An Ancient Molecular Mechanism for Establishing Embryonic Polarity

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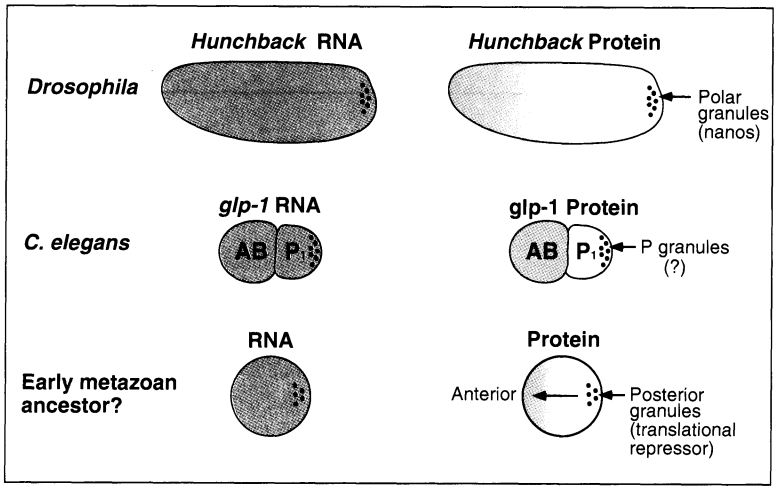
Worms, butterflies, and chimpanzees all have the same body axes—head and tail, front and back, and left and right sides. How are these axes established during development? Is there a single molecular map used by most metazoan embryos or have similar coordinates been achieved during evolution by diverse routes? A comparison of the mechanisms that establish body axes in distantly related organisms can begin to answer this fundamental question.

Progress has been spectacular in dissecting the molecular mechanisms that control axis formation in one organism, the fruit fly *Drosophila* (*1*), but much less is known about these mechanisms in other organisms. Recently, similarities have become apparent between mechanisms that govern early embryonic polarity in the nematode *Caenorhabditis elegans* and in *Drosophila* (*2*). In both species, translational repression at the posterior pole establishes asymmetry along the anterior-posterior axis (*2–4*). Nematodes and insects diverged at least 600 million years ago—when metazoans first made their appearance in the fossil record (*3*, *4*)—and so such localized translational repression may be an ancient molecular mechanism for specification of one body axis, the anterior-posterior axis that runs from head to tail. In *Drosophila*, asymmetries that are established in the oocyte generate localized protein gradients and the overall body plan during early embryogenesis (*1*). Formation of the anterior-posterior axis relies on localized maternal mRNAs—*bicoid* at the anterior and *nanos* at the posterior pole. These localized mRNAs are translated soon after fertilization to create gradients of their protein products in the early embryo. *Bicoid* encodes a transcriptional activator, which turns on zygotic expression of another gene, *hunchback*, in the anterior region; *nanos*, by contrast, represses translation of maternal *hunchback* mRNA in the posterior region and leads to its destruction. The gradient of hunchback therefore is formed by transcriptional activation at the anterior pole and translational repression at the posterior pole. The hunchback gradient, in turn, triggers a cascade of transcription factors that specify patterning along the anterior-posterior axis.

Early embryogenesis in *Drosophila* takes place within a large cytoplasm that is shared by many nuclei, the syncytial blastoderm. By contrast, most animal embryos begin life with a series of cleavage divisions that separate the zygote's cytoplasm into distinct cellular domains. Nematode embryos, for example, divide unequally at the first cleavage division, producing a large anterior daughter and a small posterior daughter. The anterior daughter generates mostly nerve and epidermis, whereas the posterior daughter forms muscle, gut, and germ cells (*5*). Amphibian embryos possess animal and vegetal poles at fertilization, which subsequently give rise to cells with distinct fates. These dramatic differences in embryonic morphology are commonly thought to reflect fundamental differences in the mechanisms that control embryonic patterning. One mechanism for generating asymmetry along the anterior-posterior axis appears to be shared by worms and flies. The glp-1 protein encoded by *glp-1*, a membrane receptor required for inductive cell interactions in the early C. *elegans* embryo (*6*), is first observed in the anterior, but not the posterior, blastomere of late two-cell embryos; this *glp-1* asymmetry is maintained in 4- to 28-cell embryos (*2*). The anterior-posterior asymmetry of glp-1 protein may be crucial for the establishment of asymmetrical patterns of cell-cell interaction, which in turn specify dorsal-ventral and left-right axes of the C. *elegans* embryo (*7–10*). In contrast to glp-1 protein, *glp-1* maternal mRNA is distributed uniformly, which eliminates two models for control of glp-1 protein asymmetry—localization of *glp-1* maternal RNA and localized control of *glp-1* RNA stability (*2*). In fact, the glp-1 pattern is controlled translationally, by the *glp-1* 3' untranslated region (3'UTR), the site of translational regulatory elements in many maternal mRNAs (*11*). Reporter RNAs carrying a naïve 3'UTR or no 3'UTR are translated in an unregulated fashion, whereas reporter RNA with the *glp-1* 3'UTR is translated in a pattern that is virtually the same as that of endogenous glp-1 protein (*2*). Specific translational regulatory elements are found within regions of the *glp-1* 3'UTR. Removal of 125 nucleotides from the 3' end of the *glp-1* 3'UTR permits translation during oogenesis, whereas removal of 61 nucleotides from the center of the *glp-1* 3'UTR permits translation in both anterior and posterior blastomeres, starting at the four-cell stage. Therefore, one type of cis-acting regulatory element appears to be located at the 3' end of the 3'UTR for repression of translation until the two- to four-cell stage; another type of element appears to be located in the central region for repression in posterior cells.



