The Role of *Hox* Genes in Female Reproductive Tract Development, Adult Function, and Fertility

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HOX genes convey positional identity that leads to the proper partitioning and adult identity of the female reproductive track. Abnormalities in reproductive tract development can be caused by *HOX* gene mutations or altered *HOX* gene expression. Diethylstilbestrol (DES) and other endocrine disruptors cause Müllerian defects by changing *HOX* gene expression. *HOX* genes are also essential regulators of adult endometrial development. Regulated *HOXA10* and *HOXA11* expression is necessary for endometrial receptivity; decreased *HOXA10* or *HOXA11* expression leads to decreased implantation rates. Alternation of *HOXA10* and *HOXA11* expression has been identified as a mechanism of the decreased implantation associated with endometriosis, polycystic ovarian syndrome, leiomyoma, polyps, adenomyosis, and hydrosalpinx. Alteration of *HOX* gene expression causes both uterine developmental abnormalities and impaired adult endometrial development that prevent implantation and lead to female infertility.

*H*OX genes comprise a family of regulatory molecules that encode highly conserved transcription factors. In the past several decades, molecular and genetic evidence indicates that *HOX* genes are expressed along anterior–posterior axes and control morphogenesis and cell differentiation during normal embryonic axial development; this mechanism for assigning differential identity along previously uniform axes is used in species as diverse as *Drosophila* and humans (McGinnis and Krumlauf 1992). *HOX* genes have a similar role in the specification of the developmental fate in individual regions of the female reproductive tract, where they regulate developmental axis in the embryonic period. *HOX* genes also give specific identity to the developing endometrium during the menstrual cycle in adults. The cyclic growth of endometrium is dependent on the ordered production of estrogen and progesterone. *HOX* gene expression is regulated by sex steroids, and this regulated expression plays an important role in endometrial development and endometrial receptivity (Taylor et al. 1997, 1998, 1999b). Here, we review the role of *HOX* genes, specifically the *HOXA*/*Hoxa* genes, in reproductive tract development, endometrial cyclic growth and embryo implantation, and the alterations in *HOXA*/*Hoxa* gene expression that can lead to infertility.

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HOX GENES AND THEIR ROLE IN THE BODY PLAN

HOX Genes

Homeobox genes (as known as *HOX* genes) comprise a group of highly conserved genes that are essential regulators of anterior–posterior (A–P) axial pattern development. In 1978, the relationship between the location of a homeotic gene and positional development identity was first recognized in *Drosophila* (Lewis 1978). Six years later, the *HOX* genes were cloned and sequenced in the fruit fly *Drosophila melanogaster* (McGinnis et al. 1984a,b; Scott and Weiner 1984). Since then, multiple *HOX* genes have been identified in many species, including humans. *HOX* genes encode proteins that act as transcription factors. In each of the *HOX* genes, a 183-bp highly conserved sequence was identified, which encodes a 61-amino acid region, called the homeodomain (HD). Structural analyses have shown that the HD can self-fold, and form a structural motif called a "helix-turn-helix motif." Through this motif, the HD, a DNA binding domain, recognizes a typical core DNA sequence, typically TAAT or TTAT, and regulates the expression of target genes, many of which play a role in axial development (Gehring et al. 1994; Krumlauf 1994; Gruschus et al. 1999; Passner et al. 1999).

Like all other insects, *Drosophila* has eight *HOX* genes, which are clustered into two complexes in close proximity, the antennapedia (Ant-C) complex and bithorax (Bx-C) complex. In mice and humans, *Hox/HOX* genes are clustered into four unlinked genomic loci, *Hox a-d* (mouse) or *HOX A-D* (human); each locus contains nine to 13 genes and all four clusters contain a total of 39 *HOX* genes. Those four paralogues, classified by sequence similarity, are located on chromosomes 6, 11, 15, and 2 in mice and chromosomes 7, 17, 12, and 2 in humans. The clustered *HOX* genes are believed to have arisen from gross duplication of a single common ancestral cluster. Presently, none of the paralogues have 13 genes, so some duplicated genes must have been lost during the course of evolution (Krumlauf 1994).

