



Review

Models for patterning primary embryonic body axes: The role of space and time



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ABSTRACT

Models for the generation and interpretation of spatial patterns are discussed. Crucial for these processes is an intimate link between self-enhancing and antagonistic reactions. For spatial patterning, long-ranging antagonistic reactions are required that restrict the self-enhancing reactions to generate organizing regions. Self-enhancement is also required for a permanent switch-like activation of genes. This self-enhancement is antagonized by the mutual repression of genes, making sure that in a particular cell only one gene of a set of possible genes become activated – a long range inhibition in the ‘gene space’. The understanding how the main body axes are initiated becomes more straightforward if the evolutionary ancestral head/brain pattern and the trunk pattern is considered separately. To activate a specific gene at particular concentration of morphogenetic gradient, observations are compatible with a systematic and time-requiring ‘promotion’ from one gene to the next until the local concentration is insufficient to accomplish a further promotion. The achieved determination is stable against a fading of the morphogen, as required to allow substantial growth. Minor modifications lead to a purely time-dependent activation of genes; both mechanisms are involved to pattern the anteroposterior axis. A mutual activation of cell states that locally exclude each other accounts for many features of the segmental patterning of the trunk. A possible scenario for the evolutionary invention of segmentation is discussed that is based on a reemployment of interactions involved in asexual reproduction.

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Development of a higher organism starts, as a rule with a single cell and proceeds, of course, under the control of genes. Since the genetic material is essentially the same in every cell, a central question is how the correct arrangement of differentiated cells is achieved. A most important step on the way from the fertilized egg to an adult organism is the setting up of the primary body axes, anteroposterior (AP) and mediolateral/dorsoventral (DV). In this process, organizing regions – small nests of cells that act as sources or sinks of signaling molecules – play an important role. The Spemann organizer is a prominent example. This organizer is usually regarded as the only organizer that exists in vertebrates, raising the question how a single organizer can specify the cells along the two major body axes that are oriented perpendicular to each other. Moreover, DV patterning has to occur along the long extended AP axis. This task cannot be accomplished by a patch-like organizer directly. A local signaling source would lead to a conical positional information profile with a constant slope into all directions, which is clearly insufficient to specify the DV axis. Models will be discussed that account for the generation and alignment of the main body axes.

The formation of organizing regions requires interactions in which local self-enhancement and long-range inhibition is involved, discussed in detail elsewhere [1–3]. The interaction of the self-enhancing Nodal with the antagonistically acting Lefty is an example [4,5]. Such interactions can generate patterns in an initially homogeneous assembly of cells. For embryos that start with a large size such as the amphibian embryo, the employment of maternal determinants is an appropriate strategy. By making only a small part of the embryo competent for organizer formation, localized determinants only allow a single organizer to be formed. Maternal determinants are not required if development starts as a small nest of cells such as it is the case in mouse or chick development. In this case, the self-regulatory features of pattern-forming reactions allow complete development in fragments even if the organizer is removed [6]. The formation of several embryos after early fragmentation of a chicken embryo is an example [7].

The generation of organizing regions requires communication between cells. If based on diffusion, the range of this signaling is restricted to short distances. Thus, these patterns can only be generated at small scales during early stages of development and have to be converted into a pattern of stable cell determinations by activating particular genes. The activities of these genes have to be maintained even if the evoking signals are no longer available. Complementary to models for setting up positional information for the body axes, models for the stable activation of genes under the influence of the resulting signal distributions will be discussed. It will be shown that activation of the correct gene at a particular position is a time-requiring process.

1. Axes formation in two steps: the head and the trunk

Understanding of the patterning along the main body axes of vertebrates is much facilitated if it is realized that different mechanisms are involved in patterning the head and in the trunk. This is true for both the patterning along the AP and the DV axes. Several observations suggest that the AP pattern in the brain is under control of a Wnt gradient that is generated at the blastopore/marginal zone [8–10]; (reviewed in [11]). The region of forebrain formation has the largest distance to the blastopore and emerges at a low WNT concentration, suggesting that the forebrain is the default state. Thus, the first steps in the AP patterning of the brain can be regarded as an example where a morphogen gradient accomplishes posteriorization by gene activation in a concentration- and thus position-dependending manner. In contrast, the AP patterning of the trunk is achieved by a sequential posterior elongation. In

cells close to the blastopore but with the exemption of the organizer region, new Hox genes become activated in a sequential way, causing specification of more and more posterior structures – a time-dependent process [12] (Durstun and Zhu, in this issue). Although both mechanisms overtly look very different, as shown below, modeling revealed that gene activation under the influence of a static gradient has also a strong time-dependent component, suggesting that interpretation of a gradient, e.g., in the brain and the time-dependent posteriorization in the trunk shares common elements.

Pronounced differences between brain and trunk patterning also exist for the patterning of the DV axis. For the patterning of amphibian brain it is crucial that cells derived from the Spemann organizer move underneath the ectoderm, forming the prechordal plate and induce neuronal tissue in the overlying ectoderm [13]. The prechordal plate is the precondition to form the midline, the dorsal-most structure from which the distance of the cells is measured, so to say, a *reference line*. In contrast, for midline formation of the trunk, cells near the blastopore (marginal zone) move toward the organizer (node), causing a conversion a ring perpendicular to the AP axis into a rod-like structure parallel to the AP axis. This process will be discussed further below in more details. The two very different functions of the organizer become established very early by a subdivision into a head- and a tail-organizer [14].

Frequently the Spemann-organizer is assumed to provide the positional information for organizing the AP axis [14]. In the view of the model proposed, this conclusion is partially misleading and results from the fact that most AP-markers are absent if the organizer is missing. However, most of these markers are neuronal markers that disappear if no midline is formed. Thus, the loss of anterior AP markers in the absence of the organizer is caused by a non-functional DV patterning. In this relation a very instructive set of experiments has been done by Ober and Schulte-Merker in the zebra fish [15]. By removing required maternal components, they obtained embryos reliably devoid of any organizer. To visualize the AP patterning they removed all BMP signaling, allowing in this way the expression of neuronal markers. Genes like *Otx* and *Krox20* were expressed at nearly normal positions but in a completely radially-symmetric way, illustrating that the activation of the anterior AP genes do not require the organizer. However, as discussed further below, the organizer plays a crucial role in the AP patterning of the trunk by terminating the time-dependent posteriorization.

2. The separation of axes formation into a brain- and a trunk-part has an evolutionary justification

Coelenterates are assumed to represent a basal branch of the metazoan evolutionary tree. A comparison of the gene expression patterns in the radial-symmetric freshwater polyp *Hydra* – a much-investigated Coelenterate – and homologous genes in higher organisms suggested that the body column of an ancestral sac-like creature with a single opening evolved into the brain of higher organisms; the ancestral oral-aboral pattern evolved in the head/brain AP-pattern [16]. *Wnt* and *Brachyury* are expressed at the tip of the hypostome and at the most posterior region in higher organisms, suggesting that, in contrast to a naïve expectation, the so-called *Hydra* head is the most-posterior structure, corresponding to the blastopore in higher organisms (Fig. 1). This view is supported by the expression patterns of several genes. *Otx*, a gene characteristic for the fore- and midbrain in vertebrates, is expressed in the whole body column of *hydra* except of the hypostome and the foot [17]. The posterior border of *Otx* expression, located in *hydra* between the tentacles and the hypostome, became an important secondary organizer in vertebrates, the midbrain–hindbrain

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