

HOX genes: The Rosetta Stone of the human cells biology

The *cell memory program* is a biological process that oversees several aspects of the cell life: i) where the new generated cell will be located ii) the fate of a new cell and the cell phenotype; iii) when it will manifest these features; iv) whether and how many cell divisions may perform; v) when will start apoptosis. Three gene families regulate the program: Polycomb family proteins induce a compact configuration of DNA-chromatin (heterochromatin) repressing HOX genes; Trithorax proteins induce an open configuration of DNA-chromatin (euchromatin), activating the HOX network. Finally, the HOX network that ensures the achievement of cell-specific gene programs mainly through the transcriptional control of the genes (Fig. 1). The Class I homeobox genes (HOX in human, Hox in mouse) are a transcription factor family, involved in embryo development containing a sequence of 183 nucleotides (homeobox) encoding a protein alpha helix-domain structure of 61 aminoacids (homeodomain); the homeodomain recognizes and binds a specific nucleotide sequence on DNA.

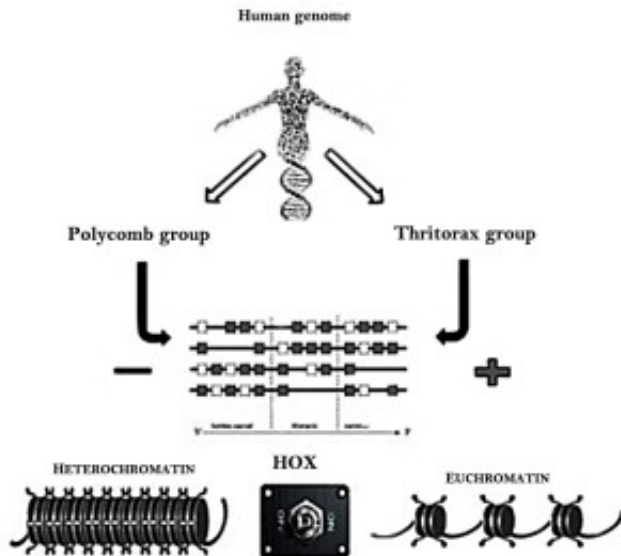


Fig. 1. The cell memory program (see the text).

The HOX gene family is arranged in four chromosomal loci each containing from 9 to 11 genes located on chromosomes: 7p15 HOXA, 17p21 HOXB, 12q13 HOXC and 2q31 HOXD. Besides, HOX can be aligned, based on the sequence similarity of the homeodomain, in 13 vertical paralogous groups following the overlapping of the 39 genes and based on homeodomain primary structure (Fig. 2). The HOX genes are involved in the hematopoietic stem cell differentiation. The HOX clusters, from HOXC4 to HOXC8 and HOXA1 are always involved in the characterization of hematopoietic stem cell phenotype, in the change of immunoglobulin class, in the permutation of the somatic cells and in lymphomagenesis. The HOX network plays a crucial role in the remodeling

of blood vessels during adult life. The meaning of HOX genes in the structuring of the heart has been shown for the first time in studies carried out on birds, *Drosophila* and the heart of amphibians. Subsequently, it has been deeply studied the role of HOX genes in determining of the anteroposterior polarity (A-P) in the vertebrates embryonic cardiac tube. The correct polarity during embryonic development of the cardiac tube in vertebrates, is crucial for the proper morphogenesis of the mature heart. The Hox genes *Hoxd3*, *Hoxa4*, and *Hoxd4* are upregulated during the early stages of heart development in chicken embryos. Moreover, *Hoxd3* is overexpressed in the region designed to the embryonic heart development, before forming of the cardiac tube.

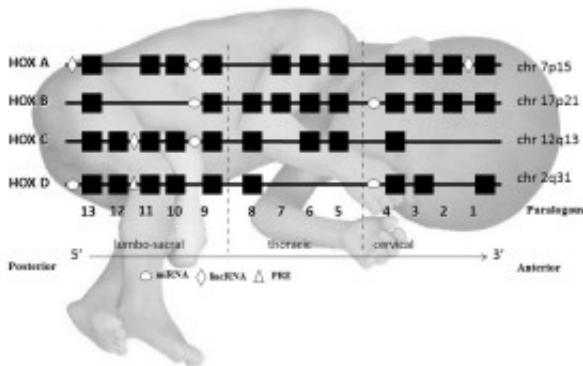


Fig. 2. Schematic representation of Class I Homeobox genes with position of lncRNA and miRNA inside the network (see the text).

Single mutations in *HOXA1* sequence, is crucial in the determination of severe cardiovascular malformations. Mice knock out for *Hoxa1*, show defects as interrupted aortic arch, aberrant subclavian artery and Tetralogy of Fallot. *Hoxa1* play a key role in the arrangement of the great arteries and heart outflow tract. Moreover, at the early stage of embryonic development, *Hoxa1* is expressed in the precursors of cardiac neural crest cells (NCCs), present into the heart. Mice knockout for *Hoxa3* gene, show cardiac abnormalities and links between circulatory and respiratory systems. The *HOXC5*, *HOXA5* and *HOXB5* expression, induce a development of new pharyngeal arches containing a new aortic arch artery with regular flow. *HOXC9* is overexpressed, in human smooth muscle cells and the cardiovascular system during embryogenesis.

The cardiovascular development represents the crucial role that HOX network plays in the arrangement of our body and structures. The cluster is able to regulate and control different gene programs, interacting with miRNAs and ncRNAs. Structural alterations: agenesis during embryonal development, adults malformation, neoplastic transformation, deregulation of physiological and metabolic processes are related to HOX gene aberrations. Maybe in the future The HOX network will be considered as "*Rosetta stone of human cell biology*".

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Publication

[Class I Homeobox Genes, "The Rosetta Stone of the Cell Biology", in the Regulation of Cardiovascular Development.](#)

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Curr Med Chem. 2016