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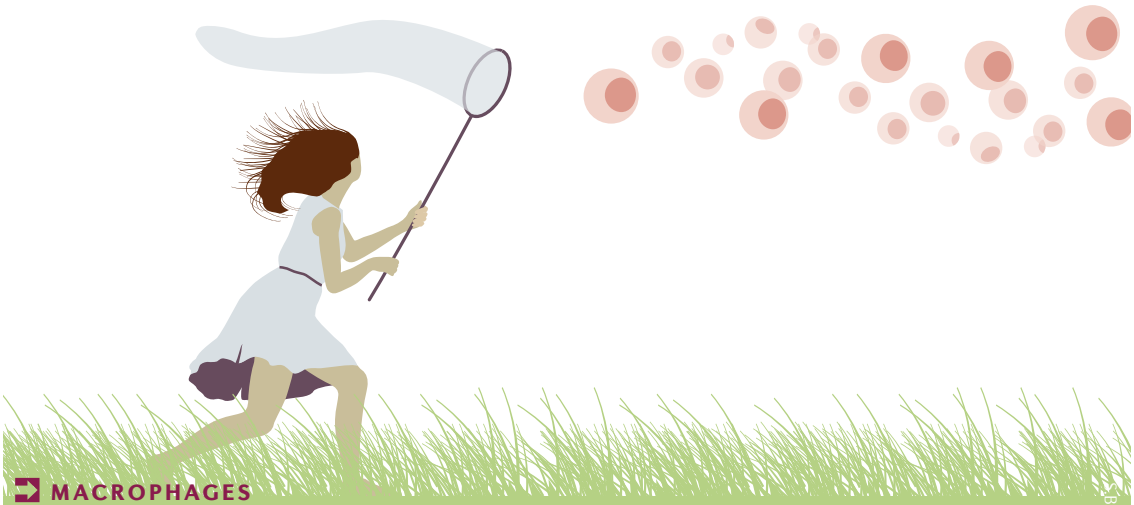

MACROPHAGES

Capturing HIV-infected T cells

In vivo, HIV-1 infects cells that express CD4, such as macrophages and CD4$^+$ T cells, but *in vitro* infection of macrophages by HIV-1 is inefficient owing to their low expression of viral entry receptors. Therefore, the mechanism by which macrophages become infected with HIV-1 *in vivo* has been unclear. Now, Baxter *et al.* show that primary monocyte-derived macrophages selectively capture HIV-1-infected CD4$^+$ T cells, which leads to efficient HIV-1 cell-to-cell spread and macrophage infection.

The authors co-cultured monocyte-derived macrophages with CD4$^+$ T cells infected with HIV-1 isolates that use either the CC-chemokine receptor 5 or the CXC-chemokine receptor 4 viral co-receptor for entry, or with uninfected CD4$^+$ T cells. Live-cell imaging showed that CD4$^+$ T cells infected with either type of virus were engulfed by macrophages, whereas uninfected CD4$^+$ T cells were not. Using multispectral flow cytometry — which measures the amount and location of multiple markers inside cells and quantifies morphologically distinct cell subpopulations — the authors quantified selective macrophage uptake of different CD4$^+$ T cell subsets that had been labelled with markers of apoptosis or necrosis. They found that both cell death and HIV-1 infection of CD4$^+$ T cells promoted their uptake by macrophages, and together they generated a stronger uptake signal. Thus, macrophages efficiently capture HIV-1-infected CD4$^+$ T cells independently of the co-receptor specificity of the HIV-1 isolate.

Uptake of HIV-1-infected CD4$^+$ T cells by macrophages could either lead to infection of the macrophages or phagolysosomal elimination of the infected cells. Macrophages and HIV-1-infected CD4$^+$ T cells were co-cultured in the presence or absence of azidothymidine — a drug that inhibits replicating HIV-1 — which showed that the viral DNA content of macrophages increased more in the absence of azidothymidine than in the presence of the drug, indicating that HIV-1 is replicating in macrophages. Furthermore, the authors found that more infectious HIV-1 was released from macrophages exposed to infected CD4$^+$ T cells than from macrophages exposed to cell-free virus. Exposing co-cultures of macrophages and HIV-1-infected CD4$^+$ T cells to inhibitors of HIV-1 T cell entry reduced macrophage infection, although infected CD4$^+$ T cells were still taken up by the macrophages. Moreover, despite the avid macrophage capture of T cells infected with non-macrophage-tropic HIV-1, these viruses were unable to infect the macrophages. Together, these results demonstrate that infected T cells are captured by macrophages and this results in subsequent macrophage infection.

Finally, the authors investigated the mechanisms of macrophage uptake of infected CD4$^+$ T cells. HIV-1 is known to spread between CD4$^+$ T cells by forming a supramolecular structure called the 'virological synapse' and this is dependent on the expression of the viral envelope glycoprotein. However, experiments using a large set of inhibitors or a virus without the envelope glycoprotein showed that macrophage uptake of infected T cells was independent of HIV-1 envelope glycoprotein–receptor interactions; thus, the uptake and spread of HIV-1 in macrophages is not mediated by conventional virological synapse signals.

In summary, these data show that macrophages capture HIV-1-infected CD4$^+$ T cells, which leads to efficient macrophage infection. This can have important implications for the spread of viruses to macrophages *in vivo*.

Elisabeth Kugelberg

> “more infectious HIV-1 was released from macrophages”

ORIGINAL RESEARCH PAPER Baxter, A. E. *et al.* Macrophage infection via selective capture of HIV-1-infected CD4$^+$ T cells. *Cell Host Microbe* http://dx.doi.org/10.1016/j.chom.2014.10.010 (2014)