Functional diversity of memory CD8 T cells is spatiotemporally imprinted

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Abstract

Tissue-resident memory CD8 T cells (T_{RM}) kill infected cells and recruit additional immune cells to limit pathogen invasion at barrier sites. Small intestinal (SI) T_{RM} cells consist of distinct subpopulations with higher expression of effector molecules or greater memory potential. We hypothesized that occupancy of diverse anatomical niches imprints these distinct T_{RM} transcriptional programs. We leveraged human samples and a murine model of acute systemic viral infection to profile the location and transcriptome of pathogen-specific T_{RM} cell differentiation at single-transcript resolution. We developed computational approaches to capture cellular locations along three anatomical axes of the small intestine and to visualize the spatiotemporal distribution of cell types and gene expression. T_{RM} populations were spatially segregated: with more effector- and memory-like T_{RM} preferentially localized at the villus tip or crypt, respectively. Modeling ligand-receptor activity revealed patterns of key cellular interactions and cytokine signaling pathways that initiate and maintain T_{RM} differentiation and functional diversity, including different TGF β sources. Alterations in the cellular networks induced by loss of TGFβRII expression revealed a model consistent with TGFβ promoting progressive T_{RM} maturation towards the villus tip. Ultimately, we have developed a framework for the study of immune cell interactions with the spectrum of tissue cell types, revealing that T cell location and functional state are fundamentally intertwined

Biography

Ananda Goldrath recently joined the Allen Institute in Seattle as the Executive Vice President and Director of the Allen Institute for Immunology after 19 years at UC San Diego where she was a Tata Chancellor's Professor in the School of Biological Sciences in the Molecular Biology Department. Her work as an Immunologist has contributed to the understanding transcriptional networks that govern the formation and maintenance of long-lived protective immunity. Dr. Goldrath's research explores the mechanistic basis underlying memory T cell differentiation by driving or suppressing target genes essential for differentiation of protective T cell subsets, by regulating metabolic pathway usage, or by controlling access to and survival in tissues. Using this information, it has proved possible to beneficially manipulate the immune system to eliminate infection and malignancies. Dr. Goldrath is a member of the American Academy of Arts and Sciences, a Pew Scholar, a Leukemia and Lymphoma Society Fellow, and a member of the Immunological Genome Project.