



Notes and Quotes

A decade of learning about the HIV reservoir: new insights into latent infection

A major barrier to curing HIV is the virus's ability to latently infect immune cells. Copies of the virus integrate into these cells' genomes; however, because the virus is transcriptionally silent, it is 'invisible' to the immune system and also impervious to antiretroviral therapy (ART). If treatment stops, the virus can emerge from its hiding spot within the cells and start replicating again.

One longstanding question is how cells become latently infected. In 2007, Saleh *et al.* [1] published an article that provided one of the first pieces of the puzzle. They demonstrated that when resting CD4⁺ T cells are incubated with certain chemokines and then infected with HIV, many copies of the virus are able to integrate into the cells' genomes. Sharon Lewin (University of Melbourne), the senior author of the article, observes that this study 'was the first to show that latency could be established by direct infection of resting T cells, in the presence of a secondary signal such as the chemokines CCL19 and CCL21, which are both abundantly expressed in lymphoid tissue. Since then, we and others have shown that other stimuli that do not activate the T cell can also facilitate latent infection. These stimuli include dendritic cells, endothelial cells, cytokines, and spinoculation.' Now, 10 years after Saleh *et al.* published their paper, two recent articles provide further insight into how the HIV reservoir is established and maintained.

In one of these articles, Descours *et al.* [2] set out to identify an effective marker for latently infected cells. After collecting CD4⁺ T cells from blood, they used green fluorescent protein to identify which cells were latently infected. Then, using ultradeep RNA sequencing, they discovered that CD32a (a low-affinity receptor for a fragment of immunoglobulin G antibodies that is expressed on the surface of dendritic cells and macrophages) was not expressed at all in uninfected T cells or T cells with productive HIV-1 infection – but was dramatically upregulated in latently infected cells. Lewin, who was not involved in the recent studies, explains, 'We now have a surface marker that can define cells enriched for latent infection. There have been many other surface markers described, but these markers only enrich for HIV by 5 to 10-fold. CD32 enriches for latent

infection 1000-fold.' The efficiency of this marker may allow scientists to study latently infected cells in a way never before possible – and could potentially help researchers target and eliminate the HIV reservoir within the body. However, Lewin cautions, 'I think the main question related to CD32 is how it works in respect to the establishment or maintenance of latent infection. The mechanism for how it works is unknown. This is really important to nut out.'

In the second recent article, Hosmane *et al.* [3] gathered resting CD4⁺ T cells from patients on long-term ART and induced cell division. They found that some cells were able to proliferate without releasing infectious virus, though these same cells were capable of producing replication-competent virus at a later point. Moreover, sequence data suggested that independent, identical isolates of replication-competent virus gathered from the same patients arose from the in-vivo proliferation of infected cells, and not from a dominant viral species infecting multiple cells. Robert Siliciano (Johns Hopkins University), senior author of the study, says these results show that 'most of the latent reservoir for HIV is actually generated by the proliferation of a smaller number of initially infected cells... These results are not consistent with the idea that *de novo* infection events maintain the reservoir.' He notes that these conclusions are supported by previous work carried out by Michel Nussenzweig (The Rockefeller University, New York City, US) and John Mellors (University of Pittsburgh, Pittsburgh, US). Lewin notes that a remaining question is, 'why the latent reservoir does not increase over time. Also, it is unclear whether virus from these expanded proliferating cells contribute to viral rebound after antiretroviral cessation.' In the future, Siliciano says that his lab plans to learn more about the factors that drive clonal expansion of infected cells, as 'understanding reservoir dynamics could lead to new approaches for curing HIV infection.'

Of the past decade, Lewin says, 'The field has progressed dramatically in multiple areas. First we know that latency is not just in resting central memory T cells; virus can also persist in other cells, such as macrophages. Second, we know that latency can be established through direct infection of T cells. Third, we know that latency can be reversed *in vitro* and *in vivo*, but latency reversal alone does not eliminate latently infected cells. Fourth, we know that cellular proliferation also plays a role in maintaining the reservoir. Finally, we know that the immune system likely plays a very important role in controlling the reservoir and

controlling viral rebound off ART. Therefore, we need strategies that tackle latency, as well as immune-mediated control. Whether proliferation itself needs to be specifically targeted currently remains unclear. In the decade ahead, we can no doubt expect further advances in this area.

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Conflicts of interest

There are no conflicts of interest.

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