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Review

Hox gene regulation and timing in embryogenesis

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ABSTRACT

Hox genes are critical regulators of embryonic development in bilaterian animals. They exhibit a unique mode of transcriptional regulation where the position of the genes along the chromosome corresponds to the time and place of their expression during development. The sequential temporal activation of these genes in the primitive streak helps determining their subsequent pattern of expression along the anterior–posterior axis of the embryo, yet the precise correspondence between these two collinear processes is not fully understood. In addition, vertebrate *Hox* genes evolved similar modes of regulation along secondary body axes, such as the developing limbs. We review the current understanding of the mechanisms operating during activation, maintenance and silencing of *Hox* gene expression in these various contexts, and discuss the evolutionary significance of their genomic organization.

Contents

1. Introduction

Development of a multicellular organism from a single cell is an intricate process. It relies on myriads of transcription factors, which must be present in the right cell at the right time. *Hox* genes, which encode homeo-domain containing transcription factors, control the patterning of bilaterian embryos along their anterior–posterior axis, from the hindbrain down to the caudal end [1]. In both fruit flies and mice, deletion of a single *Hox* gene leads to altered axial identities and transformation of specific embryonic structures into more anterior ones (*e.g.* Refs. [2–4]). Conversely, ectopic expression of a single *Hox* gene can also result in a posterior transformation or loss of the body structures [5–8]. In addition to this ancestral role, *Hox* genes also evolved novel function in the course of evolution. For instance, in tetrapods, *Hox* genes are essential for the outgrowth and patterning of limbs along both the anterior–posterior and proximal–distal axes [9].

Given the critical role of the *Hox* genes in animal development, the pattern and time of their expression must be tightly controlled. The regulation of *Hox* genes is achieved mostly at the transcriptional level, but translational control has also been documented [10]. The mechanisms of transcriptional regulation are dictated by the organization of the genes in clusters [11]. This type of genomic organization allows for the sharing of nuclear space, chromatin

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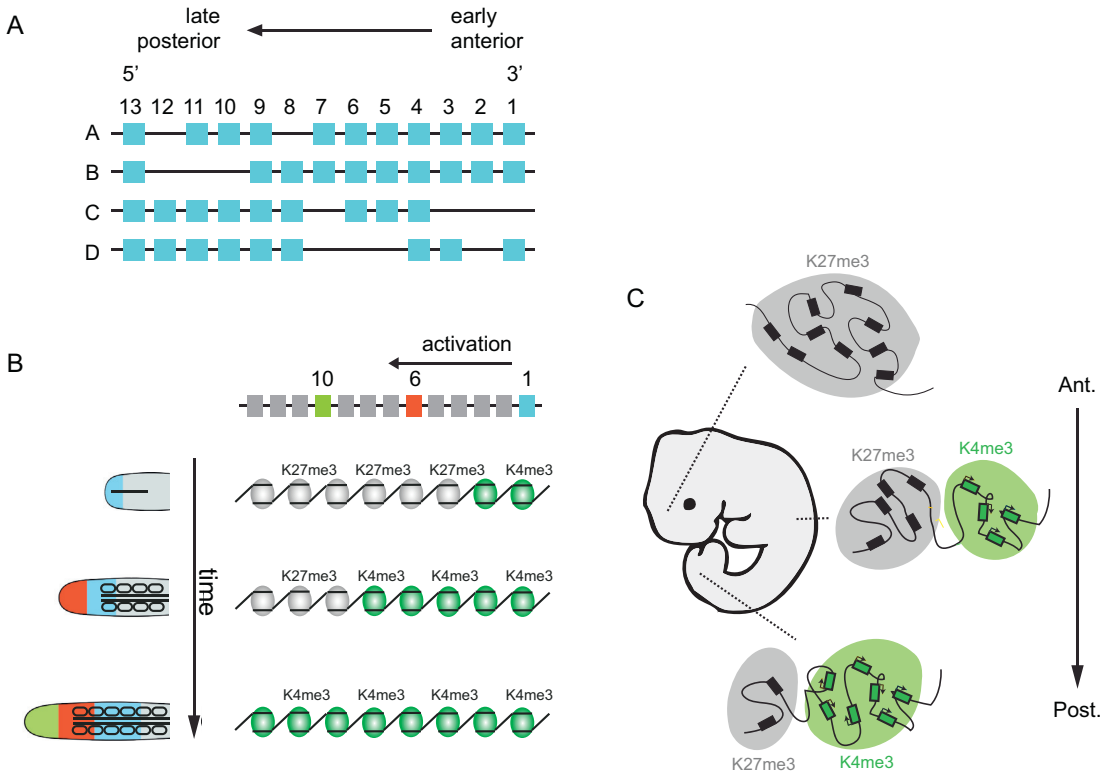

