Review Article

The Role of HOXA Cluster Genes in Human Body plan

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Abstract

Homeobox (HOX) genes are contributed in the genetic control of development of the body plan, pattern formation, and cell fate determination and the other several key developmental processes. HOX genes are also known as selector genes because expression within a given section of the embryo will cause its cells to choose a particular developmental path. HOX genes encode transcription factors that conduct embryological development as well as regulate differential endometrial gene expression with each menstrual cycle. HOX genes have been arranged in four clusters of A, B, C and D that each has parallel and overlapping expression domains. Among these clusters, HOXA cluster that is the main focus of this paper has an important role in regulating various processes in human body. In the present paper, the expression of HOXA9, HOXA10, HOXA11, and HOXA13 genes in the developmental processes related to the reproductive tract and the expression of HOXA1, HOXA2, HOXA3, HOXA4, HOXA5, HOXA6 and HOXA7 genes in the other sections of human body are highlighted.

Key words: Homebox; HOXA; Homeodomain Proteins

Introduction

Since their initial discovery in 1978, the Homeobox (HOX) genes have attracted a growing attention of diverse groups of investigators (1). HOX genes are contributed in developing most of basic genetic mechanisms of the body through creating various patterns and interfering in cell fate along the anterior and posterior axis of all metazoans (2,3). In the adult body, HOX genes are among others responsible for driving the differentiation of tissue stem cells towards their respective lineages in order to repair and maintain the correct function of tissues and organs (4). HOX gene activity results in morphological diversity of organs or structures in different species. The Abdominal-B HOX gene provides an example of such activity, as this gene suppresses the formation of the seventh abdominal segment in the adult (5). Also, despite the existence of wide difference in appearance, HOX genes do these duties in animal species (3,6). HOX proteins which contain a 61-amino acid residue polypeptide can regulate genes in adult tissues (2). 39 HOX genes are arranged in four parallel clusters of A, B, C, and D. These clusters are placed on four separate chromosomes and each of them has parallel and overlapping expression domains. Each of three clusters of B, C, and D has 9 genes and only cluster of A has 11 genes (3,6). The reason for the clustering HOX genes is not known, but some evidence shows that it preserves the proper ordered regulation of transcription of

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the HOX genes (3). Of these cluster genes, mutations in 10 HOX genes have been found to cause human disorders with critical change in their inheritance patterns, penetrance, expressivity and mechanism of pathogenesis (1). Some human disorders resulted from mutations in HOX cluster genes are given in Table 1.

HOX genes as transcriptional regulators have a critical role in the processes related to the embryo such as morphogenesis and differentiation and more likely in human implantation. The results of a recent study have also shown that HOX genes are essential for endometrial receptivity (3). It is important to note that necessary transcription factors for implantation with each menstrual cycle are encoded by HOX genes (3,6,23). Inasmuch as HOX genes are expressed within a given section of the embryo and due to this the cells choose a specific developmental path, they are known as selector genes (3).

Table 1: Some human HOX gene disorders

HOXA1	**Bosley–Salih–Alorainy syndrome**: sensorineural hearing loss, inner ear abnormalities, delayed motor milestones and internal carotid artery malformations **Athabascan brainstem dysgenesis syndrome:** profound sensorineural hearing loss, severe intellectual disability, facial and bulbar weakness, central hypoventilation and conotruncal cardiac malformations	(7,8)
HOXA2	**Autosomal recessive microtia:** poorly developed mastoid air cells, small middle ear cavity and absent inner-ear structures	(9)
HOXA11	**Thrombocytopenia:** congenital bruising and bleeding	(10)
HOXA13	**Hand–foot–genital syndrome:** limb malformations and urogenital defects **Guttmacher syndrome:** limb and urogenital malfor-mations similar to HFGS but with additional limb abnormalities	(11,12)
HOXB1	Congenital facial palsy, hearing loss, strabismus, midface retrusion and an upturned nose, feeding difficulties, speech delay, a smooth philtrum and posteriorly rotated ears.	(13)
HOXB13	Early-onset prostate cancer, possibly breast cancer and colorectal cancer	(14,15)
HOXC13	**Ectodermal dysplasia 9, hair/nail type:** hypotrichosis and nail dystrophy without other manifestations	(16)
HOXD4	Acute lymphoid malignancy with or without skeletal anomalies	(17)
HOXD10	Congenital vertical talus and Charcot–Marie–Tooth disease	(18)
HOXD13	**Synpolydactyly type II:** distal limb malformations **Brachydactyly types D and E**: Brachydactyly type D include short and broad terminal phalanges of the thumbs and halluces while brachydactyly type E consists of shortening of the metacarpals and metatarsals. **Syndactyly type V:** ulnar deviation of fingers **Brachydactyly–syndactyly syndrome:** generalized brachydactyly of the hands and feet, broad and short distal phalanges of thumbs, cutaneous syndactyly of toes	(19-22)

