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REVIEW ARTICLE

Homeobox genes for embryo implantation: From mouse to human

Bo He[1,2] | Zhang-li Ni[1,2] | Shuang-bo Kong[1,2] | Jin-hua Lu[1,2] | Hai-bin Wang[1,2]

[1]Reproductive Medical Center, The First Affiliated Hospital of Xiamen University, Xiamen, Fujian, China

[2]Fujian Provincial Key Laboratory of Reproductive Health Research, Medical College of Xiamen University, Xiamen, Fujian, China

Correspondence
Hai-bin Wang, Reproductive Medical Center, The First Affiliated Hospital of Xiamen University, Xiamen, Fujian, China.
Email: haibin.wang@vip.163.com

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Abstract

The proper development of uterus to a state of receptivity and the attainment of implantation competency for blastocyst are 2 indispensable aspects for implantation, which is considered to be a critical event for successful pregnancy. Like many developmental processes, a large number of transcription factors, such as homeobox genes, have been shown to orchestrate this complicated but highly organized physiological process during implantation. In this review, we focus on progress in studies of the role of homeobox genes, especially the Hox and Msx gene families, during implantation, together with subsequent development of post-implantation uterus and related reproductive defects in both mouse models and humans, that have led to better understanding of how implantation is precisely regulated and provide new insights into infertility.

KEYWORDS

homeobox genes, implantation, infertility, transcription factors

1 | INTRODUCTION

It is well known that the beginning of a new life starts with the union of an egg and sperm through the process of fertilization in mammals, which naturally happens in the reproductive tract of adult females. The fertilized egg then undergoes several rounds of mitosis to form a competent blastocyst. Simultaneously, the adult uterus undergoes proliferation and differentiation into specific uterine cell types to render the uterus receptive for blastocyst implantation.[1,2] With the advance of gene expression studies and the application of genetically engineered mouse models, the cellular and molecular events of implantation have been extensively explored. Like many developmental processes, numerous transcription factors are known to participate in orchestrating this process directed by ovarian estrogen (E2) and progesterone (P4) in a spatiotemporal manner.[3-5] Among a range of identified transcription factors, the homeobox transcription factors, which attracted widespread attention because of their critical role during embryonic development, have been broadly investigated in early pregnancy, such as during implantation and decidualization.

Homeobox genes are a family of regulatory genes coding for specific nuclear proteins that act as transcription factors.[6,7] They are characterized by sharing a homeobox sequence, a highly conserved 183-nucleotide sequence that encodes a 61-amino-acid domain, termed the homeodomain (HD), which is responsible for the recognition and binding of sequence-specific DNA motifs.[8,9] The homeobox genes, initially identified in *Drosophila*, can be divided into different families in mammals, such as Hox, Msx, Emx, Hmx and others.[9]

Previous studies have revealed that homeobox transcription factors encoded by the homeobox genes play important roles during various developmental and pathophysiological processes, including embryogenesis, organogenesis, tumorigenesis, and so on.[6,7,10,11] Since implantation is a complicated but precisely orchestrated

Bo He and Zhang-li Ni contributed equally to this work.

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physiological process similar to embryogenesis and tumorigenesis, the homeobox transcription factors are likely to control the dynamic expression of the implantation-related genes.[6] In fact, evidence from transgenic mouse models and human studies support the view that the homeobox transcription factors play essential roles in both the development of uterus and embryo implantation.[6,12] This review aims to illustrate progress in understanding the pathophysiological role of homeobox transcription factors, especially those encoded by the Hox and Msx genes, during the process of implantation.

