A Genetic Overview of the *Hox* Gene

by Julio Francisco

Variation in the genome can lead to new phenotypes. Such newly expressed phenotypes can be beneficial to a group of organisms allowing them to strive in their environment. An example of such evolutionary innovation was the appearance of the *Hox* genes (also known as the homeotic genes). The *Hox* genes were first identified by Bridges in Drosophila flies and have been extensively studied over the course of years (1). It was determine that the *Hox* gene controls the body plan of animals from the antero-posterior axis.The following research review will give an overview of the *Hox* genes including the expression of the *Hox* gene, and the role of *Hox* gene in both stem cell development and regeneration process. Also, this paper will address the current researches being conducted in such area.

Due to the voluminous of researches, the following review will highlight three major areas. The following are the three topics that will be address:

1. Hox Gene Expression in Vertebrate Nervous System
2. Expression of *Hox* genes in Hematopoietic Stem Cells
3. The role of *Hox* gene in limb regeneration

Overall, this literature research will provide an in-depth information of the current knowledge of the *Hox* gene.

Hox Gene Regulation

Hox gene is divided into four genomic clusters (*Hoxa, Hoxb, Hoxc,* and *Hoxd*) located on four different chromosomes, consisting of 13 paralog groups (2). Such *Hox* genes varies from species to species. Each *Hox* gene is turn ON and OFF at a narrow range of time during early development (3). Also, each *Hox* gene expression is mediated directly by enhancer- and repressor-gene interaction or through histone modification.

First, *Hox* genes are regulated by enhancer and repressor elements.These enhancer elements are required since the *Hox* gene is located considerably far distance from the promoter and surrounded by gene-poor (called "deserts") region. In the process of transcribing the *Hox* gene, "desert" genes are transcribed, too. These "desert" genes are essential for the expression of *Hox* gene in which the complete removal of the "desert" gene would lead to full loss of *Hox* expression (4).

Furthermore, the repressor turn OFF the gene by binds to the promoter region and, thus, preventing the transcription from occurring (5). However, there is not only one set of *Hox* gene expressed. There are duplications of *Hox* genes expressed (6).

In addition to the genetic regulation, histone provides an additional level of complexity to gene expression. Expression of *Hox* gene is mediated by the methylation of histone. For example, Mallo and Alonso (2013) studied the methylation of two certain *Hox* gene, H3k27m3 and H3k4m3. These gene were analyzed at tip of a mouse embryo tail. The *Hox* gene expression was followed the disappearance of H3k27m3 by a trimethylation at Lys27 of histone H3 and appearance of H3k4m3 by a trimethylation at Lys4 of histone H3. Such research demonstrated the methylated pathway of *Hox* gene expression.

Also, the position in which the *Hox* gene is located plays a vital role in expression specificities. In other words, just having the *Hox* gene in the genome is not enough to cause particular specialization. The gene has to be located at particular locus to cause specialization.

Hox Gene Expression in Vertebrate Nervous System

Despite the fact that *Hox* genes are prominent regulatory of body morphology, current researches are looking into how the *Hox* genes are expressed in the nervous system of vertebrates. This section will discuss the *Hox* gene functional roles in the nervous system.

First, the brain and central nervous system (CNS) is highly ordered and diverse. Such orderly formation of the brain and CNS is governed by genetic activities. The *Hox* gene is one of many genes that play a vital role in arranging and patterning the CNS during development. It was reported that the

Hox gene is involved mainly in specifying the rhombomeres territory (e.g. the hindbrain and spinal cord) of the CNS. (3)

Also, studies showed that the *Hox* gene plays a particular role in neuronal differentiation and identification by directing the axons to reach their targets in response to environmental cues. If there was a misexpression of the *Hox* gene, this could result in the axon to maneuver into the incorrect location. For example, the misexpression of chick Hoxc-6 in the mesoderm resulted in the outgrowth of the spinal nerve axons. This was due to the "lack of instructive mesodermal signals" (3). Overall, the *Hox* gene is necessary for proper development of the nervous system.

