Control Protein for AIDS Virus Identified

Identification of a protein that activates expression of AIDS virus genes provides another potential way to attack the virus

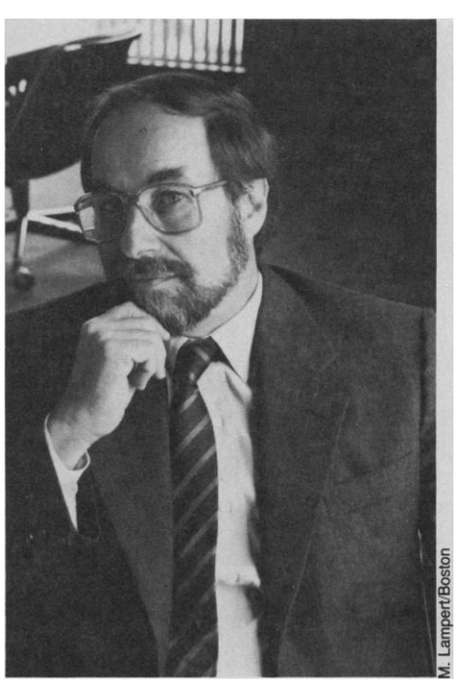
ALTHOUGH the AIDS virus infects many cell types it preferentially kills the T helper cells of the immune system. This helper cell loss is the underlying cause of the profound immune suppression in AIDS patients. In a recent development, researchers have taken a big step toward understanding what sets the lethal chain of events in motion.

Gary Nabel and David Baltimore of the Whitehead Institute for Biomedical Research in Cambridge, Massachusetts, have identified a protein, produced only by activated T cells, that turns on the AIDS virus genome, thereby enabling the virus to reproduce in—and kill—infected cells. The AIDS virus has the ability to persist in latent form in cells for many years. The current work, which is described in the 16 April issue of *Nature*, provides additional evidence that the normal immune stimulation of T helper cells, as may be caused by viral or bacterial infections, is the trigger that releases the virus from latency in those cells. But more than that, the research also provides potential new avenues to explore in the search for more effective ways of treating AIDS, or at least preventing its progression.

Nabel and Baltimore identified the regulatory protein by introducing a hybrid gene into Jurkatt cells, a line of leukemia cells of helper T cell origin. The hybrid gene was constructed by joining a sequence from the AIDS virus genome that contains the viral enhancer and promoter to a gene coding for a bacterial enzyme (called the CAT gene). Enhancers and promoters are regulatory elements needed for the first step of protein synthesis, gene transcription into messenger RNA, and the Cambridge workers showed the AIDS virus regulatory sequences only drive the transcription of the CAT gene in Jurkatt cells that were stimulated by two nonspecific activators of immune cells.

The researchers then went on to identify a protein that is made in the activated cells, but not in resting cells, and binds to the enhancer sequence of the AIDS virus. This protein turned out to be identical to "nuclear factor-kappa B" (NF-kappa B), another protein that was previously identified by the Baltimore group. NF-kappa B is so called because it is located in the nucleus of antibody-producing B cells where it turns on the expression of the gene coding for the kappa chain of antibody molecules. "We didn't know that it was found in cells other than B cells until we did these experiments," Nabel says.

The kappa chain enhancer contains a twice-repeated sequence of 11 base pairs in length that is the binding site for NF-kappa B. The AIDS virus enhancer contains a repeated sequence that is almost identical to that of the kappa chain gene and therefore the likely binding site for the protein. When Nabel and Baltimore introduced mutations into that portion of the viral enhancer, the binding of NF-kappa B was abolished. Moreover, a hybrid CAT gene with the mutated enhancer was not turned on in Jurkatt cells when they were activated. "The result is very suggestive that the protein is a critical part of the molecular switch for activating the AIDS virus," Nabel explains.



M. Lampert/Boston

David Baltimore *collaborated with Gary Nabel in identifying the T cell protein that turns on AIDS virus genes.*

The AIDS virus genome contains at least four genes that participate in regulating the synthesis of the structural proteins of the viral particle. The product of one of these genes, the *tat* gene, is a potent stimulator of the synthesis of AIDS virus proteins. Nabel and Baltimore have also shown that NF-kappa B works in concert with the *tat* gene product. The two together stimulate CAT protein synthesis much more than either does alone.

There is controversy about how the *tat* gene works, whether it acts by increasing transcription or later after transcription has occurred. (See also p. 390.) Nabel and Baltimore's findings are consistent with it acting after transcription has occurred, perhaps by stabilizing the messenger RNAs or by having a more direct effect on their translation into protein. In any event, the net result of the joint action of NF-kappa B and the *tat* product would be to greatly amplify the synthesis of AIDS virus proteins in stimulated helper T cells.

The connection of the NF-kappa B protein to AIDS virus activation provides a new target for possible AIDS therapies. "It gives us additional ways of thinking about potential treatments," Nabel says. Preventing NF-kappa B synthesis or activity might prevent T cell destruction and the development of a full-blown immune deficiency, even if the virus could not be completely eliminated from the cells of an infected individual. Whether this would have any effect on the development of the neurological symptoms that are often seen in AIDS patients and may be independent of the immune deficiency is unknown, however.

Also unclear is whether shutting off NF-kappa B activities would itself result in a crippling of the immune system. When T cells are activated by immune stimulation they produce a variety of lymphokines, proteins such as the interleukins, that are needed for mounting normal immune responses. If these are also cut off by abolishing NF-kappa B activity, then the patient might still end up seriously immunodeficient.

Nabel reports an encouraging finding in this regard, however. The lymphokine genes thus far examined do not contain the 11-base pair repeat that binds NF-kappa B. This suggests that these genes are not turned on by the protein. Even if lymphokine synthesis is affected, many of the genes have now been cloned, thus making possible the production of lymphokine proteins that might be used in replacement therapy.

A great deal more work will be required before any of this comes to pass. Nevertheless, the current results do point to another possible way of attacking the insidious AIDS virus. ■ JEAN L. MARX