Second hideout for HIV-1

Immature multipotent haematopoietic progenitor cells (HPCs) are a second reservoir of latent HIV-1 infection, according to a new report in *Nature Medicine*.

Although highly active antiretroviral therapy (HAART) has greatly reduced mortality from HIV-1 infection, it cannot completely eradicate the virus owing to viral persistence as a provirus in latently infected cells. The main cellular reservoir for latent HIV-1 infection is resting CD4⁺ T cells, and the biology of latency in these cells has been intensively investigated. However, the existence of other cellular reservoirs in which

residual virus replication occurs has long been suspected, with a key candidate being HPCs. These CD34⁺ bone marrow cells comprise a heterogeneous mixture of haematopoietic stem cells (HSCs) and multipotent progenitor cells that form as a result of HSC self-renewal and proliferation.

Collins and colleagues analysed the susceptibility of HPCs to HIV-1 infection and found that the virus can actively infect multipotent progenitor cells and cause cell death. But can HIV-1 establish a latent infection in these cells? Direct detection of latent infection involved the creation of a reporter virus expressing GFP independently of the HIV-1 long terminal repeat; this allows latently infected cells to be detected, as they express GFP but not viral proteins such as Gag. Distinct populations of actively infected (Gag⁺GFP⁺) and latently infected (Gag⁻GFP⁺) HPCs were detected, and a detailed flow cytometry analysis of the cell surface markers present on the latently infected cells revealed that they were immature multipotent HPCs.

To check whether latent HIV-1 could be reactivated from the HPC reservoir, the authors used the stimulator phorbol 12-myristate 13-acetate (PMA) to induce cellular differentiation of bone marrow-derived HPCs that were infected with HIV-1 expressing a marker protein. PMA treatment

led to a large increase in the production of virus particles and expression of the marker protein compared with a control treatment. In addition, when bone marrow-derived HPCs infected with HIV-1 were treated with the cytokines granulocyte-macrophage colony-stimulating factor and tumour necrosis factor, which stimulate HPC differentiation into the myeloid lineage, there was a rapid release of HIV-1 into the culture supernatant. Finally, the authors detected CD34⁺Gag⁺ cells in six HIV-1-infected individuals with high viral loads, and they detected HIV genomes in four out of nine individuals who had been receiving HAART for at least 6 months and in whom the viral load was undetectable.

So, in addition to the reservoir in CD4⁺ T cells, it seems that HIV-1 can persist in immature multipotent HPCs. Further work is required to investigate whether the virus is also present in CD34⁺ HSCs and whether this HPC reservoir is the source of the residual viraemia that is observed in individuals receiving HAART.

Sheilagh Molloy

ORIGINAL RESEARCH PAPER Carter, C. C. et al. HIV-1 infects multipotent progenitor cells causing cell death and establishing latent cellular reservoirs. *Nature Med.* 10 Mar 2010 (doi: 10.1038/nm.2109)

FURTHER READING Han, Y. et al. Experimental approaches to the study of HIV-1 latency. *Nature Rev. Microbiol.* 5, 96–106 (2007)