INTERNATIONAL JOURNAL OF SCIENCE AND NATURE

Www.scienceandnature.org

Review Article

HOX GENES AND ITS ROLE IN ANIMAL DEVELOPMENT

Suman Pratihar, Rudra Prasad Nath, Jayanta Kumar Kundu
Molecular Biology Research Unit, Department of Zoology, Vidyasagar University, Midnapore -721102. West Bengal.

ABSTRACT
Homeobox genes encode DNA-binding transcription regulators that participate in the formation of embryonic pattern or contribute to cell-type specificity during metazoan development. Homeobox genes that regulate axial patterning and segmental identity (Hox/HOM genes) share a conserved clustered genomic organization. Mammals have four clusters that have likely arisen from the duplication of a single ancestral cluster. Increased Hox gene complements are associated with the appearance of chordate and vertebrate characters.

KEY WORDS: Hox genes, Homeodomain, Homeobox

INTRODUCTION

Hox genes are a group of related genes that specify the anterior-posterior axis and segment identity of metazoan organisms during early embryonic development. These genes are critical for the proper number and placement of embryonic segment structures. Hox genes are defined by a DNA sequence known as the homeobox, which is a sequence of 180 nucleotides that code for a protein domain known as the homeodomain. The homeodomain protein motif is highly conserved across vast evolutionary distances. The functional equivalence of Hox proteins can be demonstrated by the fact that a fly can function perfectly well with a chicken Hox protein in place of its own. (Lutz et al., 1996) This means that, despite having a last common ancestor that lived over 670 million years ago (Ayala et al., 1998), a given Hox protein in chickens and the homologous gene in flies are so similar that they can actually take each other's places. Although the protein sequence is highly conserved, the DNA sequence from which it is made is slightly less so, a result of codon degeneracy (*i.e*., more than one codon codes for the same amino acid). The reason for this high level of conservation is related to the function of these proteins. Hox genes set up the basic regional layout of an organism, so that eyes form on the head and not on the abdomen, and limbs form at the sides and not on the head. Even a single mutation in the DNA of these genes can have drastic effects on the organism, and so these genes have changed relatively little over time. The protein products of Hox genes belong to a class of proteins known as transcription factors, all of which are capable of binding to DNA, thereby regulating the transcription of genes. The homeobox sequence codes for a 61 amino acid helix-turn-helix protein known as the homeodomain. The homeodomain acts as an "on/off" switch for gene transcription by binding to specific sequence enhancers of a gene, which either activates or represses the gene. The same Hox protein can act as a repressor at one gene and an activator at another. For example, in flies (*Drosophila melanogaster*) the protein product of the Hox gene Antennapedia activates genes that specify the structures of the 2nd thoracic segment, which contains a leg and a wing, and represses genes involved in eye and antenna formation. Thus, legs and wings, but not eyes and antennae, will form wherever the Antennapedia protein is located. (Pearson, 2005).

REGULATION OF HOX GENES

Hox genes regulate realisator genes, they are in turn regulated themselves by gap genes and pair-rule genes, which are in their turn regulated by maternally-supplied mRNA. This results in a transcription factor cascade: maternal activate gap or pair-rule genes; gap and pair-rule genes activate Hox genes; then, finally, Hox genes activate realisator genes that cause the segments in the developing embryo to differentiate. Regulation is achieved via protein concentration gradients, called morphogenic fields. For example, high concentrations of one maternal protein and low concentrations of others will turn on a specific set of gap or pair-rule genes. In flies, stripe 2 in the embryo is activated by the maternal proteins Bicoid and Hunchback, but repressed by the gap proteins Giant and Kruppel. Thus, stripe 2 will only form wherever there is Bicoid and Hunchback, but *not* where there is Giant and Kruppel. Small,1992 swaid that MicroRNA strands located in hox clusters have been shown to inhibit more anterior hox genes ("posterior prevalence phenomenon"), possibly to better fine tune its expression pattern. (Lempradl and Ringrose, 2008) The order of expression of Hox genes with a cluster is co-ordinated during development, the low number 3’ genes are expressed more anteriorly and earlier than high number 5’ genes. (Rinn et al., 2007) The groups of cells known as functional domains become committed to form body structures such as limbs and organs.

Thecombination of Hox genes expressed within the functional domains along the antero-posterior axis which results in the specifying the development of structures. In developing vertebrate Hox genes are first expressed during early gastrulation at a stage when the embryo generates its major body axis.

HOX GENE AND DEVELOPMENT

The hox genes specify regional differences along the anterior-posterior (A/P) axis of the vertebrate embryo. This function appears to reflect an ancestral role of the hox gene complex and is conserved across phyla. During the evolution of vertebrates, this gene complex has been recruited to perform other functions as well, many of which occur later in development. Although mutational analysis in the mouse is well-suited to the study of their early function, that same function limits the utility of mutational analysis in the investigation of later functions. The use of retroviral vectors to alter gene expression in the chick embryo has emerged as an effective way to address these later functions. This paper reviews that approach and its application to the study of the hox genes in the formation of the vertebrate limb. (Fraser and Bickmore , 2007) Hox genes define patterns of development in vertebrate limbs. In the chick, at least 23 Hox genes are expressed during limb development, with Hoxa9 expressed in the proximal part of the limbs where the humerus or femur develop. Hoxa9, Hoxa10 and Hoxa11 are expressed in the forelimb where the radius and ulna (or tibia and fibula) develop. Hoxa9 to Hoxa13 are expressed in the wrist (or ankle) and the digits. (Montavon, et al. 2008) Expression studies in fetal human and rodent lungs have demonstrated high expression of 3′ Hox genes in clusters A and B. There is a marked decrease in expression of most of these genes as lung development progresses suggesting that they are involved in the early stages of lung morphogenesis. For example Hoxa5, continue to be expressed at high levels throughout development and may be required for pulmonary maturation.