Figure 1 shows the homology of HOX genes between mice and humans.

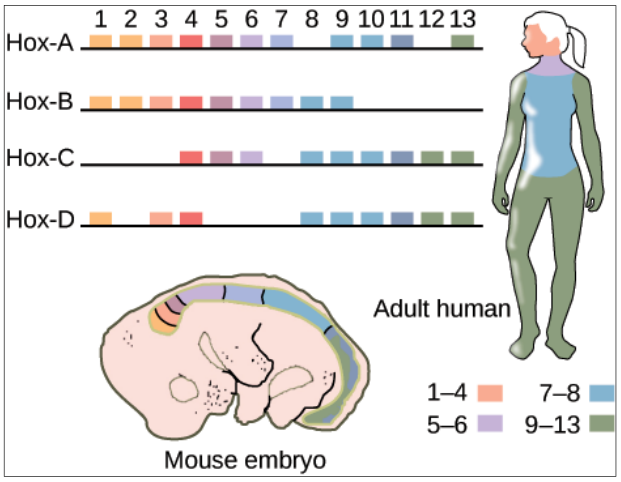

Figure 1: HOX genes in various body sections of human and mouse (24)

As shown in Figure 1, HOX genes are expressed in certain sections of the body of a human and a mouse. The expression of HOX genes in the same sections of the body of a mouse and a human has been shown in orange, pink, blue, and green colors (24).

Through doing a literature survey, we found out that there was not a comprehensive paper to investigate all 11 genes in HOXA cluster and for this reason our main focus in this paper is on genes of this cluster.

The role of HOX genes in reproductive tract

As mentioned in Introduction, HOX genes as vertebrate homologs of the Drosophila homeotic genes are expressed in the certain segments of the body (25). However, the functions of HOX genes in the adult have been poorly identified, but these genes in some processes such as the structural and functional differentiation of adult tissues probably act similar to those in embryonic developmental processes (26). The expression of HOX genes has been recently investigated in the female reproductive tract in some experimental works. These experiments have been in forms of the expression patterns, regulation of these genes in the endometrial development in human during the menstrual cycle, and implantation (3). The interference mechanisms of the HOX genes with implantation are not fully characterized (6). Effectiveness of HOX genes on endometrial development may be done in a way similar to their effects on embryonic development and this similarity is in the stages of endometrial growth, differentiation and receptivity (27). A mechanism may be provided to allow differential HOX gene expression in the reproductive tract through regulation of HOX genes by sex steroids in the uterus and also in the embryo (3). The enhanced expression seen in the midsecretory phase in the endometrium is happened at the same time with enhancement of circulating time for progesterone. In addition to retinoic acid, few regulatory molecules inducing HOX expression have been known. Estrogen and progesterone are such regulators of HOX gene expression (25). The defects observed in the expression of HOX genes in endometriosis patients confirm the functional role of these genes in human implantation. Expression of HOXD cluster genes has also been observed in the developing reproductive tract probably through contributing in determining the tissue identity during development process (3).

