Why current drug therapies don't restore the immune systems of some HIV patients

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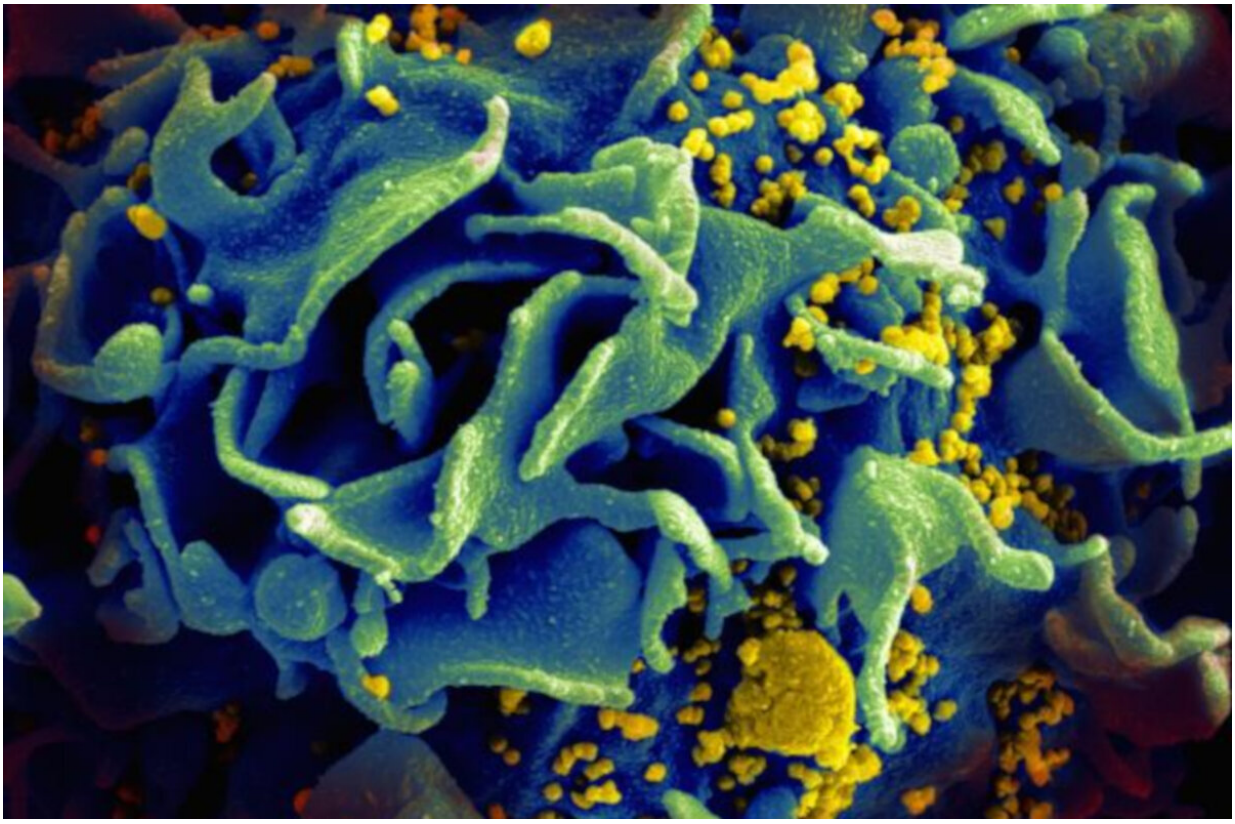

Microscopic image of an HIV-infected T cell. Credit: NIAID

A new study indicates that protein kinases, which initiate the process that erodes the body's immunity, significantly contribute to the immunodeficiency in HIV patients. Drugs that block these protein

kinases may offer a solution to treating HIV patients whose immunity is not restored by antiretroviral therapy.

HIV infections are treated with antiviral drugs which effectively prevent the disease from developing. While pharmacological HIV therapy has advanced considerably, the virus cannot be entirely eliminated from the body with currently available drugs.

However, in roughly one-fifth of HIV patients the immune system does not recover as expected: the quantity of CD4 T cells, reflecting the status of the immune system, remains low even when the quantity of HI viruses in blood is suppressed to very low levels or below the measurement threshold. In such patients, indications of chronic immune activation, which erodes the immune system, can be detected.

In cooperation with the University of Erlangen-Nuremberg in Germany, researchers at the University of Helsinki have already shown that the Nef protein, a central factor associated with the HI virus, can continue low-level production in the patient's tissues for a long time even after viral multiplication is successfully suppressed. Important to this immunity-eroding activity are extracellular vesicles generated by Nef, circulating in blood and promoting chronic immune activation.

In a new study, Professor Kalle Saksela's research group has discovered an intracellular mechanism through which the chain of events associated with immune activation is initiated.

The study was published in the *Journal of Virology*.

"The new findings demonstrate that the Nef protein kicks off this harmful chain of events via cellular signaling: it activates protein kinases of the Src family, which leads to the activation of Raf and MAPK protein kinases. As these two protein kinases are activated, the

production of extracellular vesicles, mediated by them, begins," Saksela explains.

Protein kinase inhibitors as a new treatment option?

Pharmaceutical agents that inhibit Src, Raf and MAPK protein kinases are already in clinical use, and the researchers at the University of Helsinki investigated their utility as well.

Studying the drugs in tissue cultures, they observed that it was possible to entirely prevent the production of inflammatory extracellular vesicles caused by the Nef protein using the same drug levels as in the current clinical use of protein kinase inhibitors.

"Our findings make it possible to explore novel therapies without delay in patients whose immunodeficiency is not reversed to a sufficient degree with current antiretroviral therapies. The repurposing of kinase inhibitors for treating HIV infection appears to be a very promising way of solving this significant medical challenge," Professor Saksela states.

In recent years, roughly 150 new HIV infections have been diagnosed in Finland annually. Throughout the 2000s, the number of new infections per year has remained under 200. In 2018 approximately 38 million people were estimated to be HIV positive, most of them in Africa.

More information: Zhe Zhao et al. HIV-1 Nef-induced secretion of the proinflammatory protease TACE into extracellularvesicles is mediated by Raf-1, and can be suppressed by clinical protein kinase inhibitors, *Journal of Virology* (2021). DOI: 10.1128/JVI.00180-21

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