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MILESTONE 6

Monkey insights

In 1985, following fast on the heels of the identification of HIV-1, researchers at Harvard and at the New England Regional Primate Research Center isolated virus from captive rhesus macaques in the center's colony that displayed symptoms of an immunodeficiency syndrome similar to AIDS in humans. Like HIV-1, the isolated virus—originally named STLV-III and now called simian immunodeficiency virus, or SIV—was tropic for $CD4^+$ T cells, budded from cells as viral particles and killed infected cells in culture. The findings, coupled with those of a companion study by the same researchers that demonstrated that antibodies in AIDS patients recognized SIV proteins, provided some of the first direct evidence that HIV-1 has a primate ancestor (MILESTONE 7).

Within months, these researchers formally demonstrated that the virus they had isolated from macaques (and now called SIV_{mac}) caused immunodeficiency in infected animals. By recapitulating in macaques symptoms seen in humans—including wasting, opportunistic infections and $CD4^+$ T cell depletion—the study provided experimental proof of concept that a virus causes AIDS.

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Soon after, distinct SIVs were identified that infect other nonhuman primates, including chimpanzees, African green monkeys, sooty mangabeys, gorillas and other macaque species, lending insights into the origins of HIV-1 in humans. Not all SIVs are pathogenic in their natural primate hosts, however, so the ability of SIV_{mac} to induce an AIDS-like illness in rhesus macaques made it a vital experimental tool to model HIV-1 infection and pathogenesis in animals.

Yet, studies later concluded that SIV_{mac}, unlike other SIVs, is not found in the wild. Instead, it is believed to have been generated as a function of experimentally inoculating captive rhesus macaques with SIV-infected tissue from sooty mangabeys. SIV_{smm}, which infects sooty mangabeys, is also likely the ancestor of HIV-2, a human retrovirus related to both SIV and HIV-1 (MILESTONE 7).

In spite of its lab-based origins, and some differences in disease progression in macaques as compared with humans, SIV_{mac} has become a cornerstone of HIV-1 research. But antigenic differences between the envelope (Env) glycoproteins of SIV and HIV-1, which allow the virus to bind and enter $CD4^+$ T cells, preclude the direct testing of human vaccines targeting HIV-1 Env in monkeys. In 1996, the development of chimeric simian-human immunodeficiency viruses (SHIVs) that caused AIDS-like disease in rhesus and pigtailed macaques overcame this hurdle. Whereas earlier SHIVs had not induced disease, serial passaging of SHIVs through macaques resulted in highly virulent viruses that caused rapid $CD4^+$ T cell loss and death of infected animals. The chimeric viruses incorporate the genes encoding Env and other regulatory factors from HIV-1 within an SIV backbone, thereby enabling the testing of vaccines and drugs in monkeys that target HIV-1 Env and block its role in viral infection and disease, which was previously not feasible.

These early and invaluable efforts characterizing SIV and AIDS in monkeys not only helped inform subsequent studies of HIV pathogenesis and treatment, but also shed light on the cross-species transmission patterns that gave rise to HIV-1 and related viruses.

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