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VIRUS INFECTION

HIV-1 weighs up risks and benefits

> IFN-1 sensitivity increases after transmission owing to antibody-escape mutations in Env

Type I interferons (IFN-I) induce the transcription of interferon-stimulated genes (ISGs), which have antiviral effects and limit viral growth. Interferon-inducible transmembrane (IFITM) proteins are cellular antiviral proteins that restrict the replication of several viruses, including HIV-1. IFITM1 is primarily expressed at the plasma membrane, whereas IFITM2 and IFITM3 localize predominantly to endosomal membranes, which are the main entry points for many viruses. Studies suggest that IFITM proteins inhibit HIV-1 entry, but the underlying mechanism remains elusive. HIV-1 uses the CD4 cell surface molecule as the main receptor and CXC-chemokine receptor 4 (CXCR4) and CC-chemokine receptor 5 (CCR5) as co-receptors to facilitate entry into cells. X4-tropic HIV-1 uses CXCR4 and R5-tropic HIV-1 uses CCR5, and the capacity to use alternative co-receptors confers a wider cell tropism. In this study, Foster *et al.* investigated the role of IFITM proteins in the restriction of HIV-1 strains that have different receptor tropism and identified IFITM proteins as major effectors of the innate immune response.

Testing the infectivity of HIV-1 viral envelope (Env) pseudotypes as well as replication-competent clones, the authors first showed that X4-using viruses had a greater sensitivity to IFITM2 and IFITM3 than R5 viruses, whereas R5 viruses were more sensitive to IFITM1, which suggests that co-receptor usage of the Env proteins determines restriction by the different IFTIM proteins. Furthermore, the observed IFITM inhibition phenotype correlated with the differential cellular localization of the IFITM proteins, as R5 viruses were sensitive to surface-restricted IFITM2 and IFITM3, and restriction by IFITM2 in a CXCR4 context was abolished following the relocalization of IFITM2 to the cell surface. Thus, surface-expressed IFITM1 restricts R5 viruses, whereas IFITM2 and IFITM3 that are localized to endosomal compartments inhibit X4 viruses. These findings suggest that X4 and R5 HIV-1 isolates may fuse in different subcellular compartments and that sensitivity to the different IFITM proteins depends on the route of virus entry.

The authors noticed that several viruses were almost completely resistant to IFITM protein-mediated restriction, and they identified that these viruses were transmitted founder viruses (the single viral variant that establishes a systemic infection after transmission). Interestingly, they found that consensus molecular clones of these viruses from the same infected individual isolated 6 months after infection exhibited an increased sensitivity to IFITM2 and IFITM3. An analysis of the transmitted founder viruses and their 6-month clones revealed amino acid changes in Env, although these mutations were not shared between the different pairs. The authors hypothesized that amino acid changes in Env during the transition from acute to chronic infection are associated with IFITM-mediated restriction. Importantly, in three of the six pairs, the amino acid mutations in Env of the 6-month clones were previously identified to mediate the evasion of early neutralizing antibodies. Indeed, reversion of the amino acid mutations restored IFITM resistance. As all but one of the virus pairs were R5 tropic, the authors tested the restriction phenotype in the presence of limiting surface CD4 levels. They showed that entry inhibition rendered the transmitted founder viruses sensitive to IFITM2 and IFITM3, whereas CD4 neutralization had no effect on the 6-month variants. The authors argued that the engagement of the transmitted founder virus with surface CD4 is the primary determinant for their IFITM resistance, and that mutations in Env due to immune pressure affect the cellular entry route and lead to IFITM2 and IFITM3 restriction.

Previous studies suggested that founder viruses are much less sensitive to IFN-I than virus isolates from the same individual at later time points during infection. Indeed, the authors showed that transmitted founder viruses exhibited weak sensitivity to IFN-1 treatment and that knockdown of any of the IFITM proteins had no effect. By contrast, depletion of IFITM2 and IFITM3, but not IFITM1, rescued the IFN sensitivity of 6-month viral variants in $CD4^+$ T cells. This suggests that the resistance of transmitted founder viruses to IFITMs contributes to the observed weak sensitivity to IFN-1, and that IFN-1 sensitivity increases after transmission owing to antibody-escape mutations in Env. In summary, the data implicate IFITM resistance as an essential viral attribute for HIV-1 transmission.

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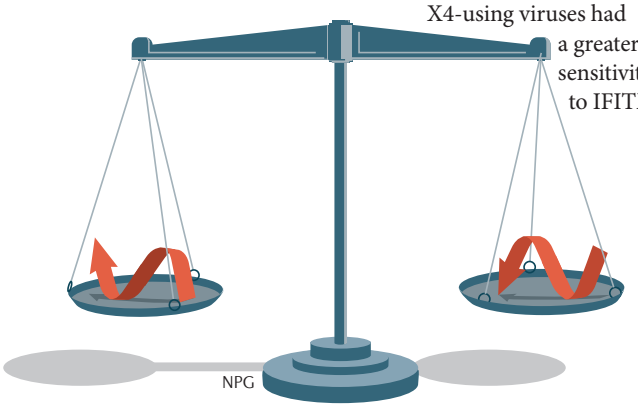

ORIGINAL ARTICLE Foster, T. L. *et al.* Resistance of transmitted founder HIV-1 to IFITM-mediated restriction. *Cell Host Microbe* http://dx.doi.org/10.1016/j.chom.2016.08.006 (2016)