Expression of Hox genes in Stem Cells

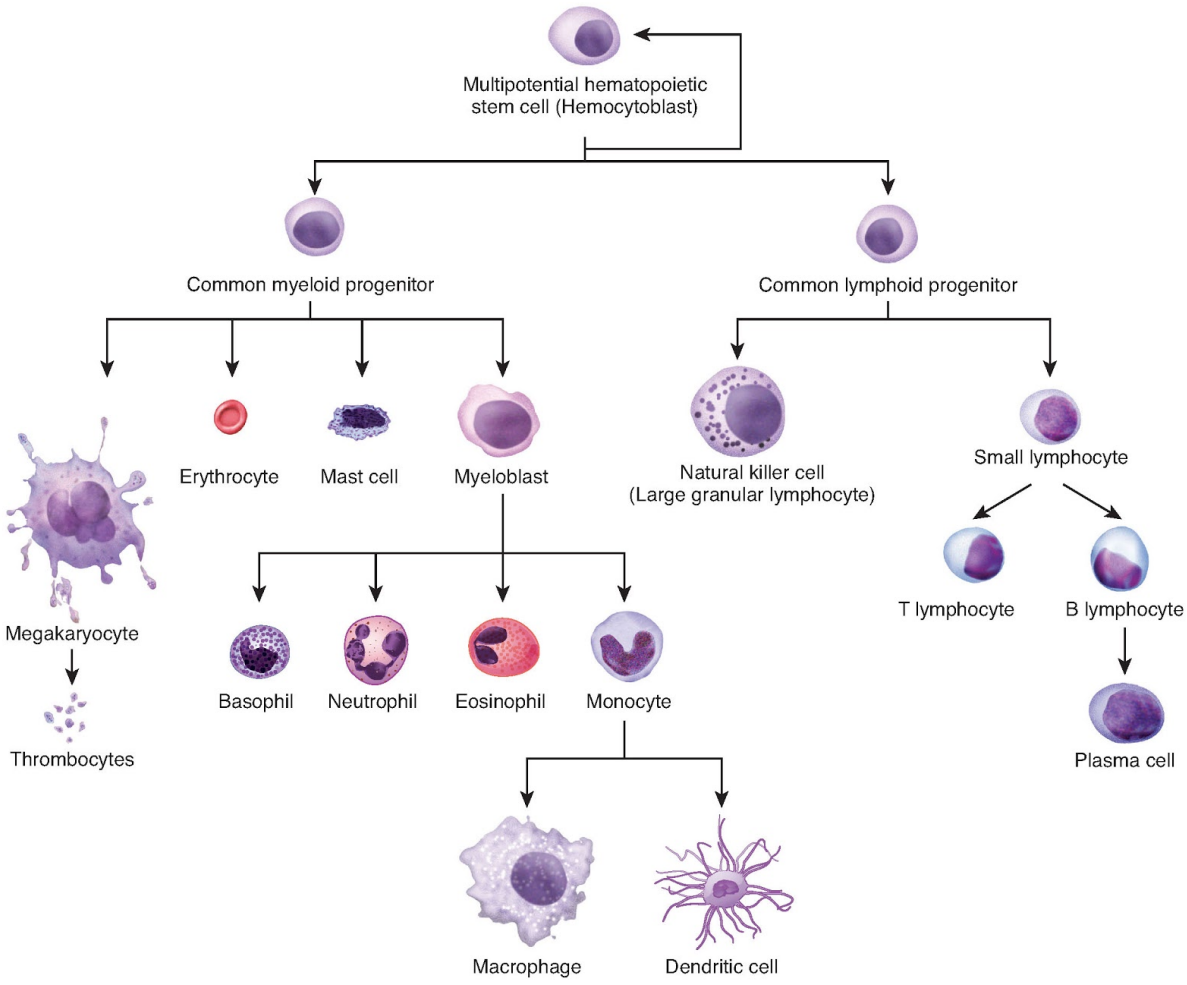
Stem cells can undergo self-renewal and differentiation into progenitor cells.There are many areas in the research of how the *Hox* genes affects stem cells. Due to the overflow of information, the following review will focus the effect of the *Hox* gene on the hematopoietic stem cells.

