SnapShot: *Hox* Gene Regulation

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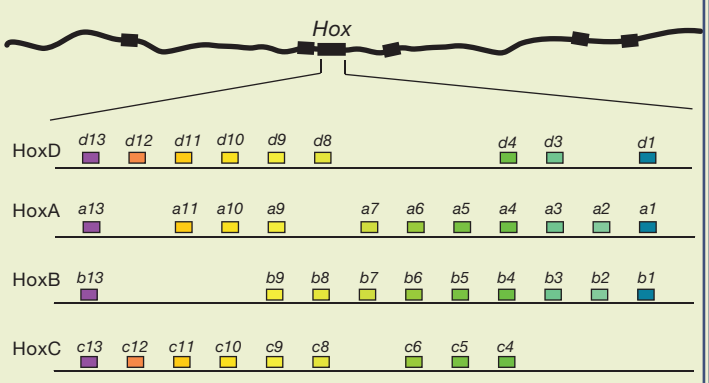
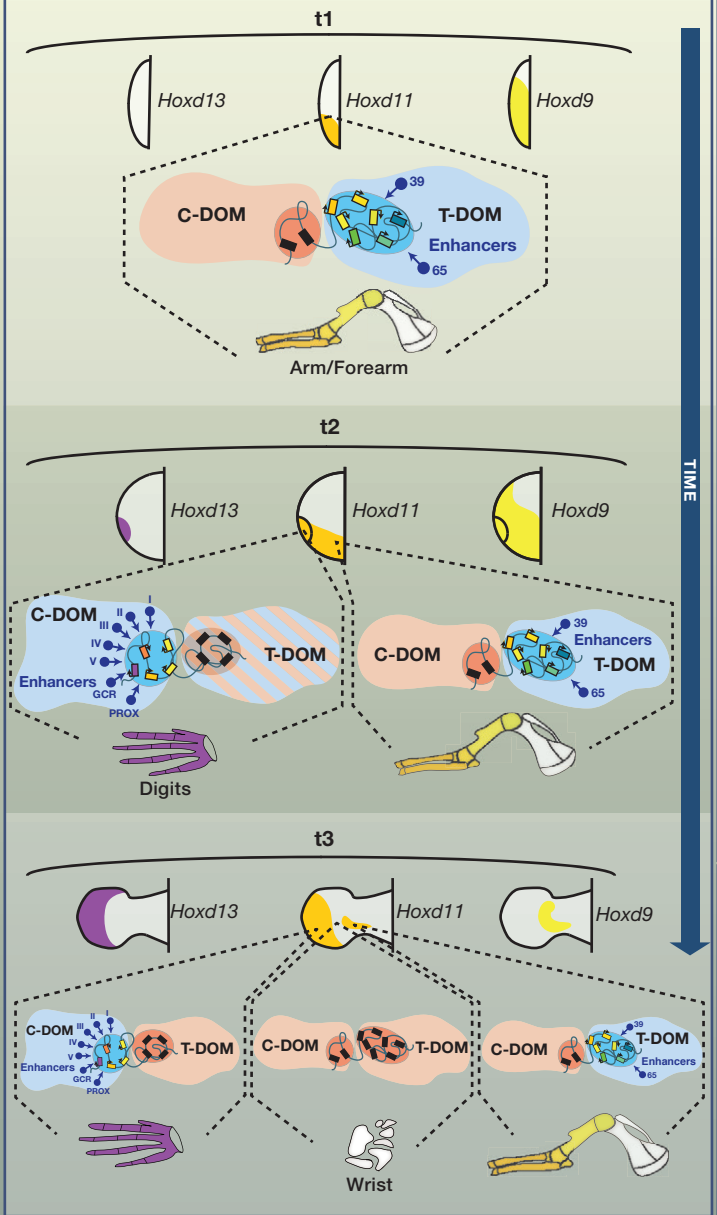
Cell