Critical role of HOXA genes

Many genes are involved in various issues related to the reproduction. For example, the Bax gene has an important role in pregnancy loss and the variations of this gene could help in the assessment of recurrent pregnancy loss, however, elaborating on this gene is not within the scope of this study and it is only as an example for genes interfering in the reproduction (28). More importantly with regards to HOXA cluster genes in the developing reproductive tract, four genes

of this cluster, namely HOXA9, HOXA10, HOXA11, and HOXA13 are expressed (2,26,27). Interestingly, HOXA10 and HOXA11 are expressed in the adult uterus as well as several other HOX genes (29). As shown in Figure 2, HOXA9, HOXA10, HOXA11, and HOXA13 are expressed in areas destined to become the Fallopian tube, in the developing uterus, in the anlage of the lower section of the uterine and cervix and in the upper vagina, respectively. A HOXA12 gene has not been identified (3) (Figure 2).

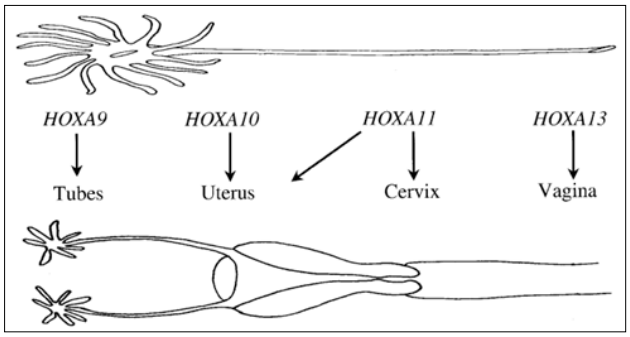

Figure 2: Expression boundary of HOXA9, A10, A11, and A13 genes in an adult reproductive tract structure (3)

HOXA10 is up-regulated by estrogen and progesterone in the adult human uterus and it has been shown that regulation of the expression of some progesterone-responsive genes is performed by HOXA10 gene (3,30,31). Also, insulin-like growth factor-binding protein 1 (IGFBP1) in murine models and in vitro has been proposed to be regulated by HOXA10. HOXA11 is induced by progesterone treatment in the uterus. HOXA11 mRNA expression is markedly reduced in the uteri of progesterone-treated HOXA10 mutant mice probably indicating co-regulation of the expression of HOXA10 and HOXA11 (31). Laparoscopic endometrioma resection increases peri-implantation endometrial HOXA10 and HOXA11 mRNA expression, proposing an improvement in endometrial receptivity (32). The highest HOXA10 expression is achieved by simultaneously administering estrogen and progesterone. It has been also demonstrated that HOXA11 is regulated similar to HOXA10. HOXA10 and HOXA11 have been identified as important mediators of sex steroid action. These two genes are expressed in the glands related to endometrium and connective tissue of the human uterus through the menstrual cycle (3) and thereafter remain in a high level during the rest of the cycle and also in the uterine lining during human pregnancy that is known as decidua (6). HOXA10 and HOXA11 have been related to endometrial receptivity. Mutations in these two genes have resulted in failure to achieve normal implantation in mice (6,33-35).

Conducting the development of morphologic structures in the female reproductive tract is one mechanism by which HOXA10 interfere with the implantation process. HOXA10 may regulate proliferation in uterine stromal cells but morphology and identity in uterine epithelial cells (36). HOXA10 gene may be important during morphogenesis for the purpose of suitable patterning of the reproduction system and in adult endometrium (33). Endometrial receptivity window is a stage that maximum expression of HOXA10 and HOXA11 is achieved. In addition to its influence on the developmental process of an embryo, HOXA10 is necessary for normal endometrial development in mouse and human implantations, humans with polycystic ovary syndrome, a genetically based disorder which reflects multiple potential aetiologies and variable clinical presentations (37), and humans with endometriosis disorder causing implantation defects. Cells in stroma of the uterine in HOXA10-deficient female mice indicate a decreasing trend in proliferation in reaction to progesterone leading to defects in decidualization (6), as a vital stage during embryo implantation that is characterized by

the differentiation of endometrial stromal cells into decidua cells (34). Similarly, HOXA11-deficient mice are infertile because of imperfections during endometrial implantation. The expression of β3 integrin as well as several other genes involved in endometrial receptivity is regulated by HOXA10 (6).

HOXA10 and HOXA11 are translated into transcription factors that regulate a battery of downstream genes necessary for growth and differentiation. Failure of the normal enhancement in HOXA10 and HOXA11 mRNA levels at the start of the window of implantation may be one mechanism responsible for endometriosis related infertility (27).

