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HIV Infection of Naïve CD4$^+$ T Cells: An Important Reservoir of Persistent HIV Infection?

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A latent viral reservoir that resides in resting CD4$^+$ T cells represents a major barrier to eradicating HIV infection [1-3]. This long-lived reservoir is not detectable by host immune responses and is impervious to combination antiretroviral therapy (cART) [4-6]. Consequently, there has been a major research effort to identify the cell populations that harbor latent HIV, and to develop pharmacologic approaches to specifically eradicate HIV from these cells.

In 2009, it was reported that resting central memory (T_{CM}) and transitional memory (T_{TM}) CD4$^+$ T cells constituted the major latent viral reservoirs in individuals on suppressive cART [7]. Effector memory (T_{EM}) CD4$^+$T cells, and to a lesser extent naïve CD4$^+$ T cells, were also found to contain integrated HIV-1 DNA, however, their overall contribution to the latent reservoir appeared to be minor. As such, recent research has largely focused on the latent HIV reservoir in CD4$^+$ T_{CM} and T_{TM} cells.

Although only regarded as a minor contributor to the latent reservoir, HIV DNA is almost always detected in naïve CD4$^+$ T cells in both viremic and suppressed individuals [8-17]. Earlier this year, it was reported that in some patients who received cART within 10 weeks of primary HIV infection, viremia could be controlled for at least 24 months post-treatment interruption [18]. Interestingly, in this patient population, HIV DNA could only be detected in naïve CD4$^+$ T cells from 2 of 11 individuals. This suggests that the HIV reservoir in naïve CD4$^+$ T cells may be more important than previously considered. Furthermore, in these patients, the short-lived T_{TM} cells and not the long-lived T_{CM} cells appeared to be the major cellular reservoir of HIV DNA [19].

The latent HIV reservoir is believed to be established early during primary infection [20-22]. In this regard, early cART administration likely reduces the size of this reservoir [23-28], and limits infection specifically in the long-lived naïve and T_{CM} CD4$^+$ T cell populations. Consequently, a shorter duration of cART may be required to achieve a functional cure. This is what has been speculated in the case of the Mississippi baby, who was born HIV positive and treated 31 hours post-partum, but subsequently, became undetectable for HIV, even after treatment was stopped at 18 months [29,30]. However, from a clinical point of view, it may not always be possible to initiate cART during primary infection because many people do not know they have been infected until clinical symptoms arise, or they live in resource poor regions where access to necessary treatment is limited.

Finding a cure for HIV has become one of the biggest global challenges of the 21st century [31]. Because of the longevity of naïve CD4$^+$ T cells and their ability to proliferate and differentiate upon antigen exposure into any of the memory cell subsets, as well as effector CD4$^+$ T cells, they undoubtedly pose a major barrier to elimination of the latent reservoir. As such, there are several important questions that need to be addressed. Are the molecular mechanisms responsible for viral latency the same in naïve and memory CD4$^+$ T cells? Are latency reversing agents, such as the histone deacetylase inhibitors vorinostat, panobinostat and romidepsin, effective in naïve CD4$^+$ T cells? Does reactivation of latent HIV infection by pharmacological agents (i.e. the kick) result in cell death in naïve CD4$^+$ T cells (i.e. the kill)? To address these questions, appropriate primary cell models of HIV latency in naïve CD4$^+$ T cells will have to be developed. Additionally, a greater focus on the latent reservoir in naïve CD4$^+$ T cells is warranted in any clinical intervention aimed at eradicating, or reducing the size of, the latent reservoir.

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