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Short Commentary OMICS International

The Role of HOX Genes in the Control of Osteogenesis

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Introduction

The osteogenesis is a complex process that involves an accurate control of bone development and growth as well as remodeling during postnatal life. Although the understanding of the transcriptional control of osteogenesis is increased considerably, the molecular regulatory basis is still poorly understood [1]. In the near future, the knowledge about the role of transcriptional factors in the control of osteoblast differentiation consequent to post-genome will be expected. In order to identify the molecular mechanisms useful in the tissue regeneration and tissue engineering methodologies of clinical practice [2]. Bone development is regulated by 500 genes, particularly Fibroblast Growth Factor-4, Bone Morphogenetic Protein-4, lymphoid enhancer binding factor-1, cyclin dependent kinase inhibitor-1 and sonic hedgehog *(FGF4, SHH, BMP4*, *LEF1* and *p21*) genes, constitute the first regulators of osteogenesis; also homeobox-containing genes as Msx sonic hedgehog, distal-less homeobox and paired box (Msx, Dlx, PAX), are the best candidates in the control of cranio-facial development and organization (Figures 1-3) [3].

HOX Genes

Class I homeobox genes (*HOX* in mice and *HOX* in humans), are 39 transcription factors, mostly involved in the regulation of embryonic development program; The *HOX* gene structure is characterized by a sequence of 183 nucleotides encoding a homeodomain of 61 amino acid, able to recognize and bind, specific sequence on DNA. Moreover, *HOX* genes are able to activate or express specific genes mainly by means of its alpha-helix structure [4,5].

The *HOX* proteins are located on four chromosomal determining four clusters or loci (*HOXA* Chr 7p15.3, *HOX*B Chr 17q21.3, *HOXC* Chr 12q13.3 and *HOXD* Chr 2q31), each containing 9-11 genes. Furthermore, the *HOX* network can be aligned in 13 paralogous groups, considering the position of each single gene within the locus and sequence similarity of the homeodomain [6].

The *HOX* network takes part at the embryonic development starting from the gastrulation, determining the generation of spatio-temporal of embryonic biological structure and also *HOX* genes play a crucial role in the control of "cell memory program".

The cell memory is a biological process controlled by specific gene program, able to regulates the body's cells fate. The "cell memory program" contains whole information about gene functions and critical information related to cell cycle that are transferred, through the genome, from a cell to another cell using cell division [7]. Thrithorax, Polycomb and *HOX* genes are involved in the control of each phase of the memory program. In details, the Thrithorax gene family, leads to the DNA-transition from heterochromatin to euchromatin, promoting an open configuration of the DNA and the *HOX* genes transcription. Conversely, Polycomb cluster is able to control the DNA-transition

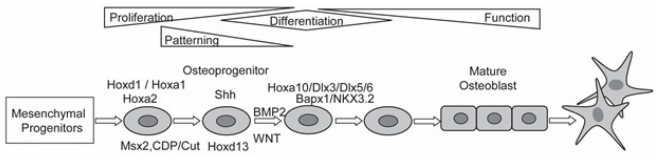

Figure 1: Mesenchymal progenitors that give rise to osteoblasts are initially marked by the transcription factor related to homeobox genes. In particolar *HOXA* and *HOXD* cluster, play a crucial role in the control of osteogenesis.

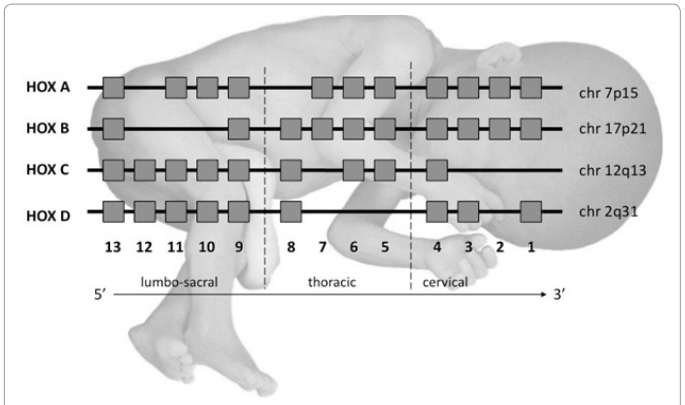

Figure 2: The *HOX* network takes part at the embryonic development starting from gastrulation.

