

RESTRICTION FACTORS TO HIV-1 REPLICATION IN MACAQUES

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HIV-1 is unable to replicate in most nonhuman primate species. The most practical animal models of human AIDS consist of infection of rhesus macaques by SIV_{MAC} or chimeras encoding the HIV-1 envelope (SHIV), both of which cause simian AIDS. Over the past few years it has become increasingly evident that primate cells express restriction factors, exemplified by TRIM5 α and APOBEC3 proteins, that inhibit infection by various retroviruses. We have previously demonstrated that the inability of HIV-1 to replicate in rhesus macaque cells *in vitro* was due solely to the blocks in the viral replication cycle imposed by these two proteins. Importantly, we have overcome these blocks and generated a recombinant virus strain, stHIV, that is ~88% HIV-1-derived and yet can replicate robustly in rhesus macaque cells *in vitro*. Nevertheless, stHIV replication in rhesus macaques *in vivo* was only modest. It is possible that stHIV replication *in vivo* might be impaired by subtle replication defects that are not obvious *in vitro* and are due to the engineering steps employed during its construction or that rhesus macaques express factors, other than TRIM5 α and APOBEC3, whose inhibitory activity against HIV-1 is only manifested *in vivo*.

In an effort to overcome these potential barriers we explored the use of alternative macaque species and in particular, pigtail macaques. We and others have recently shown that a TRIMCyp fusion protein, similar to that first identified in Owl monkeys, has arisen independently in pigtail macaques. Interestingly, unlike omkTRIMCyp, pgtTRIMCyp is completely inactive against HIV-1 even though it can restrict other lentiviruses including HIV-2, SIVagmTAN and FIV. Even though primary pigtail macaque cells did not express any restriction factors targeting the HIV-1 capsid they did express APOBEC3G that, like rhAPOBEC3G, potently inhibited HIV-1 infectivity. Therefore, we generated a variant of stHIV where the only protein derived from SIV_{MAC} was Vif, and showed that, in contrast to HIV-1, it can replicate in primary pigtailed macaque cells very efficiently. Therefore, pigtail macaques appear to express fewer restriction factors active against HIV-1 and could potentially be a model more amenable to infection by stHIV variants.