Hox Genes and Vertebrate Axial Development

In general, expression of the *HOX* genes follows a 3′ to 5′ order, which means, *HOX* genes at 3′ end are expressed earlier in development than their 5′ neighbors within the same cluster. The position in the cluster reflects both the timing and spatial position of developmental expression (Hunt and Krumlauf 1992; McGinnis and Krumlauf 1992). *HOX* genes have a well-characterized role in embryonic development, during which they determine identity along the A–P body axis. In vertebrates, gastrulation forms three germ layers: ectoderm, endoderm, and mesoderm. *HOX* genes are first expressed in the mesoderm during early gastrulation, and the 3′ genes are expressed first in anterior locations and then the 5′ genes are expressed later in the distal sacral regions. The role of mammalian *HOX* genes in regulating segmental patterns of hindbrain, skeleton axis and the limb axis is well established. In mice, gain- and loss-of-function experiments have revealed the spatiotemporal expression controlled by *Hox* genes in skeleton development (Ramirez-Solis et al. 1993; Horan et al. 1995; Fromental-Ramain et al. 1996; Favier and Dolle 1997). For instance, loss of *Hoxb4* expression leads to defects in the first and second cervical vertebrae. Targeted mutations of *Hoxa9* and *Hoxd9* result in anterior transformations of distinct lumbosacral vertebrae. There are transformations of sacral and first caudal vertebrae in *Hoxa11* knockout mice. In the vertebrate nervous system, the hindbrain or rhombencephalon develops under the regulating of such segmental patterning directed by *Hox* gene expression as well; regional expression of *Hox* genes in the hindbrain is thought to confer identity to rhombomeres (Carpenter et al. 1993; Mark et al. 1993; Goddard et al. 1996; Studer et al. 1996; Morrison et al. 1997; Manzanares et al. 1999; Ferretti et al. 2000; Yau et al. 2002). Mice harboring a *Hoxa1* mutation have alteration in hindbrain segmentation, deleting all or part of rhombomere5 (r5). The absence of *Hoxb1* function results in an apparent segmental transformation of r4 to an r2-like rhombomere identity. *Hox-* is essential for r4 development. *Hoxa3* and *Hoxb3* genes are segmentally ex-

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pressed in r4 and r6. *Hoxa4*, *Hoxb4*, and *Hoxd4* have anterior limits in the hindbrain, but map to the junction between rhombomeric segments r6 and r7. Vertebrate *HOX* genes not only specify positional identity along the A–P axis of the body plan, but also provide positional values on the axis of the developing limb (Davis and Capecchi 1996; Nelson et al. 1996; Goff and Tabin 1997; Scott 1997). The most 5′ members of the *Hoxa* and *Hoxd* clusters (*Hoxa9-13* and *Hoxd9-13*) are particularly important in vertebrate limb development. *Hoxa9* to *Hoxa10* and *Hoxd9* to *Hoxa10* are expressed in the developing upper arm/leg; *Hoxa11* and *Hoxd9* to *Hoxa13* are expressed in the development of the lower part of the arm/leg. *Hoxa13* and *Hoxd10* to *Hoxd13* are expressed during specification of the hand/foot. The first identified human limb malformation related to a defective *HOX* gene was synpolydactyly, which results from mutations in the *HOXD13* gene (Muragaki et al. 1996). The role of *HOX* genes in vertebrate axial patterning is similar to but more complex than that in *Drosophila*. In the mice and humans, *Hox*/*HOX* gene clusters provide a considerably overlapping expression pattern, which provides for the possibility of redundancy.

THE ROLE OF *HOX* GENES IN FEMALE REPRODUCTION

HOX Genes and Structure of Female Reproductive Tract

The female reproductive system is derived from the paramesonephric (Müllerian) duct, which ultimately develops into the fallopian tube (oviduct), uterus, cervix, and upper part of the vagina. The developing of female reproductive tract is patterned by the differential expression of *HOX* genes in the Müllerian duct.

In the developing Müllerian duct, a number of posterior *Abdominal B (AbdB) HOX* genes were found to be expressed in partially overlapping patterns along the A–P axis. In vertebrates, *HOX* genes in paralogous groups *Hoxa9-13* develop a characteristic spatial distribution throughout the Müllerian duct (Taylor et al. 1997; Taylor 2000; Goodman 2002). *AbdB* genes are expressed according to their 3′ to 5′ order in

the *HOX* gene clusters. *Hoxa9* is expressed at high levels in areas that will become the oviduct, *Hoxa10* is expressed in the development of the uterus, *Hoxa11* is found in the primordial lower uterus and cervix, and *Hoxa13* is seen in the ectocervix and upper vagina. No gene exists in the *Hoxa* cluster that is a paralogue of *Hoxd12* or *Hoxc12*; hence, there is no *Hoxa12* gene. This expression pattern is conserved between mice and humans (Fig. 1). Targeted mutagenesis of these genes results in region-specific defects along the female reproductive tract. *Hoxa10* deficiency causes the homeotic transformation of the anterior part of the uterus into an oviduct-like structure. *Hoxa13* null embryos show a hypoplastic urogenital genital sinus and agenesis of the posterior portion of the Müllerian duct. When the *Hoxa11* gene is replaced by the *Hoxa13* gene, posterior homeotic transformation occurs in the female reproductive tract: the uterus, in which *Hoxa11*, but not *Hoxa13* is normally expressed, becomes similar to the more posterior cervix and vagina, in which *Hoxa13* is normally expressed (Satokata et al. 1995; Benson et al. 1996; Warot et al. 1997).

