Body patterning

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Early patterning of the body during animal development is a fundamental process to subsequent events including cell differentiation, tissue and organ formation, and correct function of the adult body. We focused on two major topics: body segmentation and brain patterning, both of which are essential for conferring a functional complexity to the body, repetition of skeletal elements and complex neural network, respectively.

When we plan a new house, we first fashion a blueprint indicating the location of bedrooms, a kitchen, a living room, etc., and only subsequently do we fill each room with furniture according to the function of the room. Ontogenesis (the developmental processes of an individual animal) begins with a fertilized egg, and through proliferation, this single cell becomes many. This mass of cells becomes subdivided into distinct groups (rooms) that eventually will exhibit functional specializations (furniture) later in development. If the units fail to be correctly established in time and space, certain specializations might be entirely missing from the embryo, or cells might randomly differentiate (specialize) in the wrong place. Furthermore, cells specializing in the wrong place may end up dying because they fail to be properly integrated with the rest of the organism. All of these outcomes can have dire effects on the body (Fig. 1).

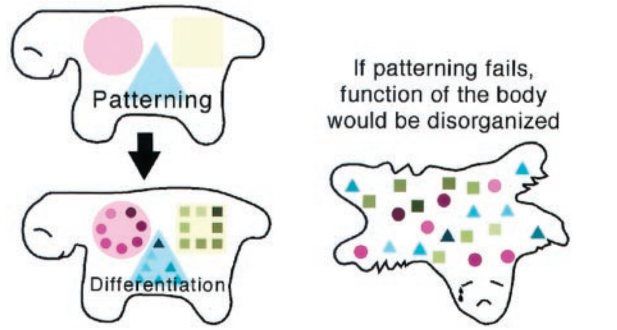

Fig. 1. Early body patterning is pivotal for development.

Progresses in the field of developmental biology have brought us a tremendous amount of knowledge concerning the mechanisms by which the early "outline" of the body is established before overt cell differentiation. The onset of organogenesis is governed by patterning processes that have gone on earlier during development that involve the actions of cell–cell signaling pathways and growth factors acting between cells and transcription factors acting within cells. In the Body Patterning session of the colloquium, we discussed two major topics, body segmentation and brain patterning, both of which are essential for conferring a highly organized functional complexity to the body. In both cases, an originally homogeneous group of cells obtains characters to give rise to particular structures and functions in a precise spatial and temporal pattern. This process gives rise to patterns such as the regular repetition of skeletal elements and the three-dimensional compartments of the brain primordium on which the subsequent complexity of the neuronal network is organized.

Segmentation

Segmentation along the antero-posterior (head-tail) axis of our body is clearly seen for vertebral bones, ribs, spinal ganglia, and so on. In addition, various other animals, which are quite distantly related to ourselves, display obvious signs of body segmentation. Among them, the fruit fly, *Drosophila melanogaster*, is the best-characterized model animal system for the genetic study of segmentation. In this insect, the entire length of the early embryo is simultaneously subdivided into segments. At a superficial level, this mode of subdivision can be analogized with the way in which a mechanical egg slicer simultaneously cuts an egg into uniform slices (Fig. 2). Genetic studies in *Drosophila* have revealed that this process of segmentation begins with gradients of maternal information established during the formation of the egg. This is then refined into blocks of gene expression by so-called gap genes whose transcription patterns are set up in response to these maternal gradients. The first periodic patterns of gene expression are revealed by pair-rule genes whose transcription is controlled by the gap genes and maternal gradients. A further step in the process is controlled by segment polarity genes, which are regulated by the pair-rule genes, and act to refine and maintain the pattern of segments (1).

Various observations in a number of other segmented animals, however, suggested that the mechanisms of segmentation in *Drosophila* might not hold true for all segmented animals. A particularly conspicuous difference involves the way in which segments appear during development. For example, in vertebrates segments are formed sequentially from anterior to posterior during an extended phase of growth and cell proliferation. Indeed, even other insects display this mode of sequential segment formation during an extended growth period. At a superficial level, this mode of subdivision can be analogized with the way yokan (a Japanese sweet pastry) is carved into slices one at a time with a knife (Fig. 2, although to be more accurate the yokan also would have to be getting longer from the posterior end part of the time). Although the process of simultaneous versus sequential subdivision appears quite different, the key question is whether or not they share a common molecular mechanism. Over the past several years, this question has been approached by molecular and genetic comparisons. Initially this was done by comparing the expression patterns of homologs of *Drosophila* segmentation genes in other animals. More recently this has also been supplemented by various func-

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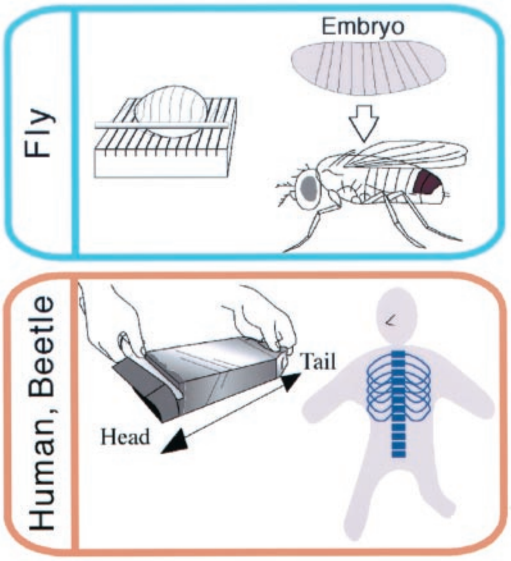

Fig. 2. Segmentation processes appear to vary between different animals.

