Project 14: Modulation of anti-parasitic immune reactions by intestinal chemosensing receptors

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The practical work for this project will be performed at the Life & Medical Sciences (LIMES) Institute, University of Bonn (www.limes-institut-bonn.de).

Background:

Chemosensing receptors recognize environmental signals, which is essential for the survival of organisms. These receptors are not only expressed in the nose or oral mucosa, they are also present in the intestinal epithelium. Here, they often sense bitter tasting substances of the diet, toxins, or components of microbial pathogens. Binding of helminth antigens to chemosensing receptors induces a type II immune response to fight these pathogens. The aryl hydrocarbon receptor (AhR) is a ligand induced transcription factor, which also senses environmental toxins or dietary components. The AhR is not only essential to coordinate immune homeostasis in the gut, but is also involved in the defense of intestinal pathogens. AhR activity is regulated by the AhR-Repressor (AhRR) in a feedback mechanism.

Own previous work:

We could show that the AhRR is also involved in the regulation of intestinal inflammation and infections. AhRR deficient mice display enhanced susceptibility to DSS induced colitis, similar to AhR-deficient mice. They also exhibit increased sensitivity to an infection with *T. gondii*, with enhanced intestinal interferon-gamma production, which possibly leads to an increased T cell response. Our group has extensive experience in the generation of genetically modified mouse models and the application of the CRISPR/Cas9 technology in vitro and in vivo, as well as experience in the generation of organoid models.

Aim of the project:

Here, we want to analyze the role of the AhR/AhRR system in intestinal immune reactions triggered by activation of chemosensing receptors. For these analyses, generation of intestinal organoids (“mini guts”) will be established and the induction of pathogen specific immune reactions will be determined after stimulation with helminth antigens and AhR ligands or by genetic inactivation of the AhR and AhRR.

Work program:

In the first part, the generation of intestinal organoids from small intestinal crypts as well as their co-cultivation with immune cells will be set up to investigate the crosstalk of intestinal epithelial cells and the immune system. Further, intestinal stem cells will be modified using CRISPR/Cas9 to generate genetically modified organoids. Using these systems, the influence of helminth antigens and AhR ligands on the expression and function of chemosensing receptors and the induction of intestinal immune reactions will be analyzed.