PERSPECTIVES: AIDS

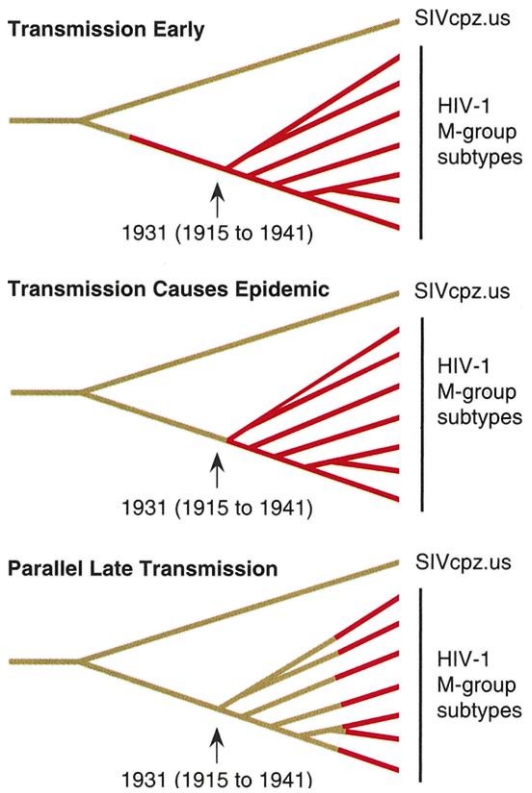
Origins of HIV

David M. Hillis

Social, economic, and political changes during the last 100 years have resulted in unprecedented contact and global movement among human populations. Under these conditions, the transmission of an animal virus to a human host (zoonotic transmission) enables the rapid spread of a virus beyond the geographic range of its original animal host. The most serious viral epidemic resulting from zoonotic transmission is AIDS caused by the human immunodeficiency viruses (HIVs). Exactly when simian immunodeficiency viruses (SIVs) were transmitted from nonhuman primates to humans and began to diversify, resulting in the emergence of HIVs, is still under investigation. Establishing the date of emergence of HIVs is imperative to elucidating how transmission occurred and to finding ways to prevent zoonotic transmissions in the future. Now, on page 1789 of this issue, Korber *et al.* (*1*) use a phylogenetic analysis, in combination with known sampling dates, to estimate the year of origin for the HIV-1 M ("main") group of viruses, the principal cause of the AIDS pandemic.

By the time that HIV-1 and HIV-2 were identified in the 1980s, several separate and widespread epidemics caused by independent HIV lineages were already under way in human populations in Africa (*2*). HIVs appear to have been transmitted to humans multiple times from at least two different nonhuman primates infected with SIVs. Lineages of HIV that were transmitted from chimpanzees are known as HIV-1, and those transmitted from sooty mangabeys are known as HIV-2. Even within each of these classes, however, HIVs seem to have been transmitted to humans more than once. Within HIV-1, the most widespread and devastating epidemic is that caused by the HIV-1 M group, which represents a single lineage with a common ancestor. Korber and her colleagues estimated the year that this common ancestor came into existence and, thus, the year that the HIV-1 M-group viruses began to diversify.

Molecular clock analyses are used to predict when lineages branch off (split) from a common ancestor in the evolutionary tree. These analyses use the age of known or previously estimated branching events to calculate the correlation between time and molecular divergence in particular genes. This correlation is then used to calculate the date of past evolutionary splits. Different models assume that the rate of change is constant through time and across lineages (*3*), or that it varies among lineages at branching events (*4*), or that it varies in any part of the evolutionary tree (*5*). By analyzing the molecular divergence of the *env* gene (encoding gp160) and applying a model of constant change, Korber *et al.* calculated a best estimate for the date when the last common ancestor of the HIV-1 M group came into existence. Their molecular clock analysis provided a date of 1931, with a 95% confidence interval of 1915 to 1941. Analysis of another gene (*gag*) or application of another model (rates allowed to change at splitting events) (*4*) gave similar results with somewhat broader confidence intervals. However, all analyses included the span of 1916 to 1941 in the 95% confidence interval of the respective estimates. Furthermore, testing a known HIV-1 group M isolate from 1959 gave an accurate estimate for the date of its origin, indicating that the assumptions of the method are reasonable.



