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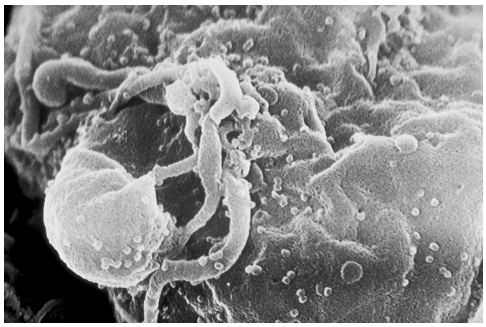
Protein wars

Vivienne Baillie Gerritsen

Face-to-face combat also exists at the molecular level. With time, animals have developed the means to fight off foreign bodies by way of a complex immune system. But it can be countered. Recently, it was discovered that the defensive effects of one protein (APOBEC3G) – found mainly in human T lymphocytes – could be wiped out by the actions of a second viral protein (VIF) which neutralises it. The net result is viral infection of human T lymphocytes. VIF belongs to Type 1 Human Immunodeficiency Virus (HIV-1) and seems to be crucial for the development of viral infection; whilst APOBEC3G, without the counter-effects of VIF, can ward off HIV-1 infection on its own. The great interest is that novel therapies developed around APOBEC3G and VIF should be of tremendous help in the endless struggle to design drugs which could fight off HIV-1 infection effectively.

APOBEC3G is found in human T lymphocytes and is predominantly a cytoplasmic protein, although some are found in the cell's nucleus. It is a cytidine deaminase nucleic acid-editing enzyme, and causes hypermutations in single-stranded DNA by deaminating cytidines. Consequently, while editing should be the source of text corrections, APOBEC3G happily creates errors – or mutations. It is not the only one of its kind but it is particular in that it has the ability to attack viral DNA – or more to the point: HIV-1 DNA.



Budding HIV on lymphocyte

Centers for Disease Control / C. Goldsmith

When HIV-1 invades a T lymphocyte, it uses the host cell and part of its machinery to reproduce virions. Mature virions are then released. In doing so, they kill the host T lymphocyte and go on to invade and infect other T lymphocytes. Thanks to APOBEC3G however, some lymphocytes do not give HIV-1 infection a chance. HIV-1 is a retrovirus, i.e. its viral RNA must first be transcribed into viral DNA. The viral DNA is then inserted into the host DNA, and the host quite innocently synthesizes copies of the viral proteins. The new viral proteins and novel copies of viral RNA are then used to make new virions. What APOBEC3G does is slip into the nascent virions to hitch a ride. And each new 'infected' virion is then released from the host cell.

APOBEC3G is not inactive once the virions have infected a T lymphocyte. During the process of viral reverse transcription, the protein spots runs of cytosine (C) nucleic acids (at least two cytosines in a row) in the newly synthesized minus viral DNA. It heads straight for them and positions itself on the nucleic acid to insert an error by swapping cytosine for uracil (U) in the nascent transcript, thus causing a guanine (G) to adenine (A) mutation in the viral DNA plus strand.

Such an action could bring about a number of consequences. The mutations could serve to disrupt a specific viral protein, resulting either in non-viable or non-infectious virions. Or they could create such havoc on the viral DNA that all novel production of virions would be

impossible. It turns out that this is precisely what happens. G to A mutations are inserted all along the viral DNA and literally break up the viral code. The resulting virions are helpless, and infection grinds to a halt.

Humans infected by HIV-1 are at a disadvantage since the virus itself is armed against the doings of APOBEC3G. Not surprisingly, the HIV-1 genome is one of the most studied genomes to date. It sports only nine genes which code for proteins, one of which – VIF or virion infectivity factor – can neutralise the action of APOBEC3G in two ways. First, it interferes with the translation of APOBEC3G thereby stunting its synthesis and secondly it clings onto the protein and triggers off its breakdown via a proteolytic pathway involving a ubiquitin-dependent proteasome. There is not much that APOBEC3G can do. The end result is that it is given no chance to insert mutations into the virions' DNA, which can continue to infect the host's immune system.

APOBEC3G would have the power to invalidate HIV-1 infection were it not for the existence of VIF. The discovery is paramount. More must be done to understand in full the molecular processes underlying the action of APOBEC3G and that of VIF. And it is not an extravagant prospect to imagine the design of drugs which could interfere either with the binding of VIF to APOBEC3G, or with APOBEC3G degradation by VIF so that APOBEC3G continues to be a threat to HIV-1, causing irreparable damage to its DNA and thereby stunting the formation of new virions and the spreading of HIV. Better still, such drugs could serve to fight off diseases other than HIV-1; APOBEC3G is non-specific enough in its action to impede the folly of other retroviruses such as Hepatitis B or certain forms of leukaemia which are also caused by retroviruses. For the time being though, VIF is the craftier of the two; the trick is to push it into the back seat.

Cross-references to Swiss-Prot

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