HIV persists in macrophages during antiretroviral therapy

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Human immunodeficiency virus (HIV) is causing one of the largest pandemics the world has ever seen. Research with antiretroviral therapy has focused on clearing the virus from T cells, a type of white blood cells in the immune system. A research team, including scientists from the Laboratory's Theoretical Division, has discovered that macrophages, another type of immune cells, can serve as a reservoir for HIV virus during antiretroviral therapy. *Nature Medicine* published their findings.

Significance of the work

Current antiretroviral treatment for HIV controls the infection, but cannot eradicate it. Treatment controls the virus to such low levels that it is barely or not at all detectable with commercial assays. Once treatment is stopped the virus almost invariably rebounds and the disease returns. To develop a cure it is important is to understand where the virus is hiding and treat the virus in the reservoirs.

University of North Carolina researchers developed a mouse model with an immune system generated from human cells but lacking T cells, which are the primary target of HIV. The absence of T cells enabled the team to discover the persistence of HIV in macrophages in animals that had received antiretroviral therapy. This research is the first direct evidence of HIV persistence in tissue macrophages *in vivo*.

These results indicate that macrophages may be a reservoir where the virus hides and that macrophages might contribute to the rebound of virus and infection after treatment. Therefore, possible therapeutic intervention to eradiate HIV may have to target two very different types of cells (T cells and macrophages). Obviously, mice are not humans. These proof-of-principle results should be considered in the context of a model of human infection. Ongoing studies are investigating whether macrophages can also be a hideout for HIV in human infection.

Achievements

The team investigated the response of macrophages to antiretroviral therapy in the mouse model and whether macrophages can serve as a reservoir for HIV virus. The investigators studied the dynamics of HIV infection and antiretroviral treatment. Los Alamos researchers **Ruy Ribeiro** and **Youfang Cao** applied their expertise in modeling

the viral dynamics of diverse infections. They analyzed the rates of viral decay and persistence during and after treatment.

The team made two surprising discoveries. 1) HIV viral loads declined very rapidly in the macrophage-only mice. This result indicated that the turnover of these infected cells is fast and indeed much faster (at least a factor of 10) than previously thought from analyses of indirect human data. 2) Interruption of therapy in macrophage-only infected mice led to a late viral rebound and resulted in disseminated infection in 33 percent of the mice. This was unexpected because it was not known that virus could hide in macrophages. Moreover, this process occurred even in the absence of T cells, which are the major target of HIV infection. The finding that HIV virus was never recovered in 67 percent of the mice after treatment ceased may indicate eradication of infection in those cases.

The research team

"HIV Persistence in Tissue Macrophages of Humanized Myeloid-Only Mice during Antiretroviral Therapy," *Nature Medicine* 638 (2017); doi: 10.1038/nm.4319. Authors: Jenna B. Honecutt, William O. Thayer, Caroline E. Baker, Rachel A. Cleary, J. Victor Garcia and Michael G. Hudgens of the University of North Carolina, Chapel Hill; **Ruy M. Ribeiro and Youfang Cao** of the Laboratory's Theoretical Biology and Biophysics group; Steven M. Lada of Veterans Affairs, San Diego Healthcare System; and Douglas D. Richman of Veterans Affairs and the University of California, San Diego.

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