Although *HOX* genes were once considered to be expressed only during embryonic development, persistent *HOX* gene expression was first well characterized in the adult female reproductive tract (Benson et al. 1996; Taylor et al. 1997). The adult reproductive tract undergoes a continuing developmental process during each menstrual cycle; proliferation and differentiation of endometrium coupled with angiogenesis leads to a new endometrium in each estrus or menstrual cycle. In both mice and humans, the expression of *Hoxa9-13*/*HOXA9-13* in the adult reproductive tract has been described as the same regions as their expression in the embryo (Dolle et al. 1991; Favier and Dolle 1997; Taylor et al. 1997; Warot et al. 1997). Specifically, *Hoxa10*/*HOXA10* and *Hoxa11*/*HOXA11* are expressed in the endometrium of the adult mice and humans. The expression of these two genes varies in an estrus/menstrual cycle-dependent manner (Fig. 2). *Hoxa10*/*HOXA10* and *Hoxa11*/*HOXA11* are expressed in the proliferative phase of the endometrium and increase during the secretory phase (Taylor et al.
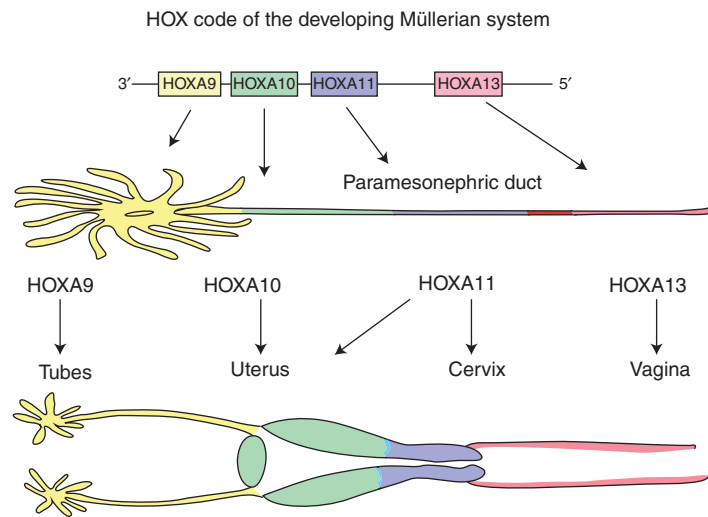
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Figure 1. *HOX* code of the developing Müllerian system (adapted from Taylor 2000).

1997, 1998, 1999b). Persistent *HOX* gene expression in the adult may be a mechanism to retain developmental plasticity in the female reproductive tract.

Emx2 is a divergent Homeobox gene, which is a mammalian homolog of the *Drosophila* empty spiracles (ems) gene. The vertebrate *Emx2* gene is located outside of the *Hox* cluster, and is expressed in the developing vertebrate brain as well as the urogenital system (Simeone et al. 1992a,b). In the embryo, *Emx2* is expressed in the epithelial components of the pronephros, mesonephros, ureteric buds, and the Wolffian and Müllerian ducts. In mouse embryos, *Emx2* expression is greatly diminished in male gonad, but strong expression remains detectable throughout the female gonad. Null mutants of *Emx2* mice fail to develop kidneys, gonads or a reproductive tract (Pellegrini et al. 1997; Svingen and Koopman 2007). In adults, *EMX2* has been detected in the human uterus. The expression of *EMX2* displayed a dynamic pattern that varied with the developmental phase of the human reproductive cycle (Fig. 2) (Troy et al. 2003).

The Role of *HOX* Genes in Female Fertility

Female fertility is a broad term, which includes the ability to reproduce or become pregnant.

Multiple factors influence female fertility, including normal aging and several disease processes. However, two processes are essential for normal female fertility: ovarian follicular maturation and embryo implantation. In vertebrates, *HOX* genes are involved in both of these processes.

Ovarian follicle development is a complex process in which many transcription factors participate. As described above, *HOX* genes containing the evolutionarily conserved HD sequence encode a family of DNA-binding transcription factors whose functions are crucial for embryonic development in vertebrates. In 1995, *HOXA4* and *HOXA7* expression was first described in the human unfertilized oocytes (Verlinsky et al. 1995). Sequence analysis of cDNA libraries generated from human unfertilized oocytes confirmed the expression of *HOXA7* (Adjaye and Monk 2000). Furthermore, in human ovarian folliculogenesis, *HOXA7* expression is nearly absent in primordial follicles but high in primary and mature follicles. During follicular maturation, the subcellular localization of *HOXA7* changes from nuclear to predominantly cytoplasmic. This differential localization indicates that *HOXA7* undergoes cell type- and stage-specific changes during the human ovarian folliculogenesis, and regulates proliferative
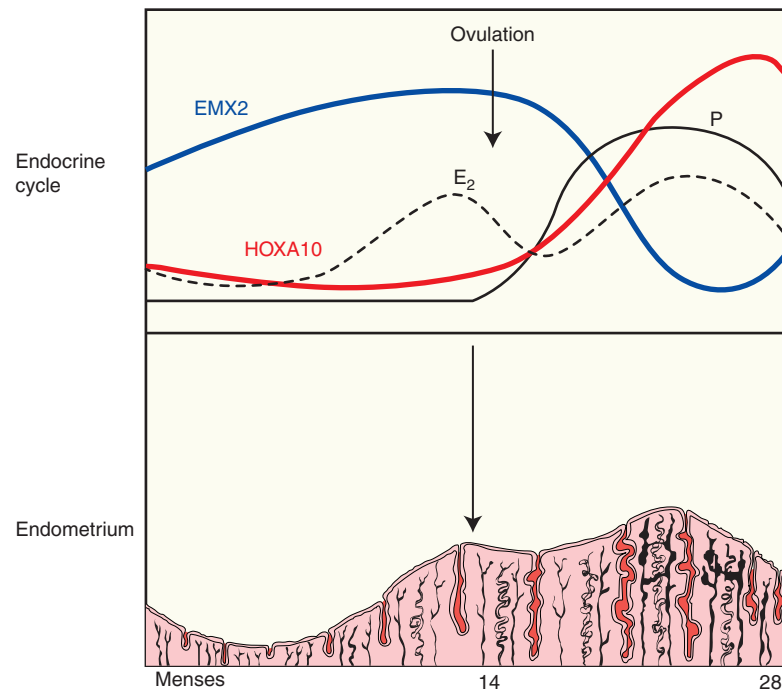
Figure 2. The pattern of *HOXA10* expression in the human endometrium through the menstrual cycle (adapted from Taylor 2000). *HOXA11* expression closely parallels that of *HOXA10*.

