Researchers find new way to defeat HIV latency
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Researchers at UC Davis Health, together with colleagues at UC San Francisco and the University of North Carolina at Chapel Hill, have found that increased crotonylation, an epigenetic mechanism that governs gene expression, might be the key to making HIV come out of hiding and become susceptible to anti-HIV drugs. Their study is published in *The Journal of Clinical Investigation*.

"Histone crotonylation regulates HIV latency," said UC Davis associate project scientist Guochun Jiang, first author on the paper. "If we can modulate that, the virus can be more efficiently flushed out."

To better understand this mechanism, the team focused on an enzyme called ACSS2, which plays an important role in fatty acid metabolism in the gut. HIV has often been linked to impairment of lipid metabolism, making ACSS2 a promising potential target for an HIV cure.

To test it out, the researchers studied peripheral blood samples from HIV-infected patients and several HIV latency cell models. Activating the ACSS2 enzyme increased viral transcription manifold. The results from patient samples were particularly encouraging.

"We examined well-characterized cell models of HIV latency and immune cells from HIV patients who had been undergoing antiretroviral therapy and had undetectable viral loads," Dandekar said. "In those samples, we were able to disrupt the HIV silencing by inducing histone crotonylation."

To further validate the results, the researchers
treated samples with an ACSS2 inhibitor, which reduced detectable virus levels, highlighting the important role of deacetylation in establishing HIV latency.

One of the more intriguing findings in the study was that increasing histone crotonylation works synergistically with other known anti-HIV latency molecules, such as the protein kinase C agonist PEP005 and the HDAC inhibitor vorinostat. Dandekar and her colleagues are now searching for more molecules that attack viral latency to develop an overall strategy of combining therapeutic agents to compel HIV expression.

"We are looking for synergistic disruption, by combining histone crotonylation with other mechanisms to reactivate HIV," Dandekar said. "This research positions us to screen and identify small molecules, which can be optimized to carry out HIV modification."


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