Pyroptosis Drives Both CD4 T Cell Death and Chronic Inflammation in HIV-Infected Lymphoid Tissues
Gilad Dotsh1, Nicole Galloway1, Xin Geng1, Kathryn Monroe1, Zhiyuan Yang1, Orlando Zepeda2, Peter Hunt2, Hiroyu Hatano2, Stefanie Sowinski1, Warner C. Greene1
1Gladstone Institute of Virology and Immunology, San Francisco, CA, United States, 2University of California, San Francisco, San Francisco, CA, United States

Background: The progressive loss of CD4 T cells in HIV-infected individuals is the over-arching cause of AIDS. Apoptosis is the mechanism by which productively infected CD4 T-cells die. In contrast, very little is known about how “bystander” resting CD4 T cells die in lymphoid tissues. These cells are refractory to productive HIV infection yet they account >95% of the CD4 T cell losses occurring in many lymphoid tissues like tonsil and spleen.

Methodology: Human lymphoid aggregated cultures (HLACs) were prepared using tonsil and spleen tissue; lymph nodes from consenting HIV-infected volunteers not on antiretroviral therapy were surgically excised and used in immuno-histological staining studies.

Results: Our finding demonstrate that productive HIV infection in activated CD4 T cells from tonsil and spleen (95%) leads to by caspase-1-mediated pyroptosis, an intensely inflammatory form of programmed cell death. In the pyroptotic death pathway, cytoplasmic contents and pro-inflammatory cytokines including IL-1β, are released into the extracellular space. Surprisingly, lymphoid CD4 T-cells, but not CD8 T cells or B cells in the same tissue, are primed to mount proinflammatory death responses as reflected by high-level expression of pro-IL-1beta. These events combine to create a vicious pathogenic cycle where dying CD4 T-cells release inflammatory signals that attract more cells to become abortively infected and die by pyroptosis causing more inflammation. Cell-to-cell transmission of HIV is obligately required to elicit this pyroptotic death response—cell free virions are ineffective Pyroptosis is efficiently blocked by VX-765, a small-molecule inhibitor of caspase-1 that has been shown to be safe in humans. Analysis of lymph nodes from HIV-infected subjects confirms caspase-1 dependent pyroptotic death of bystander CD4 T cells and release of IL-1beta.

Conclusions:
1. CD4 T-cell death in HIV-infected lymphoid tissues is principally controlled by caspase-1-mediated pyroptosis, an intensely inflammatory form of programmed cell death.
2. Pyroptosis provides a new and exciting nexus between CD4 T-cell death and inflammation with strong implications for HIV pathogenesis and disease progression.
3. Small-molecule inhibitors of caspase-1 could form a promising new “anti-AIDS” therapy that complements current treatment strategies by altering the detrimental host innate immune response to the virus rather than the virus itself.