Establishment of embryonic polarity during metazoan development.

Regulation of glp-1 asymmetry in the early C. *elegans* embryo bears a remarkable resemblance to the establishment of *hunchback* asymmetry in the early *Drosophila* embryo (see figure). Repression in the posterior region restricts translation of both *hunchback* and *glp-1* maternal transcripts to the anterior region of their respective embryos. In addition, similar cis-acting regulatory elements may be involved. In *Drosophila*, translational control depends on a short bipartite sequence motif, called the nanos response element (NRE), which resides in the *hunchback* 3'UTR (*12*). A trans-acting regulator that functions through the NREs has not been identified biochemically, but an excellent candidate is the product of the *nanos* gene (*13*). In C. *elegans*, a bipartite sequence that is strikingly similar to the *Drosophila* NRE occurs within that central region of the *glp-1* 3'UTR required for translational repression in the posterior blastomere (*2*).

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The similarity between *Drosophila* and *C. elegans* early embryos extends beyond the parallels between *hunchback* and *glp-1* translational regulation. Both embryos contain cytoplasmic "granules" in the posterior region of the zygote that are segregated ultimately to germ cell precursors during embryogenesis—the polar granules of *Drosophila* (*14*) and the P granules of *C. elegans* (*15*) (see figure). In *Drosophila*, maternal *nanos* RNA is associated with polar granules; perhaps in *C. elegans*, a homolog of *nanos* is associated with P granules.

What about vertebrates? Does translational repression in the posterior cytoplasm establish embryonic polarity in these "higher" animals? A hint that this mechanism may indeed function in vertebrates comes from the identification of a maternal transcript that encodes a nanos-like protein called Xcat-2 in *Xenopus* embryos (*16*). Although the function of Xcat-2 is unknown, its location at the vegetal pole suggests a role in early pattern formation. Furthermore, a "germ plasm" exists in the vegetal cytoplasm of amphibian embryos that may be analogous to P granules and polar granules of worms and flies (*17*). Over the past decade, a handful of molecular mechanisms have been implicated in the patterning of *Drosophila*, *C. elegans*, and *Xenopus* embryos (*1*, *18*, *19*). On the basis of the diversity of these mechanisms, the prevailing view has been that each embryo has differentially employed a handful of common molecular mechanisms to create its own coordinate system. For example, localized transcriptional activators are utilized for patterning of both *C. elegans* and *Drosophila* early embryos (*20–23*), but the mechanisms for localization, types of DNA binding protein, and specified fates are not obviously similar.

By contrast, the molecular parallels between *hunchback* and *glp-1* regulation suggest the existence of an ancient mechanism for creating asymmetric patterns of gene expression in early embryos (see figure). This mechanism is predicted to depend on a trans-acting regulator similar to nanos and to act through cis-acting sequences similar to NREs in the 3'UTRs of maternal transcripts. If this molecular machinery regulates polarity in embryos as diverse as worms, flies, and frogs, it becomes plausible that it influences axis formation in all animal embryos, including mammals. "Molecular tinkering" (*24*) may then come into play to reinforce this primitive patterning control and to derive other axes from it.

Research in *Drosophila* has pioneered our understanding of the molecular mechanisms that can establish the body axes in an early embryo. Now, phylogenetic comparisons will tell us which mechanisms are primitive and which have evolved to reinforce, modify, or extend the underlying map. Are the controls that localize translational repression conserved? Are polar granules the ancient seat of pattern governance? What links the early controls of axis formation to the later controls of homeobox genes, a highly conserved system that specifies individual regions along the anterior-posterior axis of all known metazoa (*25*)? The *hunchback* protein is a transcriptional regulator that resides at the top of a cascade of transcriptional regulators, whereas the glp-1 protein is a membrane receptor that directs inductive interactions. Clearly, these distinct modes of regulation must converge to control expression of homeobox genes. How similar are the mechanisms of convergence? Answers to these questions, among the most fundamental of all developmental biology, may be waiting around the corner.

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The Embryonic Vertebrate Forebrain: The Prosomeric Model

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The mammalian forebrain—the cerebral cortex, basal ganglia, hypothalamus, and thalamus—is the seat of higher cognitive functions. How much of forebrain development and structure is controlled by a genetic program? Although at the later stages of development incoming synaptic information from the thalamus has been shown to influence patterning in the neocortex (*1*), at early embryological stages a specific set of newly discovered genes pattern the brain into a highly organized structure—before synaptic influences are present. Furthermore, the primordia of major structural elements, such as the thalamus, are segregated by cellular boundaries that are aligned parallel to the topologically transverse and longitudinal axes of the neural tube. Specific combinations of genes that are expressed in these domains direct the unique development of each region. Finally, the organization of the forebrain indicates that it is a segmental structure.

The basic morphogenetic unit of embryonic insects is a transverse domain, or segment (*2*). The identity of each segment is determined by its position along the anterior-posterior axis and is controlled by the expression of the homeobox segment identity genes (*3*). These genes encode transcriptional regulators of specific sets of target genes, which define the unique developmental pathway of each individual segment.

It is widely held that this paradigm may apply to the organization of the somitic mesoderm (the vertebral column), the rhombencephalon (hindbrain), and the branchial arches of vertebrates. This view is based on the existence of homologs of the homeobox segment identity genes in vertebrates (the *Hox* genes) (*3*) as well as the metameric (segmental) morphological and histological features of these structures. This hypothesis has been confirmed in part by the use of genetic manipulations that al-

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