MILESTONE 17

A battle between HIV and host

Numerous positively acting cellular factors and pathways support HIV replication, but in the 1990s evidence emerged that suggested that cells express dominantly acting factors that suppress HIV replication. For instance, HIV replication is affected by the animal origin of target cells and requirements for the viral accessory genes *vif* and *vpu* vary significantly between human cell lines. These observations hinted that primate cells express antiviral proteins (termed restriction factors) that block infection. The existence of restriction factors has important implications for understanding viral replication and pathogenesis, host range and HIV evolution, and for developing animal models.

In 2002, Sheehy et al. reported the isolation of a human gene that inhibits HIV-1 infection and is suppressed by the viral Vif protein—the first identification of an HIV restriction factor. In this initial report, a subtracted cDNA screen using cells that were permissive and non-permissive to infection by *vif*-deficient HIV-1 identified the human *APOBEC3G* gene as responsible for suppression of *vif*-deficient HIV-1 infection. Subsequent studies determined that APOBEC3G can restrict HIV-1 by incorporating itself into nascent virions through its RNA-binding activity and subsequently hypermutating newly synthesized viral DNA through its cytidine deaminase activity, leading to a catastrophically altered nucleotide sequence. It was also found that Vif–APOBEC3G binding leads to degradation of the restricting factor, enabling HIV-1 to circumvent this intrinsic immune response.

This initial study represents an important milestone in HIV/AIDS research, as it revealed an integral part of the host's first line of defense against HIV and suggested that further HIV restriction factors might exist.

APOBEC3 proteins do not alone account for the observed infection restriction phenotype in non-permissive cells. Since the discovery of APOBEC3G, numerous restriction factors that target diverse components of HIV-1, HIV-2 and SIV during various stages of their life cycles have been identified. For instance, identification of the monkey TRIM5α and TRIMCyp proteins in 2004 that restrict HIV through interactions with the viral capsid revealed that this class of molecules is responsible for the majority of restriction phenomena in mammalian cells following virus entry. Later, the discovery of tetherin (also known as BST2), a transmembrane protein, revealed a crucial function of the lentiviral *vpu* gene. In the absence of *vpu* expression, tetherin physically tethers nascent virions to the surface of infected cells and the virions are subsequently internalized into endosomes, thus preventing onward transmission.

Similarly, an important function of the HIV-2 (and SIV) Vpx accessory protein was elucidated through the discovery of SAMHD1, a deoxynucleotide triphosphohydrolase that limits reverse transcription of incoming viral RNA genomes: the viral Vpx protein induces ubiquitin–proteasome-dependent degradation of SAMHD1.

More recently, further restriction factors with distinct or unknown mechanisms of antiviral activity have been implicated as having a role in the outcome of initial HIV infections (for example, Mx2, SERINC3 and SERINC5, and ZAP), highlighting the important and complex involvement of restriction factors in the life cycle of HIV and in the evolutionary battle between host and virus. Indeed, a major raison d'être for lentiviral accessory proteins is to remove or displace host antiviral proteins.

During this evolutionary battle, humans have not emerged as the victors, as HIV-related illnesses cause thousands of deaths each year. HIV has an extraordinary degree of genetic plasticity that has enabled the virus to adapt to new host proteins when crossing species barriers and during the evolutionary arms race. Despite HIV's ability to evade host restriction factors, the discovery of these factors and understanding of how they interface with viral accessory proteins provide remarkable insight into the evolution of HIV. Their discovery also provides targets for new antivirals and valuable knowledge in the development of primate animal models for HIV/AIDS, which may lead to HIV losing the battle.

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> “The existence of restriction factors has important implications for understanding viral replication and pathogenesis, host range and HIV evolution, and for developing animal models”

ORIGINAL ARTICLE Sheehy, A. M., Gaddis, N. C., Choi, J. D. & Malim, M. H. Isolation of a human gene that inhibits HIV-1 infection and is suppressed by the viral Vif protein. *Nature* **418**, 646–650 (2002)
FURTHER READING Simon, V., Bloch, N. & Landau, N. R. Intrinsic host restrictions to HIV-1 and mechanisms of viral escape. *Nat. Immunol.* **16**, 546–553 (2015)