2 | IMPLANTATION

Embryo implantation involves the first physical and physiological interaction between the embryo and uterus, which determines the success of post-implantation conceptus development and term pregnancy outcome. As the gateway to further embryonic development, successful implantation depends on the proper development of uterus to a receptive state and the synchronized development of blastocyst to a state of implantation competency.[2,4,5]

Initially, the adult uterus undergoes proliferation and differentiation in specific uterine cell types to render the uterus receptive to blastocyst implantation.[2,5] Uterine receptivity is defined as a condition in which the uterus is suitable for embryo implantation. The results from blastocyst transfer experiments suggest that the uterus is not constantly receptive to blastocysts; its receptivity lasts only for a limited time, which is defined as the "implantation window".[13] In fact, uterine sensitivity to implantation-competent blastocysts is classically divided into 3 stages: pre-receptive, receptive and refractory phases. During the pre-receptive stage, the uterus is suitable for embryo development but not ready for implantation, while during the receptive stage, the uterus can initiate implantation when there are competent blastocysts. However, during the refractory stage, implantation-competent blastocysts cannot implant into the uterus and the uterus is even hostile to blastocyst survival.[1]

It is generally accepted that the uterus is a remarkable organ which is periodically regulated by ovarian estrogen and progesterone. This periodic event is usually called the menstrual cycle and estrous cycle in humans and mice, respectively. In humans, the receptive phase can be defined based on the menstrual cycle: the first 7 days of the secretory phase of the menstrual cycle is considered as the pre-receptive stage, days 7-10 after ovulation is the receptive stage, and the rest of the secretory phase is defined as the non-receptive stage. However, in mice the receptive phase is difficult to determine based on the estrous cycle, because it is short (~4 days) and often irregular. Therefore, it is usually defined based on pregnancy: the uterus on Days 1-3 (Day 1 = vaginal plug) of pregnancy is conventionally considered to be in the pre-receptive phase in mice, in which the uterine epithelium undergoes proliferation stimulated by preovulatory estrogen. On Day 4 of pregnancy, the uterus becomes fully receptive following the priming actions of ovarian progesterone and pre-implantation estrogen, as a result, the epithelium begins to differentiate, accompanied by extensive proliferation of stromal cells. However, by late Day 5 the uterus is refractory to initiation of implantation.[1,2,5,14]

At the same time, the fertilized egg undergoes several rounds of division to form the blastocyst. The blastocyst then attains a state of implantation competency which is known as blastocyst activation. In mice, pre-implantation embryos can be suspended at the blastocyst stage without further initiation of attachment reaction during lactation, which is known as delayed implantation or embryonic diapause.[4,15-17] In addition, embryonic diapause can be induced experimentally through ovariectomy on Day 4 before pre-implantation estrogen secretion and then with daily injections of progesterone from Day 5, which can be terminated by a single injection of estrogen.[4,18] The delayed implantation mouse model makes it possible for us to explore blastocyst activation in mice. However, whether embryo diapause occurs in humans is not known.

Evidence from embryo transfer experiments suggests that implantation occurs during a limited time span when blastocyst competency is superimposed on the receptive state of the uterus, known as the "implantation window".[1,13] Any disturbance in the "implantation window" will cause implantation failure or defective implantation, and abnormal implantation can generate a range of adverse ripple effects, such as defective decidualization and placentation, eventually leading to a poor pregnancy outcome.[14] With advancing techniques and the application of genetically engineered mouse models, the molecular and cellular events that confer uterine receptivity and blastocyst competency have been extensively explored. A wide range of regulatory molecules, such as adhesion molecules, growth factors, cytokines and transcription factors, have been identified. Under the influence of ovarian estrogen and progesterone, the molecular signalling network consisting of these regulatory molecules elaborately orchestrate a successful implantation.[1-5] As summarized in Table 1, the homeobox transcription factors, especially Hox and Msx genes, are reported to be essential for implantation in mice and humans.

3 | HOMEOBOX GENES

The homeobox genes are famous for their roles in regulating the development of embryos and are characterized by the presence of a conserved DNA sequence called homeobox, which encodes a HD with a recognizable helix-loop-helix-turn-helix structure.[7,9,19] The HD is usually located at a terminal or sub-terminal position on the corresponding homeoprotein, and is responsible for recognizing and binding specific DNA sequences, which makes it possible for the homeobox transcription factors to regulate expression of target genes at transcription level, thereby leading to alterations of cellular behaviors or activities.[19] In terms of the HD, several homeobox gene families have so far been identified: Hox, Msx, Emx, Hmx, and others.[9]

The roles of homeobox genes in normal embryonic development are best represented by the Hox gene family, which is the largest family of homeobox genes. In mice and humans, Hox genes are