Uterine factor infertility with normal ovulation and embryo formation but complete implantation failure has been observed in female mice with HOXA10 removed. HOXA10 expression in the endometrium rises at the time of ovulation and has been shown to be essential for human implantation (38). At the time of implantation, HOXA10 mediates the progesterone stimulating proliferation of uterine stromal cells. On the other hand, HOXA10 mutations caused stromal cell proliferation defects that were accompanied by quantitative alterations in the expression of one cyclin-dependant kinases inhibitors (CDKIS) gene, p57 (34). Although, no mutations in HOXA10 has been observed in human, lower implantation rates have been observed in relation with HOXA10 expression during reduced secretory stage in women (23). While HOXA11 alone is a repressor on the decidual prolactin promoter, it turns into an activator when combined with a forkhead box gene, namely FOXO1A (39). HOXA10 is expressed both in the uterine anlage during morphogenesis and in the adult uterus during pregnancy. Expression at these two different time periods proposes two various models for HOXA10 function in female fertility. First model is that loss of embryonic expression of HOXA10 results in a homeotic complete change of the adjacent uterus to oviduct. The second one proposes that HOXA10 has a critical function in the adult uterus during pregnancy (29). HOXC10, HOXC11, HOXD10, and HOXD11 are all expressed in the endometrium. Unlike the HOXA cluster genes, HOXC and HOXD genes were expressed primarily in the proliferative phase endometrium and thought to regulate endometrial growth and propagation rather than the differentiated state associated with endometrial receptivity (40).

Other parts of the body

In addition to the processes related to the reproductive tract, HOX genes are involved in a number of other developmental processes in some organ systems. For example, genes in clusters of HOXA and HOXD are greatly involved in the development of mesoderm-derived tissues including limbs, the axial skeleton and kidneys. We can point to hematopoietic cells from both mouse and human bone marrow that express the majority of genes existed in the HOXA, HOXB and HOXC clusters. In this paper, we only focus on the roles of HOXA cluster genes. HOXA cluster genes are widely expressed within the hindbrain, neural tube and mesodermal layers (41). HOXA1 gene affects the development of a diverse array of tissues in the anterior domain of the embryo including the brainstem, inner ear and heart. Mice with removed HOXA1 cannot stay alive at or shortly after birth from breathing defects resulted from mis-patterning of the hindbrain. The mechanisms that HOXA1 regulates the development of neural crest cells or the inner ear are unclear (42). HOXA2 gene expression is altered by

Chromo domain, helicase, DNA-binding protein 8, an ATP-dependent chromatin, for regulation of the recruitment of chromatin modifying enzymes (43). It was found that a mutation in HOXA2 gene is responsible for autosomal-recessive microtia in an Iranian family (44). Also, HOXA2 plays a common role as its inactivation in mouse induced a mirror-image duplication of the lower jaw with two Meckel's cartilage and that HOXB2 in zebra fish may cooperate with HOXA2 in the second pharyngeal arch (45).

HOXA3 considerably improves angiogenesis and vasculogenesis processes during tissue healing and hastens the treatment of skin wounds. Prolonged expression of HOXA3 in wounds during diabetes markedly changes bone marrow-derived cells recruitment in response to wounding (46). The expression of HOXA5 is restricted to a subset of lateral sclerotome cells. It is also found that regulated expression of HOXA5 within segmented somites is important for morphology of cervical vertebrae, since spatial and temporal misexpression disrupts vertebral cartilage formation. Somites are the vertebrate axial skeleton developed from embryonic structures. HOXA5 has come under the effect of signaling pathways that pattern the somites, which may have allowed its activity to become localized within the sclerotome (47).

HOX4, HOX5 and HOX6 genes regulate the number and identity of cervical and thoracic vertebrae (41). HOXA4 is also involved in embryonic patterning. It seems that HOXA4 function in embryogenesis is not critical. HOXA4-removed mice are viable and present only some deformations of the cervical spine. Conversely, transgenic mice over-expressing the HOXA4 gene develop congenital mega-colon due to abnormalities in the enteric nervous system. Over-expression of HOXA4 further decreased cell motility and led to a corresponding increase in β1 integrin (48). HOXA5 and HOXA10 motivate the p53 promoter in breast cancer cells and develop the expression of the progesterone receptor (2). HOXA6 and HOXA7 contribute in specifying the characteristics of mesoderm derived tissues and organs.

