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Review Article

Role of Hox in Implantation and Early Embryo Development

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Abstract: Implantation and structural architecture of embryo is very crucial for development of animal. Hox genes are key regulator of implantation and structural changes of early embryo. Hox genes transcribe to form homeodomain-containing transcription factors. The different types of Homeobox genes are involved in implantation and decidualization. Post-implantation processes like limb development, lung development also involves the regulation by Hox genes. In the formation of female reproductive tract from the undifferentiated duct, the Hox plays a decisive role in deciding its fate. Different Hoxa genes are responsible for formation of the different part of the tract including oviduct, uterus and upper vagina. The development of limb is depended on several HOXD genes. HOXB clusters of homeobox genes are responsible for axial patterning. This review gives a holistic assessment on the functioning of Hox genes as regulators of numerous important roles in implantation as well as the development of embryo.

Keywords: homeodomain, decidualization, implantation, Homeobox.

Introduction:

Implantation is the attachment of the competent embryo on to the receptive maternal endometrium. Occurring after successful fertilization, it is a complex process of interaction between the embryo and the endometrium. Both the embryo and the endometrium exhibits genetical and cellular reciprocal interactions within the stipulated time frame called window of implantation. The cellular events such as proliferation and differentiation of the endometrium making it compatible for the implantation are governed by progesterone and estrogen. These two ovarian steroids act via scores of various growth factors, cytokines, and transcription factors that regulate the intricate process via autocrine and paracrine signaling to ensure successful implantation.

Transcription factors are types of proteins that bind to the upstream regulatory elements of genes in the promoter and enhancer regions of DNA and stimulate or inhibit gene expression and protein synthesis (Kulig and Lloyd, 1996; Erickson and Lloyd, 2004). Transcription factors may be tissue specific or may be present in a variety of different tissue types. Among the transcription signaling molecules, the expression of homeobox transcription factors, plays a critical role in embryogenesis and development. There are several homeobox transcription factors like Msx, Hox, Wnt, Rbpj etc. Among these the Hox family is the largest group and is found to be invincible for the proper implantation and early embryo development. The numerous genes constituting the Hox family of genes are responsible for modulating the physiologic changes during implantation and post-implantation. So, these factors are of very much interest in contemporary research. Reports suggest that along with the implantation

they are also involved in other functions like embryogenesis, organogenesis, tumorigenesis etc. This review presents a detailed discussion on the Hox family of Homeobox-containing transcription factors.

Homeobox(Hox) family:

Hox/HOX genes are a group of homeobox-containing transcription factors that belongs to a multigene family. These developmentally regulated transcription factors are known for their role in patterning the body plan of animals. Homeobox is a conserved sequence element of 183bp, which encodes a 61-amino acid domain, termed as the homeodomain. Typically invertebrates possess a single Hox cluster containing 8 to 15 genes, as seen in Drosophila (HOM-C), whereas vertebrates possess multiple clusters that differ among different taxas (Pascual-Anaya *et al.,*2013). Mammals possess four clusters of Hox genes (HoxA, B, C, and D) which are found to have evolved by two rounds of gene duplication (McGinnis and Krumlauf, 1992; Krumlauf, 1994).

The Hox genes were first identified in *Drosophila melanogaster* and are found to have a major role in establishing segmental identity along the anterior-posterior (A-P) axis in the fly. In Drosophila, eight Hox genes called the homeotic complex (HOM-C), clustered on a single chromosome, are found which are divided into two groups named the Antennapedia complex (ANT-C) and Bithorax complex (BX-C). ANT-C comprises of five Hox genes namely labial(lab), proboscipedia(pb), Deformed(Dfd), Sexcombsreduced(Scr) and Antennapedia (Antp). The BX-C consists of three Hox genes namely Ultrabithorax (Ubx), Abdominal-A (Abd-A), and Abdominal-B (Abd-B)(Taniguchi, 2014). On the other hand 39 Hox genes present as four cluster HoxA, HoxB, HoxC and HoxD are found to be located on different chromosomes, at 7p15, 17q21.2, 12q13, and 2q31 in human and 6C2, 11B4, 15F2 and 2C3 in the mouse. Each cluster consists of 13 paralog groups (PGs) with nine to eleven members assigned on the basis of sequence similarity and relative position within the cluster. A high degree of homology is evident between the human HOX genes and the Hom-C genes of Drosophila, (He *et al.,* 2018). Thus the human paralog groups 1-8 are more closely related to antennapedia (Antp), with groups 9-13 more closely related to abdominal-B (Abd-B).