EVOLUTION OF HOX GENES:

In Ecdysozoa, there are approximately ten Hox genes. Vertebrates have four duplicates (paralogues) of these ten genes, known as Hoxa, Hoxb, Hoxc, and Hoxd. These four paralogous clusters are a consequence of the ancestral vertebrate genome being twice duplicated in its entirety. (Dehal and Boore, 2005) The first occurred before the Cnidaria-Bilateria split, the second during the evolution of the fishes. The arrows represent Hox genes arrayed along a chromosome. The bottom line represents the ten Hox genes seen in most invertebrates, and is the ancestral complement of the vertebrates. The top four lines represent the four duplicated clusters of these ten genes seen in vertebrates. In order from left to right (anterior to posterior), they are: labial, proboscipedia, zerknullt, Deformed, Sex combs reduced, fushi tarazu, Antennapedia, Ultrabithorax, Abdominal-A and Abdominal B. Arrows with the same color came from the same ancestral gene. Although these vertebrate genes are duplicates of the same genes seen in the Ecdysozoans, the four copies are not actually identical. Each copy has accumulated its own unique mutations over time, producing proteins with distinct functions. Some have actually been deleted entirely or duplicated again in certain vertebrate groups. For example, Hoxa and Hoxd are involved in the segment identity along the limb axis. Hox expression in the limb has two phases, an early wave of expression for the arm and a late wave for the digits, which involves Hoxd 8 – 13 and has a separate regulatory region 5' of Hoxd 13 which is not found in teleost fish (Deschamps, 2007).

CONCLUSION:

The body development of an embryo provides insights into the evolutionary origin of the animal. Groups of animals that pass through a similar embryonic stage are descended from a common ancestor. During evolution, the development of structures can be altered so that they acquire new functions. The development of insects and vertebrates limbs involves the same set of pattern-establishing genes, reflecting the evolution of limb development from an ancestral mechanism for specifying body appendages. The body plan of all animals is defined by patterns of Hox gene expression that provide positional identity, the interpretation of which has changed in evolution.

REFERENCES:

Lutz, B., Lu, H. C., Eichele, G., Miller, D., and Kaufman TC. (1996) Rescue of Drosophila labial null mutant by the chicken ortholog Hoxb-1 demonstrates that the function of Hox genes is phylogenetically conserved. *Genes & Development.* **10**, 176–184.

Ayala, F.J. and A. Rzhetskydagger (1998) Origin of the metazoan phyla: Molecular clocks confirm paleontological estimates". *Proc Natl Acad Sci*. **95** (2), 606–11.

Pearson, J. C., D. Lemons, and W. McGinnis (2005) Modulating Hox gene functions during animal body patterning. *Nature Rev. Genet*. **6**, 893–904.

Small, S. (1992) Regulation of even-skipped stripe 2 in the Drosophila embryo. *EMBO J*. **11(11),** 4047-57.

Lempradl, A. and L. Ringrose (2008) How does noncoding transcription regulate Hox genes? *Bioessays*. **30(2),**110-21.

Rinn, J.L, Kertesz, M, Wang, JK., Squazzo, SL., Xu, X., Brugmann, SA., Goodnough, LH., Helms, JA., Farnham, PJ., Segal, E., Chang, HY., (2007) Functional demarcation of active and silent chromatin domains in human HOX loci by noncoding RNAs. *Cell*. **129(7),** 1311-23.

Fraser, P. and Bickmore, W. (2007) Nuclear organization of the genome and the potential for gene regulation. *Nature*. **447(7143)**, 413-7.

Montavon, T., Le Garrec JF., Kerszberg, M., Duboule, D. (2008) Modeling Hox gene regulation in digits: reverse collinearity and the molecular origin of thumbness. *Genes Dev*. **22(3),** 346-59.

Dehal, P, Boore, JL. (2005) Two Rounds of Whole Genome Duplication in the Ancestral Vertebrate. *PLoS Biol* **3(10)**, e314.

Deschamps, J (2007) Ancestral and recently recruited global control of the Hox genes in development. *Curr Opin Genet Dev*. **17(5),** 422-7.

Fig1: Hox gene cluster

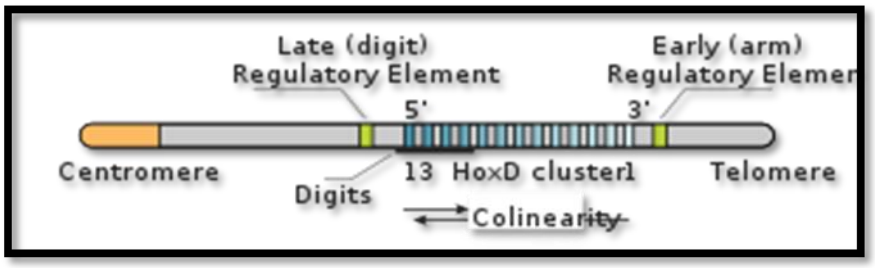

FIGURE 2:-A representative dendrogram illustrating the evolution of Hox clusters. Hox gene clusters are thought to have developed by a process of duplication and divergence from a primordial homeobox gene estimated to have arisen about 1,000 million years ago.