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REVIEW

Epigenetic control of embryo–uterine crosstalk at peri-implantation

Shuangbo Kong[1,2] · Chan Zhou[2] · Haili Bao[2] · Zhangli Ni[2] · Mengying Liu[2] · Bo He[2] · Lin Huang[1,2] · Yang Sun[1,2] · Haibin Wang[1,2] · Jinhua Lu[1,2]

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Abstract

Embryo implantation is one of the pivotal steps during mammalian pregnancy, since the quality of embryo implantation determines the outcome of ongoing pregnancy and fetal development. A large number of factors, including transcription factors, signalling transduction components, and lipids, have been shown to be indispensable for embryo implantation. Increasing evidence also suggests the important roles of epigenetic factors in this critical event. This review focuses on recent findings about the involvement of epigenetic regulators during embryo implantation.

Keywords Implantation · Epigenetic regulation · Uterine receptivity · Blastocyst activation decidualization

Introduction

Embryo implantation, the process during which blastocyst embed into the maternal uterine wall, is a critical step during mammalian pregnancy, and any disturbance to implantation will lead to pregnancy-related complications, such as infertility and recurrent pregnancy loss. Implantation only occurs within a limited time duration, which is defined as the window of implantation. During this window, the uterus is in the receptive state, and the blastocyst, must acquire implantation competency, a state of embryo differentiation that can initiate crosstalk with uterine cells to implanting into the uterus for further in vivo development of the embryo. This concept of uterine receptivity was first raised and established by studies employing the embryo transfer technique in the 1960s [1]. Based on the previous findings, uterine sensitivity to implantation-competent blastocysts is classically divided into three stages: pre-receptive, receptive, and refractory. During the pre-receptive stage, the uterus is favourable for embryo development, but not suitable for implantation. The uterus at the receptive stage can initiate implantation when there are competent blastocysts. During the refractory stage, however, implantation-competent blastocysts cannot implant in the uterus and the uterus is even adverse to the survival and development of blastocysts [2]. The uterus is mainly composed of three different cell types, the epithelium, stroma, and myometrium. The coordination of these different endometrial cell types makes the uterus to be receptive mainly underling the regulation of progesterone (P4) and estrogen (E2) [3]. Before implanting into the uterus, the embryo must develop to form a blastocyst, which comprises of the outer trophectoderm (TE), and the inner cell mass (ICM), which further differentiate into the primitive endoderm and epiblast (Fig. 1). The reciprocal embryo transfer experiments using the delayed implantation model also indicated that blastocyst state of activation is also a critical determinant for implantation in the receptive uterus [4].

During peri-implantation, different uterine cell types respond to changing E2 and P4 levels specifically. On day 1 (day 1 = see vaginal plug) of pregnancy in mice, the uterine epithelium undergoes extensive proliferation under the influence of a preovulatory E2 surge. From day 3 onward, P4 secreted by the newly formed corpus luteum inhibits epithelium proliferation, and initiates stroma cell proliferation. On day 4, a pre-implantation ovarian E2 surge superimposes on P4 signalling to induce the establishment of uterine receptivity and the acquisition of implantation competency

✉ Haibin Wang
haibin.wang@vip.163.com

✉ Jinhua Lu
jinhua888@126.com

1 Reproductive Medical Center, The First Affiliated Hospital of Xiamen University, Xiamen 361003, Fujian, People's Republic of China

2 Fujian Provincial Key Laboratory of Reproductive Health Research, School of Medicine, Xiamen University, Xiamen 361102, Fujian, People's Republic of China

