Department of Biological Sciences

VISITOR'S TALK

Speaker: Dr. Kushagra Bansal, PhD

Harvard Medical School, USA

Date/Time: Friday, September 1st, 2017 at 05:15 pm

Venue: L1, LHC

Title: Thymic induction of immunological self-tolerance: the role of AIRE and its partners

Immunological self-tolerance, an intricate network of 'central' and 'peripheral' mechanisms, is a fundamental property of the immune system which not only averts autoimmune responses, but is also highly relevant to cancer immunity. Central tolerance is shaped in the thymus, where medullary thymic epithelial cells (mTECs) orchestrate the negative selection of a nascent repertoire of autoreactive T cells and positive selection of regulatory T cells (Treg). Although the cellular mechanisms involved in establishment and maintenance of immunological self-tolerance are significantly well-characterized, the molecular events preceding these mechanisms remain an area of intense investigative research. We investigated the molecular cascade promoting central tolerance in the thymus using the murine counterpart of a rare monogenic human autoimmune disorder, Autoimmune Polyendocrinopathy Candidiasis Ectodermal Dystrophy (APECED), caused by mutations in the Autoimmune Regulator (AIRE) gene, as an experimental model. AIRE is a transcriptional regulator which drives the expression of scores of loci encoding tissue-specific self-antigens in mTECs, and ensures selective removal of thymocytes bearing T cell receptors that recognize these antigens. Combining a series of multidisciplinary experimental approaches, ranging from transcriptomics (RNA-seq, microarray) and epigenomics (ChIP-seq, ATAC-seq) to genetic perturbation in mice, we uncovered a novel epigenetic regulatory layer in the molecular circuitry of AIRE, and identified potential novel targets for patients with AIRE mutations. Comprehensive analyses of AIRE's protein partners revealed its close relationship with the regulators of DNA topology and genomic superstructure, and pharmacological intervention of the components of this network promoted autoimmune responses in mice. Our findings provide mechanistic framework for establishment of immunological self-tolerance in the thymus, and yield novel cell-intrinsic regulators of this crucial mechanism of the immune system, with implications for therapeutic and diagnostic strategies.