

Mechanistic Basis for HIV-1 Coreceptor Switch

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ABSTRACT

The human immunodeficiency virus (HIV) enters target cells via interaction of the viral glycoprotein with the cellular receptor CD4 and two principal coreceptors, CCR5 (R5 viruses) and CXCR4 (X4 viruses). Most HIV-1 transmissions result in a predominantly R5 virus infection. With time, X4 variants arise and coexist with R5 virus variants in ~50% of subtype B infected individuals. The underlying basis for virus coreceptor switch late in infection remains an enigma, but will be important to understand given that the appearance of X4 virus in HIV-1 infected patients inevitably heralds an unfavorable clinical outcome. We recently documented the emergence of X4 viruses in rhesus macaques infected with a CCR5-tropic simian-human immunodeficiency virus (SHIV_{SF162P3N}) that rapidly progressed to disease in the absence of strong antiviral responses. Emergence of X4 variants followed rather than preceded or coincided with the onset of precipitous peripheral CD4⁺ T cell loss, strengthening the notion that X4 dominance is the consequence rather than the cause of immune failure. Furthermore, and the emerging X4 variants were more neutralization sensitive than the inoculating virus, supporting an inhibitory role of antiviral antibodies in HIV-1 coreceptor switch *in vivo*. Nevertheless, the finding that expansion or switch to CXCR4 usage was evident only in two of six SHIV_{SF162P3N}-infected macaques that progressed to disease in the presence of transient seroconversion suggests that although the inability to maintain antibody-selective pressure promotes the emergence of CXCR4-using viruses, it may be in itself insufficient to drive coreceptor switch. Comparison of the viral burden and target T cell availability in R5 SHIV_{SF162P3N} infected macaques with (n=2) or without (n=4) coreceptor switch revealed no difference in the proliferation rate of naive CD4⁺ T cells that express CXCR4 but not CCR5. However, the percentage of CCR5 expressing peripheral CD4⁺ target T cells (p = 0.005) and overall viral burden were significantly higher in macaques with switch than those without (p = 0.002), with the rate of CD4⁺ T cell loss being faster in macaques with switch than those without (p=0.05). Thus, a certain amount of viremia is needed to generate the mutations and conditions optimal for coreceptor switching. The time required for accumulation of envelope substitutions necessary to confer CXCR4 usage, and for the immune system to collapse thereby removing the immune suppression of the evolving X4 viruses likely explains the infrequent and long delay in their appearance.