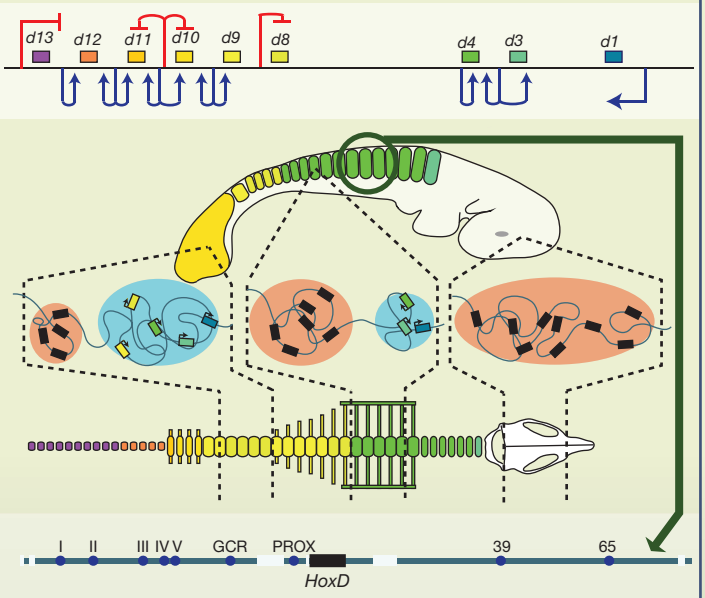
The mammalian Hox clusters



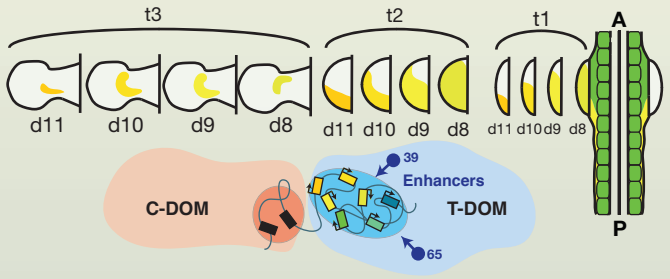
Switch in regulatory controls: the limb model



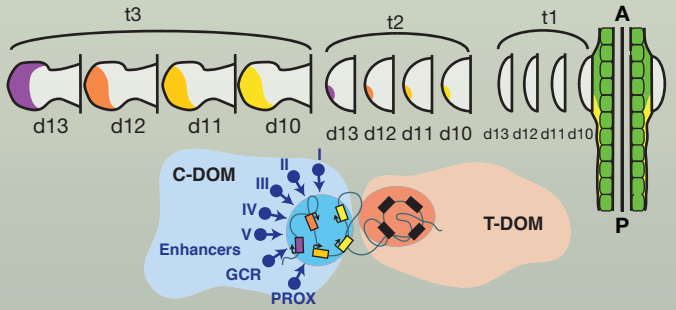
Regulation of *HoxD* gene in primary and secondary axes



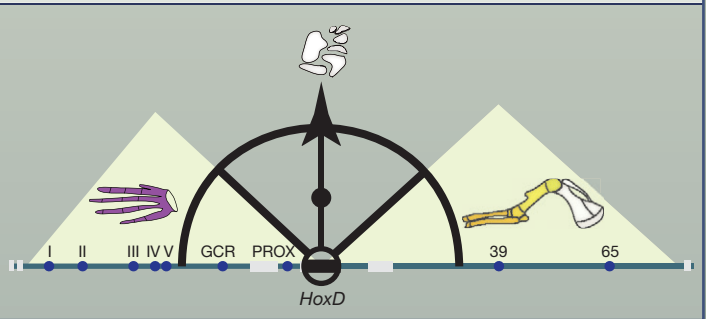
EARLY-PROXIMAL CONTROL OF HOXD EXPRESSION



LATE-DISTAL CONTROL OF HOXD EXPRESSION



Mechanism of *HoxD* collinear regulation in limbs



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Cell

The Mammalian *Hox* Clusters

In mammals, *Hox* genes are found in four genomic clusters—*HoxA*, *B*, *C*, and *D*—produced after two genome duplications occurring at the root of vertebrates. They encode a family of transcription factors that are critical for the organization of the body plan during animal development (Duboule, 2007; Krumlauf, 1994). *Hox* genes carrying the same number in different clusters are paralogous. That is to say that they derive from the same ancestral gene. Among the 13 groups of *Hox* genes, the paralogy is complete only in groups 13, 9, and 4, which contain all four genes. All *Hox* genes have the same 3′-to-5′ orientation, and the color code corresponds to the schemes below.