A deadly evolutionary tree. Three hypotheses for the origin of the HIV-1 M group of viruses from SIVcpz (the virus infecting chimpanzees). Beige lineages indicate the presence of SIVcpz in chimpanzee populations and red lineages the presence of HIV-1 M-group viruses in humans. Korber *et al.* (*1*) have established that the common ancestor of the HIV-1 M group came into existence in the early 1930s. Three different hypotheses for the transmission of immunodeficiency viruses from chimpanzees to humans—Transmission Early, Transmission Causes Epidemic, and Parallel Late Transmission—are consistent with this date.

What does establishing a date in the early 1930s for the last common ancestor tell us about the origins of the HIV-1 M group and of the AIDS pandemic it caused? As Korber *et al.* note, the date of the last common ancestor only identifies when this viral lineage began to diversify; it does not identify when the virus was transmitted from chimpanzees to humans. One could envisage at least three hypotheses to explain the date of this transmission event (see the figure). The virus could have been transmitted to humans in the 1800s or early 1900s perhaps through the hunting of chimpanzees for food. It then would have remained isolated in a small, local human population until about 1930, when it began spreading to other human populations and to diversify (Transmission Early hypothesis). In this case, socioeconomic and political changes in Africa could account for the increasing spread of the virus in humans (*6*). A second possibility is that the virus was transmitted from chimpanzees to humans around 1930, and immediately began to spread and diversify in human populations (Transmission Causes Epidemic hypothesis). A third possibility is that multiple strains of SIV were transmitted from chimpanzees to humans at about the same time in the 1940s or 1950s (Parallel Late Transmission hypothesis). It has been suggested that parallel transmission could have occurred through contamination of poliovirus vaccines with multiple SIVs. Poliovirus was cultured in chimpanzee kidney cells and oral polio vaccines were administered in Central Africa between 1957 and 1960 (*7*). However, this mechanism of transmission seems highly unlikely given the small number of chimpanzee kidneys used for preparing oral polio vaccines, the rarity of SIV infections in chimpanzee populations, and the

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lack of known strains of SIVcpz (the SIV strain that infects chimpanzees) in the cluster of M-group viruses.

Of the three hypotheses, the data of Korber and co-workers best support the Transmission Early hypothesis, although they do not rule out the other two. Additional sampling of SIVcpz lineages in chimpanzee populations will help resolve this issue. The Transmission Early hypothesis will continue to be supported if additional sampling shows that all SIVcpz lineages are only distantly related to the HIV-1 M group. The Transmission Causes Epidemic hypothesis would be supported if it were found that an SIVcpz lineage branches off close to the last common ancestor of the HIV-1 M group (see the figure). Finally, the Parallel Late Transmission hypothesis would be supported by the finding that multiple SIVcpz lineages are embedded within the HIV-1 M group.

If HIV has been present in human populations since at least the 1930s (and probably much earlier), why did AIDS not become prevalent until the 1970s? The phylogenetic trees of HIV-1 indicate that the spread of the virus was initially quite slow—by 1950 there existed 10 or fewer HIV-1 M-group lineages that left descendants that have survived to the present. The epidemic exploded in the 1950s and 1960s, coincident with the end of colonial rule in Africa, several civil wars, the introduction of widespread vaccination programs (with the deliberate or inadvertent reuse of needles), the growth of large African cities, the sexual revolution, and increased travel by humans to and from Africa. Given the roughly 10-year period from infection to progression to AIDS, it was not until the 1970s that the symptoms of AIDS became prevalent in infected individuals in the United States and Europe.

The conditions that gave rise to the HIV-1 M-group pandemic probably included the same factors that gave rise to the parallel epidemics caused by other HIVs. From the standpoint of viruses that can infect humans, the world is a much smaller place today than it was at the turn of the last century. As we head into the 21st century, human populations will have to deal with many more zoonotic viral epidemics.

