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.

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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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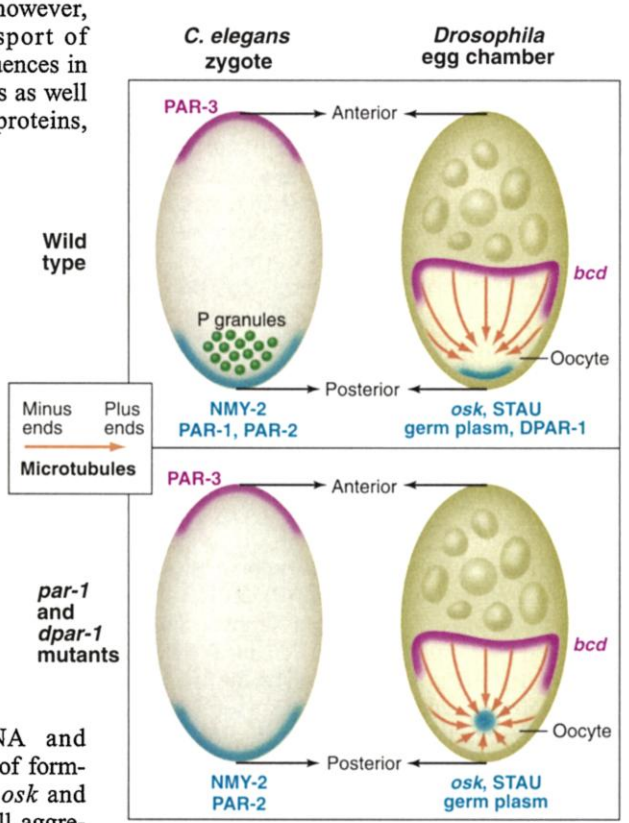
terior cell fate determinants *bicoid* (*bcd*) and *oskar* (*osk*). *Bcd* mRNA moves along the microtubules toward the minus ends at the anterior, and *osk* mRNA moves in the opposite direction toward the plus ends at the posterior (see the figure). The exact mechanisms by which *bcd* and *osk* mRNAs are moved along the cytoskeleton are not known. There is, however, good evidence that transport of these mRNAs requires sequences in their 3′ untranslated regions as well as specific RNA binding proteins, such as STAUFEN (*12*).

In the new work, Shulman *et al.* (*5*) and Tomancak *et al.* (*6*) describe the molecular characterization and mutant phenotypes of the *Drosophila par-1* homolog, *dpar-1*. Reminiscent of its *C. elegans* homolog, DPAR-1 is found at the posterior pole of the *Drosophila* oocyte. Mutations in *dpar-1*, just like mutations in *par-1* of *C. elegans*, affect posterior pattern formation. Embryos from mutant *dpar-1* mothers do not have abdomens and fail to form germ cells. DPAR-1 is required for the posterior localization of *osk* mRNA and STAUFEN protein. Instead of forming a tight posterior cap, *osk* and STAUFEN cluster in a small aggregate in the middle of the mutant oocyte (see the figure). TGF-α/*gurken* and *PKA* mutants also result in mislocalization of *osk* mRNA and STAUFEN protein and their aggregation in the center of the oocyte. This mislocalization is the result of defective disassembly of the MTOC at the posterior pole. The same defect causes *bcd* mRNA to move to both poles instead of being sequestered at the anterior pole (*11*).

The disruption of microtubule organization appears to be different in *dpar-1* mutant fruit flies compared with *gurken* and *PKA* mutants. Using markers for the minus and plus ends of the microtubule network, Shulman and co-workers show that the MTOC is properly disassembled at the posterior pole and reassembled at the anterior pole in *dpar-1* mutant fly oocytes. Indeed, the minus ends of the microtubules seem less affected than the plus ends in these mutants, and *bcd* mRNA localization is essentially normal. Overall microtubule organization, however, is affected in *dpar-1* mutants—microtubules are found along the entire periphery of mutant oocytes, whereas in wild-type oocytes they do not extend from the posterior pole (*5, 6*). In the fruit fly mutant, the microtubule plus ends appear oriented toward the oocyte's center. This may explain why *osk* mRNA (which associates with the plus ends of the microtubules) aggregates in the center of the oocyte. These results raise the possibility that PAR-1 is required to maintain a microtubule gradient, ensuring that microtubules extend from the oocyte's anterior pole but are largely absent from its posterior pole. This microtubule polarization is necessary for localization of factors such as STAUFEN protein and *osk* mRNA to the posterior pole (*5, 6*).



Which end is up? PROTEINS and *mRNAs* determine either an anterior (pink) or posterior (blue) cell fate in the fertilized egg (zygote) of the worm *C. elegans* and in the oocyte of the fruit fly *Drosophila*. PAR-1 is necessary for correct localization of posterior cell fate determinants. Fly and worm *dpar-1* and *par-1* mutants, respectively, show aberrant polarization of cell fate determinants and lack posterior structures and germ cells.

The PAR-1 proteins of *Drosophila* and *C. elegans* are strikingly similar in their distributions within cells and their effects on the localization of posterior and germ line cell fate determinants. Proposing a unifying model for *par-1* activity in fruit fly and worm is, however, problematic because axis determination in the two systems depends on different cytoskeletal systems. The results of Shulman, Tomancak, and their colleagues suggest that DPAR-1 destabilizes the microtubule network in the *Drosophila* oocyte. Anterior-posterior polarity in *C. elegans* requires an intact actin cytoskeleton, but a direct effect of *par-1* on actin stability or organization has not yet been demonstrated. Also, PAR-1 localization has different requirements in the two systems. In *C. elegans*, the earliest acting element of the *par* pathway, *non muscle myosin II* (*nmy-2*), is localized to the posterior pole independently of *par* gene activity. Posterior localization of PAR-1 depends on *nmy-2* and also on *par-2* and *par-3*, whereas *par-1* mutations do not affect the localization of NMY-2, PAR-2, or PAR-3 (*7, 13, 14*). In *Drosophila*, mutations in the *nmy-2* and *par-3* genes do not alter DPAR-1 localization. Instead, DPAR-1 localization depends on *osk* mRNA, which has no identified homolog in *C. elegans* (*5*). Although the PAR-1 localization machinery does not seem to have been conserved between the two systems, the function of PAR-1 may have been conserved.

What part does PAR-1 play in the anterior-posterior determining pathways of the fruit fly and worm? A clue to its function comes from studies of mammalian MARK proteins, which destabilize the microtubule network by phosphorylating microtubule-associated proteins (*15*). Perhaps these proteins are also downstream targets of PAR-1 and DPAR-1. Now that the fly and worm genome sequencing projects are complete, it should be possible to identify other components of the axis determination machinery—for example, the *staufen* homolog in *C. elegans* and the *pie-1*, *mex5/6* homologs such as *Tis11* in *Drosophila* (*16*). If the PAR-1 family acts in a universal pathway to polarize cells, then homologies between flies and worms should be extended to include regulators and targets of PAR-1. If PAR-1 is the only factor that the two systems have in common, then it is more likely that the PAR-1 protein family was recruited independently several times in evolution (*6*).

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