ABSTRACT

Mucosal immune system comprises not only the major compartment of the immune system but also important interface with the outer environment. It is responsible in maintaining an intricate balance with the danger and non-danger stimuli of the outer world by employing specific anatomical features and unique functional mechanisms. Mucosal immune system has been long understudied, perhaps due to the limited accessibility, and its biological importance is thus still underevaluated. However, it has become evident that it is important to study mucosal immune system not only in local mucosal affections but also when uncovering pathogenic mechanisms and novel prevention strategies of organ specific autoimmune diseases such as type 1 diabetes.

Thus, the first, more clinically oriented part of this thesis is focused on mucosal immune system of the upper respiratory tract in disease conditions - in nasal polyposis (NP).

Because there is a substantial accumulation of eosinophils and neutrophils in the most frequent type of NP, we investigated and described increased expression of chemokine receptors CCR1 and CCR3 in NP versus nasal mucosa. Both innate immune mechanisms as well as homeostasis of epithelial cells may participate in NP. We have documented increased numbers of iNOS-positive and insulin-like growth factor-1 receptor (IGF-1R)-positive cells in both stroma and epithelium of NP.

The second part of the thesis deals with the interplay of the mucosal immune system, dietary gluten or gliadin in pathogenesis and a novel prevention strategy of autoimmune type 1 diabetes (T1D).

Because gluten-free (GF) diets highly prevent T1D in animal models we investigated the effect of dietary gluten on the mouse mucosal immune system. In the first two papers, we compared the effects of the standard, diabetes permissive vs. the diabetes preventive GF diet and found changes in proportion of mucosal γδ T cells, Th17 cells as well as a more proinflammatory cytokine signature associated with the standard, diabetes-permissive diet. Since not many studies addressed in detail the innate immune mechanisms of gliadin we next investigated innate signaling pathways utilized by gliadin fragments. We documented that apart from IL-1β induction, TLR2/4/MyD88/TRIF/MAPK/NF-κB innate signaling pathway and NLRP3 inflammasome activation are involved in wheat proteins signaling. Finally, we tested intranasal (i.n.) administration of gliadin as a novel vaccination strategy - using an environmental compound that may have etiological role in T1D. We showed that i.n. gliadin is able to substantially reduce diabetes incidence in NOD mice and also reduce diabetes incidence when applied much later to already prediabetic mice. The effect was associated with increased proportion of potentially regulatory γδ T cells, and to a lesser extent also $CD4^{+}Foxp^{+}$ Tregs, in mucosal compartments as well as with changes in their cytokine signatures.

In conclusion, this thesis deals with the mucosal immune system. We addressed some pathogenic processes in a local mucosal affection - NP as well as studied interactions of environmental factors and mucosal immune system in pathogenesis and also as possible novel prevention strategy in T1D.

Keywords: mucosal immune system; nasal polyposis; type 1 diabetes; pathogenesis; prevention.