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Oral presentation

An unprecedented and simple gp120 switch mechanism enables HIV-1 to overcome multiple entry inhibitors and tropism limitations

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We previously isolated HIV-1JRCSF variants that efficiently use mutant CCR5 coreceptors, including CCR5(D18) lacking the important tyrosine sulfate-containing amino terminus. The relationship between mutant CCR5 concentrations and HIV-1 infectivities in HeLa-CD4 cell clones implied that multiple virus-associated CCR5s (~3–6) are required. We now describe HIV-1JRCSF variants that efficiently use CCR5(HHMH), a chimera containing murine extracellular loop 2. Interestingly, the adapted virus causes large syncytia and has three gp120 mutations previously found in CCR5(D18)-adapted virus, two in variable region 3 (S298N and V313L) and one eliminating an N-glycan in variable region 4 (N403S). Accordingly, virus adapted to CCR5(HHMH) uses CCR5(D18), but not a double mutant damaged in both regions, whereas wild-type HIV-1s require both regions. This suggests that these adaptive mutations function by lowering the activation energy barrier for infection rather than by increasing viral affinity for specific CCR5 sites. Infectivity assays using HeLa-CD4/CCR5(HHMH) clones with distinct coreceptor quantities and studies with entry inhibitors demonstrate that highly adapted HIV-1s require one coreceptor, whereas maladapted viruses require several. Thus, gp120 adaptations lower the activation energy for membrane fusion, enabling portions of CCR5 to suffice, reducing stoichiometries of CCR5 required in fusion-active complexes, and facilitating infections of cells having low CCR5 concentrations. Stoichiometric shifts caused by a small number of common gp120 substitutions profoundly control cell tropisms and sensitivities to entry inhibitors. These results provide a novel foundation for understanding HIV-1 adaptations and entry inhibitors including antibodies.