References

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PERSPECTIVES: DEVELOPMENT

PARallels in Axis Formation

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The anterior-to-posterior axis of a fruit fly or worm embryo is determined even before the first division of the fertilized egg. As the embryo undergoes successive cell divisions, cells at one end are destined to produce anterior structures (such as the fruit fly head or worm pharyngeal muscle cells), whereas cells at the other end are destined to produce posterior structures (such as the germ cells that give rise to egg and sperm).

In the fruit fly *Drosophila* and the worm *Caenorhabditis elegans*, this asymmetry is achieved by segregating specific mRNA and protein products (which determine either anterior or posterior structures) to one pole of the egg or the other. These anterior and posterior "cell fate determinants" are produced by the mother during oogenesis. Mutations that impair either their synthesis or segregation (localization) affect the establishment of the body axes of the fly and worm embryo.

Surprisingly, with the exception of the germ line factors *nanos* and *vasa/glh* (*1*, *2*), there seems to be little commonality between the two systems. For example, drugs that disrupt either the actin or tubulin (microtubule) cytoskeleton reveal that the embryonic axis of *Drosophila* requires an intact microtubule network, whereas polarization of the *C. elegans* embryo requires an intact actin network (*3*, *4*). This is set to change with the recent reports of Shulman *et al.* (*5*) in *Cell* and Tomancak *et al.* (*6*) in *Nature Cell Biology*. The two groups demonstrate that a putative serine-threonine kinase, PAR-1, known to determine asymmetric segregation of cell fate determinants in the worm embryo (*7*), also affects their localization in the *Drosophila* embryo. Intriguingly, *par-1* and other *par* genes have homologs that establish cellular asymmetries in other systems—for example, the segregation of factors required for neural development in *Drosophila* and the distinction between apical and basolateral surfaces in human epithelial cells (*8*, *9*). These homologies suggest that the mechanisms regulating cell asymmetry in different species and cell types may be more similar than previously thought.

Anterior-posterior polarity in *C. elegans* is established after fertilization by the point of sperm entry, which becomes the embryo's posterior pole. Subsequently, during division of the fertilized egg, the mitotic spindle localizes near the posterior pole, and the egg divides to produce a large anterior and small posterior cell. Just before this division, several maternally synthesized proteins determining anterior and posterior cell fate become localized to their respective poles (*10*). In addition, P granules containing mRNAs and proteins that instruct differentiation of germ line cells become localized at the posterior pole (see the figure). It is known that both asymmetric cell division and segregation of cell fate determinants depend on a network of actin microfilaments because the drug cytochalasin (which prevents actin polymerization) induces a symmetric first division and prevents the localization of P granules (*4*). Mutations in several *par* genes also disrupt asymmetric cell division and P granule localization. Most PAR proteins are asymmetrically segregated: PAR-1 and PAR-2 are sequestered at the posterior pole, PAR-3 at the anterior pole (*7*, *10*).

In *Drosophila*, polarization of the oocyte's microtubule network is important for the establishment of anterior-posterior and dorsoventral patterning in the embryo. Microtubules (polymers of tubulin subunits) have slow-growing minus ends and more dynamic plus ends. The minus ends are anchored at the microtubule organizing center (MTOC) at one pole of the cell. Motor proteins directed toward either the plus or minus microtubule ends transport mRNAs and proteins along the microtubule cytoskeleton to the cell poles. In the early *Drosophila* oocyte, the MTOC is at the posterior pole. Reciprocal signaling between the oocyte and the surrounding follicle cells leads to a reorganization of the microtubule network. The oocyte releases transforming growth factor–α (TGF-α)/GURKEN, which binds to its receptor on a subset of follicle cells marking them as "posterior." Through the protein kinase A (PKA) signaling pathway, these posterior follicle cells induce a reorganization of the microtubule network in the oocyte. A new MTOC is established at the anterior of the oocyte, and the old one at the posterior disappears (*11*). This new polarity of the microtubule cytoskeleton leads to the sorting of mRNAs encoding the anterior and pos-

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