TABLE 1 Homeobox genes implicated in embryo implantation: from mouse to human

Gene	Family	Reproductive phenotype in gene-knockout mice	Related reproductive process and diseases in humans	References
Hoxa9	Hox		Implantation	56
Hoxa10	Hox	Homeotic transformation of the anterior part of the uterus into an oviduct-like structure; defective decidualization	Implantation; highly expressed in endometriosis	41,42,51,91,92
Hoxa11	Hox	Fewer glands; Infertility due to defective implantation and decidualization	Implantation and decidualization; decreased expression results in lower implantation rates	45,48-50
Hoxa13	Hox	Hypoplastic urogenital genital sinus and agenesis of the posterior portion of the Müllerian ducts	Hand-foot-genital syndrome	43,44
Msx1/2	Msx	Implantation failure	Decreased expression associated with infertility	64,67
Emx2	Emx	Abnormal development of the reproductive tract	Implantation; endometriosis	46,47,57,58
Hmx3	Hmx	Impaired implantation and decidualization		37

termed Hox and HOX genes, respectively.[6,7,20,21] There are at least 39 genes arranged in 4 clusters and designated as Hoxa, Hoxb, Hoxc, Hoxd or HOXA, HOXB, HOXC, HOXD. Each cluster is located in different genomic loci and consists of 9-11 genes. Specifically, Hoxa-d/HOXA-D are located on chromosome 6, 11, 15 and 2 in mice and chromosomes 7, 17, 12 and 2 in humans. Both in the mice and humans, Hox/HOX gene clusters usually show a considerably overlapping expression pattern, which suggests the possibility of redundancy.[6,22-24] Hox genes have a well-characterized role in embryonic development, which determines identity along the anteroposterior (A-P) body axis. For example, loss- and gain-of-function experiments suggest that Hox/HOX genes play important roles in regulating segmental patterns of hindbrain, skeleton axis and the limb axis.[7,11,20,21] The development of female reproductive tracts is also directed by Hox/HOX genes in an A-P pattern during embryogenesis in both mice and humans,[6] which will be discussed further below.

In mammals, muscle segment homeobox (Msx) genes are unlinked and related to the *Drosophila* muscle segment homeobox (msh) gene.[25,26] Unlike the Hox/HOX genes, Msx genes encode HD transcription factors usually characterized as transcriptional repressors.[27-29] In mice and humans, Msx/MSX genes consist of different members: *Msx1/MSX1*, *Msx2/MSX2*, *Msx3/MSX3*, which share 98% homology in the HD.[30] Consistent with Hox/HOX genes, Msx genes also exhibit overlapping expression patterns during embryogenesis and play important roles in the process of organ development, such as neural development and craniofacial development.[31,32] For example, loss of *Msx1*, *Msx2*, or both, adversely affects many developmental processes and even leads to perinatal lethality.[27-29,33] However, little is known about the role of *Msx3* and further research is needed in the future.

The Hmx homeobox gene family was first identified in humans, and the widespread existence of Hmx genes in the animal kingdom suggests that this gene family is of ancient origin.[34,35] In mice and humans, the Hmx gene family has at least 3 members: *Hmx1*, *Hmx2* and *Hmx3*.[36] The overlapped expression of these genes suggests a common functional role in sensory organ development and pregnancy.[37]

4 | THE ROLES OF HOMEOBOX GENES DURING IMPLANTATION

The generally accepted view is that successful pregnancy depends on a well-developed and functional female reproductive tract, consisting of oviduct, uterus and vagina, and any disturbance occurring in the development of female reproductive tracts will lead to pregnancy complications or infertility.[38] In the course of development, the female reproductive tracts arise from structures known as the Müllerian ducts (MDs).[14,38] As mentioned above, the A-P patterning of MDs proceeds in a particular order, developing into the oviduct, uterus, cervix, and upper vagina, which seems to be governed primarily by 5′ genes of the homeobox A cluster (Hoxa) in mice.[6,39] For example, *Hoxa9* is expressed in areas which will become the oviduct, *Hoxa10* is expressed in the developing uterus, *Hoxa11* is found in the primordia of the lower uterine segment and cervix, and *Hoxa13* is expressed in the upper vagina.[40] The critical roles of the Hox genes in the development of female reproductive tracts are evidenced by targeted mutagenesis of these genes, which leads to region-specific defects along the reproductive tract. In detail, *Hoxa10* deficiency causes the homeotic transformation of the anterior part of the uterus into an oviduct-like structure.[41,42] *Hoxa13*$^{-/-}$ females show a hypoplastic urogenital genital sinus and agenesis of the posterior portion of the MD in mice. Expression of the Hoxd cluster genes has also been observed in the developing reproductive tract. For example, *Hoxd13* is highly expressed in the developing reproductive tract, with a similar expression pattern to *Hoxa13*. *Hoxa13*$^{+/-}$ and *Hoxd13*$^{-/-}$ females show malpositioning of the vagina and

