AIDS virus

More and better *trans*-activation

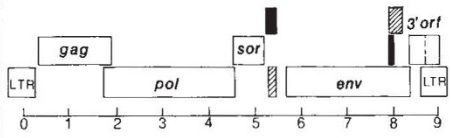
from A. Burny

THE virus that causes acquired immune deficiency syndrome (AIDS) is a sophisticated weapon aimed at the human T4 lymphocyte, a key cell of the immune response. This highly cytopathic virus, called HTLV-III, LAV or, most recently, HIV (see ref. 1), is endowed with the means to stimulate its own replication in an infected cell. One gene involved in this autostimulation is *tat III* (refs 2–4), a bipartite gene encoding a protein that interacts with receptor sequences near the upstream (5′) end of the viral messenger (m)RNA. On page 412 of this issue[5], Bill Haseltine and his colleagues describe the discovery of a new bipartite gene, *art*, of HIV that is also involved in autostimulation. The product of the gene activates the expression of the *gag* and *env* genes of HIV (encoding, respectively, the capsid and envelope proteins) and thereby regulates virus replication.

The discovery of *art* (for anti-repressor translation) is an intellectual and technical achievement. Haseltine's group recently investigated[4] the mechanism of *trans*-activation by the *tat III* gene product and observed that elevation of long terminal repeat-directed gene expression in cells expressing the tat III protein reflects an increase in protein synthesis without a comparable rise in the steady-state level of the respective mRNAs. Deletion analysis of the HIV long terminal repeat demonstrated that the sequence necessary for *trans*-activation (the TAR sequence) is located between nucleotides −17 and +80, that is, 3′ (downstream) from the mRNA initiation site (the cap site). Taken together, the lack of effect of *tat III* on viral mRNA concentration and the presence at the 5′ side of viral mRNAs of nucleotide sequences responsive to tat III protein regulation prompted Haseltine and co-workers to establish experimentally that *trans*-activation by *tat III* is mediated via a post-translational mechanism[6].

Continuing their deletion analysis of the HIV proviral genome, Haseltine and colleagues have now identified a seventh viral gene. Their approach consists of the transfection of matched cell lines with intact or deleted proviral DNA constructs and determination of the amounts of virus and viral antigens produced. It became obvious that a new gene was involved when deletions located in the 3′ region of the first exon of the *tat III* gene, but not extending into the *env* gene, prevented virus production even in the presence of a functional tat III product supplied in *trans*. A second set of mutations (insertions and deletions) located further down the proviral DNA to the 3′ side of the second exon of *tat III* and overlapping *env* yielded proviruses that failed to express viral gag and env proteins. Finally, new plasmids designed to express the putative new open reading frame but not *env* were demonstrated to allow *env* production by proviruses containing mutations in the new open reading frame. As the phenotypes induced by both sets of mutations performed are similar, Haseltine and colleagues conclude that they have identified a new gene.

The protein product of the gene, 116 amino acids long, has no effect on viral



Map of the genes encoding the AIDS virus. Black boxes, the two coding exons of the *tat* gene; hatched boxes, those of the *art* gene; *pol*, *sor*, genes for other viral proteins; *orf*, open reading frame. Scale, kilobases.

mRNA concentrations but is required for expression of the HIV gag and env proteins. The inescapable conclusion of these experiments is that the *art* gene product specifically allows translation of HIV *gag* and *env* mRNAs, thus unlocking the block imposed on virus expression. The discovery of *trans*-activation of retroviral long terminal repeats or mRNAs will be important for understanding virus persistence and latency, cell killing and cell transformation.

The *tat* and *art* gene products are clearly potent regulators of viral gene expression, and are most probably involved in the successive cycles of latency and expression that characterize the life-span of the AIDS virus. Fine tuning of *tat* and *art* genes must allow silent accumulation of *gag* and *env* mRNAs. Expression of tat and art proteins switches on a burst of expression of *gag* and *env* components that initiates virus production. Such a mechanistic design predicts that *tat* and *art* mRNAs must be translatable in conditions that preclude translation of *gag* and *env* mRNAs. Detailed analysis of the 5′ end of the corresponding mRNAs, and identification of the tat and art protein interactions with their target nucleic acids, are urgent tasks.

As Haseltine and co-workers point out, the new data are highly suggestive of the existence of an early–late switch in HIV infections and in infections mediated by similar agents such as visna virus and caprine arthritis encephalitis virus. The two latter systems are characterized by persistence and latency[7–9], and *trans*-activation has been demonstrated in visna virus-infected cells[9].

Retroviruses, DNA viruses and other systems involving production of a lethal product obey the biological paradigm that production of the product is best achieved if delayed to late stages of the life-span of the cell. Regulation of translation of accumulated mRNAs is an elegant manner of complying with this requirement. □

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Gravitational waves

Observatories of the future

from M.G. Edmunds

THE direct observation of gravitational waves, the ripples in space-time generated by the motions of masses, is one of the last-known windows that remains to be opened on the Universe. Although detections have been promised within five years for at least the past fifteen years, it does at last seem that the hopes will develop into real data within six years from now, as concluded at a recent meeting* by members of groups working on the problem. This optimism springs from a consensus on the theoretical estimates of the expected strength of cosmic sources of gravitational radiation, as well as growing confidence that the technological advances required for interferometric detectors of sufficient sensitivity can be made.

An interferometric gravitational-wave detector (see Fig. 1) basically consists of three suspended masses arranged at the corners of an L. The two arms of a Michelson interferometer formed with mirrors attached to the masses measure the rel-

*The Interferometric Gravitational Wave Detectors meeting was held at Cardiff University on 17 February 1986.