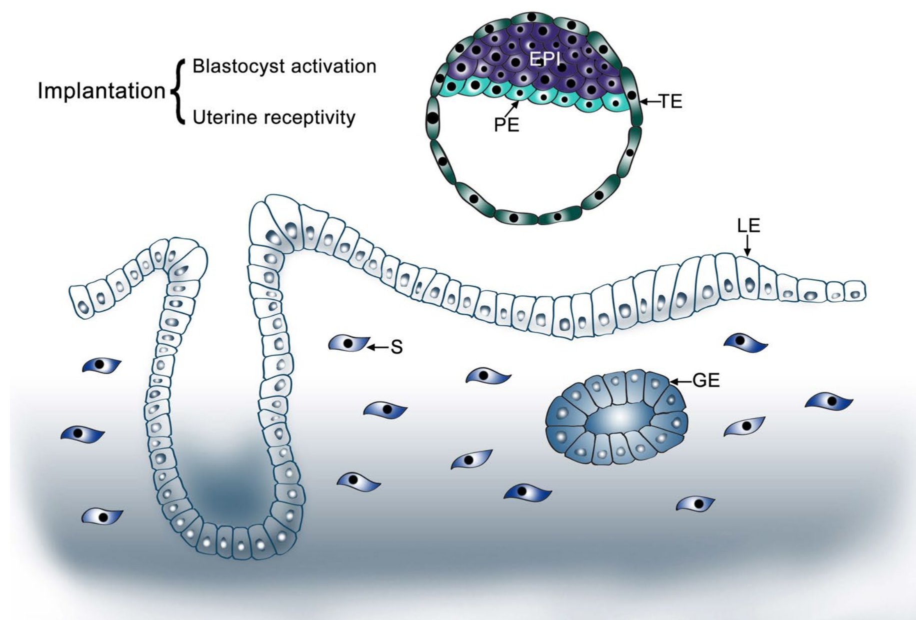

Fig. 1 Diagram of embryo implantation in mice. For successful implantation, the embryo at blastocyst stage must acquire implantation competency through a process defined as blastocyst activation, and the uterus, mainly involved the epithelium and stroma, must differentiate into a unique state-uterine receptivity to be conducive for embryo implantation. The synchronization between the blastocyst activation and uterine receptivity determined the window of implantation. TE trophectoderm, EPI epiblast, PE primitive endoderm, LE luminal epithelium, GE gland epithelium, S stroma

of blastocysts. Ovariectomy on day 4 morning, before this pre-implantation E2 surge, induces delayed implantation and embryonic diapause, a state that can be maintained by daily P4 injection from day 5 and terminated by the re-supplement of E2 [3, 5]. Similar fluctuation of P4 and E2 hormones is also observed in humans, with high levels of E2 in the proliferation stage and increased P4 levels in the secretory phase, of which the window in human is usually regarded as 5–7 days post P4 stimulation [6]. It is still unclear whether embryonic diapause also occurs in humans.

The process of implantation is divided into three stages: apposition, attachment (adhesion), and penetration. During the apposition stage, blastocysts are distributed evenly along the whole uterine horn in rodents, and the trophoblast layer of the embryo becomes closely apposed to the uterine luminal epithelium. At the attachment stage, the association of the trophoblast and luminal epithelium is strong enough to resist dislodging of the blastocyst when the uterine lumen is flushed. The first sign of the attachment reaction, which occurs at day 4 night in mice, coincides with a localized increase in stromal vascular permeability at the site of blastocyst attachment and can be visualized by tail vein injection of blue dye before sacrifice. Penetration is the process by which the embryo invades into the uterine stroma through the luminal epithelium and basal lamina to establish a vascular relationship with the uterus. After embryo implantation, the uterus undergoes significant changes to support the further development of the embryo until the establishment of a functional placenta; specifically, the uterine stromal cells proliferate and differentiate to form the decidual cells, a process termed stromal–decidual transformation (also called decidualization) [5, 7]. While embryo implantation is a dynamic process controlled strictly by molecules such as transcription factors and signalling pathway components, it is also regulated by epigenetic factors.

Aspects of epigenetic regulation

Unlike genetic regulation which functions by altering the DNA sequence, epigenetic regulation is defined as stably heritable changes in a chromosome without changing the DNA sequence [8]. Epigenetic processes mainly include DNA methylation, histone modification, and non-coding RNAs, which can influence the expression of target genes [9].

DNA methylation

DNA methylation, the best-characterized epigenetic modification, is achieved by adding a methyl group (–CH3) to the fifth carbon of the cytosine ring to form methyl cytosine, during which S-adenosylmethionine acts as the methyl donor [10]. DNA methylation is catalysed by the enzymes DNA methyltransferases (DNMTs): DNMT1, DNMT3A, DNMT3B, and DNMT3L. DNMT1 is a methylation-maintaining enzyme responsible for restoring the hemi-methylated sites to full methylation after DNA replication, whereas DNMT3A and DNMT3B are mainly involved in methylating new sites, called de novo methylation [11]. DNMT3L, without DNA methyltransferase activity in itself, is reported to regulate DNA methylation [12, 13]. In humans and other mammals, DNA methylation occurs predominantly on the cytosine base of a cytosine guanine (CG) dinucleotide in the

DNA sequence [14]. These CG dinucleotides are often clustered in small stretches of DNA, called CpG islands, which are often associated with promoter regions and at the 5′ end of the gene [15]. In general, CpG islands in gene promoters are unmethylated, which allows active gene transcription, and methylated CpG islands associated with gene promoter regions would silence gene expression. However, most CpG sites outside of CpG islands are methylated, suggesting its role during the global maintenance of the genome [14, 16]. All of epigenetic modifications should be reversed biochemically, and many years after the finding of DNMT, the TET family proteins have been shown to be responsible for DNA demethylation [17]. TET proteins are capable of catalysing the conversion of 5mC into 5hmC, and then 5hmC serves as an intermediate product for DNA demethylation in an indirect demethylation manner through passive or active pathways [17].

