IMMUNE EVASION

Overcoming host defences

The powerful anti-viral effects of the cytidine deaminase APOBEC3G (apolipoprotein B mRNA-editing enzyme, catalytic polypeptide-like 3G) can be counteracted by Vif (viral infectivity factor) — a protein encoded by HIV-1. The mechanisms by which Vif suppresses the host defence have remained poorly defined, but now three studies published in *Molecular Cell* and *Nature Medicine* have shown that Vif depletes cells of APOBEC3G, thereby preventing its anti-viral function.

Cells expressing endogenous APOBEC3G are 'non-permissive' for the production of fully infectious Vif-mutant virus, whereas cells deficient for APOBEC3G are 'permissive' for virus production. To elicit its anti-viral effect, APOBEC3G must be incorporated into Vif-mutant virion particles for transport to the virion's target cell. After entry into a new host cell, APOBEC3G deaminates cytidine residues in the viral DNA generated during reverse transcription, causing calamitous mutations to the viral DNA-replication intermediates.

In each of these new reports, APOBEC3G was found to be absent from virions that were generated in the presence of Vif and so its anti-viral potential was suppressed. Vif-mediated exclusion of APOBEC3G from virions was shown to occur independently of other viral proteins and to be associated with the depletion of APOBEC3G protein from the cell, although APOBEC3G messenger RNA levels were not reduced.

Pulse-chase radiolabelling studies carried out by all three groups showed that in the presence of Vif, the half-life of APOBEC3G was markedly reduced. This decrease in APOBEC3G protein levels was abrogated in the presence of proteasome inhibitors, indicating that Vif either targets APOBEC3G to the proteasome for degradation or enhances the natural turnover of the protein. In addition, using immunofluorescence, Marin *et al.* showed that APOBEC3G and Vif expression was restricted to separate cells in cultures co-transfected with APOBEC3G and Vif DNA, and that in the presence of protease inhibitors cells could express both proteins. These data provide further evidence to indicate that APOBEC3G is eliminated in a proteasome-dependent manner from cells co-expressing APOBEC3G and Vif.

Sheehy *et al.* and Marin *et al.* then showed that ubiquitylated APOBEC3G accumulates in the presence of Vif, implying that Vif enhances APOBEC3G turnover by inducing its ubiquitylation and thereby targeting it to the proteasome for degradation. By designing a series of Vif deletion mutants, Marin *et al.* determined that Vif contains two regions that are important for its effect on APOBEC3G, one of which has amino-acid sequence similarities with other molecules that target proteins for ubiquitylation and degradation, such as human suppressor of cytokine signalling 6 (SOCS6), and therefore this motif probably directs the ubiquitylation of APOBEC3G and its subsequent destruction. The other region of Vif that is crucial for APOBEC3G elimination was found to mediate the association of Vif with APOBEC3G.

Stopak *et al.* observed that levels of APOBEC3G were diminished in the presence of Vif even at the early time points of the pulse-chase radiolabelling studies, indicating that Vif might impair translation of APOBEC3G mRNA. They were able to confirm this in both *in vitro* translation assays and additional short-term radiolabelling studies, in which Vif had a dose-dependent inhibitory effect on APOBEC3G translation.

These studies have identified two mechanisms — inhibition of APOBEC3G mRNA translation and enhanced proteasomal degradation of APOBEC3G protein — by which the HIV-1 virulence factor Vif overcomes the anti-viral host defence provided by APOBEC3G. The combined effect of this bimodal action is that APOBEC3G protein is depleted from the host cell and therefore is absent from the virion particles generated. Further understanding of the molecular mechanisms by which Vif mediates these effects could lead to the generation of a new class of anti-viral drug that impedes Vif function.

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References and links

ORIGINAL RESEARCH PAPERS Stopak, K. *et al.* HIV-1 Vif blocks the antiviral activity of APOBEC3G by impairing both its translation and intracellular stability. *Mol. Cell* **12**, 591–601 (2003) | Sheehy, A. M. *et al.* The antiretroviral enzyme APOBEC3G is degraded by the proteasome in response to HIV-1 Vif. *Nature Med.* 5 October 2003 (doi:10.1038/nm945) | Marin, M. *et al.* HIV-1 Vif protein binds the editing enzyme APOBEC3G and induces its degradation. *Nature Med.* 5 October 2003 (doi:10.1038/nm946)

IN THE NEWS

Vatican in HIV row

A television documentary by the British Broadcasting Corporation (*Panorama — Sex and the Holy City*) has reported that the Roman Catholic church is claiming that condoms can not stop the spread of HIV. Cardinal Alfonso Lopez Trujillo, President of the Vatican's Pontifical Council for the Family, told the BBC that as "the AIDS virus is roughly 450 times smaller than the spermatozoan ... [it] can easily pass through the ... condom." Pope John Paul II opposes any form of contraception that breaks the link between sex and procreation. The Roman Catholic church teaches abstinence as the best way to prevent the spread of HIV. The Archbishop of Nairobi, Kenya, said that "AIDS ... has grown so fast because of the availability of condoms," which promote promiscuity (*Panorama*).

To counter these claims, the World Health Organization (WHO) refers to a study carried out in 2001 by the WHO and the United States National Institutes of Health, which showed that condoms are 90% effective against HIV/AIDS. The remaining 10% of cases of transmission are caused by incorrect use. Condoms are "essentially impermeable to particles the size of [sexually transmitted disease] pathogens" (Fadela Chaib, WHO). The Roman Catholic position is "dangerous when we are facing a global pandemic which has already killed more than 20 million people," said Chaib.

Meanwhile, in the United States, President Bush has received criticism over his stipulation that one-third of the funding for his anti-AIDS initiative is used to encourage sexual abstinence until marriage. An article in *The New York Times* said it "looks as if the administration is more interested in showing that it shares the Christian Right's sexual squeamishness than in fighting AIDS."

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