Tampering with transcription

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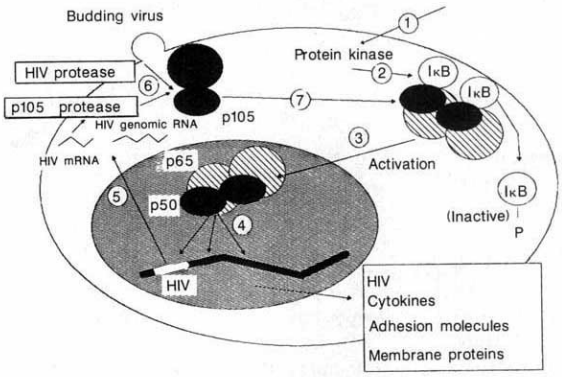
CONCEALED within a cell, the human immunodeficiency virus (HIV) quietly subverts a host that would otherwise seek to destroy it. Productive HIV infection reflects a delicate balance between the needs of the host cell and the demands of the virus. It is now clear that this balance has not been left simply to chance — two studies, one that appeared in last week's *Nature*[1], the other reported on page 709 of this issue[2], show that sophisticated strategies have evolved to alter cellular transcription and facilitate viral replication. Many cellular proteins contribute to the replication of HIV, including NF-κB, an inducible transcription factor that binds to regulatory sites in the HIV enhancer sequence and increases viral transcription after T-cell activation[3]. It now seems that NF-κB is also specifically induced during the course of infection[1], and that it may be regulated by a viral gene product, the HIV-1 protease[2].

Like all viruses, HIV is an intracellular parasite. Beginning with its entry into its host cell by way of the CD4 glycoprotein, the virus interacts with many cellular proteins to complete its life cycle. The importance of these host-cell factors became apparent during early attempts to isolate the virus. Propagation was much more successful when the host T cell was activated by mitogens[4,5], which causes an increase in NF-κB binding to DNA; and the two κB elements in the HIV-1 regulatory region, although not indispensable for replication[6], are responsible for the increase in stimulation through the enhancer sequence seen in activated T cells.

In cells infected by HIV, including T cells and some monocytes, NF-κB resides within the cytoplasm in an inactive form, complexed to an inhibitor, IκB. Cellular activation by mitogens or cytokines releases the active DNA-binding complex, which is composed of distinct DNA-binding (p50) and transactivation (p65) subunits (see figure). This process is regulated at several levels — phosphorylation by protein kinases, for example, causes IκB to disengage from the p50/p65 complex[7]. Another regulatory step probably involves the DNA-binding subunit of NF-κB. This protein is synthesized as a precursor of relative molecular mass 105,000 (M_r 105K) and requires processing to generate the active binding protein of M_r 50K.

Bachelerie and co-workers have now shown that infection by HIV stimulates binding of NF-κB to DNA[2]. In a promonocytic line, infection leads to a marked increase in NF-κB binding activity and function, raising the possibility that NF-κB has a part in perpetuating the infection and that viral genes activate NF-κB. Several mechanisms could account for the increase in binding activity; the induction of cellular protein kinases, transcriptional activation of p105 and/or p65, inhibition of IκB synthesis or activation of a protease might all serve this function. Rivière *et al.*[1] provide evidence for an intriguing possibility: the HIV protease, thought normally to regulate maturation of the virus by cleavage of the HIV polyprotein within budding forms, might also contribute to NF-κB activation. They have detected a smaller form of the processed p105 DNA-binding subunit. This smaller protein, of M_r 45K, is also generated by cotransfection with the HIV protease, and a potential aspartyl protease cleavage site has been identified which could give rise to this protein. Incubation of p105 NF-κB with the HIV protease *in vitro* also generates the protein. Normally, a yet undefined cellular protease is likely to serve this function.



Mechanism of NF-κB activation and its relationship to HIV infection. (1) Cells are activated by cytokines or mitogens. (2) Cellular protein kinases are induced, causing phosphorylation of IκB and other potential regulatory proteins. The phosphorylated form of IκB does not complex to p50/p65. (3) Dissociation of p50/p65 from IκB allows its translocation to the nucleus. (4) Nuclear NF-κB stimulates increased transcription of HIV and other cellular genes, including those responsible for cytokines, adhesion molecules and cell-surface glycoproteins. RNA (5) Viral RNA is synthesized, including messenger RNAs encoding structural proteins, such as the HIV protease, and genomic HIV RNA. (6) Activation of the HIV protease stimulates cleavage of the p105 precursor of the DNA-binding subunit of NF-κB. Infection or cellular activation could also induce cellular proteases, including the endogenous p105 protease. (7) The p50 DNA-binding subunit is incorporated into the p50/p65 complex.

These findings are an elegant example of the precision of viral/host cell interactions, and raise additional questions about the molecular activation of HIV during infection and the role of NF-κB. The HIV protease has been thought to be confined to the budding virus particle. This assumption must now be reassessed. Another possibility is that the virus particle can deliver sufficient protease to the cell to stimulate proteolysis of p105. At the same time, the possibility remains that HIV activates other cellular proteins, including protein kinases, cellular proteases or IκB, which regulate NF-κB.

Taken together, the observations raise the possibility that NF-κB maintains viral replication once it has been initiated. How might this occur? The most likely explanation is that NF-κB participates in the activation of a cellular gene required for later steps in the infectious cycle, and there is no shortage of cellular genes which could serve this function. The cytokine TNF-α, for example, stimulates NF-κB binding activity and HIV replication, and it has κB regulatory elements that regulate its expression. Although Bachelerie *et al.* found no extracellular TNF-α, the cytokine might act in an autocrine or intracrine fashion[8]. Many cellular genes could also code for proteins having this role, including other cytokines, growth factor receptors, adhesion molecules and membrane proteins which can be regulated by NF-κB. Possibly, it is not a single gene, but a set of coordinately activated host cell genes, which facilitates infection.

The alternative of NF-κB binding activity simply being a consequence of infection and having no active role in infection seems less likely. In addition to its association with HIV infection, the κB regulatory element has been found in many primate viruses and NF-κB is induced during their course of infection[9]; HTLV-I and Epstein–Barr virus, for example, contain specific viral transactivators which stimulate κB-dependent transcription by different mechanisms (refs 10 and 11; M.-L. Hammarskjold, personal communication).

Apparently, there is a common theme in infection by these different viruses which is not yet understood. As viral genes help to define critical steps in the regulation of cellular gene expression, these new insights may allow us to learn what the virus has already discovered. □

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