improper separation of the vagina from the urogenital sinus, also suggesting that *Hoxd13* plays important roles in the development of the female reproductive tract. In humans, expression of HOXA genes in the developing female reproductive tract seems to be similar to that in mice, suggesting a similar role in the development of female reproductive tracts between mice and humans.[43-45]

Apart from the Hox genes, *Emx2*, a member of EMX gene family, is expressed in the epithelial cells of MDs of the embryo, and loss of Emx2 causes development of the reproductive tract in mice to fail.[46,47] However, little is known about the role of other homeobox genes during development of the female reproductive tract.

As described above, successful implantation depends on the proper development of uterus to a state of receptivity and the synchronized development of blastocyst to a state of implantation competency. Fundamental to this process are the dynamic and ordered molecular and cellular events that direct the uterus-embryo crosstalk, which are precisely regulated by large numbers of transcription factors under the guidance of ovarian hormones.[1-3,5] Among them, homeobox transcription factors encoded by homeobox genes, such as Hox and Msx genes, are of great interest.[6,12] Although Hox genes are considered to be typically expressed during embryonic development, the persistent expression of Hox genes has also been noted in the adult uterus during the peri-implantation stage in mice and humans. Early in 1995, Satokata et al[42] reported that *Hoxa10* was expressed in luminal and glandular epithelium of mouse uterus before Day 1.5; the expression of *Hoxa10* shifted to the stroma underlying the epithelium on Day 4, and targeted disruption of the *Hoxa10* led to female infertility. Furthermore, Benson et al[41] found that loss of *Hoxa10* has no adverse impact on the survival of embryos throughout embryo transfer experiments, but mainly influences uterine function and implantation. *Hoxa11*, another member of the Hoxa cluster, is also expressed in uterine stromal cells during implantation, and loss of this gene leads to female infertility.[48,49] The overlapping expression patterns of *Hoxa10* and *Hoxa11* suggest that these 2 genes may play a similar role in the process of implantation. In fact, initial uterine attachment of blastocysts can occur and *Lif* and *Hbegf* genes are normally expressed in *Hoxa10*$^{-/-}$ mice, suggesting that *Hoxa10* is not crucial for uterine receptivity.[41,42] In contrast, *Hoxa11*$^{-/-}$ uteri are hypoplastic, with fewer glands, and gland-derived *Lif* is absent in *Hoxa11*$^{-/-}$ uteri, indicating that *Hoxa11* may be crucial for uterine receptivity and later events of implantation.[48-50] Although no human females with mutations in *HOXA10* and *HOXA11* have been reported, both *HoxA10* and *HoxA11* are upregulated in the human uterus during the secretory phase, which suggests that they might have a role in uterine receptivity and implantation.[6,40,49,51] Consistent with this, patients with implantation defects usually have lower *HOXA10* and *HOXA11* expression, as well as aberrant post-translational modifications of HOXA10 expression, such as sumoylation and acetylation.[52-55] In addition to *HOXA10* and *HOXA11*, a recent study found that other HOX genes, such as *HOXA9*, *HOXB6* and *HOXD10*, also show increased expression in the human endometrium during the mid-secretory phase of the menstrual cycle,[56] suggesting that these HOX genes are also involved in endometrial receptivity in humans.

