Core and pathogen-specific transcriptional networks of T follicular helper cells

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Abstract

Interactions between T follicular helper (Tfh) cells and germinal center (GC) B cells promote the generation of high-affinity class switched antibodies, long-lived plasma cells, and memory B cells. Tfh cells provide co-stimulatory signals through cognate interactions and secreted cytokines to tailor B cell responses in a pathogen-specific manner. Tfh differentiation is instructed by the transcription factor Bcl6, which acts through repression of target genes to inhibit alternative CD4+ helper T cell fates. However, we and others have shown that Tfh cells can co-express the lineage-defining transcription factors of T effector subsets, such as T-bet in type 1 inflammatory responses. We propose that dynamic transcriptional networks enable functional heterogeneity of Tfh cells to tailor pathogen-specific GC responses. Using ZsGreen-Tbet reporter mice, we have explored diverse Tfh responses in distinct viral, bacterial, and helminth infections. We show that T-bet is expressed in Tfh cells in a context dependent manner, where high and low T-bet expression correlate with specific Tfh-produced cytokines. To explore this hypothesis beyond known lineage-defining transcriptional regulators, we have built a transcriptional map of Tfh heterogeneity using diverse infectious challenges in mice, paired with human tonsil Tfh and circulating Tfh. Gene expression analysis highlighted a core Tfh signature that is distinct from T effectors and T follicular regulatory cells in each infection. Further, we identify infection-dependent networks of known and previously unknown factors, that provide insight into the mechanism of Tfh flexibility that tailors GC B cell responses in a pathogen-specific manner. Our results define a blueprint of Tfh diversity and may identify ways to direct this process for immunotherapies for antibody-mediated diseases, such as Lupus and asthma, where skewed Tfh diversity impacts disease.