Activation of HOX genes during differentiation

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Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

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Literature references


Reactome database release: 69

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Activation of HOX genes during differentiation

Stable identifier: R-HSA-5619507

Hox genes encode proteins that contain the DNA-binding homeobox motif and control early patterning of segments in the embryo as well as later events in development (reviewed in Rezsohazy et al. 2015). Mammals have 39 Hox genes arrayed in 4 linear clusters, with each cluster containing 9 to 11 genes. Based on homologies, the genes have been assigned to 13 paralogous groups. The nomenclature of Hox genes uses a letter to indicate the cluster and a number to indicate the paralog group. For example, HOXA4 is the gene in cluster A that is most similar with genes of paralog group 4 from other clusters.

One of the most striking aspects of mammalian Hox gene function is the mechanism of their activation during embryogenesis: the order of genes in a cluster correlates with the timing and location of their activation such that genes at the 3' end of a cluster are activated first and genes at the 5' end of a cluster are activated last. (5' and 3' refer to the transcriptional orientation of the genes in the cluster.) Because development of segments of the embryo proceeds from anterior to posterior this means that the anterior boundaries of expression of 3' genes are more anterior (rostral) and the anterior boundaries of expression of 5' genes are more posterior (caudal).

Expression of HOX genes initiates in the posterior primitive streak at the beginning of gastrulation at approximately E7.5 in mouse. As gastrulation proceeds, further 5' genes are sequentially activated and they too undergo the same chromatin changes and migration. After formation of the axis of the embryo, similar waves of activation of HOXA and HOXD clusters occur in developing limbs beginning at about E9. Retinoids, especially all trans retinoic acid (atRA), participate in initiating the process via retinoid receptors. Other factors such as FGFs and Wnt, also regulate Hox expression. After activation, Hox genes participate in maintaining their own expression (autoregulation), activating later, 5' Hox genes, and repressing prior, 3' Hox genes (crossregulation). Differentiation of embryonal carcinoma cells and embryonic stem cells in response to retinoic acid is used to model the process in vitro (reviewed in Gudas et al. 2013).
Activation of Hox genes is accompanied by a change from bivalent chromatin to euchromatin (reviewed in Soshnikova and Duboule 2009). Bivalent chromatin has extensive methylation of lysine-9 on histone H3 (H3K9me3), a repressive mark, with interspersed punctate regions of methylation of lysine-4 on histone H3 (H3K4me2, H3K4me3), an activating mark. Euchromatization initiates at the 3' ends of clusters and proceeds towards the 5' ends, with the euchromatin migrating to an active region of the nucleus (reviewed in Montavon and Duboule 2013). This change in chromatin reflects a loss of H3K27me3 and a gain of H3K4me2,3. Polycomb repressive complexes bind H3K27me3 and are responsible for maintenance of repression, KDM6A and KDM6B histone demethylases remove H3K27me3, and members of the trithorax family of histone methylases (KMT2A, KMT2C, KMT2D) methylate H3K4.

**Literature references**


**Editions**

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Activation of anterior HOX genes in hindbrain development during early embryogenesis

Location: Activation of HOX genes during differentiation

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In mammals, anterior Hox genes may be defined as paralog groups 1 to 4 (Natale et al. 2011), which are involved in development of the hindbrain through sequential expression in the rhombomeres, transient segments of the neural tube that form during development of the hindbrain (reviewed in Alexander et al. 2009, Soshnikova and Duboule 2009, Tumpel et al. 2009, Mallo et al. 2010, Andrey and Duboule 2014). Hox gene activation during mammalian development has been most thoroughly studied in mouse embryos and the results have been extended to human development by in vitro experiments with human embryonal carcinoma cells and human embryonic stem cells.