The critical roles of *Hoxa10*/*HOXA10* during implantation are evidenced by transgenic mouse model experiments and decreased implantation rates in women with altered *HOXA10* expression. Like many other transcription factors, *Hoxa10*/*HOXA10* exerts pleiotropic effects through repressing or activating the downstream target genes in many physiological processes, including implantation.[57] For example, Troy et al[58] found that *Emx2*, a downstream target gene of *HOXA10*, exerts anti-proliferative effects in the adult endometrium and is cyclically expressed in an inverse spatiotemporal manner to *HOXA10*, suggesting a negative regulatory role. According to its expression pattern during pre-implantation, *Hoxa10* seems to promote the proliferation of epithelial and stromal cells during implantation by suppressing the expression of *Emx2*. In contrast to these inhibitory effects, decreased expression of *Wnt4* and FKBP52 was observed in the uteri of *Hoxa10*$^{-/-}$ mice,[59,60] suggesting a positive regulatory role of *Hoxa10* during peri-implantation. Furthermore, putative *Hoxa10* target genes have been systematically identified by microarray analysis employing a murine model of transient *Hoxa10* expression during the anticipated implantation window.[61] In humans, *HOXA10* can also upregulate expression of the cell adhesion molecule β3 integrin in endometrial epithelial cells, which is suggested to be positively correlated with the formation of pinopods on the epithelial cells during peri-implantation.[62,63] Although these results regarding the downstream target genes of Hox transcription factors are only the tip of the iceberg, they provide us with new insights into how implantation is precisely orchestrated by the homeobox transcription factors.

In recent years, considerable progress in understanding the role of Msx genes during implantation has been made.[5,12] A role of Msx genes in implantation was noted following the aberrant expression of *Msx1* in the uterus of *Lif*$^{-/-}$ mice,[59] which suggests it is cross-regulated with *Lif* during implantation.[64] In contrast to the constitutive contributions of *Hoxa10* and *Hoxa11*, Msx genes are distinctly and transiently expressed in the epithelium prior to implantation. Specifically, *Msx1* is expressed in the luminal and glandular epithelium of the pre-implantation uterus and has a transient peak expression during the receptive phase on Day 4, but is not expressed in the uterus thereafter for the remainder of the pregnancy. While mice with uterine deletion of *Msx1* show deferred implantation outside the normal window that results in compromised pregnancy outcomes, mice with uterine deletions of both *Msx1* and *Msx2* exhibit implantation failure, suggesting that *Msx2* compensates for the loss of *Msx1* in *Msx1*$^{d/d}$ uteri. The absence of Msx genes cause implantation failure by impeding transitions of the uterine luminal epithelium from a higher to a less polar state, which is conducive to blastocyst attachment. Accordingly, loss of the unique epithelial expression patterns of *Claudin-1* and *Sprr2* at the implantation chamber (crypt) are observed in luminal epithelium of uteri in *Msx1*$^{d/d}$*Msx2*$^{d/d}$ mice on Day 5.[64,65] In addition, there is evidence that Msx genes regulate epithelial cells

through paracrine factors secreted by the stromal cells.[66] Consistent with these results, *Msx1* was upregulated between the late proliferative and early secretory phase and then downregulated prior to receptivity for implantation in humans. Moreover, reduced expression of *Msx1* in human endometrial tissue is linked to infertility.[67] These results suggest that Msx genes are critical for implantation in both mice and humans. Meanwhile, persistent expression of *Msx1* has been shown in the uterus of the experimentally induced delayed implantation mouse model, followed by downregulation with estrogen-induced blastocyst reactivation and implantation. On inactivation of *Msx1* and *Msx2*, blastocysts in the uterus fail to achieve diapause and reactivation due to compromised blastocyst survival, suggesting that uterine Msx genes are important for survival of dormant blastocysts. Further study disclosed that the Msx genes direct and sustain embryonic diapause and blastocyst survival by limiting inflammation in the uterus. The roles of Msx genes in embryonic diapause may be conserved between species, which is evidenced by the similar expression pattern of *Msx1* during diapause in unrelated mammalian species.[68,69] In addition, evidence from mouse studies suggests that the effects of Msx genes in both uterine receptivity and embryo diapause are mediated through repressing *Wnt5a*, a known transcriptional target of uterine Msx genes.[64,68] The delayed implantation mouse model is an important means of studying blastocyst activation, and the unique expression pattern of Msx genes in the uterus of delayed implantation mice suggests a possible mechanism for blastocyst activation.[12] However, whether Msx genes play a role in human blastocyst development or not is not known because of lack of knowledge on the diapause in humans. But in general, all these results have demonstrated the critical roles of Msx genes in implantation in mice and humans.

