HTLV-III and LAV: Similar, or Identical?

Early in 1985, the precise genetic sequences of three viruses isolated from patients with AIDS and AIDS-related symptoms were published in the scientific literature.* The publications removed any doubt that the three isolates are variants of the same virus, but they immediately raised speculation about the relationship of the isolates to each other. This speculation has now become part of a patent dispute between the U.S. government and the Pasteur Institute.

The viruses, isolated by teams headed by Robert C. Gallo of the National Cancer Institute (NCI), Luc Montagnier of the Pasteur Institute, and Jay Levy of the University of California at San Francisco, have been given different names. Gallo's is called HTLV-III (for human T-lymphotropic virus type III), Montagnier's is called LAV (for lymphadenopathy/AIDS virus), and Levy has named his ARV (for AIDS-related virus). The sequence data indicate that HTLV-III and LAV are very similar to each other, while ARV is substantially different. With a genome of almost 10,000 nucleotides, LAV and HTLV-III differ by only about 150 nucleotides; ARV differs by almost 600.

Innuendoes immediately started circulating around the scientific community that HTLV-III and LAV are in fact the same virus. These allegations rest in part on the fact that Montagnier sent Gallo a sample of supernatant containing a small amount of LAV in September 1983.

These innuendoes have intensified in recent weeks as the result of a study by a group headed by Malcolm Martin of the National Institute of Allergy and Infectious Diseases. Martin has constructed restriction enzyme maps of 12 AIDS virus isolates, including HTLV-III, LAV, and ARV, indicating the points at which seven enzymes cleave the viral genomes. These maps provide an indication of genetic differences among the isolates. Martin's data show that the restriction maps of HTLV-III and LAV are identical, while those of all the other isolates differ from each other. Although Martin's paper has not yet been published (it is currently in press in *Science*), it has been widely circulated around the scientific community.

One complicating factor in comparing HTLV-III and LAV is that the virus that Gallo's group sequenced came from a cell line infected with virus isolates from ten different patients. There are at least four different viruses integrated into the cells in that line, and different clones will produce different but closely related, viruses.

Mikulas Popovic, a cell biologist in Gallo's lab who infected the cell line, used multiple isolates because he found that some viruses "take" more readily than others. However, a short time later, Popovic also established virus-producing lines infected with isolates from single patients. One of these, infected with virus from a Haitian, was included in the patent application for the method of mass-producing HTLV-III. This virus has since been sequenced and it is as different from LAV as ARV is.

Gallo argues that this ought to silence any speculation that he deliberately grew the French virus. If he already had other lines infected with other viruses, why would he sequence the virus from a line he had infected with the French isolate?

Gallo also notes that his group had several virus isolates before Montagnier's sample arrived. "It was no big deal to get supernatant. We got that from many patients for a long, long time before he sent us this virus," Gallo says. "Am I going to throw away [my reputation] for a virus that is simple to isolate, and then publish its sequence with multiple collaborators? It just doesn't make sense."

Moreover, the sample of supernatant that Montagnier sent contained only a small amount of virus. According to Gallo and Popovic, it contained 11,000 counts per minute of reverse transcriptase activity, a level that Gallo says is considerably less than is required to productively infect a cell line. At the time it arrived, Gallo's group had not developed its permissive cell line and they were having difficulty getting virus isolates to grow. Gallo and Popovic say they infected fresh lymphocytes with the virus Montagnier sent, but when the reverse transcriptase activity declined they put the material in the freezer.

Could the line that Popovic infected with multiple isolates have been accidentally contaminated with LAV? Contamination of cultures is not uncommon. Moreover, one scientist who has worked with several AIDS virus isolates says that LAV grows more readily than others, perhaps because it has been propagated in vitro for a long time.

In response, Gallo points out that the genetic sequences of the two viruses are not identical. Others note, however, that some of the differences are due to deletions of small segments of the genome, and they argue that if these are discounted, the viruses are very similar. But one scientist who is not favorably disposed toward Gallo concedes that "there are point mutations that are difficult to explain" if HTLV-III and LAV are indeed the same virus.

Gallo also argues that, as more and more isolates are examined, some very closely matched pairs are being found. In a paper published by his lab, for example, out of 18 isolates examined by restriction enzyme mapping, two were very closely related, differing by only one restriction enzyme site. Gallo says that some regions of the genomes of this pair have now been sequenced, and they are as closely related as HTLV-III and LAV.

Further evidence to support this argument comes from research by Dino Dina and his colleagues at Chiron Research Laboratories in Emeryville, California. Dina has developed probes for the most variable regions of the genes that code for envelope proteins of the AIDS virus. At a meeting at Cold Spring Harbor in September, he reported that in random sampling of virus isolates he found several that are very similar to HTLV-III and LAV in these variable regions.

Few scientists contacted by *Science* were willing to discuss on the record the similarities between HTLV-III and LAV. The general consensus, however, appears to be that, although the degree of similarity between the two viruses is unusual, not enough is known about the genetic heterogeneity of the AIDS virus or its natural history to draw any conclusions.—**C.N.**

*S. Wain-Hobson *et al.*, *Cell* **40**, 11 (1985); L. Ratner *et al.*, *Nature (London)* **313**, 277 (1985); R. Sanchez-Pescador *et al.*, *Science* **227**, 484 (1985); and M. Muesing *et al.*, *Nature (London)* **313**, 450 (1985).