Structure and Expression pattern of Hox genes:

Hox genes are those transcription factors that contain a unique conserved sequence of 182bp called the homeobox sequence. This sequence encodes a 61 amino acid domain called the homeodomain. The Hox genes of mammals are small in size, each containing only two exons separated by one intron which can vary from around 200 bases to several kilobases. The conserved homeobox sequence is found to be always present within the second exon of the Hox genes. This property of the Hox genes shows a high degree of homology among these genes, especially within paralog groups. The Hox proteins contain an acidic tail at the C-terminus and a pentamer upstream of the homeodomain that binds the TALE (three amino acid loop extension) proteins which act as cofactors. The homeodomain is a highly conserved motif of 60 amino acids (Lewin, 2000).

The order of expression of HOX genes within a cluster is coordinated during development. The cells require positional information to ensure that the uncommitted cells differentiate into tissue appropriate for its location within the developing embryo. During the early gastrulation of the developing vertebrates, the Hox genes are first expressed when the embryo generates its major body axis (Duboule, 1994). The pattern of Hox gene expression is spatial wherein the 3‘ genes are expressed earlier than 5‘ and 5‘ genes are expressed as the embryo develops more progressively. This pattern of expression of Hox gene is termed as “temporal colinearity” (Shah and Sukumar, 2010).

Function of Hox genes during endometrial receptivity and Implantation:

Implantation occurs within the limited span of time termed as “implantation window”, in which the uterus is at the receptive state towards a competent blastocyst (Paria *et al.,* 1993; Wang

and Dey, 2006). Any discrepancy within this window can lead to numerous adverse effects like defective decidualization and placentation etc. (Lim and Wang, 2010). Of lately scores of regulatory factors such as cytokines, growth factors, adhesion molecules and transcription factors are identified to have worked together as a network under the influence of estrogen and progesterone hormones for a successful establishment of implantation. (Wang and Dey, 2006; Cha *et al.,* 2012; Zhang *et al.,* 2013; Tu *et al.,* 2014). Among these molecules, Homeobox transcription factors especially Hox family of genes are found to have vital roles in implantation in human and mice (Taylor, 2000).