Regulation of *HoxD* Genes in Primary and Secondary Axes

During the development of the main body axis, *Hox* genes are activated in the mesoderm of the future somites, in the neural tube, and in the lateral plate mesoderm according to their position within their respective gene clusters: 3′ *Hox* genes, such as *Hoxd1*, are expressed early on and at anterior locations, whereas 5′ *Hox* genes, such as *Hoxd13*, are expressed later and more posteriorly. The correspondence between gene topology and the place and time of transcription are referred to as spatial and temporal collinearities, respectively. As exemplified with the *HoxD* locus, such regulatory controls mostly rely upon sequences located within the cluster (Tschopp et al., 2009) either with a positive (blue arrows) or negative (red arrows) effect. This axial collinear distribution of *Hox* transcripts is accompanied by the unfolding of a 3D chromatin domain (Noordermeer et al., 2011; Soshnikova and Duboule, 2009) composed of two antagonist compartments containing either active genes marked with H3K4me3 (light blue) or inactive genes marked with H3K27me3 (red). At different body positions, the sizes of these two compartments vary, with the positive domain increasing toward the posterior end.

Hox genes also control the morphogenesis of secondary axes such as the limbs. As the limb bud emerges from lateral plate mesoderm (green arrow), *HoxD* genes are activated by remote enhancers located within two gene deserts flanking the cluster. Initially, an early transcriptional activation relies on enhancers present within a telomeric regulatory landscape, matching a topological domain (T-DOM). This phase organizes proximal limb structures such as the arm and forearm (Andrey et al., 2013; Tarchini and Duboule, 2006). Subsequently, a second wave of transcription occurs, controlled by the opposite regulatory landscape (C-DOM), which accompanies the emergence of digits (Montavon et al., 2011). Genes at the extremity of the cluster, such as *Hoxd13* and *Hoxd12*, only respond to the later phase, whereas genes in the center of the cluster, such as *Hoxd8*, mostly respond to the former. Genes located in between, including *Hoxd11*, *Hoxd10*, and *Hoxd9*, respond to both types of regulation in different cells (Kmita et al., 2002).

Switch in Regulatory Controls: The Limb Model

First, the telomeric enhancers are recruited to control the expression of *Hoxd8* to *Hoxd11* during the early phase of limb budding. These genes are localized in the T-DOM. In contrast, *Hoxd12* and *Hoxd13* reside in the C-DOM, which is inactive at this early time point (Andrey et al., 2013). Second, as this phase continues in the proximal part of the limb bud (scheme on the right), the late phase starts in a subset of cells located at the posterior-distal aspect of the bud (scheme on the left). In these latter cells, centromeric enhancers are progressively recruited and activate the transcription of *Hoxd12* and *Hoxd13*. Some of the genes that are active during the early phase, such as *Hoxd11* and *Hoxd9*, reallocate their contacts from the T-DOM toward the C-DOM enhancers. In these presumptive digit cells, the telomeric enhancers are progressively disconnected from their target genes and are switched off.

Because the limb grows distally, cells implementing the C-DOM regulation at the distal tip will progressively separate from the proximal cell population. As a consequence, an intermediate cellular territory will appear, where cells implement neither C-DOM nor T-DOM regulation and are thus negative for *HoxD* transcripts. This domain, which eventually generates the mesopodium (wrist or ankle), contains cells that have switched off their T-DOM enhancers and have turned to the C-DOM regulation. However, the latter is not actively maintained due to an ever-increasing distance to a potential source of signals released from the distal tip.

Mechanism of *HoxD* Collinear Regulation in Limbs

Two distinct regulatory landscapes, functionally and topologically independent from one another, regulate *HoxD* gene transcription during tetrapod limb development. The ability of each gene to respond to one of these two types of regulation is determined by its capacity to make physical contacts with the corresponding enhancers, and this capacity is determined by the position of the gene within the cluster. This bimodal regulation eventually sets the final dosage of various *HoxD* transcripts within each presumptive limb segments, thereby patterning the final morphology of the appendages. This regulatory system gives a mechanistic ground to *HoxD* gene collinearity in tetrapod limbs and provides a framework for understanding *Hox* gene regulation in other contexts.

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