activities of ovarian follicles (Ota et al. 2006). Granulosa cells surround the developing oocyte, providing a critical microenvironment for follicular growth. During this process, the oocyte and the granulosa cells establish mutual interactions and their growth is regulated by coordinated paracrine mechanisms. *HOXA7* modulates granulosa cell growth and proliferation not only via the regulation of the epidermal growth factor receptor (EGFR), but also forms dimers with the *HOX* gene cofactor pre-B-cell leukemia transcription factor 2 (PBX2) to bind the specific promoter regions in the human granulosa cells. *HOXA7* plays an important role in ovarian follicular maturation (Ota et al. 2008; Zhang et al. 2010).

Embryo implantation is critical for female reproduction. This process is a complex event requiring synchronization between a developing embryo and receptive endometrium. Fundamental to this process is the dynamic and precisely ordered molecular and cellular events that drive and stabilize the interaction between

the developing embryo and its host endometrium. As described above, *Hoxa10*/*HOXA10* and *Hoxa11*/*HOXA11* are expressed in endometrial glands and stroma throughout the estrus/menstrual cycle. These two *HOX* genes are essential for embryo implantation in both mice and humans (Hsieh-Li et al. 1995; Satokata et al. 1995; Benson et al. 1996; Gendron et al. 1997). Targeted mutation of either *Hoxa10* or *Hoxa11* in the mice leads to infertility related to defects in uterine receptivity. Embryos produced by *Hoxa10* deficient mice are viable and can successfully implant in wild-type surrogates. However, those embryos are not able to implant or survive in the uteri of *Hox* gene knockout mice. Although the uteri of these knockout mice appear anatomically normal, they do not support the development or implantation of their own embryos, nor of embryos from the wild-type mice. Histologic abnormalities were noted in the *Hoxa10* deficient mice, resulting in a homeotic transformation of the anterior part of the uterus into an oviduct-like structure. Similarly,

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the mice with a homozygous mutation in the *Hoxa11* gene are infertile because of implantation defects. Those mice have reduced endometrial glands and decreased leukemia inhibitory factor (LIF) secretion. Targeted mutation of orthologous *Hox* genes such as both *Hoxd9* and *Hoxd10* in mice does not result in abnormalities on uterine structure or position (De La Cruz et al. 1999). Although no human females with mutations in *HOXA10* and *HOXA11* have been described, it has been reported that patients with lower implantation rates have lower *HOXA10* and *HOXA11* expression in the secretory phase, which indicates that maternal *HOX* gene expression is conserved and necessary for endometrial receptivity (Taylor et al. 1999b; Bagot et al. 2000; Taylor 2000).

Estrogens and Progesterone Regulate *Hox* Gene Expression in the Reproductive Tract

So far, few regulators of *HOX* gene expression have been identified. Sex steroids have been investigated in the regulation of the *HOX* genes at the 5′ end of the cluster, which determine the posterior development, including the development of female reproductive tract (Taylor et al. 1997, 1998, 1999b; Ma et al. 1998; Cermik et al. 2001; Goodman 2002). During each reproductive cycle, endometrial epithelial and stromal cells display a well-defined cyclic pattern of functional differentiation under the influence of estrogen and progesterone. Menstrual cyclicity is regulated by timed expression of estrogen and progesterone, which act both independently and in concert to up-regulate *HOXA10* and *HOXA11* expression in the endometrium. In normal cycling women, *HOXA10* and *HOXA11* levels increase, reaching maximal expression during the mid-secretory phase, and remaining elevated throughout the secretory phase. In endometrial stromal cells, 17β-estradiol and progesterone significantly increase *HOXA10* and *HOXA11* expression. *HOXA9* is under the control of both estrogen and progesterone as well. The regulation of *HOX* gene expression in the adult uterus by ovarian steroids is related to its position within the cluster and mediated by the direct action of estrogen and progesterone receptors on these genes.