Apart from Msx/MSX genes, the Hmx gene family is also reported to be upregulated in the myometrium of the uterus during pregnancy, and targeted disruption of the *Hmx3* gene results in implantation failure owing to the perturbation of *Wnt* and *Lif* gene expression,[37] which suggests that Hmx genes also play a critical role in implantation. Above all, the results from genetically engineered mouse models suggest that homeobox genes may play central roles in both the development of female reproductive tracts and implantation. Despite all the significant advances in our understanding of the roles of Hox and Msx genes in implantation, it is far from clear whether the other homeobox genes, such as Emx and Pax, are involved in implantation.

5 | THE ROLES OF HOMEOBOX GENES IN THE DEVELOPMENT OF POST-IMPLANTATION UTERUS

Blastocyst attachment to the luminal epithelium is followed by the development of the post-implantation uterus, in which stromal cells surrounding the implanting blastocyst undergo extensive proliferation and differentiation into morphologically and functionally distinct cells types; this process is also called decidualization.[1] As mentioned above, many homeobox genes, such as *Hoxa10*, *Hoxa11*, *Msx1*, and so on, are dynamically expressed in the uterus during implantation. Some of these homeobox genes, especially *Hoxa10* and *Hoxa11*, are persistently expressed in the post-implantation uterus, suggesting important roles in the development of the post-implantation uterus. In pregnant mouse uterus, the expression of *Hoxa10* is first detectable in the epithelial cells on Day 1.5. It shifts to the stroma underlying the epithelium on Day 4, increases in the stroma surrounding the embryo with the onset of the attachment reaction at midnight of Day 4, and is further enhanced on Day 5 and beyond. By Day 6, the *Hoxa10* is strongly expression throughout the whole stroma.[41,42] This spatiotemporal expression of *Hoxa10* implies an important role during decidualization, which is evidenced by decreased decidualization in response to artificial stimuli in the *Hoxa10*$^{-/-}$ mice.[41] Furthermore, dysregulation of cyclin D3 and loss of region-specific expression of CDK4 and CDK6 has been shown in the decidual bed of *Hoxa10*$^{-/-}$ female mice,[70-72] and overexpression of cyclin D3 can improve decidualization defects in *Hoxa10*$^{-/-}$ mice.[73] Beyond that, the cell cycle inhibitors p15 and the negative cell cycle regulators cyclins G1 and G2 are all abnormally induced in *Hoxa10*$^{-/-}$ mice.[74,75] More recently, Gao et al[76] suggest that FoxM1 and cyclin D3, as the downstream targets of *Hoxa10*, play crucial roles in normal regional decidualization. All these results suggest that *Hoxa10* may be at the control point of cell cycle progression and cellular differentiation during decidualization. Furthermore, *Hoxa10* deficiency compromises natural killer cell differentiation and alters expression of region-specific genes such as *Gdf10*, *Snail2*, *Hgf* and others, during decidualization.[77] Collectively, *Hoxa10* influences a host of genes necessary for normal decidual development. In humans, *HOXA10* is highly expressed in the endometrium cell during the mid-secretory phase of the menstrual cycle, in which the stroma initiates decidual differentiation, suggesting an essential role of *HOXA10* during decidualization. In fact, *HOXA10* gene are reported to regulate the expression of the decidualization marker IGFBP-1.[78] In addition, there is also evidence that *HOXA10* plays an essential role in decidualization in humans through regulating the expression of the cell cycle inhibitor P57, and interleukins IL-11 and IL-15 during steroid hormone-mediated decidualization of human endometrial stromal cells *in vitro*.[79,80] Although the more severe phenotype in *Hoxa11*$^{-/-}$ mice prevents us from examining the function of *Hoxa11* during decidualization, overlapping expression patterns of *Hoxa10* and *Hoxa11* were also observed in mouse decidua, suggesting a similar role in the process of decidualization.[1,6,14] All these results suggest that *Hoxa10* and *Hoxa11* play crucial roles in the decidualization in both mice and humans. In contrast to *Hoxa10*/*Hoxa11*, the Msx genes have been shown to be strictly silenced during decidualization, suggesting that Msx genes may be dispensable during development of the post-implantation uterus.[3,64] Beyond that, there are no reports showing that the other homeobox genes are critical for decidualization. Nevertheless, it is clear that precisely regulated homeobox genes are essential for normal uterine decidualization.

