Integration logistics

HIV-1 'preferentially' integrates into a subset of transcriptionally active host genes, but how some of these genes are selected remains unclear. In *Nature*, Marini *et al.* show that HIV-1 DNA integration occurs in genes located near the outer shell of the nucleus that are marked by active transcription chromatin marks and are proximal to the nuclear pore. The identification of genes that undergo recurrent HIV-1 integration and mapping them in the nuclear architecture or the direct visualization of HIV-1-integration sites in CD4$^+$ T cells shows 'preferential' localization of viral DNA next to the nuclear envelope. In contrast, the virus 'disfavors' heterochromatic regions in the nuclear periphery or more centrally located transcriptionally active regions. Once integrated, the HIV-1 DNA makes contact with subunits of the nuclear pore complex called nucleoporins; silencing of several nucleoporins diminishes HIV-1's transcriptional activity. These observations suggest that HIV-1 DNA integrates in the first open chromatin regions encountered in the nucleus, which might be related to the short lifetime of the viral integrase. ***IV***

***Nature* (2 March 2015) doi:10.1038/nature14226**

HIV keeps DCs immature

HIV-1 infection is characterized by dysregulation of the immune system and is thought to be due at least in part to the impaired function of dendritic cells (DCs). In *The Journal of Immunology*, Geijtenbeek and colleagues investigate the changes that occur in DCs following exposure to HIV-1 *in vitro* to gain insight into the systemic disruption of the immune system seen during infection. The literature is divided about whether DCs can be infected by HIV-1; however, these authors find that DCs can be readily infected with both R-tropic HIV-1 and pseudotyped HIV-1. Despite efficient infection, DCs fail to be activated and maintain an immature state with a poor ability to stimulate T cell proliferation. Moreover, HIV-1 infection suppresses DC activation that is otherwise strongly triggered by ligands of Toll-like receptors. Although the mechanism of this suppression is unclear, it is independent of the HIV-1 envelope but dependent on viral replication. *ZF*

J. Immunol. (30 March 2015) doi:10.4049/jimmunol.1403016

Passive protection

Broadly neutralizing antibodies (bNAbs) can confer protection against HIV-1 infection in humanized mice and in primate models, but whether immunotherapy with a monoclonal bNAb can control HIV-1 in humans remains unclear. In *Nature*, Nussenzweig and colleagues describe a phase I clinical trial designed to elicit passive anti-viral protection by the potent bNAb 3BNC117, which recognizes the CD4-binding site in HIV-1 Env and can neutralize 195 of 237 HIV-1 strains across six clades. A single infusion of a high dose of 3BNC117 elicits a transient drop in viral load (differing from baseline by 0.8–2.5 $\log_{10}$) in 10 of 11 HIV-1-infected volunteers, with the non-responder harboring a 3BNC117-resistent virus. The authors observed evidence of antibody-mediated viral selection in some patients, whereas others maintained their sensitivity to 3BNC117 for as long as it remained in circulation. These findings suggest that passive immunization, paired with other anti-HIV-1 treatment modalities, may protect infected people. ***LAD***

***Nature* (8 April 2015) doi:10.1038/nature14411**

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Neutralizing antibody evolution

Effective, broadly neutralizing antibodies (bNAbs) to HIV-1 are observed many years after infection and show unusual features, such as long and protruding heavy-chain CDR3 regions, unusual post-translational modifications and extensive somatic hypermutation (SHM). In *Cell*, Shapiro and colleagues investigate the ontogeny of the bNAb lineage VRC01, which targets the site of engagement of the coreceptor CD4 by HIV-1, through longitudinal sampling of peripheral B cell transcripts over 15 years and co-crystal structures of members of this lineage. The VCR01 lineage shows very high diversity, due to a high rate of SHM during the course of the infection. The structures indicate that amino acid changes enhance antibody-antigen interactions, while the lineage conserves the binding mode and core interactive residues. SHM persists during the course of infection with rates of about two substitutions per 100 nucleotides per year, comparable to that of HIV-1 evolution. These results suggest that just a few highly diverse antibody lineages may be critical for the control of HIV-1. *IV*

Cell (9 April 2015) doi:10.1016/j.cell.2015.03.004

HIV-1 in the driving seat

The accumulation of macrophages in tissues such as the kidneys, liver and intestine has been reported during infection with HIV-1 and simian immunodeficiency virus. In *Blood*, Maridonneau-Parini and colleagues investigate the mechanistic basis of altered macrophage distribution during HIV-1 infection. Using *in vitro* models of macrophage migration, they find that HIV-1 infection selectively increases the mesenchymal mode of macrophage migration at the expense of amoeboid movement. This is relevant to tissue invasiveness because mesenchymal migration is characterized by podosomes and is proteolytic, which allows penetration of substrates with low porosity. Adoption of the mesenchymal mode depends on HIV-1's expression of functional negative factor protein (Nef). Indeed, mice with transgenic expression of Nef show a proclivity for mesenchymal macrophage migration as well as enrichment for macrophages in tissues or implanted tumors. Nef operates by activating a Hck-WASP–mediated pathway required for the formation and stability of podosomes. These findings suggest that Nef-triggered redistribution of macrophages to tissues might therefore contribute to the dissemination of HIV-1 and pathogenesis of AIDS. ***ZF***

***Blood* 125, 1611–1622 (2015)**

HIV entry

HIV-1 enters T cells by interaction of its envelope glycoprotein gp120 with the receptors CD4 and CXCR4 or CCR5, followed by gp41-assisted fusion with the host-cell plasma membrane. In *Nature Chemical Biology*, Yang *et al.* show that viral fusion occurs at edges of cholesterol-rich lipid-raft domains. Liposomes containing the gp41 fusion peptide 'preferentially' associate with membranes at the boundaries between lipid phases and fuse their contents by coalescence with similar patches on the opposing host-cell membrane. These lipid-phase boundaries are thought to be more deformable and could lower the energetic barriers associated with membrane fusion and thereby facilitate entry of the virus into the host cytoplasm. In *Virology*, Mefford *et al.* report two polymorphisms in gp120 that increase viral trophism for macrophages, which express CCR5 but express less CD4 than T cells. Enhanced gp120-CCR5 interactions occur and might explain the increased infection of macrophage-rich tissues such as brain. *LAD*

Nat. Chem. Biol. (27 April 2015) doi:10.1038/nchembio.1800 & *Virology* **481**, 210–222 (2015)