Medical University of Graz

The role of JAK/STAT signaling in different asthma phenotypes

Summary

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Supervisors:	PD Dr. Eva Sturm Dr. Philipp Douschan
Availability:	This position is available.
Offered by:	Medical University of Graz
Application deadline:	Applications are accepted between March 24, 2021 00:00 and May 05, 2021 23:59 (Europe/Zurich)

Description

Background:

Most proinflammatory cytokines and growth factors utilize the Janus kinases (JAK)-signal transduction and activator of transcription (STAT) pathway, which has been linked to various inflammatory and autoimmune diseases. In mammals, *there* are *four members* of the *JAK family* and seven STAT molecules. Several JAK inhibitors have already been approved or under development for a variety of inflammatory disease. As different JAK inhibitors have different specificities for JAK isoforms or TYK2, there is an ongoing discussion regarding which profile of JAK inhibition would be optimal for which specific disease. During the last decade, promising experimental data from JAK inhibitors have also been published in asthma research. For instance, it was demonstrated that the JAK3 inhibitor tofacitinib, which shows less affinity to JAK1 and JAK2, suppresses cytokine production in bronchoalveolar lavage (BAL) cells from asthmatic and healthy donors (1) and reduces the number of infiltrating eosinophils in the BAL fluid of OVA-challenged mice (2). More recently, intratracheal or inhaled application of non-selective JAK inhibitors has been shown to reduce allergen-induced airway inflammation and airway hyperresponsiveness in mice (3). Thus, current literature indicates that JAK/STAT inhibitors promote regulatory effects on inflammatory cells *in vivo* and *in vitro*; however, the exact mechanisms are still unclear. Moreover, so far neither *in vitro* nor *in vivo* studies have specifically investigated and compared the role of JAK/STAT signaling in allergic *versus* non-allergic asthma.

Hypothesis and Objectives:

Our recent data provides evidence that JAK/STAT signaling plays a crucial role in the pathophysiology of allergic disorders by regulating eosinophil function. In this project we will investigate the activation pattern of the JAK/STAT pathway in different peripheral blood leukocyte populations such as eosinophils, neutrophils, basophils, monocytes and T cell subsets from allergic and non-allergic asthmatic patients as compared to healthy controls. As JAK/STAT signaling can change upon cell activation, we will define the JAK/STAT activation status of infiltrated leukocytes in BAL fluid and nasal mucus from patients. To prove the *in vivo* relevance of these approaches mouse models of allergen-induced and chemical-induced asthma will be used.

Methodology:

The PhD student will learn how to isolate different leukocyte populations from peripheral blood. JAK/STAT expression and activation will be quantified by real-time PCR, western blot, fluorescence microscopy and flow cytometry (Year 1). The student will investigate the biological relevance of JAK/STAT inhibition in human leukocytes by different functional assays (i.e. migration, degranulation, apoptosis, cytokine production) (Year 2). In a translational aspect, the student will use well established experimental mouse models for allergic and non-allergic asthma to investigate the therapeutic effect of JAK/STAT inhibition on lung function (using Flexivent measurements) and leukocyte recruitment (multicolor flow cytometry). Cytokine profiles will be determined by multiplex ELISA. Lung tissue will be stained by immunohistochemistry. Lipid mediators will be determined by LC-MS (Year 3-4).

References:

1. Southworth T, Plumb J, Gupta V, Pearson J, Ramis I, Lehner MD, et al. Anti-inflammatory potential of PI3Kdelta and JAK inhibitors in asthma patients. Respiratory research. 2016;17(1):124.

2. Kudlacz E, Conklyn M, Andresen C, Whitney-Pickett C, Changelian P. The JAK-3 inhibitor CP-690550 is a potent anti-inflammatory agent in a murine model of pulmonary eosinophilia. Eur J Pharmacol. 2008;582(1-3):154-61.

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3. Calbet M, Ramis I, Calama E, Carreno C, Paris S, Maldonado M, et al. Novel inhaled pan-JAK inhibitor, LAS194046, reduces allergen-induced airway inflammation, late asthmatic response and pSTATs activation in Brown Norway rats. The Journal of pharmacology and experimental therapeutics. 2019.