Expression of a typical anterior Hox gene has an anterior boundary located at the junction between two rhombomeres and continues caudally to regulate segmentation and segmental fate in ectoderm, mesoderm, and endoderm. Anterior boundaries of expression of successive Hox paralog groups are generally separated from each other by 2 rhombomeres. For example, HOXB2 is expressed in rhombomere 3 (r3) and caudally while HOXB3 is expressed in r5 and caudally. Exceptions exist, however, as HOXA1, HOXA2, and HOXB1 do not follow the rule and HOXD1 and HOXC4 are not expressed in rhombomeres. Hox genes within a Hox cluster are expressed colinearly: the gene at the 3’ end of the cluster is expressed earliest, and hence most anteriorly, then genes 5’ are activated sequentially in the same order as they occur in the cluster.

Activation of expression occurs epigenetically by loss of polycomb repressive complexes and change of bivalent chromatin to active chromatin through, in part, the actions of trithorax family proteins (reviewed in Soshnikova and Duboule 2009). Hox gene expression initiates in the posterior primitive streak that will contribute to extraembryonic mesoderm. Expression then extends anteriorly into the cells that will become the embryo, where expression is first observed in presumptive lateral plate mesoderm and is transmitted to both paraxial mesoderm and neurectoderm formed by gastrulation along the primitive streak (reviewed in Deschamps et al. 1999, Casaca et al. 2014).
Prior to establishment of the rhombomeres, expression of HOXA1 and HOXB1 is initiated near the future site of r3 and caudally by a gradient of retinoic acid (RA). (Mechanisms of retinoic acid signaling are reviewed in Cunningham and Duester 2015.) The RA is generated by the ALDH1A2 (RALDH2) enzyme located in somites flanking the caudal hindbrain and degraded by CYP26 enzymes expressed initially in anterior neural ectoderm of the early gastrula and then throughout most of the hindbrain (reviewed in White and Schilling 2008). HOXA1 with PBX1,2 and MEIS2 directly activate transcription of ALDH1A2 to maintain retinoic acid synthesis in the somitic mesoderm (Vitobello et al. 2011). Differentiation of embryonal carcinoma cells and embryonic stem cells in response to retinoic acid is used to model the process of differentiation in vitro (reviewed in Soprano et al. 2007, Gudas et al. 2013).

HOXA1 appears to set the anterior limit of HOXB1 expression (Barrow et al. 2000). HOXB1 initiates expression of EGR2 (KROX20) in presumptive r3. EGR2 then activates HOXA2 expression in r3 and r5 while HOXB1, together with PBX1 and MEIS:PKNOX1 (MEIS:PREP), activates expression of HOXA2 in r4 and caudal rhombomeres. AP-2 transcription factors maintain expression of HOXA2 in neural crest cells (Maconochie et al. 1999). HOXB1 also activates expression of HOXB2 in r3 and caudal rhombomeres. EGR2 negatively regulates HOXB1 so that by the time rhombomeres appear, HOXB1 is restricted to r4 and HOXA1 is no longer detectable (Barrow et al. 2000). EGR2 and MAFB (Kreisler) then activate HOXA3 and HOXB3 in r5 and caudal rhombomeres. Retinoic acid activates HOXA4, HOXB4, and HOXD4 in r7, the final rhombomere. HOX proteins, in turn, activate expression of genes in combination with other factors, notably members of the TALE family of transcription factors (PBX, PREP, and MEIS, reviewed in Schulte and Frank 2014, Rezsohazy et al. 2015). HOX proteins also participate in non-transcriptional interactions (reviewed in Rezsohazy 2014). In zebrafish, Xenopus, and chicken factors such as Meis3, Fgf3, Fgf8, and vHNF regulate anterior hox genes (reviewed in Schulte and Frank 2014), however less is known about the roles of homologous factors in mammals.

Mutations in HOXA1 in humans have been observed to cause developmental abnormalities located mostly in the head and neck region (Tischfield et al. 2005, Bosley et al. 2008). A missense mutation in HOXA2 causes microtia, hearing impairment, and partially cleft palate (Alasti et al. 2008). A missense mutation in HOXB1 causes a similar phenotype to the Hoxb1 null mutation in mice: bilateral facial palsy, hearing loss, and strabismus (improper alignment of the eyes) (Webb et al. 2012).

**Literature references**


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