A network of different transcription factors work together under the regulation of ovarian steroids for the orderly feto-maternal crosstalk which is the fundamental for the implantation to take place successfully (Paria *et al.,* 1993; Tu *et al.,* 2014). Among them the family of homeobox transcription factors such as Hox and Msx are of great importance (Cha and Dey, 2014; Du and Taylor, 2015). In a study done by Satokata and team (Satokata *et al.,* 1995), it is revealed that Hoxa10 is expressed in the luminal and glandular epithelium before Day 1.5 in mice and later on Day 4 the expression shifts to stroma underlying the epithelium. It is also found that the targeted deletion of Hoxa10 within this time causes female infertility. Embryo transfer experiment conducted by Benson *et al.,* in 1996, revealed that Hoxa10 loss do not hinder the embryo survival during the embryo transfer but impacts the uterine function and implantation. Another member of Hoxa cluster, Hoxa11 is also found to be expressed in the uterine stromal cells during implantation, loss of which leads to female infertility (Hsieh-Li *et al.,* 1995; Taylor *et al.,* 1999).Hoxa11$^{-/-}$ uteri are found to be hypoplastic, decreasing number of glands and absence of gland derived Lif expression, showing its functional importance during uterine receptivity and implantation (Hsieh-Li *et al.,* 1995; Gendron *et al.,* 1997; Taylor *et al.,* 1999). No cases of HOXA10 and HOXA11 mutations in human females are reported till date. Both Hoxa10 and Hoxa11 genes show overlapping expression pattern as well as upregulated expression during the secretory phase, suggesting their role in uterine receptivity and implantation (Benson *et al.,* 1996; Taylor *et al.,* 1997; Taylor *et al.,* 1999; Du and Taylor, 2015). It is evidenced that HOXA10 and HOXA11 expression is lower in the patients facing implantation defects. Additionally, females with implantation defects are also found to have anomalous posttranslational modifications such as sumoylation and acetylation of HOXA10 (Fischer *et al.,* 2011; Jana *et al.,* 2013; Zhu *et al.,* 2013; Jiang *et al.,* 2017). Xu and team recently reported the expression three other Homeobox gene alongwith HOXA10 and HOXA11 genes in human uterus. During the mid secretory phase of menstrual cycle in human females increased expression of HOXA9, HOXB6 and HOXD10 gene is seen in the endometrium suggesting their involvement in human endometrial receptivity (Xu *et al.,* 2014).

It is seen that Hoxa10/HOXA10 genes exerts is effect through repressing or activating cascade of downstream genes in various physiological processes like implantation (Daftary and Taylor, 2004). Through microarray analysis in murine model during the implantation window forty (40) statistically significant genes regulated by HOXA10 were identified (Vitiello *et al.,* 2008). In mice, Hoxa10 is found to promote the proliferation of epithelial as well as stromal cells during implantation by downregulating the expression of the downstream gene Emx2(Empty Spiracles Homeobox 2) showing inhibitory effect. On the other hand Hoxa$^{-/-}$ mice uterus showed decrease in the expression of Wnt4 and FKBP52 downstream targets showing the positive regulatory function of Hoxa10 in peri-implantation period of gestation (Daikoku *et al.,* 2004; Daikoku *et al.,* 2005). Bagot and coworkers demonstrated that Hoxa10 is very much important for the pinopod development explaining its inevitable contribution for successful blastocyst implantation (Bagot *et al.,* 2001).In humans also the HOXA10 gene is found to target the downstream gene Emx2 as seen in mice. In human Emx2 gene exerts proliferative effects in the adult endometrium and exerts a negative role by cyclically expressing in an inverse spatiotemporal manner to HOXA10 (Troy *et al.,* 2003). HOXA10 is also found to upregulate the expression of the

cell adhesion molecule â3 integrin in endometrial epithelial cells (Daftary *et al.,* 2002).

Homeobox gene: Its role during postimplantation period and decidualization of pregnant mice uterus

After the successful implantation of the blastocyst, the stromal cells surrounding the blastocyst transform into morphologically and functionally distinct cells called decidual cells through a process called decidualization (Okada *et al.,* 2018).Two of the major Hoxa cluster genes, Hoxa10 and Hoxa11 are expressed in the uterus post-implantation implying their role in the post implantation processes taking place in the uterus. There is spatiotemporal change in the expression of Hoxa10 in the pregnant mouse uterus. Hoxa10 is first expressed on Day 1.5 in the epithelial cells. On Day 4 during the onset of the attachment of the blastocyst to the competent uterus, Hoxa10 is detectable in the stroma underlying the epithelium. Post the attachment reaction the expression is further enhanced on Day 5. On Day 6 the expression spreads throughout the whole stroma (Satokata *et al.,* 1995; Benson *et al.,* 1996).The importance of Hoxa10 in the mice uterus during periimplantation is substantiated by decreased decidualization in response to artificial stimuli in the Hoxa10^{-}/$^{-}$ mutant mice (Benson *et al.,* 1996). Furthermore, Hoxa10^{-}/$^{-}$ female mice showed dysregulation of cyclin D3 and loss of region-specific expression of CDK4 and CDK6 and abnormal induction of the cell cycle inhibitors p15 and the negative cell cycle regulators cyclins G1 and G2(Das *et al.,* 1999; Tan *et al.,* 2002; Yao *et al.,* 2003; Tan *et al.,* 2004; Yue *et al.,* 2005). As reported by Gao *et al,* (2015), FoxM1 and cyclin D3, the other two downstream targets of Hoxa10 also plays an important role in normal regional decidualization. The above results indicate that Hoxa10 may act as the control point of the cell cycle progression and cellular differentiation during decidualization. In addition to that, reports shows that, Hoxa10 deficiency also effects natural killer cell differentiation and alters the expression of region-specific genes such as Gdf10 (Growth differentiation factor 10) also known as BMP-3B(Bone morphogenetic factor-3B), Snail2 (Snail family zinc finger 2), Hgf (Hepatocyte growth factor) and others, during decidualization (Rahman *et al.,*2006).

