ABSTRACT

Immune tolerance to host own tissues and cells is the fundamental attribute of properly working immune system. The repertoire of effector T-cells, which possess randomly generated antigen-specific receptors, is during their development shaped by central immune tolerance to retain only those specificities which do not recognize self-antigens. In addition, various mechanisms of peripheral tolerance keep in check potentially self reactive cells which escaped from the protective mechanism of central tolerance. Thus, a tight regulation of tolerance, operating at several anatomical places in the host body, collectively imposes immune homeostasis and well-being of the organism. The breach of central tolerance can have far reaching consequences, as demonstrated by mutations in Autoimmune regulator gene. These mutations lead to the development of severe autoimmune disease, comprising several clinical components, gastrointestinal associated symptoms including. We have shown, that in the absence of Autoimmune regulator, the occurrence of gastrointestinal symptoms is associated with the loss of thymic-mediated central tolerance to enteric α-defensins, essential antimicrobial peptides produced by intestinal Paneth cells. The loss of tolerance leads to the escape of defensin-specific T-cells to immune periphery and consequently, to their attack on Paneth cells, resulting in their diminishment. This, in turn, impacts the composition of intestinal microbiota, affecting the polarization of T-cells in the gut towards Th17 phenotype which further provides a milieu supporting inflammatory autoimmunity and perturbations in intestinal homeostasis. Moreover, we showed the importance of several members of Wnt signaling cascade in the regulation of intestinal homeostasis and their impact on immune-mediated dysfunction of intestinal epithelia.