (IL-10)-10 in NSCLC
IL-10 is one of the major cytokines which is significantly involved in immunosuppressive and pro-tumoral processes in the immune system. IL-10 is mainly produced by tumor asso-
associated macrophages (M2), T regulatory cells (Treg) and Th2 cells, but also by bronchial epithelial cells which are the initial source of NSCLC. Moreover, IL-10 is able to inhibit Th1 cells, antigen presenting cells (APC) and classical-activated macrophages (M1) which play an important role in tumor defense.

In our working group we analyze the role of IL-10 and its impact on the immune system during lung tumor development. A better understanding of the cytokine IL-10 is of crucial importance to develop improved immunotherapy methods.

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 (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) has been recruiting healthy and asthmatic school children (6 to 10 years) 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. 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- or IL-17-deficient mice, 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 those research topics:

- Role of the transcription factor NFATc1 in allergic asthma
- Determining the role of acid sphingomyelinase (ASM) in allergic asthma
- Interferon type I and type III immune responses to rhinovirus infections in asthma
- Role of TGF-β in anti-rhinovirus immune responses in asthmatic patients
- IL-33/ST2 immune responses to respiratory bacteria and viruses in pediatric asthma
- The Role of Innate lymphoid cells type 2 (ILC2) in experimental allergic asthma.

Teaching

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

Selected Publications

Koch S, Reppert S, Finotto S. NFATc1 deletion in T lymphocytes inhibits the allergic trait in a murine model of asthma. Clin Exp Allergy. 2015 Aug;45(8):1356-66