Humans are exposed to a wide variety of chemicals that have estrogenic properties. Those estrogenic compounds show profound and lasting effects on essential developmental genes in female reproductive tract. They have potential to alter the expression of estrogen responsive genes, such as *HOX* genes. These changes are likely to influence reproductive competence. Diethylstilbestrol (DES) is a nonsteroidal estrogen, a well-known teratogen. This chemical alters the localization of *Hox* gene expression along the axis of the developing murine reproductive tract, and induces developmental anomalies of female reproductive tract (Ma et al. 1998; Akbas et al. 2004). DES exposure in utero shifts *Hoxa9* expression from the oviducts to the uterus and leads to decreases in both *Hoxa10* and *Hoxa11* expression in the uterus. The decreased expression of the *Hoxa* genes may cause a "T-shaped" uterus, a structure that is characterized by branching and narrowing of the uterus into a tube-like phenotype. This phenotype is likely caused by expression of the *Hox* gene that controls tubal identity (*Hoxa9*) ectopically in the uterus. Because the multiple *HOX* gene clusters provide an overlapping expression pattern in the mice and humans, the complete transformation into an oviduct is probably prevented.

Studies on xenoestrogens, such as methoxychlor (MXC) and bisphenoyl A (BPA), have shown that exposure to these chemicals also alters the *Hoxa10* expression in female reproductive tract (Block et al. 2000; Suzuki et al. 2004; Fei et al. 2005; Markey et al. 2005; Sugiura-Ogasawara et al. 2005; Daftary and Taylor 2006; Smith and Taylor 2007). MXC is a pesticide and this chemical is associated with female reproductive defects after either prenatal or postnatal exposure. MXC specifically alters *Hoxa10* gene expression, specifically the *Hoxa10* gene expression. This *HOX* gene is responsible for normal uterine development and fertility, and its expression is permanently repressed in the uterus of mice exposed to MXC in utero. This effect is mediated through the *HOXA10* estrogen response element (ERE) in a dose-dependent pattern.

BPA, another xenoestrogen, is a common component of polycarbonate plastics, epoxies used in food storage, canned goods, and dental sealants. BPA is also associated with adverse reproductive outcomes in both animal models and humans. After exposure to BPA in utero, *Hoxa10* expression is increased in female mice and this altered expression persisted in adults. The alternation of the gene expression persists long after exposure and alters the normally precise, temporal regulation of *Hoxa10* in reproductive tract development. This permanently modified expression of *Hoxa10* contributes to the decline in female reproductive potential. Despite its opposite effect on *HOX* gene expression in vivo, BPA behaves similarly to MXC in vitro by stimulating the *HOXA10* ERE. The difference seen after in utero exposure likely represents the unique molecular signals present in the embryo and underlies the increased risk of exposure to environmental chemicals during critical periods of development. Exposure to various xenoestrogens alters *Hoxa10* gene expression in the developing reproductive tract, and these exposures may lead to permanent alteration of gene expression in the adult (Fig. 3) (Taylor 2008).

HOX GENES AND INFERTILITY

HOX genes are essential for endometrial development and embryo implantation in both mice and humans. As described above, the association between alteration of *Hoxa* gene expression and fertility is evident in animal models (Fig. 4) (Paria et al. 2002). The *Hoxa10*/*HOXA10* and *Hoxa11*/*HOXA11* genes act as important transcriptional moderators that either activate or repress the downstream target genes; these targets include β3-integrin and *Emx2*/*EMX2*, which are themselves important for embryo implantation. As discussed earlier, in normal cycling women, there is a surge of *HOXA10* and *HOXA11* expression during the mid-secretory phase; diminished *HOXA10* and *HOXA11* expression in the secretory phase leads to low embryo implantation rates. Impaired uterine receptivity has been studied in several gynecological diseases that lead to infertility. These include endometriosis, polycystic ovarian syn-

drome, leiomyoma, and hydrosalpinx. Compared with controls, there is diminished *HOXA10* and *HOXA11* expression in woman with each of those disorders (discussed in detail below). Although differential mechanisms may lead to decreased expression, it appears that altered *HOX* gene expression is so central to the process of implantation that decrease of their expression is required to diminish implantation. Alterations in the expression of *HOX* genes cause infertility in humans primarily by endometrial receptivity defects and impaired implantation.

