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Chronic human herpesviruses such as cytomegalovirus (CMV) and Epstein-Barr virus (EBV) cause lifelong persistent infections in nearly all of the population. Viral reactivation can lead to life threatening disease or malignancy in individuals with impaired immune systems due to HIV/AIDS, immunosuppression for transplantation or autoimmunity, chemotherapy for cancer and in the elderly. Despite advances in antiviral medication, CMV remains the commonest infection post-transplantation leading to direct end-organ disease such as pneumonitis, as well as indirect effects such as allograft rejection and opportunistic infection. In the elderly persistent CMV infection is associated with accelerated aging of the immune system, several age-related diseases and reduced survival. Moreover, EBV-related lymphoproliferative disorder (PTLD) occurs in 1-16% of transplant recipients, particularly pediatric recipients, and carries a mortality rate of 30-70%³. There are no vaccines for CMV or EBV and there are limited safe and effective treatment options. Our ability to make significant advances in immune-based therapies for persistent herpes viruses is impeded because these viruses persist and become reactivated in multiple lymphoid and tissue sites, while study of the human anti-viral response is largely limited to the sampling of peripheral blood. As T cell immunity is critical for control of persistent, intracellular viruses and blood contains only 2-3% of total T lymphocytes in the body, it is unclear how the function and features of circulating T cells relate to their protective efficacy. Our laboratory has set up a novel tissue resource in which we obtain multiple lymphoid and mucosal tissues from organ donors, providing us unique access to study T cell responses in the sites where they become activated and maintained. Our central hypothesis is that the functionality of T cells specific for CMV and EBV in healthy humans will vary depending on tissue site and the presence of persisting or latent virus. We will perform an in-depth analysis of T cell responses to CMV and EBV in healthy humans in blood and multiple tissue sites within an individual and between individuals across the human lifespan in the setting of local CMV and EBV activation. Understanding how human T cells mediate control of persistent herpesviruses in healthy humans will provide the basis for translational studies in the immunosuppressed and elderly to determine how pathways mediating CMV and EBV immune control are disrupted and to identify protective pathways. Results from these studies will provide novel targets to improve treatments through vaccination or immunotherapy, and discover new predictive blood biomarkers of viral-related disease progression.