

Reversible Reprogramming of Circulating Memory T Follicular Helper Cell Function during Chronic HIV Infection

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Despite the overwhelming benefits of antiretroviral therapy (ART) in curtailing viral load in HIV-infected individuals, ART does not fully restore cellular and humoral immunity. HIV-infected individuals under ART show reduced responses to vaccination and infections and are unable to mount an effective antiviral immune response upon ART cessation. Many factors contribute to these defects, including persistent inflammation, especially in lymphoid tissues, where T follicular helper (T_{fh}) cells instruct and help B cells launch an effective humoral immune response. In this study we investigated the phenotype and function of circulating memory T_{fh} cells as a surrogate of T_{fh} cells in lymph nodes and found significant impairment of this cell population in chronically HIV-infected individuals, leading to reduced B cell responses. We further show that these aberrant memory T_{fh} cells exhibit an IL-2-responsive gene signature and are more polarized toward a Th1 phenotype. Treatment of functional memory T_{fh} cells with IL-2 was able to recapitulate the detrimental reprogramming. Importantly, this defect was reversible, as interfering with the IL-2 signaling pathway helped reverse the abnormal differentiation and improved Ab responses. Thus, reversible reprogramming of memory T_{fh} cells in HIV-infected individuals could be used to enhance Ab responses. Altered microenvironmental conditions in lymphoid tissues leading to altered T_{fh} cell differentiation could provide one explanation for the poor responsiveness of HIV-infected individuals to new Ags. This explanation has important implications for the development of therapeutic interventions to enhance HIV- and vaccine-mediated Ab responses in patients under ART. *The Journal of Immunology*, 2015, 195: 5625–5636.