Similarly, HOXA10 in humans is expressed in the endometrial cells during mid-secretory phase of the menstrual cycle, in which decidual differentiation is initiated by the stroma. In vitro experiments conducted on endometrial stromal cells have shown that HOXA10 regulates the expression of p57, a cell cycle inhibitor (Qian *et al.,* 2005), interleukins IL-15 and IL-11(Godbole and Modi, 2010) and also the decidualization marker IGFBP-1(Insulin like growth factor binding protein-1) (Kim et al, 2007) suggesting its essential role during decidualization.

Role of Hox genes during the embryonic development:

A. Development of reproductive tract

In terms of presence of Homeodomain, the Homeobox transcription factors are broadly divided into Hox, Emx, Msx, Hmx and others. Among these the "Hox family" is the largest family and their roles in implantation and embryonic development are found to be more evident. The formation of the antero-posterior body axis of developing embryo is one of the well characterized roles of Hox genes. Several studies have revealed that HOX/Hox genes plays crucial role in regulating the segmental pattern of hindbrain, skeleton axis and the limb axis (McGinnis and Krumlauf, 1992). Along with this, they also direct the development of female reproductive tract in both humans and mice (Hunt and Krumlauf, 1992; Krumlauf, 1994; Grapin-Botton and Melton, 2000; Du and Taylor, 2015).

Well developed female reproductive system is the key factor to fertility and successful pregnancy. Any disturbance in proper formation of vagina, uterus and oviduct may lead to several pregnancy issues and also infertile female (Kobayashi and Behringer, 2003). Although as described earlier, the Hox genes are found to be expressed in the adult uterus during peri-implantation period in both mice and human, they are also expressed in the developing female reproductive tract. The female reproductive tract is developed from structures

known as the Mullerian ducts. The development of oviduct, uterus and upper vagina of reproductive tract proceed in peculiar A-P order patterning of Mullerian ducts (Ma *et al.,* 1998; Kobayashi and Behringer, 2003; Lim and Wang, 2010). Studies have found that different Hoxa genes are expressed in different region of developing reproductive tract, Hoxa9 is expressed in areas determined to become the oviduct, Hoxa10 is expressed in the developing uterus, Hoxa11 is expressed in the primordia of the lower uterine segment and cervix, and Hoxa13 is found in the upper vagina (Taylor *et al.,* 1997). The gene targeted studies reveals that mutagenesis of these genes causes region specific impairments along the developing reproductive tract, showing there important role.

