HIV can remain “hidden” in a latent form for years, even after long-term suppression with highly active antiretroviral therapy. Moreover, viral drug resistance represents a formidable problem, creating an urgent need for new classes of antiretrovirals.

HIV begins its assault by injecting its core, which contains single-stranded RNA, into a host cell. Once inside, the viral RNA is converted into double-stranded DNA—a process known as reverse transcription—and the original viral RNA is degraded. Another enzyme, integrase, mediates the final step of the genome conversion, where the viral double-stranded DNA slips into the host’s DNA, allowing it to take advantage of the host cell’s genetic machinery to replicate and propagate itself.

During these early steps of infection, the virus relies heavily on its host cell to lend a helping hand, which makes it particularly vulnerable to antivirals and host defense mechanisms.

To identify cellular processes that participate during this critical time period, Young and his collaborators disrupted the function of individual genes in the genome of host cells. They then screened the mutagenized cells for their ability to resist infection with murine leukemia virus (MLV), a virus often used as a convenient, harmless stand-in for HIV.

Their experiments revealed a previously unknown regulatory step during MLV and HIV infection that uses sulfonation—a type of chemical modification—to boost the production of new viral particles. When sulfonation was impeded genetically or through chemical inhibitors during or shortly after viral DNA integration into a chromosome, the virus’s ability to reproduce was comprised. A closer look revealed that sulfonation was required to fully activate the viral long terminal repeat (LTR) promoters that flank the viral genome. LTRs function as regulatory regions that interact with cellular and viral factors to trigger gene expression as well as production of the viral genomes that are packaged into the next generation of virus particles.

This discovery might open up new avenues for the development of drugs that specifically interfere with this newly revealed aspect of retroviral biology and render host cells resistant to HIV infection.

For more information, please visit salk.edu/faculty/young.html

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“One of the major long-term goals of our work is to uncover the cellular protein machinery required for replication steps of viruses such as HIV, the cause of AIDS. Knowledge of this machinery provides brand-new insights into the cell biology of virus infections and could suggest new broad-spectrum antiviral approaches.”