Universität Basel

Research Project

Intestinal macrophages and dendritic cells in oral tolerance and colitis

Third-party funded project

Project title Intestinal macrophages and dendritic cells in oral tolerance and colitis
Principal Investigator(s) Niess, Jan ;
Project Members Melhem, Hassan ;
Organisation / Research unit
Bereich Medizinische Fächer (Klinik) / Gastroenterologie (Niess)
Department
Project start 01.09.2018
Probable end 31.08.2022
Status Completed

Although macrophages and dendritic cells (DCs) have been identified as important cell populations for the establishment of oral tolerance and the development of colitis, intestinal macrophages and DCs are cells with a rather undefined function. The analysis of a reporter mouse line, in which the fractalkine receptor CX3CR1 can be tracked by expression of the green fluorescent protein (GFP) has led to the identification of phagocytes that extend processes between intestinal epithelial cells into the intestinal lumen (Science. 2005; 307, 254). Further characterization revealed that CX3CR1+ phagocytes express CD68 and are likely macrophages, from which DCs can be discriminated by the expression of the integrin alpaE (CD103) (J Immunol. 2010; 15, 2026). Intestinal macrophages capture and process antigens and microbial compounds in the intestine and deliver these antigens to DCs, which migrate to the mesenteric lymph nodes (MLN) to prime naïve T cells (Mucosal Immunol. 2014; 7, 533). Our preliminary work shows that macrophages and DCs express the G protein coupled receptor GPR35, that has been identified as the receptor for the chemokine CXCL17 and for which a single nucleotide polymorphism has been described to be associated with ulcerative colitis and primary sclerosing cholangitis, but whose function in the gastrointestinal tract is largely unknown. OBJETIVESIn this proposal we will investigate if intestinal DCs and macrophages express GPR35 and if GPR35 is needed for the establishment of oral tolerance and for the development of colitis. Specifically, the following aims will be addressed: 1. The cells that express GPR35 will be defined. 2. Whether GPR35 is required for the establishment of oral tolerance, and 3. whether GPR35 regulates the migration of macrophages and DCs to the inflamed colon during colitis will be examined. METHODSA GPR35-tdTomato reporter mouse line has been generated in order to identify the cells that express GPR35. After identification of the cell that expresses GPR35, the function of GPR35 for the establishment of oral tolerance. In this model, mice will be gavaged with Ovalbumin (OVA), mice will be then immunized with OVA, and splenocytes will be isolated and will be tested for their ability to produce IFN? after restimulation with OVA. The development of colitis will be investigated by giving Dextran Sodium Sulfate (DSS) to the drinking water. SIGNIFICANCEThis proposal aims to identify the cell that expresses GPR35 and to examine the function of GPR35, which has been identified as a chemokine receptor for the chemokine CXCL17. The migration of DCs and macrophages into the lamina propria of the small and large intestine and trafficking of DCs from the lamina propria to the mesenteric lymph nodes are of importance for the establishment of oral tolerance and the development of colitis. Whether GPR35 influences the trafficking of DCs and macrophages and contributes to the establishment of oral tolerance and the development of colitis is not known. The better understanding of the mechanism underlying the migration of macrophages and DCs to the lamina propria and trafficking of DCs to the MLN will give insights how inflammatory bowel disease (IBD) develops and may potentially uncover a novel target to treat IBD.

Financed by
Swiss National Science Foundation (SNSF)

Add publication

Add documents

Specify cooperation partners