Fig. 1. *Hox* gene clusters and collinearity. (A) In mammals, four *Hox* genes clusters (*HoxA–D*) share similar organization. *Hox* genes are classified in 13 paralogy groups. Genes located on the 3′ side of each cluster are activated early in development, and in anterior tissues, while 5′ located genes are expressed progressively later and in more posterior regions (temporal and spatial collinearity). (B) Chromatin dynamics and temporal collinearity. A transition in histone modifications over the cluster accompanies transcriptional activation during axis extension. The whole cluster is initially labeled with the repressive mark H3K27me3 (grey). This mark is progressively erased and replaced by H3K4me3 (green) in parallel with gene activation. The schemes on the left illustrate the progressive activation of *Hox* genes along with the extension of the anterior–posterior axis, with the expression of representative genes from different paralogy groups: *Hox1* (blue), *Hox6* (red) and *Hox10* (green). (C) Higher-order chromatin organization and spatial collinearity. *Hox* clusters adopt compact structures in regions of the embryo where they are silent, such as the forebrain (top). Along the anterior–posterior axis, active and silent genes segregate in separate compartments (middle), labeled by H3K4me3 (active, green) or H3K27me3 (silent, grey). In more posterior areas, the majority of *Hox* genes are found in the active compartment. Panels B and C are inspired by Refs. [22] and [55], respectively.

structure, common regulatory elements, such as enhancers, and even promoters. As a result, the time and place of *Hox* genes expression are largely determined by the relative position of each gene within its cluster [11]. This review addresses our current knowledge of the mechanisms controlling *Hox* genes expression during embryogenesis, focusing largely on the mammalian *Hox* clusters and including possible insights that can be gained from other species. For a more comprehensive review of *Hox* regulation in Drosophila, we recommend several recent articles [12,13].

2. Genomic organization and collinear expression of *Hox* genes

In many animal species *Hox* genes are clustered, and the conservation of gene order between distant species indicate that this organization is ancestral [11]. Invertebrates and chordates possess a single *Hox* cluster containing 8–15 genes [14]. In contrast, vertebrates have four *Hox* clusters (*HoxA*, *B*, *C* and *D*) as a result of two rounds of whole genome duplications (Fig. 1A) [11,15]. The ancestor of teleost fishes experienced another duplication of genome, which produced additional *Hox* gene clusters [14]. Based on sequence homology and chromosomal location *Hox* genes are assigned to 13 paralogy groups, where *Hox1* lies at the 3′ and *Hox13* is at the 5′ end of the cluster.

This exceptional genomic organization has important functional consequences, since the transcriptional activity of a given *Hox* gene depends on its position within the cluster, a phenomenon referred to as collinearity. Three distinct modes of collinearity have been reported: (1) spatial collinearity is a correspondence between the position of each *Hox* gene within the cluster and its anterior boundary of expression (Fig. 1) [16,17]. Accordingly, the genes located at the 3′ end of the cluster are transcribed in more anterior regions of the embryo compare to the genes situated at the 5′ end, which are expressed in more posterior areas. Spatial collinearity was observed in all bilaterians; even in species where genomic clustering was completely lost, as in the larvacean Oikopleura, *Hox* genes are expressed in nested anterior–posterior territories reminiscent of the patterns observed for their orthologous counterparts in species that kept the clustered organization [18]. The presence of *cis*-regulatory elements in close proximity to the *Hox* genes (see below) might explain why disintegration of the clusters in two or more pieces would be compatible with correct spatial expression patterns of *Hox* genes during development [11].

(2) In vertebrates, *Hox* genes become activated in the posterior part of the primitive streak in a time order that reflects their location within the clusters. Genes at the 3′ end of the clusters are activated first, whereas genes located at more 5′ positions are activated subsequently, a process referred to as temporal collinearity (Fig. 1A) [19]. This process takes place in parallel with the progressive extension of the anterior–posterior body axis in vertebrates. A proper timing of *Hox* genes activation is necessary for the correct specification and growth along the anterior–posterior axis as precocious activation of the 5′ located genes results in premature truncation of the embryos or loss of axial structures [7,20,21]. Genetic studies in mice demonstrated that *Hox* cluster integrity is essential for temporal collinearity [7,20,22], and accordingly, this

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