Medical University of Graz

Inflammation and immune system dynamics in pathologic conditions

Summary

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Supervisor:	Prof. Dr. Thomas Pieber
Availability:	This position is available.
Offered by:	Medical University of Graz
Application deadline:	Applications are accepted between February 10, 2020 00:00 and March 30, 2020 23:59 (Europe/Zurich)

Description

Background:

Inflammation and immune system regulation play an important but complex role in many pathological conditions.

In atopic dermatitis the immune profile in affected as well as non-lesional skin is as of yet not very well understood. The immune response can vary greatly between affected subjects and hence not all treatments are equally effective.

However, atopic dermatitis is often characterized by increased levels of interleukin 4 (IL-4), interleukin 13 (IL-13), interleukin 22 (IL-22) and interleukin 31 (IL-31) combined with a T-helper type 2 (Th2) profile. (Sidbury und Khorsand 2017)

In March 2017 a human monoclonal antibody called Dupilumab was approved by the FDA for treatment of moderate to severe atopic dermatitis in adults. Dupilumab binds to the shared alpha subunit of IL-4 and IL-13 receptors and hence interferes with the activation of T-cells and blocks the synergistic effects of IL-4 and IL-13 on allergic inflammation. (Cabanillas et al. 2017; Deleanu und Nedelea 2019)

The technology of dOFM allows collection of diluted but otherwise unchanged interstitial fluid (ISF) which provides a detailed look into the dermal tissue environment. Interstitial fluid contains various cytokines, immune cells and metabolites, hence it provides a great opportunity to elucidate the presence and real-life dynamics of immunological processes behind various pathological conditions and can be coss-referenced with blood samples and punch biopsies. (Bodenlenz et al. 2013)

Preliminary testing successfully established the ISF sampling and analytical methods in pigs and healthy subjects. Now we aim to elucidate complex immune pathways that are affected in atopic dermatitis in particular, but possibly also other diseases.

Type 1 diabetes, for example, is characterized by the autoimmune reaction and eventual destruction of beta cells in the islets of Langerhans leading to an eventual cessation of insulin production. The student will be involved in a deep-immune phenotyping study in mice to investigate the immunome during the process of beta cell destruction.

With a thorough and comprehensive analysis we want to unravel the mechanisms of pathologic immune reactions and better understand the pathways that many drugs and diseases exploit.

Hypothesis and Objectives:

The hypothesis is that the clinical treatment effect of Dupilumab is linked to the degree of inhibition of the IL-4 and IL-13 signaling in affected skin. By measuring a broad range of biomarkers and immune cells the individual clinical treatment effect and its variability may be elucidated.

Firstly**,** we aim to investigate the pharmacodynamic effect of dupilumab treatment on inflammatory cytokine and chemokine levels, eicosanoids, on local immune-cell populations and on the metabolomic profile in dermal interstitial fluid (ISF) of lesional and non-lesional skin and blood of AD patients in correlation to its clinical treatment effect.

Secondly, changes in gene expression and the relation to changes in inflammatory biomarkers and immune cell patterns will also be a focus of this thesis.

The aim in analyzing the immunome in type 1 diabetes will be the elucidation of immune cell infiltration and interaction of immune cells and beta cells in different stages of type 1 diabetes progression in a mouse model.

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Methodology:

Flow cytometry, qPCR, Immunehistochemistry

References:

Bodenlenz, M.; Dragatin, C.; Hoefferer, C.; Birngruber, T.; Priedl, J.; Feichtner, F. et al. (2013): Certified dOFM sampling devices provide access to target tissue in pharmaceutical trials. In: *Biomedizinische Technik. Biomedical engineering* 58 Suppl 1. DOI: 10.1515/bmt-2013-4133.

Cabanillas, Beatriz; Brehler, Ann-Christin; Novak, Natalija (2017): Atopic dermatitis phenotypes and the need for personalized medicine. In: *Current opinion in allergy and clinical immunology* 17 (4), S. 309–315. DOI: 10.1097/ACI.0000000000000376.

Deleanu, Diana; Nedelea, Irena (2019): Biological therapies for atopic dermatitis: An update. In: *Experimental and therapeutic medicine* 17 (2), S. 1061–1067. DOI: 10.3892/etm.2018.6989.

Sidbury, Robert; Khorsand, Kate (2017): Evolving Concepts in Atopic Dermatitis. In: *Current allergy and asthma reports* 17 (7), S. 42. DOI: 10.1007/s11882-017-0710-5.