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PRESS RELEASE

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The flaws of HIV

Discovery of a new antiretroviral protein, SERINC5

HIV is a complex virus. Though research carried out over the past 30 years has helped to understand most of its biology, its infectious process still contains grey areas. One of these has to do with the exact role played by Nef, an HIV accessory protein, during infection. Without it, the weakened HIV virus loses much of its pathogenic ability. It was therefore necessary to identify the exact mechanism by which HIV infectivity is destroyed, and which cell protein is responsible. Researchers from the Universities of Geneva (UNIGE) and Trento have deciphered this important flaw in the virus arsenal of attack by identifying the SERINC5 protein. This discovery can be read in Nature.

To defend themselves against viral infections, our cells use a variety of biological weapons. But viruses mutate faster than the eukaryotic cells we are made of, that is why they have so-called «countermeasure» proteins that allow them to divert the effectiveness of our immune system. The Nef protein appears to be one of them. It is indeed known to play a fundamental role in HIV replication and the development of AIDS. It is in fact capable of enhancing the infectivity of viral particles.

«When the virus replicates in a cell, it utilizes Nef in order to neutralize a specific protein whose function is to protect this cell against HIV. Our goal was therefore to identify this unknown protein to understand why some cells are more susceptible to HIV than others,» explains Federico Santoni, co-author of the study, bio IT specialist and computational biologist within Prof. Stylianos Antonarakis' research group at the Faculty of Medicine of UNIGE.

Finding the protein that defends our cells

The researchers examined cell lines from different organs in order to identify those that were most and least likely to be infected with HIV. To do so, they removed Nef from the virus – the manipulated virus is called HIV–Nef – to determine which microbiological elements, usually inhibited by Nef, could explain this greater or lesser sensitivity to infection. The scientists found that in the least sensitive to HIV–Nef cell lines, a membrane protein called SERINC5 was highly expressed, while it was not – or almost not – expressed in cell lines susceptible to the virus.

Massimo Pizzato, an HIV virologist at the University of Trento and coordinators of the study, details how Nef is able to inhibit this protein and favor HIV infection: «This mechanism takes place in two stages. When HIV is Nef protein free, it successfully penetrates a cell to infect it. The virus then replicates normally. But when it comes out again to continue its destructive work in another cell, it takes away a

part of the infected cell membrane to build its own membrane. With it, it also carries the SERINC5 protein found on the membrane of the attacked cell. From then on, when the virus tries to infect a second cell, SERINC5 acts as an alarm signal and warns the cell that the pathogen is coming. The virus is therefore no longer able to penetrate the cell.» Nef, by inhibiting SERINC5, is therefore a crucial element for HIV infectivity.

Strengthening SERINC5

Usually, Nef is able to neutralize SERINC5. Nevertheless, the study shows that if SERINC5 is highly expressed, Nef is no longer able to counteract it, which greatly reduces the virus infectivity. The goal is therefore to reverse the balance of power to favor SERINC5. «SERINC5 is not the first antiretroviral factor discovered. For sure, we have identified a new element, but, most importantly, we deciphered a mechanism that works very differently from the others. Moreover, contrary to the antiretroviral factors previously discovered, which are activated by interferon (a protein substance produced by certain cells of the immune system in response to a pathogen), SERINC5 is expressed continuously in all cells of our immune system» states Federico Santoni.

“We now need to carry on working on this defensive mechanism to evaluate how to exploit this flaw in new therapeutic strategies, either by strengthening the presence of SERINC5 in all cells, or by modifying its structure to enable it to escape Nef inhibition. We have some long-term research ahead of us!”

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