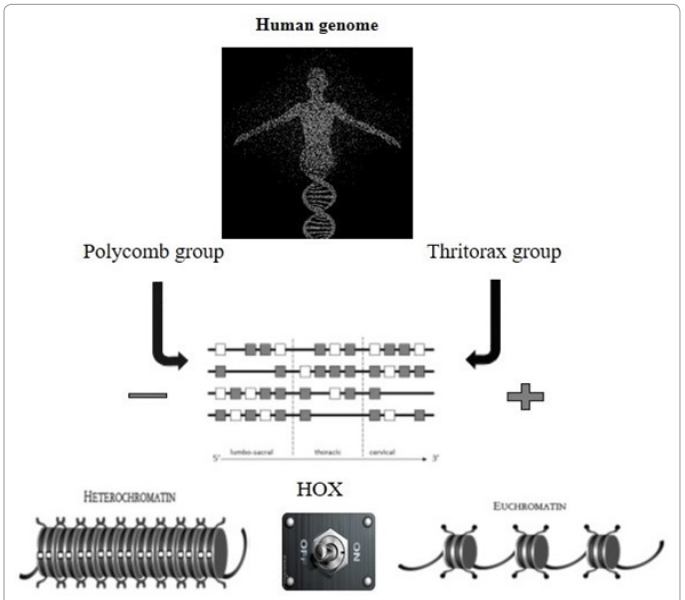

Figure 3: The *HOX* genes are the controller of the epigenetic change in the chromatin structure.

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from euchromatin to heterochromatin, blocking the *HOX* gene expression [7]. The *HOX* network, ensures the achievement of cell-specific gene programs through the transcriptional control of the gene expression [8]. Finally, Class-I homeobox proteins, regulate the stem cells differentiation in one of approximately 300 cellular phenotypes present in our body, mainly by means of accurate control of the cell-fate memory program [9].

Lymphoid-specific helicase (LSH) functions as a chromatin remodeling ATPase in mammals [10]. Since LSH also regulates the accessibility of DNA to de novo DNA methyltransferases [11] and LSH null mice lose up to 70% of DNA methylation globally [12], it has been suggested to play a role in the establishment and maintenance of DNA methylation during differentiation of embryonic lineage cells. Recent observation revealed that together with histone methyltransferases G9a/GLP complex, LSH is involved in the developmentally programmed DNA methylation, especially at the *HOX* loci [13]. Mechanistically, Lsh and G9a/GLP complex are very likely to maintain the DNA methylation via recruitment of DNMTs to the *HOX* loci [14]. As precise regulation of *HOX* genes is essential for the osteogenesis, investigation the chromatin loading of Lsh and the patterns of DNA methylation might create a novel direction for the study of the molecular basis that required for the osteogenesis. Many evidences have shown the involvement of Homeobox genes in bone formation. The upregulation of *HOX*A2 is crucial for repress osteogenesis [10,15]. Recently, it has been studied the role of *HOX*A10 in the control of osteoblasts differentiation; hyper-expression of *HOX*A10 was able to activate several osteoblast related genes like Osx; Osterix controls bone mineralization and osteoblasts differentiation. Therefore, *HOX*A10 gene was considered a key factor for: i) the proper timing, expression of specific osteogenesis markers; ii) correct mineral and matrix deposition during osteoblasts maturation [11,16].

Conclusion and Future Prospects

Class I homeobox genes are arranged like a biological chip able to decode the mechanism that controls the phases of cell differentiation. Furthermore, the *HOX* proteins and could be used like a model to study the ability of the cell to assume a specific phenotype during embryonic development. The limit of the tissue regeneration is related to the difficult at reproduce each single embryonic stage that characterized the cell differentiation because the sequence of the activation and repression of the specific molecular targets, is not clear yet. Moreover, it has not been understood, which system is able to control the determination of the different cell phenotypes. In my opinion, The *HOX* genes are the best candidates to play this function. Many evidences confirm the role of *HOX* genes in the control of the cell phenotype and their deregulation determine changes in the program of the cell memory, inducing morphological malformation, cellular neoplastic transformation and recently it has been demonstrated the involvement of *HOX* genes in different metabolic pathologies [3,17,18]. In conclusion, I consider the *HOX* cluster like "the Rosetta stone" of human cell biology.

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