Histone modification

Chromatin is mainly composed of genomic DNA and the nucleosome. The nucleosome is a histone octamer consisting of two copies of each of the four core histones (H2A, H2B, H3, and H4), around which approximately 146 bp of the DNA is wrapped. These nucleosomes are linked by loops of DNA and the linker histone H1 to form chromatin. The N terminal tails of the histones protrude from the chromatin to be subjected to post-translational modification. It has been shown that nucleosomal histones are subject to numerous covalent modifications, including methylation, acetylation, phosphorylation, sumoylation, glycosylation, and ubiquitination, at specific tails of selected amino acids. A variety of enzymes are involved in the modification of histone tails, including histone methyltransferases (HMTs), acetyltransferases (HATs), kinases, and ubiquitin ligase functioning as the "writer", as well as the eraser such as histone demethylases, deacetylases (HDACs), and phosphatases, which are able to remove the modification marks from the histone tails [18]. These modifications impose either transcriptionally repressive or transcriptionally permissive chromatin structures [19, 20]. For instance, histone acetylation usually renders active genes as does the di- or trimethylation of lysine residue four in histone H3 (H3K4me2, H3K4me3), while H3K9me2/3 and H3K27me3 modifications repress gene expression [21, 22]. Moreover, proteins, known as epigenetic "readers", can directly bind to these specific modifications and exert repressive or stimulating effects on gene activity [23]. In general, different from DNA methylation which is believed to be a more stable and long-term silencing mechanism, various histone modifications seem to exert short-term, flexible regulation that is important for the plasticity of development [24–26].

Non-coding RNAs

Non-coding RNAs are transcribed from the genome, but generally are not translated into proteins. They can be classified into two subgroups according to their length: long non-coding RNAs (lncRNAs) containing more than 200 nucleotides and short ncRNAs (< 200 nucleotides), which include microRNAs (miRNAs), short interfering RNAs (siRNAs), piwi-interacting RNAs (piRNAs), and so on [27–29]. Alternatively, non-coding RNAs could also be classified based on their function: housekeeping ncRNAs, including ribosomal RNA (rRNA), transfer RNA (tRNA), small nuclear RNA (snRNA), and small nucleolar RNA (snoRNA), which are expressed in all cell types and carry out essential functions in the cells and regulatory ncRNAs, including several classes of small and long molecules, are involved in the regulation of gene expression [30]. When ncRNAs act in *cis*, they are able to regulate the expression of one or more genes nearby in the same chromosome. However, when ncRNAs act in *trans*, they are able to regulate the expression of one or more genes in different chromosomes or regulate mature RNAs in the cytoplasm [31]. Examples of the well-studied mammalian lncRNAs are Xist (inactive X-specific transcript) and Tsix (X-specific transcript), which are involved in X chromosome inactivation in female mammals [9, 32]. Recent findings demonstrate that non-coding RNAs (ncRNAs) are often accompanied by epigenetic events that are important for the regulation of gene transcription, protein translation, genomic stability, and chromatin modifications [33–37].

miRNAs, which are approximately 22 nucleotides in length, are a class of small non-coding RNAs that function as post-transcriptional regulators of gene expression. They usually bind to the 3′ untranslated regions (UTRs) of their target messenger RNAs (mRNAs) through complementary base pairing, and regulate target gene expression by either degrading or translationally repressing target mRNAs [38, 39]. It has been shown that a single miRNA is potentially responsible for repressing hundreds of mRNA targets, since the recognition of a target mRNA mainly depends on a small seed region within the mature miRNA. However, the targets of miRNAs responsible for different phenotypes have been proposed to be tissue or cell specific [40]. In recent years, it has been shown that small non-coding miRNAs are important components of epigenetic post-transcriptional regulators [41–45]. lncRNAs, transcripts longer than 200 nucleotides, are the most heterogeneous class of non-coding RNAs. They can regulate gene expression at different levels, including chromatin modification, alternative splicing, protein localization and activity, and increasing mRNA stability by protecting the 3′ UTR of mRNAs from miRNA binding [46]. Increasing evidence has shown that lncRNAs are involved in many different biological processes, such as proliferation, differentiation, pluripotency, and cell death [47, 48].

