Another step towards a cure Vitamin A transporter reactivates latent HIV

Human immunodeficiency viruses (HIV) are insidious. They can evade the immune defence and antiviral drugs by becoming "latent". In this state, they are largely invisible and unassailable. As long as these dormant viruses persist, there is no cure for HIV/AIDS. However, researchers at Ulm University Hospital have discovered a new way to reactivate latent HI viruses. This is made possible by the body's own protein RBP4, a transporter for vitamin A – and provides a new starting point for HIV cure approaches.

"We have discovered a natural active substance that can 'startle' 'hidden' HI viruses, making them vulnerable to the immune system," says Professor Frank Kirchhoff, Director of the Institute of Molecular Virology at Ulm University Hospital. The natural active agent is the retinol-binding protein RBP4, which is known as a vitamin A transporter. Kirchhoff coordinated the study, which was recently published in the highly renowned journal "Signal Transduction and Targeted Therapy", which is part of the Nature group.

The international research group, including scientists from the USA, Vienna and Ulm, subjected the human blood peptidome to a comprehensive screening. A large number of small proteins and peptides from human blood were analysed for their ability to activate latent HIV, using a model cell line for latently HIV-infected T lymphocytes. These immune cells play a key role in defence, but are also preferentially infected by the HI virus. "Although the virus is inactive in the latent state, the immune cells carry the viral genetic material and can start to produce infectious viruses again even after long time periods," explains Dr Chiara Pastorio, postdoc at the Institute of Molecular Virology. The scientist, who was recently awarded the Jutta and Wilfried Trumpp Foundation Prize of the International Graduate School in Molecular Medicine Ulm, is the first author of the study.

In cooperation with a US research group, the team was also able to show that latency reversal with RBP4 is successful in cells from HIV-positive people who had an undetectable viral load under long-term therapy. Physiological concentrations of RBP4 – those naturally present in the human body – were sufficient to awaken the "dormant" viruses. The international research team also discovered that only the vitamin A carrier loaded with retinol can activate the latent viruses, whereas the unloaded transporter protein was inactive. However, retinol or retinoic acid itself was not sufficient for latency reversal. Instead, the virologists demonstrated that activation of a special signalling pathway (NF-κB), which plays a key role in immunological and cell division processes and is amplified by other signals, is critical for this effect.

"With the retinol-binding protein RBP4, we have found a natural factor that may be capable of reactivating latent HIV reservoirs. This is a further step towards a possible cure for this insidious disease," emphasise the Ulm researchers. The discovery could open new possibilities for the "shock-and-kill" strategy, which aims to activate "sleeping" viruses so that they can be eliminated by the immune system. The project, which offers new therapeutic perspectives, was funded by the German Research Foundation through the Collaborative Research Centre (SFB) 1279 "Use of the human peptidome to develop new antimicrobial and anti-cancer therapeutics". Further support came from partner institutions in Philadelphia and Vienna, as well as from the German Centre for Neurodegenerative Diseases (DZNE).

Publication:
Pastorio, C., et al. Retinol Binding Protein 4 reactivates latent HIV-1 by triggering canonical NF-κB, JAK/STAT5 and JNK signalling. Sig Transduct Target Ther 10, 326 (2025). https://doi.org/10.1038/s41392-025-02424-3.

Press release

09-Oct-2025
Source: Ulm University

Further information

- Ulm University