Several studies have shown that deficiency in Hoxa10 causes the homeotic transformation of the anterior part of the uterus into an oviduct-like structure (Satokata *et at.,* 1995; Benson *et al.,* 1996). Hypoplastic urogenital sinus and agenesis of the posterior portion of the mullerian duct is seen in Hoxa13$^{-/-}$ mice. Alongwith the Hoxa cluster genes the Hoxd cluster genes are also expressed in the developing reproductive tract. The Hoxd13 gene shows similar pattern of expression as that of the Hoxa13 gene. The crucial role of presence of Hoxd13 gene is understood by a study on Hoxa13$^{+/-}$ and Hoxd13$^{-/-}$ deficient female mice. In both the cases the mice shows malpositioning of the vagina and improper separation of the vagina from the urogenital sinus. Similarities in the expression of human HOXA genes to the mice indicate a similar role in the development of female reproductive tracts both in mice and humans (Mortlock and Innis, 1997; Warot *et al.,* 1997; Taylor, 2000).

B. Limb development in embryo:

Several Hox genes are related to development of limb in the developing embryo of human.HOXD13 is a gene of HOXD cluster which is responsible for the limb development in a growing embryo. It is found that any mutation in this gene leads to synpolydactyly(SPD),a rare limb malformation which is dominantly inherited, with a combination of syndactyly(fusion of digits) and polydactyly (extra digits)(Sayli *et al.,*1995; Sarfarazi *et al.,* 1995; Muragaki *et al.,* 1996). People who are homozygous for SPD, shows Brachydactyly, a condition in which there is shortening of the digits (Muragaki *et al.,* 1996). Similarly, Hypodactyly a condition with loss of digit development is seen in mice. A semi dominant syndrome with homozygous hypodactyly showing hindrance in digital arch formation is seen in mice with Hoxa13 deletion (Mortlock et al, 1996).

C. Hox genes and development of Lung:

The development of lung is associated with synchronized expression of large network of genes in spatio-temporal manner. A high expression of 3' Hox genes in clusters A and B is found in fetal rodents and human lung development in various studies (Molard and Dziadek, 1997; Golpon *et al.,* 2001). Moreover, as lung development progresses the expression of most of the genes are found to be lowered suggesting their involvement in the early stages (airway branching etc.) of the lung morphogenesis. On the other hand, expression of Hoxa5 gene of the Hoxa cluster is found high throughout the development suggesting its role in the later stages like the pulmonary maturation (Kim and Nielson, 2000). Mice with reduced or deleted Hox genes show strong evidence of the role of Hox genes in the structural development of the respiratory system and regulation of pulmonary surfactant production. In mice with reduced Hoxb5 genes shows reduction in the degree of branching morphogenesis (Volpe *et al.,* 2000). Additionally, Hoxa5 knock-out mice die in early neonatal period. Though these knockout mice develop full term they could not survive due to tracheal occlusion and reduced levels of expression of surfactant proteins (Aubin *et al.,* 1997).

Studies reveal that various lung abnormalities are associated with abnormal HOX gene expression in human. Over expression of HOXB5 is found in both bronchopulmonary sequestration (Volpe *et al.,* 2000) and congenital cystic adenomatoid malformation characterized by deregulated patterns of morphogenesis in primordial lung tissue (Golpon *et al.,* 2001). Several acquired disorders like emphysema, primary pulmonary hypertension and lung carcinomas are also characterized by altered pattern of expression of HOX gene (Calvo *et al.,* 2000; Volpe *et al.,* 2003).

D. Hox genes in Axial patterning of Embryo

As stated earlier Hox genes plays an important role in AP axis patterning in vertebrate. Anatomically, the vertebral column can be divided in 5 different regions as cervical, thoracic, lumbar, sacral, and caudal. In particular, it is thought that speciûc combinations of Hox genes along the AP axis are responsible for the generation of vertebrae with distinct anatomical properties (Wellik, 2007). A large number of studies, mainly using the mouse as a model, have highlighted the complexity of the Hox patterning activities leading to the production of a properly organized axial skeleton (Mallo *et al.*, 2010). In vertebrates, Hox gene expression is initiated in cells of the posterior primitive streak that contribute to extraembryonic mesoderm and then expands anteriorly into prospective cells of the embryo proper (Deschamps *et al.*, 1999). Sequential activation of Hox genes directly reûects their position within the cluster, with expression of more posterior (50) genes being progressively initiated at later developmental time points (Izpisua Belmonte *et al.*, 1991). The initial Hox expression domains are transmitted to the nascent paraxial mesoderm during gastrulation, creating the ûrst Hox.

