CD4–HIV-1 Envelope Interactions: Critical Insights for the Simian/HIV/Macaque Model

Amit Sharma^{1,2} and Julie Overbaugh¹

Abstract

The macaque models of HIV-1 infection have been a cornerstone of research on transmission, pathogenesis, and prevention. In particular, the infection of macaques with chimeric simian/HIV-1 viruses (SHIVs) is central to the vaccine development pipeline because SHIVs encode the key target of HIV-1-neutralizing antibodies, the HIV-1 envelope (env) protein. In this review, we highlight some of the recent studies that have improved our understanding of the CD4–HIV-1 env interaction, which are crucial for development of SHIV/macaque models of HIV-1 infection.

Keywords: CD4, HIV-1 envelope, SHIV/macaque model

MOST OF THE WIDELY utilized simian/HIV-1 viruses (SHIVs) were generated by trial and error, encode HIV-1 envelopes (env) from laboratory-adapted viruses, and were biasedly selected for high replication and pathogenicity in macaques. We now have greater appreciation that laboratory-adapted viruses are phenotypically different from the transmitted HIV-1 variants. There are a limited number of SHIVs encoding transmitted HIV-1 envs, in part because such SHIVs replicate poorly and are nonpathogenic in macaques. The mechanistic reasons behind this were until recently unknown.

The first study to uncover the molecular mechanism of SHIV restriction in macaque cells revealed that the macaque CD4 (mCD4) does not function as an efficient receptor for transmitted HIV-1 envs from multiple subtypes, suggesting that this is a common feature of transmitted variants.¹ It was further revealed that the inability of most transmitted envs to utilize mCD4 maps to species-specific single amino acid difference at residue 39 in the D1 domain of CD4 [human CD4 (hCD4) encodes asparagine and mCD4 encodes isoleucine]. Thus, asparagine at position 39 is critical for mediating entry of transmitted HIV-1 envs. This study provided key insights into why very few SHIVs based on transmitted envs have been successful and why development of SHIVs generally require extensive adaptation of virus in macaques, at least, in part, to optimize mCD4-mediated entry. A recent study shed more light on this issue and discovered that the adaptation of HIV-1 envs to mCD4 alters the conformational and antigenic properties of envs, thus severely limiting their

translational utility of SHIVs.² In particular, it was demonstrated that the adaptation to mCD4 induces conformational changes that disrupt quaternary epitopes in the native env trimer and exposes epitopes present in the CD4-induced open conformation of env. Thus, it is critical to focus resources for development of SHIVs that encode transmitted HIV-1 envs that can replicate in macaques without passage and retain the biological characteristics of transmitted HIV-1 variants.

Recent studies suggest that it is possible to develop a pathogenic SHIV encoding transmitted HIV-1 envs that can replicate in macaques without passage, including by *in vivo* selection of such env variants by inoculating macaques with a pool of SHIVs. These studies provide proof-of-principle that there are rare transmitted HIV-1 envs that can utilize mCD4 without the need for extensive adaptation, but also highlighted the fact that the majority of SHIVs encoding transmitted HIV-1 envs do not replicate in macaques. Given the fact that the mCD4–HIV-1 env interaction is a major determinant for establishing persistent SHIV infection in macaques, it is logical to apply rational design approaches to bolster this interaction in the context of the engineered SHIVs. In line with this, a recent study performed the sequence and structural comparisons of hCD4 and mCD4 in their interaction with HIV-1 env and quantified the positive evolutionary selection at CD4-binding residues in env from a broad array of primate lentiviruses.³ Based on these analyses, the authors substituted serine at position 375 in diverse HIV-1 envs with corresponding hydrophobic and basic residues from SIV envs. These substitutions resulted in increased

¹Division of Human Biology, Fred Hutchinson Cancer Research Center, Seattle, Washington.

²Department of Veterinary Biosciences, Department of Microbial Infection and Immunity, The Ohio State University, Columbus, Ohio.

mCD4 binding, improved viral entry, and enhanced replication of SHIVs in macaques.

Finally, a recent study explored the bold concept that other nonhuman primates (NHPs) could serve as alternative models for HIV-1 infection. Using an evolutionary biology approach, the authors sampled the *CD4* genetic diversity across the primate phylogeny and discovered that some Spix's owl monkeys encode *CD4* alleles that encode asparagine at position 39.⁴ These alleles encode functional receptors for entry by HIV-1 envs isolated from transmitted HIV-1 variants representing all of the major HIV-1 group M clades. It is interesting to note that the New World monkeys, to which the owl monkey family belongs, present minimal cellular blocks to HIV-1 infection. Thus, if NHP models are to continue to be important for HIV-1 prevention and vaccine research, it is worth exploring the genetic repertoire of New World monkeys for functional HIV-1 receptors and minimal cellular barriers to HIV-1 replication compared with macaques.

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Address correspondence to:

Amit Sharma

Department of Veterinary Biosciences

Department of Microbial Infection and Immunity

The Ohio State University

Columbus, OH 43210

E-mail: sharma.157@osu.edu