Some studies propose that the helpful/extra interaction of HOXA6 and HOXA7 controls the expression of genes involved in early germ layer characteristics (49). HOXA7 was seen to be expressed most strongly over spinal ganglia 6–9 and 13-19 of the mouse and of the chick, respectively. HOXA10 and HOXA6 like HOXA7 were found to be strongly expressed in spinal ganglia of both mouse and chick, while HOXA9 was seen to be more weakly expressed in both species (50). Figure 3 shows the expression domain of HOXA6, HOXA7, HOXA9, and HOXA10 in both mouse and chick. HOXA9 directly regulates flt3, a receptor tyrosine kinase enriched in primitive hematopoietic progenitors. The flt3 signaling is vital for the maintenance of lymphoid progenitors from which B cell precursors are derived (51).

In general, the region-specific expression of HOXA4-A9 was observed in the visceral mesoderm and had common posterior expression boundaries at the cecum/rectum junction (52). HOXA13 and HOXD13 are particularly expressed in the rear section of the alimentary canal (hindgut), cloacal mesoderm and endoderm, but not in the esophagus (53). HOXA13 expression enhances tumor growth in vitro and in vivo, and is a negative independent predictor of disease-free survival of patients with esophageal squamous cell carcinoma as the sixth most common cancer in the world (53). A number of typical manifestations of HOXA13 deletion, such as speech delay, short stature, small feet with brachydactyly, bilateral mild hypoplasia of distal phalanges

of some fingers of the hands, and some mildly dysmorphic facial features have been observed in a girl (54) (Figure 3).

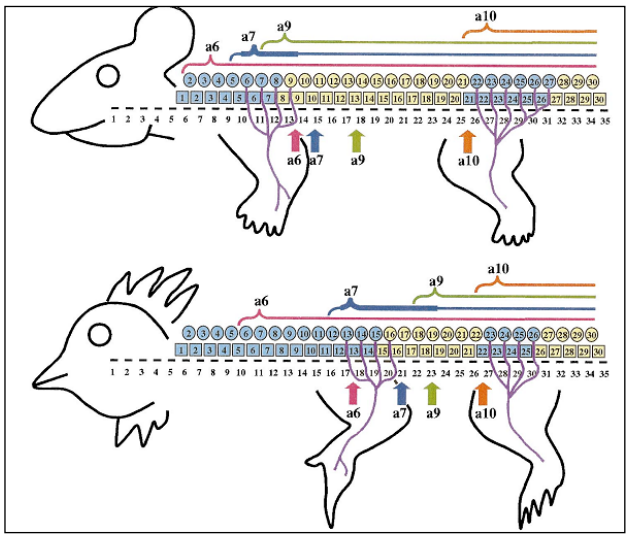

Figure 3: HOXA6, A7, A9, and A10 expression domains (shown in brackets) in spinal ganglia of mouse and chick (50)

Conclusion

A review on HOX genes with a main focus on the role of HOXA cluster genes in various sections of human body was done within the scope of this study. This kind of gene cluster is important in the genetic control of developmental processes. The effect of HOXA1 in the anterior domain of the embryo including the brainstem, inner ear and heart, the effect of HOXA2 gene on regulating the recruitment of chromatin modifying enzymes, the significant role of HOXA3 in tissue repair and cutaneous wound healing, interference of HOXA4 in embryonic patterning, restricted expression of HOXA5 in a subset of lateral sclerotome cells, the roles of HOXA6 and HOXA7 in specifying the characteristics of mesoderm derived tissues and organs, and finally very significant expression of HOXA9, HOXA10, HOXA11, and HOXA13 genes in embryonic and endometrial developmental processes related to the reproduction system. Also, recent studies have shown that a mutation in HOXA2 gene is responsible for autosomal-recessive microtia in an Iranian family.

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