Translational Medicine

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Perspective

CTL Penetration to HIV Reservoirs in All Locations

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One of the most challenging barriers for HIV eradication is the prevalence of HIV reservoir cells in a wide variety of tissues and with distinct viral and cellular signatures. Even when effective CTL responses are stimulated and maintained, HIV can still evade being cleared given the poor accessibility of some tissue reservoirs and reduced CTL penetration into these compartments [1].

Because of the high susceptibility of follicular CD4+ T cells to HIV infection, poor follicular CTL penetration, and significant extracellular HIV virion accumulation on the surface of follicular dendritic cells (FDCs), B cell follicles are considered a critical sanctuary for HIV replication and persistence. HIV-specific CTL are abundant within lymphoid tissues, but fail to accumulate within lymphoid follicles where HIV-1 replication is concentrated. Recent work by Louis Picker validated that productive SIV infection in rhesus monkey elite controller is restricted to follicular CD4+ T helper cells (TFH)) due to the physical exclusion of CD8+ T cells from B cell follicles [2]. A study of peripheral blood from chronically HIV-infected individuals on ART also showed that within central memory CD4+ T cells, peripheral T follicular helper cells are the most significant HIV reservoirs. Follicular cytotoxic T cells, a group of cytotoxic T cells expressing CXCR5, were found to localize to B cell follicles and control viral infection of TFH cells. Thus, boosting cytotoxic CTLs with specific homing signatures like CXCR5 could be valuable in eliminating the viral reservoir in B cell follicles. An alternative strategy could be to chemically induce or genetically engineer CTL to express CXCR5. Indeed, transduction with CXCR5 effectively localized CTL to B cell follicles in rhesus macaques, but if these cells were enough to clear the B-follicular HIV reservoir remains unknown. Other strategies include treatment with IL-15, use of bispecific antibodies and disruption of the follicle by medication such as rituximab [3].

The central nervous system (CNS) is another compartment that might not be easily targetable for vaccine mediated HIV reservoir elimination approaches. While it is populated with macrophages and astrocytes that might be susceptible to HIV infection these cell types are potentially less responsive to CTL elimination. Furthermore, the blood-brain barrier (BBB) by regulating the trafficking of cells might prevent the free influx of vaccine induced T-cell responses and if prior therapeutic vaccines have induced relevant HIV specific CD8+ T cell response in the CNS has not be examined. Finally it remains questionable if highly cytolytic CD8+ T cell response should be induced in the CNS via therapeutic vaccination, as massive infiltration by polyfunctional CD8+ T-cell could result in uncontrolled astrocytic and microglial activation with detrimental consequences for the vaccines [4].

Other cell types than CD4+ T-cells, in particular macrophages; serve as harbor for latent HIV. Traditionally, macrophages are believed to have a moderate life span and lack self-renewing potential, but recent data suggested the role of these cells as long-lived HIV reservoirs even during active ART. Moreover, Clayton et al. showed that macrophages were intrinsically more resistant to CTL mediated killing relative to CD4+ T cells. New strategies to enhance CTL activities towards HIV-infected macrophages remain to be investigated.

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