Hox Genes in Hematopoietic Stem Cells Development

Blood cells are classified into two main groups: lymphoid cells (lymphocytes, lymphoblasts, and plasma cells) and myeloid cells (granulocytes and monocytes; Fig. 2). These blood cells possess short lifespan and must be constantly self-renewed. All blood is derived and self-renewed from pluripotent cells called hematopoietic stem cells (HSCs; 3). The differentiation and proliferation of HSC is mediated by an organism's gene.

Genetic manipulation through amplification or deprivation of the *Hox* gene in HSC has provided valuable data on the effect of *Hox* gene differentiation and proliferation. For example, overexpression of *Hoxa10*, *Hoxb3*, and *Hoxb6* in mouse BM cells had profound effects such as inhibiting the differentiation of B- and T-cell, impairing erythropoiesis, and inducing myeloproliferative disorder and leukemia. Also, data showed that *Hoxb4*-deficient mouse exhibit reduction in HSC. Studies showed that the role of the *Hoxb4* gene is to stimulate HSC expansion. Such

expansion promote symmetrical self-renewal. However, *Hoxb4* gene was not the only *Hox* gene that promoted expansion, other *Hox* genes (e.g. *Hoxb3*) has this expansion ability (2)



From http://cnx.org/contents/966c32cc-3d6f-4f4e-af4f-ea0c975e825c@4/Cellular_Differentiation

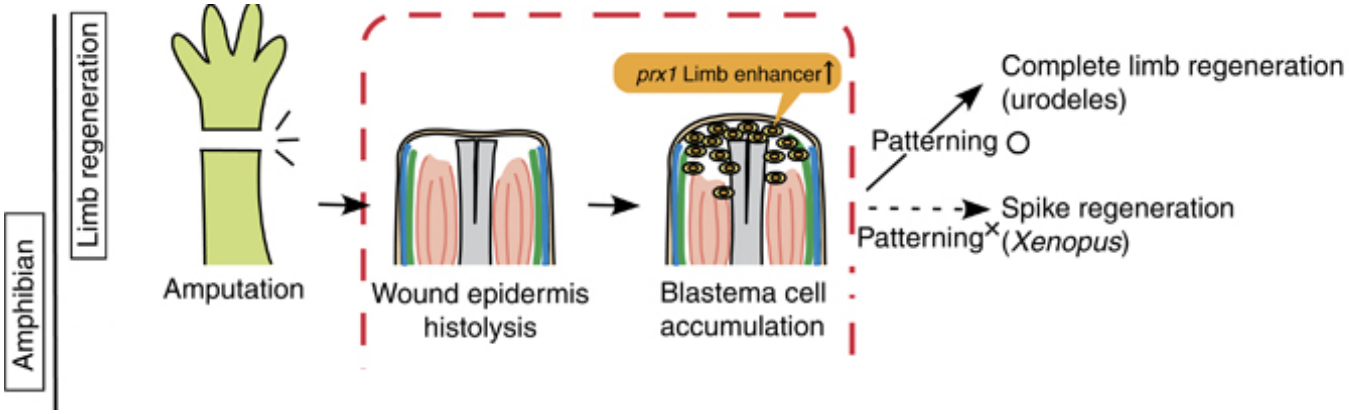
Figure 2. An overview of the production of mature blood cells by the proliferation and differentiation of hematopoietic stem cells.

Hox gene and limb regeneration in Urodeles

Urodeles (i.e. salamanders and newt) has been the model animal in the study of limb regeneration. Urodeles regeneration ability is not limited to only the limbs and appendages. Many

organs can reform including the “lens, retina, intestine, cardiac ventricle, upper and lower jaws, and tail” (8). To understand the function of *Hox* genes in regeneration of limbs, a foundational knowledge of the cellular mechanism of the limb regeneration in urodeles must be recognized.