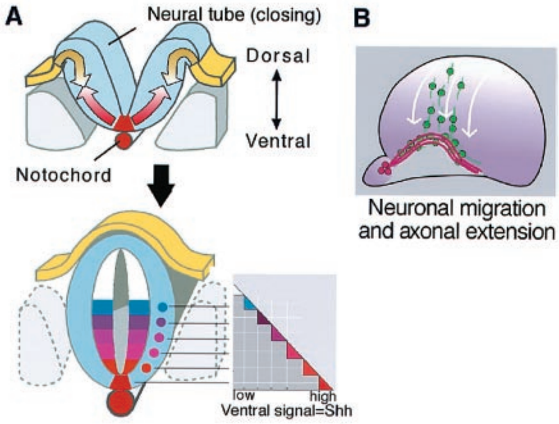

Fig. 3. Gradient signals define the neuronal patterning. (*A*) When the neural tube forms by a closure of the neural plate, signals acting from the dorsal and ventral aspects (yellow and red) eventually define several distinct regions in the neural tube. These events include different concentrations of Shh factor emanating from the ventral end. (*B*) An established pattern of the brain also instructs migration of the neuron precursors and pathways of axonal extension.

tional analyses and independent genetic investigations in other segmented animals.

Within the insects, these comparative studies have shown that insects in which segments appear sequentially (such as beetles and grasshoppers) can indeed use similar mechanisms to those in insects that segment simultaneously (such as *Drosophila*), but the mechanisms are not necessarily identical, suggesting that evolutionary changes in the molecular mechanisms of segmentation have occurred during insect evolution (2). Between more widely diverged animals, such as between *Drosophila* and vertebrates, the picture is less clear at the moment. In large part, it appears that homologous genes are not involved in setting up segments in vertebrates and *Drosophila*, but a recent series of experiments does suggest that the vertebrate homologs of the pair-rule gene *hairy* of *Drosophila* is involved in generating segments in vertebrates, therefore suggesting that there might be some molecular similarities between segmentation in these widely diverged animals (3). Alternatively, this may represent independent co-option of the same gene for this process in each lineage. Further investigation, including the analysis of segmentation in additional animal groups, should help improve our picture of how segmentation has evolved, and what relationship, if any, exists between all animals that display segmented body plans.

Patterning the Brain

The brain serves diverse, yet precise, functions that are built on numerous networks connecting its various parts. Each region of the brain is highly specialized both in its architecture and the precise types of differentiated cells that it contains. How is such regional specificity established? The brain starts to develop from a simple sheet called the neural plate. Neurulation converts the neural plate into a neural tube, which is subdivided into a series of vesicles constituting the primordia of the major brain regions: the forebrain, midbrain, and hindbrain. As development proceeds, transverse constrictions further subdivide the brain into neuronal segments, or neuromeres. Generation of the neuromeres is controlled by the antero-posterior patterning system (4). A distinct dorso-ventral (back-belly) patterning system induces the longitudinal organization of the central nervous system. Induction signals in the form of chemical compounds from the dorsal side include molecules of the transforming growth factor β superfamily and function to dorsalize the neural tube. Conversely, signals emanating from the ventral midline structures, including the notochord, control the position of ventral cells such as motor neurons (Fig. 3). This ventral signal appears to be the Sonic hedgehog (Shh) protein (5). Other local cues are also important in patterning the brain, and in later development various neuronal cell types are generated in specific locations according to their positions along the antero-posterior and dorso-ventral axes of the patterned brain. This initial level of cellular patterning also functions to generate the scaffolds for neuronal cell migration and axonal extension. Whereas some neurons migrate along the boundary between neuromeres or domains, others migrate within a single neuromere to reach its boundary where they then stop and take up residence. Thus early brain patterning itself plays a key role in the formation of later neuronal networks.

Perspective

It is now widely accepted that similar sets of factors are shared by different animal species and also by distinct processes in the course of early patterning of organogenesis. During animal evolution a "prepattern" of fundamental organs emerged relatively early. Then a next question is what distinguishes our brain from the brain of a fly, or what distinguishes the brain from the leg in a single organism, both of which use Shh for its development? Developmental and evolutionary biologists are now beginning to tackle such questions.

Comparative studies of segmentation have taught us that similar morphologies can be achieved through different molecular mechanisms, but at the same time seemingly different processes can actually depend on similar molecular mechanisms. It will be a challenge to unveil the mechanisms of segmentation in non-*Drosophila*-type animals and compare these to find out what evolutionary linkages exist, if any, between all segmented animals. Thus, our efforts to understand the molecular and genetic mechanisms of body patterning are now revealing opportunities to combine developmental biology, evolutionary biology, and even paleontology, in a coherent manner. Future progress in this area also will depend on combining the macroevolutionary data from comparisons of various species with microevolutionary studies to understand how variation actually arises.

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