HOX Genes and Endometriosis

Endometriosis is an estrogen-dependent benign inflammatory disease defined by the presence of viable endometrial tissue outside the uterine cavity. The prevalence of endometriosis has been estimated as up to 10% to 15% of reproductive-age women and 30%−50% of women with endometriosis have infertility (Verkauf 1987; Olive and Pritts 2001). Multiple factors are considered to contribute to endometriosis related infertility, including altered folliculogenesis, impaired fertilization, poor oocyte quality, and defective implantation. Here, we will focus on the role of diminished implantation as it is related to diminished *HOX* gene expression. In patients with endometriosis, implantation rates are reduced during both natural and assisted reproductive technology cycles, even in patients with minimal disease (Barnhart et al. 2002). Two of the *HOXA* genes, *HOXA10* and *HOXA11*, involved in uterine embryogenesis and endometrial receptivity, have been implicated in the pathogenesis of endometriosis-associated infertility. In humans, the expression of both *HOXA10* and *HOXA11* rises dramatically during the implantation window and remains elevated throughout the secretory phase. However, patients with endometriosis do not show this rise in *HOXA10* and *HOXA11* (Taylor et al. 1999a; Kim et al. 2007; Lee et al. 2009).

HOXA10 downstream target genes are also involved in this pathologic mechanism. As discussed above, *EMX2* is a divergent Homeobox gene, cyclically expressed in the adult
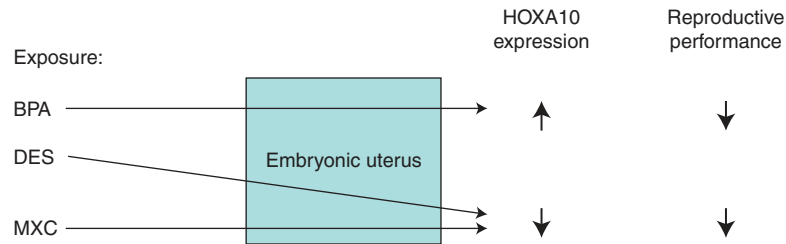
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Figure 3. Exposure to various xenoestrogens alters *HOXA10* gene expression in the developing reproductive tract. BPA, bisphenol A; DES, diethylstilbestrol; and MXC, methoxychlor.

endometrium. Endometrial *EMX2* expression is directly regulated by endogenous endometrial *HOXA10*. Normally *EMX2* expression is down-regulated in the peri-implantation period; however, this regulated expression fails in women with endometriosis (Troy et al. 2003; Daftary and Taylor 2004). Further demonstrating the important role of this target gene, altering the endometrial *Emx2* levels is not only associated with defective implantation, but also reduces litter size in mice (Taylor and Fei 2005). Aberrant endometrial *EMX2* expression in women

with endometriosis is mediated by altered *HOXA10* expression.

Furthermore, another biomarker of endometrial receptivity to embryonic implantation is also found to be decreased in endometriosis. Integrins are ubiquitous cell adhesion molecules that participate in cell–cell and cell–substratum interactions. These molecules undergo dynamic alterations during the normal menstrual cycle in the human endometrium. β3-integrin is expressed in endometrium at the time of implantation, and the disruption of in-
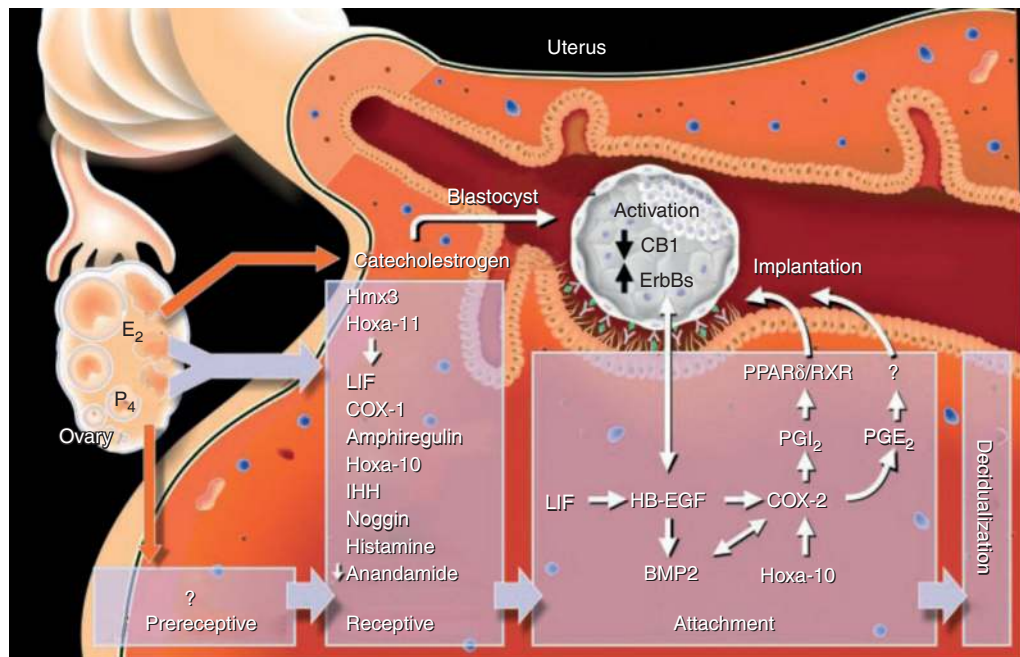

Figure 4. Molecular signaling during implantation in the mouse and human. (From Paria et al. 2002, reprinted, with permission, from The American Association for the Advancement of Science ©2002.)

