ABSTRACT

Enteric α-defensins belong to a superfamily of antimicrobial peptides representing the humoral branch of innate immunity. They are produced by intestinal Paneth cells and play an irreplaceable role in the homeostasis of small intestine by modulation of its bacterial composition and the protection of intestinal stem cells residing in the intestinal crypts. Unexpectedly, the tissue-specific gene expression screening of enteric alpha-defensins on a panel of rat tissues revealed their presence in the thymus. The characterization of their cellular source pointed to the $CD45^-$ $MHCII^+$ $AIRE^+$ medullary thymic epithelial cells (mTECs). The subsequent analysis further confirmed that, analogous to the rat model, mouse enteric α-defensins (cryptdins) are in the thymus expressed exclusively in the mTECs. It is now well established that autoimunne regulator (AIRE)-dependent transcription of peripheral tissue restricted antigens (TRAs) and their presentation by mTECs leads to a deletion of self-reactive thymocytes. This process of negative section represents the central mechanism of immunological tolerance. Predictably, mutations and malfunctioning of AIRE lead to aberrations in the negative selection, occurrence of self-reactive T-cells and subsequent production of autoantibodies against TRAs. Consistent with this finding, we detected the presence of autoantibodies against human enteric defensin-5 (HD-5) in the serum of autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) patients suffering from AIRE gene mutations. Thus, this study for the very first time identifies enteric α-defensins as immunologically targeted peripheral antigens, tolerance to which is regulated by its AIRE-controlled transcription in the thymus. Moreover, our results provide a new molecular basis for possible explanations of clinical symptoms seemingly unrelated to the nature of APECED disease such as malabsorption and gastritis. They also extended the list of mTEC's expressed TRAs. This study thus warrants further investigation into the mechanism of central and peripheral tolerance and the role of defensins in the development of autoimmune diseases.