Medical University of Graz

Short chain fatty acids and pulmonary endothelial function

Summary

Akos Heinemann & Thomas Baernthaler, Division of Pharmacology, Medical University of Graz

Supervisors:	Prof. Dr. Akos Heinemann Dr. Thomas Bärnthaler
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: Short chain fatty acids (SCFA) such as acetate, propionate and butyrate, are produced in high concentration via fermentation in the human gut by commensal bacteria and are taken up into the bloodstream. SCFA have been shown to have strong anti-inflammatory properties by the production of mediators like PGE_2 and inhibition of cytokine release. Accordingly, allergic germ-free mice show exaggerated airway eosinophilia and increased levels of TH2 cytokines when compared to recolonized mice and nutrient fiber content strongly correlates with the extent of allergic inflammation and lung eosinophilia, which was also alleviated by treatment with propionate in a mouse model of house-dust mite allergy. SCFA are natural ligands for the free fatty acid receptors FFA2 (GPR43) and FFA3 (GPR41), which belong to the family of seven transmembrane spanning G protein-coupled receptors. SCFA have also been shown to regulate gene transcription via the inhibition of histone deacatylase (HDAC) activity. Their anti-inflammatory properties are at least partially mediated by NFκB inhibition and subsequent repression of related cytokines.

Hypothesis and Objectives: Based on preliminary data from our laboratory we hypothesize that SCFA are capable of regulating endothelial function which translates to an anti-inflammatory action. We will further characterize the effects of SCFA on pulmonary microvascular and arterial endothelial cells regarding barrier function, expression of adhesion molecules, intracellular signaling pathways and interaction of the endothelium with immune cells. Proof of concept studies will be performed in diverse mouse models of asthma and asthma exacerbations.

Methodology: The PhD student will learn how to isolate leukocytes from peripheral blood of human volunteers and patients and how to cultivate endothelial cells from lungs. FFA2 and FFA3 expression will be quantified by real-time PCR, Western blot, fluorescence microscopy and multi-colour flow cytometry. Endothelial barrier function will be investigated by electrical impedance measurements (ECIS), transendothelial diffusion assays, VE-cadherin/actin staining of monolayers and systems of isolated whole lung perfusion. Cytokine profiles will be determined by multiplex ELISA. Lipid mediators will be determined by LC-MS. Moreover, the student will investigate the role of SCFA and their receptors in experimental mouse models for allergic asthma and non-allergic Fra-2 transgenic asthma mouse model that are already available within the consortium and international collaborators. The occurrence of SCFA-producing microbiota strains in stool samples of animal models and patients with chronic asthma will be investigated.

References:

1. Theiler A, Bärnthaler T, Platzer W, Richtig G, Peinhaupt M, Rittchen S, Kargl J, Ulven T, Marsh LM, Marsche G, Schuligoi R, Sturm EM, Heinemann A. Butyrate ameliorates allergic airway inflammation by limiting eosinophil trafficking and survival. J Allergy Clin Immunol. 2019 Sep;144(3):764-776. doi:10.1016/j.jaci.2019.05.002. PMID: 31082458.

2. Bärnthaler T, Theiler A, Zabini D, Trautmann S, Stacher-Priehse E, Lanz I, Klepetko W, Sinn K, Flick H, Scheidl S, Thomas D, Olschewski H, Kwapiszewska G, Schuligoi R, Heinemann A. Inhibiting eicosanoid degradation exerts antifibrotic effects in a pulmonary fibrosis mouse model and human tissue. J Allergy Clin Immunol. 2020 Mar;145(3):818-833.e11. doi: 10.1016/j.jaci.2019.11.032. PMID: 31812575.

3. Konya V, Üllen A, Kampitsch N, Theiler A, Philipose S, Parzmair GP, Marsche G, Peskar BA, Schuligoi R, Sattler W, Heinemann A. Endothelial E-type prostanoid 4 receptors promote barrier function and inhibit neutrophil trafficking. J Allergy Clin Immunol. 2013 Feb;131(2):532-40.e1-2. doi:10.1016/j.jaci.2012.05.008. PMID: 22704539.