Assessing Immune-Mediated Elimination of Natural HIV Reservoirs

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Abstract

Although modern therapies have greatly improved the lives of HIV-positive people with access to care, a cure remains elusive. Curing infection would likely require therapies that combine the ability to force the virus out the ‘latent state’ in which it hides, with immune responses able to kill unmasked infected cells, the so-called “shock and kill” strategy. Cytotoxic T-lymphocytes (CTL), which specialize in killing cells that express intracellular viral antigens, hold particular promise as immune effectors for shock and kill approaches to eradicating the latent reservoir in HIV-infected individuals.

The make-up of the viral reservoir in antiretroviral-treated individuals is complex. The large majority of proviruses are defective, containing deletions and other mutations that render them replication-incompetent. Although these defective proviruses have generally been considered to be inert, we show that a subset can be expressed as antigens, resulting in CTL recognition. By combining CTL clones with potent killing activity with effective latency-reversing agents we have achieved reductions in cell-associated HIV DNA from ex vivo patient samples. Surprisingly, however, this was not associated with reductions in infectious virus as measured by quantitative viral outgrowth assays.

Our results support that the recognition of cells infected with defective HIV proviruses may distract CTL from eliminating cells harboring infectious proviruses, representing a previously unappreciated barrier to curing infection. The lack of any reduction in infectious virus in our assay may also point to additional barriers to eradication, such as HIV-Nef-mediated immune evasion, which may have to be overcome in order to cure infection.

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