Identification of Extra-thymic Aire-expressing Cells (eTACs) in Human Tissue and Comparison between Type-1 Diabetic and Non-diabetic Controls

Eileen J. McMahon[1], Todd C. Metzger[2], and Mark S. Anderson[2]
[1]Westmont College, Santa Barbara, CA; [2]Diabetes Center, University of California – San Francisco

Purpose: Autoimmune regulator (Aire) was identified in 1997 as the gene mutated in autoimmune polyendocrine syndrome type I (APS-1), a disease in which patients develop a wide range of autoimmune diseases including type I diabetes (T1D). Aire is known to be highly expressed in medullary thymic epithelial cells where it upregulates tissue-specific antigens (TSAs) for negative selection of T cells. Recently, using transgenic reporter mice, our lab has characterized a rare population of cell in secondary lymphoid organs that also expresses Aire. Furthermore, these eTACs (extra-thymic Aire-expressing cells) could promote peripheral tolerance to prevent autoimmune diabetes in an antigen-specific manner. The goal of this study was to identify and characterize eTACs in human lymph node and spleen and to compare eTACs in T1D samples and healthy controls.

Methods: Immuno-fluorescent staining with anti-Aire antibody was used to identify eTACs in human pancreatic and non-pancreatic LN (PLN and nPLN, respectively). Sections were also co-stained for MHC class II and CD11c, a prototypical dendritic cell marker. RNA was isolated from frozen whole PLNs and from sorted populations from fresh spleen. Quantitative PCR was used to measure relative Aire expression and to identify potentially Aire-regulated TSAs.

Summary of Results: Aire+ cells were readily identified by immuno-staining in both PN and nPLN sections. Like in mouse, human eTACs were relatively rare but localized outside the B-cell follicles and stained with the hallmark “nuclear speckling” pattern. Furthermore, the eTACs were ubiquitously positive for MHC class II but lacked high expression of CD11c, calling into question their identification as a known resident DC population. Quantitative PCR confirmed the expression of Aire in whole PLN and in sorted CD45+, MHC class II+ populations from fresh human spleen. No difference was found in the relative expression of Aire between T1D, no diabetes, and pre-T1D PLN specimens. However, the expression of ladinin-1, a putative Aire-regulated TSA in mouse eTACS, was positively correlated with Aire expression, suggesting that it might be an Aire-regulated TSA in humans as well.

Conclusions: Overall, our data confirm that Aire is indeed expressed outside the thymus in humans and that human eTACs appear analogous to the more fully characterized murine eTACs. Their potential for promoting peripheral tolerance in a therapeutic setting remains an exciting possibility.