6 | REGULATION OF HOMEOBOX GENES BY ESTROGEN AND PROGESTERONE IN EARLY PREGNANCY

As previously described, precisely regulated homeobox genes are essential for implantation in both mice and humans, but few regulators of homeobox gene expression have been identified so far. Sex steroids, which are secreted periodically during each reproductive cycle, have been investigated in studies of the regulation of the homeobox genes. The major steroids that specify implantation are the ovarian steroids E2 and P4, which regulate uterine growth and differentiation.[1,2,4,5] With techniqual advances and the application of genetically engineered mouse models, many genes necessary for implantation, such as cytokines, growth factors and so on, have been shown to be induced and regulated by E2, P4 or both,[3] and expression of the homeobox genes seems also to be directly or indirectly regulated by these 2 hormones in mice and humans.

The periodical expression pattern of the homeobox genes in the uterus during peri-implantation in mice and the menstrual cycle in humans suggests the regulatory roles of E2 and P4,[6,45] but direct evidence for such regulatory roles comes from studies in mouse models. Specifically, *Hoxa10* expression in the adult uterus is strongly activated by progesterone and the progesterone receptor antagonist RU486 is able to block this induction, but is repressed by estrogen in a protein synthesis independent manner.[39] Correspondingly, decreased expression of *Hoxa10* has been shown in progesterone receptor null mice.[81] Furthermore, analysis of adjacent Hoxa genes reveals that *Hoxa9* and *Hoxa11* are also activated in a collinear fashion by progesterone.[39] These results suggest that the regulation of Hox gene expression in the adult uterus by ovarian steroids is a property related to position within the cluster, mediated by the direct action of estrogen and progesterone receptors upon these genes. Beyond that, the expression of *Hoxa10*/*HOXA10* and *Hoxa11*/*HOXA11* in developing female reproductive tracts is also regulated by hormonal factors in both mice and humans, as evidenced by the repression of *Hoxa10*/*HOXA10* and *Hoxa11*/*HOXA11* when developing female reproductive tracts were exposed to the synthetic estrogen diethylstilbestrol (DES) during reproductive tract morphogenesis.[82-84]

Apart from the Hox/HOX genes, Msx genes, another homeobox gene family that profoundly influences receptivity and implantation in mice, are not obviously regulated by these hormones in ovariectomized mouse models.[3] Even so, the persistent expression of *Msx1* in the delayed implantation uterus and rapid loss of expression following a single injection of estrogen suggests that the expression of *Msx1* is repressed by estrogen.[68] In fact, rapid Lif induction by E2 is responsible for the loss of *Msx1* in the delayed implantation uterus because E2 failed to downregulate *Msx1* expression in *Lif*$^{-/-}$ uteri. In addition, *Msx1* expression was downregulated if P4 treatment was combined with Lif, suggesting a direct regulatory role of Lif on *Msx1*.[59,64,68,69] All these results suggest that E2 regulates the expression of *Msx1* in an indirect manner at peri-implantation.

Although the way in which homeobox genes are precisely regulated remains largely unknown, the existing evidence is sufficient to demonstrate that the ovarian hormones induce and regulate the expression of homeobox genes directly or indirectly during peri-implantation.

7 | HOMEOBOX GENES AND INFERTILITY

As described above, a well-orchestrated temporal and spatial expression pattern of homeobox genes is essential for implantation in both mice and humans. Any alterations in the regulation of homeobox gene expression in the developing female reproductive tracts or the adult uterus may lead to disorders of reproductive function.[14,85,86] Therefore, studies on the roles of the homeobox genes during implantation will provide information to help us prevent and treat infertility.