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tegrin expression is associated with decreased uterine receptivity and infertility (Lessey and Young 1997). Interestingly, β3-integrin subunit is a direct *Hoxa10* downstream target gene, and directly regulated by *HOXA10* in endometrial cells. Aberrant expression of both *HOXA10* and integrins have been described in the endometrium of women with endometriosis (Lessey et al. 1994; Lessey and Young 1997; Daftary et al. 2002; Klemmt et al. 2006; Cakmak and Taylor 2011).

Recent studies indicate that epigenetic modifications may play an important role in pathological process in endometriosis. Epigenetics refers to heritable alteration of DNA by long-lasting covalent methyl modification without DNA sequence changes. These epigenetic changes have been described in numerous studies including hypermethylation of *HOXA10*, progesterone receptor-β, and E-cadherin or hypomethylation of genes for estrogen receptor-β and steroidogenic factor 1 (Guo 2009; Senapati and Barnhart 2011). In both murine and baboon endometriosis models, hypermethylation of the promoter region of *Hoxa10/HOXA10* and decreased expression of *Hoxa10/HOXA10* genes were shown in eutopic endometrium (Kim et al. 2007; Lee et al. 2009). In humans, hypermethylation of *HOXA10* was identified in the endometrium of women with endometriosis (Wu et al. 2005). The DNA methyltransferase (DNMT) is a family of enzymes, which catalyze the transfer of a methyl group to DNA. DNMT 1, 3A, and 3B were found to be overexpressed in the epithelial component of endometriotic implants. However, only DNMT3A was found to be up-regulated in eutopic endometrium of women with endometriosis (Wu et al. 2007). A recently published study, using a genome-wide methylation array, shows that *HOXA10* expression was repressed and methylation of *HOXA10* gene was altered by 1.3-fold in human endometriosis (Naqvi et al. 2014). Other *HOX* genes, such as *HOXD10* and *HOXD11*, also showed significantly altered methylation in endometriosis (Naqvi et al. 2014). Epigenetic programming of *HOX* gene expression in endometriosis leads to lasting alterations in endometrial receptivity.

HOX Genes and Polycystic Ovarian Syndrome

Polycystic ovarian syndrome (PCOS) is a common endocrine disease, afflicting 5% of women of reproductive age. It is characterized by anovulation and elevated androgen action. Infertility associated with PCOS derives from chronic anovulation. Despite the ability to correct ovulatory disorders, pregnancy rates remain paradoxically low, and spontaneous pregnancy loss rates are high. In women with PCOS, between 30% and 50% of all conceptions miscarry (Giudice 2006). Some data also suggest that poor oocyte quality, implantation failure, and higher rates of miscarriage further complicate achieving and maintaining a pregnancy in women with this disorder. Women with PCOS are also at significantly higher risk of endometrial hyperplasia (Niwa et al. 2000). PCOS may have complex effects on the endometrium, contributing to the infertility. Furthermore, increasing evidence and emerging data have shown that endometrial receptivity contributes to the infertility of PCOS even in the setting of ovulation induction (Giudice 2006). An increase in the expression of *HOXA10* in the endometrium is necessary for receptivity to embryo implantation. However, endometrial biopsies obtained from women with PCOS in ovulatory cycles have shown that *HOXA10* expression is decreased compared with normal fertile women during the secretory phase (Cermik et al. 2003). In vitro, *HOXA10* expression is repressed by testosterone (Cermik et al. 2003). Testosterone also prevents the increased expression of *HOXA10* induced by estradiol or progesterone. Dihydrotestosterone produced an effect similar to that of testosterone, whereas flutamide blocked the testosterone effect. Diminished uterine *HOXA10* expression may contribute to the diminished reproduction potential of women with PCOS, illustrating a significant effect of the disease on receptivity. Elevated androgen levels may induce infertility associated with PCOS by altering *HOX* gene expression.

As discussed above, β3-integrin, a biomarker of endometrial receptivity to embryonic implantation, is a *HOX* target gene that is

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directly regulated by *HOXA10* in endometrial cells. The expression of this biomarker is decreased in endometrium from women with PCOS compared with fertile controls (Apparao et al. 2002). Also, as described above, after ovulation induction treatment of infertility in PCOS, implantation rates remain low. In fertile women, when ovulation is induced with clomiphene citrate, the treatment provokes the expression of endometrial integrins at the implantation window. Interestingly, integrin is decreased in endometrial biopsy specimens from women with PCOS even after clomiphene citrate treatment (Gonzalez et al. 2001; Jakubowicz et al. 2001).

HOX Genes and Leiomyoma

Leiomyomas (fibroids) are the most common benign uterine tumor of reproductive age women. The growth of leiomyoma is strictly related to sex steroids and their receptors. Their presence is associated with menorrhagia and poor reproductive outcomes. The prevalence of uterine fibroids approaches to 33% of women of reproductive age based on clinical assessment, and up to 50% on ultrasound scans. This disorder presents in 5%–10% of women with infertility (Payson et al. 2006; Revel 2012).

