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"Defining the role of CD9 expressing T follicular helper cells in infection and autoimmunity."

By

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M.D./Ph.D. Program
B.S., Biology, 2020, College of Charleston, Charleston, SC

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Friday, March 21st, 2025
10:00A.M.
Cancer Center, G1196

Join Zoom presentation
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ABSTRACT

T follicular helper (Tfh) cells are a subset of CD4 T cells that facilitate humoral responses following vaccination and infection. In secondary lymphoid tissues, Tfh cells progressively differentiate within T cell zones, B cell follicles, and germinal centers (GCs), where they secrete cytokines such as IL-21 and IFN-γ to regulate B cell activation and differentiation. Tfh cells that enter the GC provide critical signals to B cells to aid in their proliferation, survival, and selection and promote the differentiation of these B cells into memory B and long-lived plasma cells. Additionally, Tfh cells that remain in the follicle are required to generate $Tbet^{+}CD11c^{+}$ B cells (TBCs, DN2), a unique subset of tissue-resident memory B cells. In infection and autoimmunity, Tfh cell-derived IL-21 and IFN-γ are essential for protective and pathogenic B cell responses, but only about one-third of Tfh cells actively secrete cytokines.

In this thesis, a population of Tfh cells that have elevated surface expression of the tetraspanin CD9 ($CD9^{hi}$) was identified using an acute LCMV infection. $CD9^{hi}$ Tfh cells were characterized to be the active IL-21 and IFN-γ-secreting Tfh cells. Despite residing in both the GC and the follicle, $CD9^{hi}$ Tfh cells display enhanced proliferation, VLA-4 integrin expression, and migratory capacity toward a CXCL13 chemokine gradient. $CD9^{hi}$ Tfh cells exhibited transcriptional profiles and chromatin architecture distinct from their $CD9^{lo}$ counterpart. Deletion of CD9 resulted in a reduction of IL-21 and IFN-γ-secreting Tfh cells and a subsequent decrease in TBCs and class-switched virus-specific antibody responses but not GC B cells. As IL-21 and IFN-γ-producing Tfh cells are critical drivers of disease in lupus, we found that $CD9^{hi}$ circulating Tfh cells (cTfh) were expanded in PBMCs from lupus patients compared to healthy controls. The increased frequency of $CD9^{hi}$ cTfh cells in lupus patients was positively correlated with the expanded DN2 B cell population. Moreover, co-culturing $CD9^{hi}$ or $CD9^{lo}$ cTfh cells with DN2 B cells from lupus patients demonstrated that these B cells required the $CD9^{hi}$ cells to survive. Therefore, CD9 identifies and regulates the cytokine-producing Tfh cells, which impact TBCs and the humoral response during infection and autoimmunity.