The best-known example is that humans are easily exposed to a wide variety of chemicals that have profound and lasting effects on development of female reproductive tracts. These chemicals influence reproductive competence by altering the expression of the homeobox genes necessary for development of female reproductive tracts, such as the HOX genes.[87-89] For example, perinatal exposure of humans to DES produces uterine, cervical, and oviductal malformations by altering the expression of *HOXA9-11* genes, and this exposure may lead to permanent alteration of gene expression in the adult.[39,88] A persistent abnormality of *HOXA10* may be one of the main causes of infertility. These results suggest that keeping mothers and newborns away from exposure to such chemicals is one of the best ways to prevent infertility. Another example of the role of homeobox genes in infertility is endometriosis, which is considered to be a chronic, recurrent and progressive disease.[6,14,85] On one hand, infertile patients with endometriosis do not show a mid-secretory rise in *HOXA10* and *HOXA11* expression, which normally occurs in each menstrual cycle.[49,90] This could explain why the endometrium of the endometriosis patient is less receptive to implantation. On the other hand, *HOXA10* is reported to be expressed in human peritoneal, ovarian and lung endometriosis, as well as rectosigmoid endometriosis.[91] This ectopic expression of *HOXA10* in endometriotic lesions outside the normal domain raises the supposition that *HOXA10* might be necessary for "de novo" development of endometrial tissue, which normally occurs in the development of uterus during embryogenesis.[6,85] These results may provide new insight into the etiology of endometriosis, about which we know little, and could be helpful in the treatment of the pathology. In addition, there is also evidence that reduced expression of *Msx1* in human endometrial tissue is linked to infertility.[67] However, whether other homeobox genes are involved in infertility and whether the abnormal expression of homeobox genes in infertile patients is a defect inherent in the endometrium or secondary to the endometriosis is still unknown, and needs to be explored in the future.

8 | CONCLUSION

Implantation is the gateway to further embryonic development and is therefore considered to be the critical event during the pregnancy, involving the first physical and physiological interaction between the embryo and uterus.[1,14] Clinically, disrupted endometrial receptivity and blastocysts of poor quality also largely account for low pregnancy success rates in assisted reproductive technique programs.[2,4,5] Therefore, it becomes more and more important for us to understand the molecular mechanisms of implantation.

Despite recent progress in elucidating the roles of Msx genes in uterus receptivity and blastocyst diapause, and previous studies on the Hox genes that have greatly increased our knowledge on implantation, the roles of the homeobox genes encoding homeobox transcription factors are far from clear. For example, regarding the molecular mechanisms underlying their functions, we still need to understand whether the other homeobox genes apart from Hox and Msx genes are involved and what roles they play during implantation. One cause of this lack of clarity is the fact that homeobox genes form a superfamily of regulatory genes, which can be divided into different families, each with many different clusters. It is difficult to confirm the function of each gene in the short term. Genome-wide deletion of the homeobox genes results in embryonic lethality or developmental defects of female reproductive tracts, which limits further research on their roles in implantation. Fortunately, the widely used Cre-Loxp transgenic mouse models provide a feasible strategy to further explore the roles of homeobox genes during implantation. Recent studies on the role of Msx genes in implantation are excellent examples of the application of conditional knockout mouse models.

In fact, one of our purposes in conducting mouse uterus research is to portray the complexity of the human endometrium, given the impossibility of genetically manipulating human uteri. As mentioned above, the expression pattern similarities of homeobox genes in mouse and human, together with the aberrant expression patterns in female infertility, suggest the conserved roles of these genes, which made it feasible to translate research findings in mouse models to humans. In conclusion, subsequent studies will identify other homeobox genes and their target genes to further illuminate the complex regulatory network that is critical for implantation in mouse and human, which ultimately will provide information for the diagnosis and treatment of the female-related infertility.

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CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTION

HBW designed this review and agreed the analysis plan. BH and ZLN collected literature and sorted out the information. SBK and JHL wrote the original draft of this review, with all other authors provideding comments. HBW acts as guarantor. All authors read and approved the final manuscript.

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