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VIRAL INFECTION

When two become one

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HIV-1 entry begins with the binding of the viral envelope protein (Env) to CD4 receptors and co-receptors on the surface of host cells. This interaction triggers a complex series of events that result in the fusion of viral and host membranes. The early stages of HIV-1 entry have been studied extensively; however, the molecular details of the initial fusion events remain unresolved, and the contribution of intracellular signalling to fusion is controversial. Now, two recent studies provide new insights into the fusion stage of HIV-1 entry.

In the first study, Ozorowski, Pallesen *et al.* used cryo-electron microscopy (cryo-EM) to investigate conformational changes in the Env glycoprotein (composed of three gp120 and three gp41 subunits) that occur after HIV-1 binding and might drive fusion. They compared cryo-EM maps of a fully glycosylated SOSIP (a solubilized and stabilized version of the Env trimer) in complex with CD4 and antibodies that recognize the co-receptor-binding site with pre-fusion SOSIP trimers, and report receptor-induced structural rearrangements in Env. These conformational changes affected both the surface gp120 subunits and the transmembrane gp41 subunits, and included changes to the V1/V2 and V3 loops, the formation of a helix and a large rearrangement of the gp41 fusion peptide following receptor binding into a newly formed pocket. The repositioned fusion peptide was found to be stabilized by many newly formed interactions within Env itself, which, when mutated, resulted in decreased viral infectivity. The authors hypothesize that these molecular rearrangements result in the formation of a stable fusion intermediate and prime the viral glycoprotein for further transitions that occur following co-receptor binding.

In a second study, Zaitseva *et al.* observed that Env binding to its receptors induces the redistribution of phosphatidylserine to the host cell surface and that this promotes viral fusion. First, the authors found that infection with pseudoviruses expressing HIV-1 Env or recombinant gp120 induced the redistribution of phosphatidylserine from the inner leaflet of the plasma membrane to the cell surface. Moreover, inhibition of host anoctamin 6 (a regulator of the lipid redistribution) decreased fusion in a dose-dependent manner, which suggests that viral fusion requires anoctamin 6-mediated externalization of phosphatidylserine. In agreement with this, the authors report that the addition of exogenous phosphatidylserine or phosphatidylserine-binding proteins promoted or reduced Env-mediated fusion, respectively. Previous studies had shown that the induction of Ca^{2+} signalling in response to the binding of HIV-1 to host receptors is important for viral fusion. The authors of this study show that Ca^{2+} signalling is linked to the externalization of phosphatidylserine and the increased efficiency of viral fusion. Interfering with intracellular Ca^{2+} signalling caused a decrease in Env-mediated fusion, and this decrease could be rescued by the addition of phosphatidylserine. Phosphatidylserine-dependent fusion was found to occur after viral attachment and gp20–co-receptor interactions but before the outer leaflets of the host membranes merge (termed hemifusion), as evidenced by the accumulation of fusion intermediates when anoctamin 6 was inhibited. The authors suggest that cell surface phosphatidylserine engages in electrostatic interactions with the Env trimer to promote fusogenic restructuring in Env.

Together, these two studies provide new insights into the receptor-mediated fusion stage of HIV-1 entry, which could lead to new approaches for the development of antiretrovirals.

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> “new insights into the receptor-mediated fusion stage of HIV-1 entry”

ORIGINAL ARTICLES Ozorowski, G., Pallesen, J. *et al.* Open and closed structures reveal allostery and pliability in the HIV-1 envelope spike. *Nature* http://dx.doi.org/10.1038/nature23010 (2017) | Zaitseva, E. *et al.* Fusion stage of HIV-1 entry depends on virus-induced cell surface exposure of phosphatidylserine. *Cell Host Microbe* **22**, 99–110. e7 (2017)