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Review

Review: Time–space translation regulates trunk axial patterning in the early vertebrate embryo

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ABSTRACT

Here, we review a recently discovered developmental mechanism. Anterior–posterior positional information for the vertebrate trunk is generated by sequential interactions between a timer in the early non-organiser mesoderm and the Spemann organiser. The timer is characterised by temporally colinear activation of a series of Hox genes in the early ventral and lateral mesoderm (i.e., the non-organiser mesoderm) of the Xenopus gastrula. This early Hox gene expression is transient, unless it is stabilised by signals from the Spemann organiser. The non-organiser mesoderm (NOM) and the Spemann organiser undergo timed interactions during gastrulation which lead to the formation of an anterior–posterior axis and stable Hox gene expression. When separated from each other, neither non-organiser mesoderm nor the Spemann organiser is able to induce anterior–posterior pattern formation of the trunk. We present a model describing that NOM acquires transiently stable hox codes and spatial colinearity after involution into the gastrula and that convergence and extension then continually bring new cells from the NOM within the range of organiser signals that cause transfer of the mesodermal pattern to a stable pattern in neurectoderm and thereby create patterned axial structures. In doing so, the age of the non-organiser mesoderm, but not the age of the organiser, defines positional values along the anterior–posterior axis. We postulate that the temporal information from the non-organiser mesoderm is linked to mesodermal Hox expression. The role of the organiser was investigated further and this turns out to be only the induction of neural tissue. Apparently, development of a stable axial hox pattern requires neural hox patterning.

Contents

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Introduction Hox colinearity, and A–P patterning

It has long been known that vertebrate Hox genes are closely clustered in genetic complexes that show temporal and spatial colinearity. The time and (axial anteroposterior) position of expression of each hox gene correlate with its genetic position in the complex. The most 3′ gene is expressed first and most anteriorly and the most 5′ gene last and most posteriorly. It has been argued that temporal colinearity is the primary property. This close clustering and colinearity is a rare characteristic in evolution. In its extreme form, it is limited to the vertebrates [1]. Hox colinearity is at the centre of modern thinking about vertebrate hox genes. It obviously provides a potential mechanism for patterning hox expressing structures like the main body axis and the developing limb. Although this aspect is clearly very important, the question of how temporal colinearity could pattern an axis has not received much attention. There are a few ideas about this. Duboule proposed that localised growth control could combine with temporal colinearity to pattern an axis in his Einbahnstrasse model [2]. Iimura and Pourquie [3] proposed that this patterning occurs via temporally collinear control of gastrulation cell movements by hox genes. But there is very little research into these concepts nor any detailed mechanistic explanation or model as to how hox temporal colinearity could pattern an axis. Nearly all extant models concern morphogen gradients and use hox genes only as individual targets of gradient morphogens (e.g., 4, 5, 6, 7). The purpose of this article is to review and discuss studies that have investigated the connection between Hox colinearity and axial patterning. These studies led to a specific model featuring time space translation and an interaction between hox expressing non-organiser mesoderm and the Spemann Organiser.

The mechanism of hox colinearity

It is evident that Hox genes lie at the heart of axial patterning [8]. Their temporally colinear expression in the Xenopus non-organiser mesoderm coincides with the generation of A–P identities in this tissue. How temporal colinearity in the Hox clusters is achieved is not yet clear. Global control regions outside the Hox clusters might play a role in this [9]. Progressive opening of the chromatin in the Hox clusters has also been proposed as part of the mechanism [10]. At any rate, all who have speculated about the nature of Hox colinearity have assumed that this is regulated at the level of transcription. More recently, it became clear that the transcription of the Hox clusters is more complex than the simple expression of the individual Hox genes. Mainguy et al. [11] have shown that the mouse and human Hox clusters generate many polycistronic transcripts and that large parts of them are transcribed both in the sense and the antisense directions. Differential splicing of large transcripts and sense-antisense pairing of mRNAs can also be ways by which the abundance of Hox gene transcripts are regulated, and temporal colinearity could be achieved at the posttranscriptional level. MicroRNAs are also known to regulate the expression of other genes posttranscriptionally (see for review [12]. Genes encoding small non-coding RNA's of the Mir family have been found in the Hox clusters and have been shown to regulate the availability of Hox mRNA's [13,14].

The confusion of the axes

The A–P axis of vertebrates arises during gastrulation. The internalizing mesoderm sets up the A–P axis. The first (organiser) mesoderm to internalize makes the head. The last forms the tail [15–17].

This process has been studied in Xenopus and zebrafish, where there is however also evidence for prelocalisation of A–P identity across the dorsoventral axis in earlier pregastrula embryos [18–22]. This appears to reflect a predisposition of more ventral early mesoderm to become more posterior later. What is confusing about this is that, at this early stage of development, the future A–P axis coincides with what is called the future D–V axis and this seems to be reflected by polarisation of genes concerned with both of these axes and of upstream factors common to both. Meinhardt [23] has pointed out that one reference point (organiser) cannot set up two axes. We think the axes separate at least partly due to a space time translation mechanism during gastrulation. We agree with Stern [24,25] that the A–P axis is at least partly a time axis. There are systematic differences in the timing of the relevant gastrulation movements of mesoderm at different d/v locations.

Spemann organiser (SO) and non-organiser mesoderm (NOM)

The early dorsoventral differences in the embryo cause the Xenopus gastrula to contain two kinds of mesoderm: Spemann organiser (SO), which is dorsal, and non-organiser mesoderm (NOM), which is ventrolateral. At one stage it was thought that the organiser provided the A–P positional information. Spemann published a paper in 1931 which proposed head and tail organisers [26] and there were even proposals of head, tail and middle organisers [27–30]. More recently, it has become clear that, while there is a head organiser that encodes head specificity, by blocking Wnt signalling [31] and a trunk organiser that does not block Wnt., at least some of the spatial information in the posterior (trunk), hox expressing part of the axis, comes from the NOM and its derivatives [5,6,32,33]. We show, in fact, below, that the trunk organiser is not informational for A–P positional values. In general, it has become clear that an important aspect of the genesis of A–P pattern is the transfer of A–P information from NOM mesoderm to neurectoderm, during regionalisation of the central nervous system [5,6,30,32]. We conclude (below) that the trunk organiser provides no positional information but enables transfer of this information from NOM to the neurectoderm.

Hox genes in early Xenopus development and a comment on early embryos of other vertebrates

There is a comparable early pattern of hox expression in embryos in gastrulae of each of the families of vertebrates that have been well studied. Fish (zebrafish) [35], amphibians [33], birds (chicken) [36], and mammals (mouse) [37].

In the following paragraphs, we review our earlier findings [33,38].

In *Xenopus laevis*, there is a temporally colinear sequence of hox gene expression in the non involuted ventrolateral non-organiser mesoderm (NOM) in the gastrula but no axial hox pattern. The first hox gene (Hoxd1) starts expression at the beginning of gastrulation (st. 10.25). The rest follow in a temporally collinear sequence during the course of