There are three stage in the reformation of a limb (Fig. 2). The first stage begins after the limb of an urodele is amputated. The wound healing process begins. Within the first hour the basal epithelium cells at the edge of the wound start to migrate across the amputated section. This process of covering the wounding site with epithelium cell is known as epithelialization. It typically takes 24 hours to cover the entire amputated site with epithelium cells. The newly formed epithelium cells begins to thicken within few days due to epidermis cells called keratinocytes that migrate and proliferate, forming a “wound epithelium.” Leukocytes such as macrophage begin to accumulate at the injured site (8). Next, mature cells underneath the formed epithelium begins to dedifferentiate in order to proliferate into blastema. In the second stage, the blastema begins expansion and growth. In the third stage, the cell start to differentiate and grow into a newly developed limb (9).



From http://www.nature.com/jid/journal/v131/n12/fig_tab/jid2011223f6.html#figure-title

Figure 2. A general overview of limb regeneration in urodeles. There are three stage of development in urodeles. In the first stage, the wound is covered up with wound epithelium, and the mature tissue under the epithelium begins to dedifferentiate. These undifferentiated and proliferating cells form blastema. In the next stage, the blastema expands and starts to grow . In the last stage, the cells differentiate and reforms the missing limbs (16).

Researchers demonstrated the important role of *Hox* gene in wound healing and the dedifferentiation process. For example, Christen, Beck, Lombardo, and Slack (2003) studied the expression of three *Abdominal B*-type *Hox* gene (XHoxc10, XHoxa13, and XHoxd13) in *Xenopus*. The researchers demonstrated that these *Hox* genes are expressed during different temporal and spatial settings. It was reported that XHoxc10 is up-regulated at the site of dedifferentiated and undifferentiated cell are recruited. XHoxa13, on the other hand, is expression during the proliferation of the blastemal cells. Overall, the expression of the *Hox* gene is crucial for the regeneration of a new limb.

Concluding Remark

Hox gene plays a critical role in the many biological process. In fact, the loss of the *Hox* gene can lead to major deficits. For example, the disruption of Hoxa3 result in the loss of the thymus. Also, the loss of the Hoxa1/ Hoxd11, and Hoxc11 can result in the loss of function of the metanephric kidney (10).

To describe the complete role of the *Hox* gene is beyond the limit of this report, but the overall function is to determine the anterior and posterior body plan of an organism.

LITERATURE CITED

1. Gehring W.J. 2007. The homeobox as a key for understanding the principles of the genetic control of development. In *HOX Gene Expression*, 1-13. Springer New York
2. Argiropoulos B & Humphries RK. 2007. Hox genes in hematopoiesis and leukemogenesis. *Oncogene*. 26 : 6766–6776
3. Estacio-Gómez A, Díaz-Benjumea F,J. 2014. Roles of hox genes in the patterning of the central nervous system of drosophila. *Fly*. 8 : 26-32.
4. Soshnikova N. 2014. Hox genes regulation in vertebrates. Developmental Dynamics. 243 : 49-58.Jacob F, Perrin D, Sanchez C, Monod J. 1960. Operon: a group of genes with the expression coordinated by an operator. C. R. Hebd. Seances Acad. Sci. 250: 1727-29.
5. Duboule, D. 2007. The rise and fall of the Hox gene clusters. Development 134: 2549-60.
6. Gunsilius E, Gastl G, Petzer AL. 2001. Hematopoietic stem cells. Biomedicine & Pharmacotherapy. 55 : 186-94
7. Mescher, A. L. 1996. The cellular basis of limb regeneration in urodeles. Int. J. Dev. Biol. 4: 785-795.
8. Christen B, Beck CW, Lombardo A, Slack JMW. 2003. Regeneration-specific expression pattern of three posterior hox genes. Developmental Dynamics. 226 : 349-55
9. Gouti M, Gavlas A. 2007. Hox genes amd stem cells. In HOX Gene Expression, ed. Spyros Papageorgiou, 111-129. New York, NY: Springer.
10. Mallo M, Alonso CR. 2013. The regulation of hox gene expression during animal development. Development. 140 : 3951-63.