PRESS RELEASE

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The Wistar Institute and University of Pennsylvania Scientists Identify Potential Target Gene within Certain HIV Reservoir Cells

Drs. Lieberman, Collman, and Co-Authors Link RSAD2/Viperin Gene with Certain Chronically HIV-Infected Cells

PHILADELPHIA — (October 3, 2024) —New findings could lead to different research tactics for scientists investigating a cure for HIV. Results from The Wistar Institute's Lieberman lab, led by Hilary Koprowski, M.D., Endowed Professor Paul M. Lieberman, Ph.D., and researchers at the Perelman School of Medicine's Center for AIDS Research and center director Ronald G. Collman, M.D. — have identified the RSAD2/Viperin gene as a potential HIV treatment target within certain HIV reservoir cells. Their The results were published in the paper, "HIV-induced RSAD2/Viperin supports sustained infection of monocyte-derived macrophages," in the *Journal of Virology*.

HIV does not have a cure because there is no known method — yet — for eliminating the virus from the body once infected. Although HIV can be managed with antiretroviral therapy (ART), the virus persists in infected cells throughout the body, called "HIV reservoirs." Reservoirs not only serve as the main barrier in HIV cure research, which focuses in large part on strategies to destroy these HIV reservoirs, but also contribute to chronic inflammation and comorbidities in people living with HIV.

A certain type of immune cell — myeloid cells, including macrophages and microglia — often serves as an HIV reservoir because, unlike other cells infected with HIV, these cells tend not to be killed by HIV's viral replication. Due to their comparative longevity as reservoirs and prevalence within the nervous system, HIV-infected macrophages often cause neurocognitive complications in people with HIV that develop even despite antiretroviral treatment (ART).

Lieberman and Collman, joined forces to research the genetics of macrophages that might play a role in maintaining the HIV reservoir status quo. Their investigation revealed a surprising candidate in the gene RSAD2/Viperin — which usually *fights* viruses. In HIV-infected macrophages, RSAD2/Viperin expression was quite high compared both with controls and HIV-infected CD4+ T cells (the other major type of cell that can become a viral reservoir of HIV).

RSAD2/Viperin is a gene associated with interferon response, and typically, both the gene itself and the interferons that trigger its activation have antiviral effects. However, certain interferons have been found to play paradoxical roles in chronic HIV by enabling the virus' persistence, and upon finding RSAD2/Viperin's elevated expression in reservoir macrophages, the researchers hypothesized that the gene must be abetting HIV's continued presence within these cells.

To test this, the research team used the siRNA method to target and reduce RSAD2/Viperin's expression in macrophages infected with HIV. Once they reduced the gene's expression, several measures of HIV's presence and activity fell, including viral transcripts, p24 protein production, and multinucleated giant cells (another indicator of active viral activity). Reduced RSAD2/Viperin also altered histone modification of HIV genomes — that is, the control of HIV's latency by chromatin and epigenetic factors. These findings suggest a novel role for RSAD2/Viperin in regulating chromatin that otherwise might suppress HIV replication during latency.

"Looking closely at RSAD2/Viperin in these HIV-infected MDMs, we've identified yet another paradox of HIV infection," said Lieberman, program leader, Genome Regulation and Cell Signaling Program, Ellen and Ronald Caplan Cancer. "Our data show that while, yes, this is an antiviral gene that can come to the body's defense against the virus at first, it also seems to maintain HIV's ability to persist as a chronic infection. That makes RSAD2/Viperin a compelling candidate for further research and possible targeting of HIV reservoirs — which is critical to future cure research."

"We've come to understand yet another facet of chronic HIV infection's complexity," agreed Collman. "We're hopeful that these findings will be helpful as the field continues to pursue possible therapeutic interventions that would eliminate the viral reservoir in the search for an HIV cure, or reduce negative consequences of infection that can persist even despite effective therapy, such as neurocognitive decline."

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