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Interferon-I: The Pièce de Résistance of HIV-1 Transmission?

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Abstract

Despite the extensive viral quasispecies that develops in an individual during the course of HIV-1 infection, transmission is typically established by a single donor viral variant. Recent studies now provide insight into the phenotypic properties influencing this selection process at transmission including the contribution of resistance to type I interferons.

Keywords

HIV; transmission; bottleneck; interferon; resistance; mucosal

HIV-1 mucosal transmission is an inherently inefficient process with less than 1% of unprotected sexual exposures leading to clinical infection. A central hallmark of transmission is the appearance of a severe population bottleneck whereby, in 80% of sexual transmission cases, infection is established by a single genetic variant (1). As recently summarized by Joseph *et al.* (2), the mechanism for this bottleneck includes a complex interplay of various anatomical and physiological barriers coupled with host innate immune responses that limit early viral replication and dissemination. This raises the question of whether these bottlenecks represent a stochastic process, in which any reasonably fit virus can establish a new infection, or whether there are selective forces favoring particular genotypic and phenotypic properties. Delineating the viral traits that correlate with transmission could advance strategies aimed at preventing HIV-1 transmission. To date, numerous studies have identified an array of genetic signatures specific to transmitted/founder (TF) viruses, including residues clustering near the Env glycoprotein's CD4-binding site (1). More intriguingly, a recent study by Carlson *et al.* characterizing 137 linked transmission pairs determined that mucosal transmission selects for viruses with a more consensus-like sequence, a bias that is mitigated by genital ulcers and inflammation (3). Such studies suggest that broader underlying phenotypic determinants may be augmenting the selection of viruses at transmission.

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In a recent study, Iyer and colleagues identified several biological features linked to enhanced transmission fitness (4). Owing to the labor intensiveness of molecular cloning they implemented a limiting dilution virus isolation approach to generate single virion plasma-derived HIV-1 isolates from eight epidemiologically-linked transmission pairs. By conducting *in vitro* replication assays on 300 virus isolates from the plasma of matched donor and recipients they found that recipient founder isolates were three times more infectious, had a 1.4-fold higher ability to replicate and were more efficiently released from infected cells than corresponding non-transmitting donor viruses (4). Most prominently, they found that recipient isolates required 8-fold and 39-fold higher concentrations of IFNα2 and IFNβ respectively to achieve a 50 percent reduction in replication, thus demonstrating that founder viruses were uniformly resistant to type I interferons (IFN-I) which form part of the innate immune response against infection (4). In addition, pre-treatment of $CD4^+$ T cells with IFNβ alone selected for donor isolates with a phenotype that mirrored that of founder viruses. This study is congruent with their prior report demonstrating that founder viruses exhibit greater infectivity, bind to dendritic cells more efficiently and are resistant to inhibition by IFNα2 when compared to viruses derived from chronic infections (5). Taken together, these studies suggest that there is selection during the HIV-1 transmission bottleneck for virus variants that are adept at evading host innate responses.

In contrast, similar studies by Deymier *et al.* (6) and Oberle *et al.* (7) failed to find any significant difference in IFNα resistance between TF and non-transmitted viruses. Differences in study designs could account for these discrepancies, including HIV-1 clade-specific effects, utilization of plasma-derived versus archived virus in peripheral blood mononuclear cells (PBMC) or molecular clones versus cultured virus isolates, as well as quantitation of input virus by particles versus infectious units. Notably, each of these studies, including Iyer *et al.*, utilized transmission pairs to enable direct comparison of recipient founder viruses to their contemporaneous donor non-transmitted viruses. This is important because the wide range of viral phenotypes otherwise observed between chronically infected subjects could obscure the identification of more subtle phenotypes (4, 6, 7). However, since IFNα resistance appears to decrease shortly after infection and increase again during late-stage chronic infection (4, 8), donor differences in the length of time since infection could also influence these findings.

Questions also remain regarding the specific viral genes responsible for mediating resistance to IFNα. Foster *et al.* now provide strong evidence for interferon-induced transmembrane protein (IFITM) resistance as a major determinant of HIV-1 transmission fitness, and demonstrate that this resistance is conferred by *env* (8). Specifically, neutralizing antibody escape mutations that accumulated after transmission were associated with enhanced sensitivity to IFITM-mediated restriction, suggesting that escape from adaptive immunity may render the virus more susceptible to restriction mediated by the innate immune system at the time of transmission. This observation is consistent with the findings from Carlson *et al.*, where polymorphisms associated with immune escape were selected against during transmission (3). Of note, this selection bias was observed in *gag*, *pol*, and *nef*, suggesting that viral genes outside of *env* may also be influencing transmission fitness. Although this selection for consensus-like genomes was hypothesized to reflect higher *in vivo* fitness, follow-up studies by Deymier *et al.* found no association with *in vitro* replication capacity

(RC) (6). The authors did, however, observe that *in vitro* RC largely determined growth in the presence of IFNα, highlighting a clear correlation between IFNα resistance and the inherent ability of the virus to replicate (6). A recent study by Sutherland *et al.* observed a similar association between the *in vitro* RC of MJ4/*gag* chimeric viruses and their resistance to protease inhibitors (PI), with high RC viruses exhibiting lower PI susceptibility than low RC viruses (9). Therefore, the inherent *in vitro* RC of a virus may be influencing '*in vivo* resistance' to a number of external selection forces and thus will need to be carefully considered when exploring factors influencing transmission, as will the impact of utilizing highly activated $CD4^+$ T cells to derive viral isolates and to assay RC.

In summary, the extreme selection bottleneck that occurs during transmission provides a unique opportunity to identify virological attributes critical to the successful early replication of HIV-1. Iyer *et al.* now identify that resistance to IFN-I may reflect a key component of this early immunological bottleneck. In line with these findings, recent work by Sandler *et al.* demonstrate that pre-challenge administration of IFN-α2a prevented systemic SIV infection and limited the number of TF viruses in rhesus macaques (10). As such, further *in vivo* studies may help to clarify the role of IFN resistance and refine our understanding of the selective forces mediating HIV-1 transmission.

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