MILESTONE 16

Latent inducible HIV-1 in T cells

The advent of combination therapy for HIV treatment in the mid-1990s had a huge impact on patient morbidity and mortality (MILESTONE 14). Together, reverse-transcriptase inhibitors and newly developed protease inhibitors caused plasma virus to fall to undetectable levels within 2–4 months. It was presumed that integration of HIV-1 DNA into the host genome could enable persistence of the virus, and indeed, a 1995 paper by Chun et al. had detected integrated proviruses in some infected patients. These proviruses were found in resting CD4$^+$ T cells, which did not produce virus unless activated. But in 1995 it was not clear how much of an obstacle this potential latent reservoir of integrated proviruses would be to ultimate eradication of the virus by the new combination therapy.

A 1997 paper from the group of David Ho described two phases of viral decline in infected patients treated with combination therapy: a first phase in which virus levels dropped by around 99% within the first two weeks of treatment and a second phase of slower decline, which the authors concluded was driven by loss of long-lived infected cells. Extrapolating from these decay characteristics, they predicted that around 2–3 years of effective treatment would be required to eradicate HIV-1, perhaps longer if the virus persisted in sanctuary sites. Sadly, this estimate proved too optimistic.

Papers from the groups of Robert Siliciano and Douglas Richman, published in 1997, began to characterize and quantify the latent reservoir of HIV-1 virus in patients. Chun et al. provided the first snapshot of the latent reservoir of virus, in a group of 14 asymptomatic HIV-1-infected donors. Looking in the lymph nodes, the authors found that around 0.5% of resting CD4$^+$ T cells harbored HIV-1 DNA, but that less than 0.05% of resting cells contained integrated provirus. The relatively small size of this latent reservoir was a surprise, but the authors cautioned against underestimating its importance, due to the long survival of memory CD4$^+$ T cells. In work published later that year, Finzi et al. looked at 22 patients successfully treated with drugs for up to 30 months and reported the sobering finding that, despite apparently complete suppression of virus replication, highly purified resting CD4$^+$ T cells from each of these individuals could be induced to make replicating virus. Furthermore, levels of inducible replication-competent virus did not decline with increasing time on therapy and the inducible viruses had not acquired mutations conferring drug resistance, suggesting that they were derived from long-lived cells that were infected before the initiation of therapy. Similar findings were also reported in the same issue of *Science* by Wong et al. and in *PNAS* by Chun et al.

> “the latent reservoir of HIV-1 is a formidable obstacle to eradication of the virus”

Today, we know that the latent reservoir of HIV-1 is a formidable obstacle to eradication of the virus. We know that the reservoir is maintained at least in part by clonal expansion of CD4$^+$ T cells containing integrated provirus and that it is hard to measure, as the vast majority of integrated proviruses are defective. The reservoir also extends beyond quiescent cells in the blood and lymph nodes, to sanctuary sites such as the brain that are poorly penetrable to antiretroviral drugs. Nevertheless, achieving at least a functional cure of HIV infection remains a hotly pursued goal and there is intense interest in learning more about the HIV reservoir and how to prevent the virus from rebounding so that medication might be stopped.

Clare Thomas, *Nature*

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