HIV tamed by designer 'leash'

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Researchers have shown how an antiviral protein produced by the immune system, dubbed tetherin, tames HIV and other viruses by literally putting them on a leash, to prevent their escape from infected cells. The insights reported in the October 30th issue of the journal *Cell* allowed the research team to design a completely artificial protein -- one that did not resemble native tetherin in its sequence at all -- that could nonetheless put a similar stop to the virus.

"Tetherin is essentially a rod with anchors at either end that are critical for its function," says Paul Bieniasz of Howard Hughes Medical Institute and the Aaron Diamond AIDS Research Center at The Rockefeller University. Either one of those anchors gets incorporated into the envelope surrounding HIV or other viruses as they bud through the plasma membrane of an infected cell. "One anchor gets into the virus and the other in the cell membrane to inevitably form a tether.

"We showed we could design a completely different protein with the same configuration - a rod with lipid anchors at either end - and it worked very well," he continued. The finding helped to confirm that tetherin is capable of acting all on its own, he added.

They also explain tetherin's broad specificity to protect against many viruses. "It is just targeting lipids," Bieniasz said. "It's not about viral proteins." That's conceptually important, he continued, because there is no specific interaction between tetherin and any viral protein, which makes it a more difficult problem for viruses to evolve resistance. Rather than tweaking an existing protein-coding gene, "the virus has to

make the more difficult adjustment of acquiring a new gene antagonist [of tetherin]."

Unfortunately, many viruses have managed to do just that. In the case of HIV, a protein called Vpu counteracts tetherin. They now show it does so by sequestering the host protein, which prevents its incorporation into the virus. The new insight into tetherin's and Vpu's modes of action, however, may lead to the development of Vpu blockers that could free up the innate host defense and inhibit HIV's spread, Bieniasz suggests.

Bieniasz said there is some possibility that tetherin exists in different forms that might explain differences among people in the progression of HIV or other viral infections. However, the only common variation they've seen in the tetherin gene so far does not appear to affect its function. The tetherin sequence does vary quite a lot from one species to the next, he added, as is often the case due to strong selection when host defense genes meet viral inhibitors.

To place the findings in context, Bieniasz says it is worth noting that tetherin is encoded by just one of more than 900 genes that get switched "on" in response to interferon, a cell signaling protein of the immune system.

"There are hundreds of interferon-induced genes," he said. "The functions are known for only a very small number - less than a dozen. There are potentially a large number of antiviral mechanisms we still know nothing about."

Going forward, his team intends to look more closely at many of those others, and Bieniasz suspects more surprising mechanisms will be in store.

Source: Cell Press (news : web)