The presence of a distorted uterine cavity caused by leiomyomas significantly decreases in vitro fertilization (IVF) pregnancy rates. Fortunately, myomectomy can increase the pregnancy rates in patients with leiomyoma-related infertility (Bulletti et al. 1999; Surrey et al. 2001). However, the mechanisms by which leiomyoma cause infertility are not fully known. *HOXA10* is expressed in human myometrium and its expression also has a menstrual cycle-dependent pattern. In vitro, *HOXA10* expression is induced in endometrial stromal cells by progesterone, but in the primary myometrial cells, progesterone suppresses *HOXA10* expression (Cermik et al. 2001; Matsuzaki et al. 2009; Rackow and Taylor 2010; Sinclair et al. 2011). It is clear that there are different factors involved in the regulation of *HOXA10* by progesterone in myometrium than endometrium. Further, independent of any change in progesterone con-

centration, endometrial *HOXA10* and *HOXA11* expression are significantly decreased in uteri with submucosal myomas compared with controls. This effect is not localized to the endometrium overlying the myoma; rather the decreased *HOXA10* expression is seen throughout the endometrium. This global effect of the myoma on endometrium suggests the presence of a diffusible factor that would influence endometrial receptivity remote from the myoma itself. Indeed, we have recently reported that TGFβ secreted by myomas leads to decreased BMP receptor expression and subsequent *HOXA10* repression (Sinclair et al. 2011). Leiomyoma alter endometrial receptivity by secreting TGFβ and altering genes including *HOXA10* that are required for implantation.

HOX Genes and Hydrosalpinx

Hydrosalpinx is an inflammatory disease involving the oviduct. The prevalence of hydrosalpinges in patients suffering from tubal disease is relatively common and ranges from 10% to 13% when diagnosed by ultrasound, and up to 30% when diagnosed by hysterosalpingography or at the time of surgery (Cakmak and Taylor 2011). Women with hydrosalpinges have decreased implantation rates in IVF, and their pregnancy rates can be improved with salpingectomy before IVF. The hydrosalpinx generates an inflammatory fluid that may interfere with endometrial receptivity and embryonic implantation mechanically or chemically (Zeyneloglu et al. 1998; Camus et al. 1999). Although a study has shown that culturing mice embryos in the medium containing hydrosalpinx fluid can suppress embryo maturation and promote degeneration, this toxic effect does not affect human embryos. (Mukherjee et al. 1996; Strandell et al. 1998) We performed an in vitro study demonstrating that hydrosalpinx fluid decreased endometrial *HOXA10* mRNA expression in a dose-dependent pattern. Subsequently, studies on women with hydrosalpinges show that the expression of *HOXA10* was significantly lower in women with hydrosalpinges compared with fertile controls. After salpingectomy, *HOXA10* expression in infertile women with hydrosal-

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pinges was similar to that of age-matched fertile women, indicating that salpingectomy restores *HOXA10* expression to physiological levels (Daftary and Taylor 2002; Daftary et al. 2007).

As described above, β3-integrin subunit is a well-characterized endometrial receptivity marker, directly regulated by *HOXA10* in endometrial cells. In women with the presence of hydrosalpinges, the expression of β3-integrin is also reduced. Interestingly, two thirds of patients with hydrosalpinx who underwent salpingectomy also showed return of *HOXA10* and β3-integrin back to normal levels (Bildirici et al. 2001).

SUMMARY

All metazoans use *HOX* genes to regulate embryonic patterning. *HOX* genes play a fundamental role in morphogenesis during embryonic development. Well-characterized examples include the role of *HOX* genes in the patterning of the vertebrate hindbrain, skeleton, and limbs. In reproduction, *HOX* genes determine positional identity during embryonic development of the female reproductive tract. Abnormalities in reproductive tract development are related to *HOX* gene mutations and to alterations in the normal *HOX* gene expression patterns. This has been clearly shown in mice with targeted *Hox* gene mutations as well as in mice exposed to chemicals with estrogenic properties such as DES. In the adult, the endometrium undergoes an ordered process of differentiation leading to receptivity to implantation. *HOX* genes are also essential to this process. As transcription factors, *HOX* genes control cyclical endometrial development and receptivity by activating or repressing the expression of target genes. *HOXA10* and *HOXA11* expression increases drastically in the mid-secretory phase, the time of implantation, and they remain elevated throughout the secretory phase. This increased expression is necessary for embryonic implantation; decreased *Hoxa10*/*HOXA10* and *Hoxa11*/*HOXA11* expression at this time leads to decrease implantation rates in both mice and humans. Impaired uterine receptivity has been studied in several infertility-related gynecolog-

ical diseases, such as endometriosis, polycystic ovarian syndrome, leiomyoma, and hydrosalpinx. Alternation of *HOXA10* and *HOXA11* expression has been identified as a mechanism of the decreased implantation associated with these disorders. Alteration of *Hoxa* gene expression causes both uterine developmental abnormalities and impaired adult endometrial development that prevent implantation and lead to female infertility.

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