No Free Lunch: HIV-1 Pays a Price to Infect Macaque Cells

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The most recent World AIDS Day serves as a timely reminder that an HIV-1 vaccine remains a major goal in biomedical science. Macaque models of HIV-1 infection have been instrumental in pre-clinical and passive immunization studies. However, due to species-specific barriers, HIV-1 cannot establish a long-term infection in macaque cells. Therefore, modeling HIV-1 infection in macaques often requires use of chimeric SIV (simian immunodeficiency virus)/ HIV viruses (SHIVs). Chimeric SHIVs require adaptation to persistently infect macaques, presumably due to differences between macaque CD4 (mCD4) and human CD4, the receptor for HIV-1. The envelope glycoprotein of HIV-1 (Env) is the major target of the host immune response and is the focus of most vaccine development strategies. Previous studies had isolated two independent Env mutations (A204E and G312V) that enabled a 100-fold increase in CD4-mediated entry into macaque cells. However, the consequences of adaptation to a macaque host for the antigenic properties of Env had remained unaddressed. This is important because if the SHIV Env would not faithfully recapitulate the immunological properties of Env from circulating HIV-1 subtypes infecting humans, their use as models for vaccine development could be limited. This question was recently addressed by a Fred Hutch study published in the *Journal of Virology*, and led by graduate student David Boyd in the lab of Dr. Julie Overbaugh (Human Biology and Public Health Sciences Divisions).

As a first test to determine to what extent, if any, the antigenic properties of Env changed during adaptation, the authors introduced the A204E and G312V mutations either alone, or in combination, into Env proteins derived from representative sub-Saharan African HIV-1 subtypes. While introduction of both mutations simultaneously resulted in non-functional Envs, five out of seven Envs permitted mCD4-mediated infection with either A204E or G312V, whereas for the remaining two, only the A204E mutation enabled mCD4-dependent entry. These A204E or G312V-containing Envs that could replicate in a CD4-dependent manner are hereafter collectively referred to as mCD4-adapted Envs. The Env protein exists as trimer, and engagement by CD4 results in a more open conformation (see figure). The researchers hypothesized that mCD4-adapted Envs exhibited a similarly open conformation, which would render them more sensitive to antibodies specific for antigens that are not accessible in the closed conformation. To test this hypothesis, the researchers used a panel of neutralizing antibodies that recognize either quaternary epitopes (PG9, PG16,

PGT145, VRC03; only present in closed conformation trimer) or CD4-induced epitopes (sCD4, 17b; exposed in the open conformation). Strikingly, the authors found that a subset of mCD4-adapted Envs became resistant to neutralization by antibodies that target quaternary epitopes while becoming sensitive to CD4-induced epitopes. "Our results suggest that there are antigenic consequences of adapting HIV-1 envelope to the macaque CD4 receptor and help explain why it has been so difficult to generate challenge viruses that are representative of HIV-1 variants circulating in people," said Mr. Boyd.

Next, the investigators assessed the neutralization profiles of Envs derived from either pathogenic SHIVs or CD4-independent strains of HIV-1. Notably, both types exhibited neutralization profiles similar to that of mCD4-adapted Envs, suggesting that comparable conformational changes accompany CD4-independence and adaptation to mCD4. Finally, the researchers determined if the ability to use mCD4 as a receptor could predict the neutralization profile of Envs. To this end, the authors compared the ability of Envs isolated from 48 recently transmitted variants to infect cells expressing either mCD4 or human CD4, yet found that the ability to use mCD4 is not a determinant of sensitivity to the quaternary PG9/PG16 antibodies. Overall, this study demonstrated that adaptation of HIV-1 to mCD4 results in significant structural and functional changes in Env, and informs the design of future SHIV models.

"We did identify a subset of HIV-1 envelopes that are able to use macaque CD4 for entry and maintain key antigenic properties of transmitted viruses. We are now interested in developing novel challenge viruses based on these envelopes", concluded Mr. Boyd.

Boyd DF, Peterson D, Haggarty BS, Jordan APO, Hogan MJ, Goo L, Hoxie JA, Overbaugh J. (2014). Mutations in HIV-1 envelope that enhance entry with the macaque CD4 receptor alter antibody recognition by disrupting quaternary interactions within the trimer. J Virol. Nov 5. pii: JVI.02680-14.

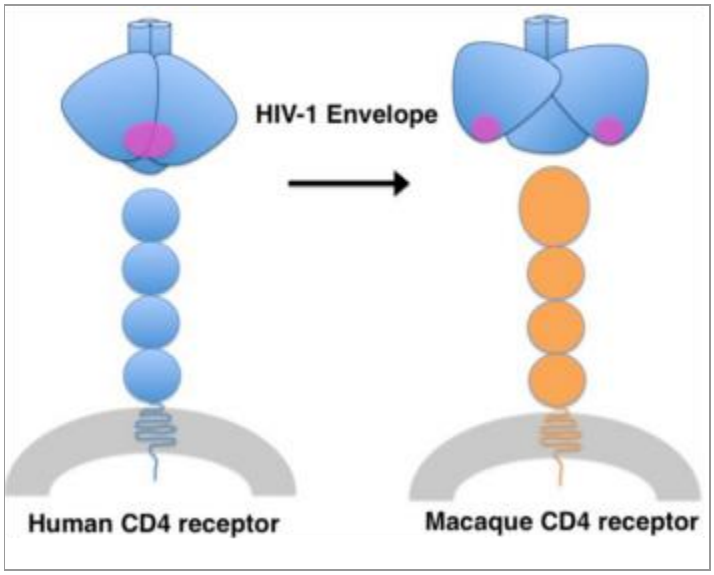

Image provided by Mr. Boyd

HIV-1 Envelope (Env) interacts with the human CD4 receptor to infect cells and establish infection (left panel). The CD4 proteins of most other species do not function as a receptor for HIV-1. The macaque CD4 protein can function as receptor for some strains of HIV-1, particularly for those adapted in culture, but not for HIV-1 Envs from most globally circulating variants relevant to the HIV pandemic. The study of Boyd and colleagues suggests that mutations that allow HIV-1 Env to use the macaque CD4 receptor for entry induce conformational changes in Env that disrupt important epitopes (highlighted in magenta) that are currently the focus of HIV-1 vaccine design.