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Tracking the birth of an evolutionary arms race between HIV-like viruses and primate genomes

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Using a combination of evolutionary biology and virology, scientists at Fred Hutchinson Cancer Research Center have traced the birth of the ability of some HIV-related viruses to defeat a newly discovered cellular-defense system in primates.

The research, led by Michael Emerman, Ph.D., a member of the Hutchinson Center's Human Biology and Basic Sciences Division, and Harmit Malik, Ph.D., a member of the Center's Basic Sciences Division, was published online Jan. 26 ahead of the Feb. 16 print issue of *Cell Host & Microbe*.

The work, which also involved researchers in the Hutchinson Center's Computational Biology Program, hinges on the recently discovered cellular-defense protein called SAMHD1, which protects some key cells of the immune system from infection by HIV-1. The protein likely accomplishes this by reducing the available nucleotides, or DNA building blocks, the virus needs for replicating. In response, some viruses related to HIV-1, such as HIV-2 and some simian immunodeficiency viruses that infect other primates, produce a protein called Vpx that binds to SAMHD1 and targets it for destruction.

HIV-1, however, does not encode Vpx, but it does encode a related protein called Vpr. Emerman and colleagues tried to address the question of whether HIV-1 lost the ability to degrade SAMHD1 or whether this

ability was gained only in the minority of lentiviruses that encode a Vpx protein.

To distinguish between these possibilities, the researchers tested both Vpx as well as the related Vpr proteins from a panel representing all currently known primate lentiviruses for their ability to bind and degrade SAMHD1. When the phylogenetic history, or evolutionary relatedness, between these two viral proteins was mapped on top of their functions, the researchers found that SAMHD1-degrading ability was acquired first by the Vpr protein before the Vpx protein was even "born."

This new function occurred only once, in a single evolutionary lineage representing three of eight currently known primate lentivirus types. "This means that the ability of lentiviruses to degrade primate SAMHD1 is a newly acquired trait," Emerman said. "However, HIV-1 does not have the capacity to degrade SAMHD1 because its Vpr gene derived from a lineage of viruses in primates that never evolved to gain this function."

The researchers also found that Vpr/Vpx proteins have highly species-specific abilities to degrade primate SAMHD1. Thus, while a lentivirus can degrade SAMHD1 within a single primate species, it cannot bind and degrade the SAMHD1 protein from a more distantly related species. The specificity of the virus for its particular host and the fact that SAMHD1 degradation was an evolutionary novelty among lentiviruses suggests that SAMHD1 from some primates is locked in an "evolutionary arms race" with Vpx/Vpr proteins.

Such genetic tugs of war exemplify what is known among evolutionary biologists as the Red Queen Principle, a phrase borrowed from the Red Queen in Lewis Carroll's "Through the Looking Glass" that refers to the paradox of running as fast as you can just to stay in place. "Red Queen conflicts" typically put pressure on both sparring partners to continually

evolve new ways to outsmart and overcome each other just to stay in the game. In this case, the host proteins evolve to evade degradation by the newly evolved viral proteins.

To assess molecular signatures of these evolutionary arms races, first author Efrem Lim, a graduate student in Emerman's lab, compared the evolutionary rates of SAMHD1 across primate evolution. He found that prior to 23 million years ago, there was very little evidence for rapid evolution of SAMHD1. In contrast, SAMHD1 proteins in Old World monkeys that harbor Vpr/Vpx-containing lentiviruses have evolved rapidly for millions of years.

"We have not only recreated the birth of SAMHD1-degrading activity in these viruses but also have captured the immediate evolutionary consequence on the host genes they antagonize," said Malik, an evolutionary geneticist. "While such arms races between viruses and host genomes have been documented previously, this is the first instance where the beginning of the Darwinian arms race has been captured in both viral and primate genomes."

Emerman, a virologist, speculates the research may have direct implications for HIV-1 and AIDS. "It is possible that HIV-1 is so pathogenic because it needs to grow rapidly in order to compensate for the lack of the ability to deal with SAMHD1," he said.

Provided by Fred Hutchinson Cancer Research Center

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