Numerous reports have shown that targeted mutations of Hox genes reflected that mutations in genes from Hox3 to Hox 11 generate axial skeleton defects (Wahba et al., 2001; Wellik and Capecchi, 2003, McIntyre *et al.*, 2007). Study on expression of Hox genes have shown that 3- genes exhibit phenotypes in anterior region of the axial vertebrae and 5- hox genes display phenotypes in posterior displaying the collinear expression. This phenomenon is also reflected in the study wherein it is seen that loss of Hoxd3 function results in defects of the ûrst and second cervical vertebrae, C1 and C2, while loss of Hoxd11 function causes changes in sacral patterning (Condie and Capecchi 1993; Davis and Capecchi, 1994).

Downstream genes of Hoxa10:

HOXA10 is found to exert its effect in the endometrium through various downstream target genes. Among them are IGFBP1 (Kim *et al.,* 2003), p/CAF (Sun *et al.,* 2009), EMX2 (Troy *et al.,* 2003), â3 Integrin subunit (Daftary *et al.,* 2002). It has been also shown at molecular level that the expression of cyclinD3, a cell cycle regulator (Das *et al.,* 2009)is perturbed during the decidual progression in mice with Hoxa10 null mutation (Rahman *et al.,* 2006; Das *et al.,* 1999), indicating its importance downstream of Hoxa10 during decidualization. It is further reported by Gao et al. (Gao *et al.,* 2015) that the expression of Forkhead box M1 (FOXM1), during decidualization is regulated by Hoxa10 at the transcriptional level, shown by the significant reduction of FoxM1 expression at the SDZ in Hoxa10$^{-/-}$ mice causing impaired regional decidualization. Further Hmgn5 is another gene involved in the regulation of cellular proliferation and differentiation of uterine stromal cells by acting downstream of Hoxa10 (Li *et al.,* 2016).

Table 1. Functions associated with different Hox genes.

Hox gene	Animal	Process associated
Hoxa5	Mice	Pulmonary maturation
Hoxb5/HOXB5	Mice, Human	Branching morphogenesis of lung
Hoxa9/HOXA9	Mice, Human	Developing oviduct
Hoxa10/HOXA10	Mice, Human	Endometrial receptivity, Implantation & decidualization, developing uterus
Hoxa11/HOXA11	Mice, Human	Endometrial receptivity, Implantation, developing lower uterine segment & cervix
Hoxa13/HOXA13	Mice, Human	Developing upper vagina
HOXA9	Human	Endometrial receptivity
HOXB6	Human	Endometrial receptivity
HOXD10	Human	Endometrial receptivity
HOXD13	Human	Limb development

Discussion

Implantation and decidualization is a complex process that involves interplay of numerous genes and pathways. Techniques involving gene silencing in combination with microarray analysis with the use of bioinformatics tools have made it feasible in contemporary time to define a role for particular factor of interest during decidualization. Among such factors, Homeobox (Hox) gene family has been found to have essential role in the regulation of embryonic and post natal physiologic developmental processes. As with other homeobox genes, HOXA10 is a regulator of embryonic morphogenesis and differentiation (McGinnis and Krumlauf, 1992) and is essential in determining body pattern along the

anterior–posterior axis. HOXA10 is necessary for the development and differentitation of the reproductive tract (Izpisua-Belmonte *et al.*, 1991).The Hox comes together to set up the axis and provide constant input in different tissues, thus orchestrating the developmental sequence sublimely. *In vivo* studies alongwith genome editing tools to study the Homeobox genes as well as non-coding DNA becomes very important to identify specific gene products involved in the orchestration which might ultimately become feasible target for therapeutic intervention.

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