CALIFORNIA HIV/AIDS RESEARCH PROGRAM

Tissue-resident Memory T cells and HIV Latency in the Gut

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In most developed countries, highly active antiretroviral therapy has transformed HIV infection into a manageable chronic disease. Despite systemic viral suppression, however, HIV survives, and patients continue to suffer from non-AIDS morbidities. The main barrier to eradication is a small proportion of latently infected cells that harbor the virus in a form that is invisible to the immune system and protected from the effects of antiretroviral drugs. As these cells reactivate over time, the latent reservoir continues to cause residual immune activation and chronic systemic inflammation. The increased inflammation contributes to a higher incidence of cardiovascular disease, certain cancers, cognitive and renal impairment, bone demineralization, and immune dysregulation. One of the main sites for latent and productively infected cells is the gut. During acute infection, HIV initiates a vicious inflammatory cycle by causing damage to the mucosal barrier of the gut, leading to systemic exposure to microbial products and increased activation of T cells. Since disruption of the mucosal barrier is a key contributor to the excess inflammation, it is critical to better identify latently and productively infected cells in the gut to specifically target and eliminate them. However, the HIV reservoir in the gut is poorly understood, in part because of the difficulty of obtaining gut biopsies. Moreover, the gut contains resident memory T cells with unique functional, phenotypic, and survival properties that are distinct from those in lymphoid tissues and blood. We propose to isolate various memory populations from gut biopsies of HIV-positive patients and healthy controls and use highly sensitive methods to determine which memory population harbors the most latent and productive HIV. To better understand factors that promote latency or viral replication, we will also analyze global gene expression in these cell populations and determine how the gut microenvironment contributes to their long-term survival. Understanding the mechanisms by which the gastrointestinal niche contributes to the maintenance of latently infected cells will provide knowledge required to develop therapies to eliminate the HIV reservoir in the gut. The ultimate goal is to repair mucosal barrier function and decrease systemic inflammation, with the hope of restoring normal health and reducing comorbidities in HIV-positive patients.

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