circRNAs, covalently closed continuous loop RNA lacking both a 5′ cap and a 3′ tail, are a special class of endogenous non-coding RNAs (ncRNAs) with higher stability and are expressed in a tissue-specific manner [49]. It has been suggested that circRNAs function in five putative manners: (1) promoting transcription of their parental genes; (2) competitively influencing the biogenesis and processing of the mRNA transcribed from their parental genes; (3) acting as miRNA sponges to competitively bind with miRNAs by their conserved binding sites for these miRNAs to block the binding between miRNAs and their target mRNAs; (4) functioning as RNA binding protein (RBP) sponges to regulate the function of RBPs; and (5) encoding proteins due to some circRNAs containing internal ribosome entry sites that allow the binding of ribosomes for protein translation [50].

Epigenetic regulation of the embryo–uterine crosstalk during peri-implantation

Epigenetic control of the embryo preparation for implantation

The embryo is at the blastocyst stage when it can implant into the uterus, and the blastocyst needs to acquire implantation competency. During the pre-implantation embryo development process, the terminally differentiated gametes, the egg and sperm, fuse to form a zygote, which then undergoes several rounds of mitosis. During this process, the embryo acquires totipotency, as the single embryonic cell can contribute to both the embryonic and extra-embryonic lineage. Increasing evidence has demonstrated that many different types of epigenetic regulation, including histone modifications, DNA methylation, chromatin accessibility, and 3D chromatin organization, are all involved in this short and highly effective epigenome transforming event.

For the DNA methylation dynamics in the early embryo, the highly methylated paternal genome is actively demethylated mainly through the TET-mediated hydroxylation [51]. Passive demethylation is also thought to play a role due to the inactivation of DNA methyltransferase and rapid cell proliferation in early embryos. Both the paternal and maternal genomes lose their DNA methylation until the blastocyst stage. This highly DNA demethylation process contributes to the activation of the early embryo transcriptional network and pre-implantation embryo development. For the histone modification, the immunofluorescence staining of different histone modifications in different species has suggested dynamic changes of histone modifications in the parental pronuclei after fertilization and during pre-implantation development [52, 53]. Recently, the highly developed low-input genome-wide analysis technologies have drastically stimulated the development of this field in both mice and humans. For example, it was found that both the distribution pattern and regulation for binding genes of H3K4me3 are not similar to the other cells. In the full-grown oocytes and metaphase II (MII) oocytes with the genome transitions to a silenced state, it was defined as a noncanonical pattern of H3K4me3 (ncH3K4me3), since it was wide spread [54]. The oocyte-specific pattern of the histone epigenome will undergo rapid erasure and re-establishment during fertilization and pre-implantation development. Other dynamic changes for epigenetic regulation, such as H3K27me3 histone modification and chromatin accessibility, have also been extensively explored during pre-implantation embryos [55, 56]. For more detailed information about the epigenome in early embryo development, please refer to other special reviews which address these progresses thoroughly [57, 58]. Based on these valuable data, the following challenges will be the functional dissection of different epigenetic regulations during totipotent acquirement and pre-implantation embryo development to form the blastocyst.

In normal pregnancy, when the embryo develops into the blastocyst stage and enters into the uterine cavity, it initiates the crosstalk with the endometrium, and the attachment reaction can usually be observed in mice on day 4 night. However, this sequence is interrupted in delayed implantation, which can be induced experimentally in mice and rats by ovariectomy before the pre-implantation ovarian E2 surge and maintained by injection of P4. In the delayed implantation, the blastocyst is metabolically dormant and incompetent to initiate attachment in the uterus. This phenomenon can also naturally occur in some species and in lactating rodents [59]. In the dormant blastocyst, beyond metabolism, the transcriptional activity generally shut down, which is consistent with the observation that the chromatin structure was well compacted with more heterochromatin in the dormant blastocyst [60]. The latest reports of manipulating the c-Myc and mTOR pathway can mimic the dormant state in delayed implantation [61, 62], further confirming the low metabolism and transcription activity for cells entering the dormant state. During the blastocyst acquiring the implantation competence, the microRNA Let-7a was downregulated, associated with upregulated miRNA processing enzyme Dicer. In addition, both forced expression of Let-7a and Dicer knockdown can compromise implantation competency of the blastocyst [63, 64]. In humans, the embryo can secrete miRNAs into the culture medium in IVF practice, and these miRNAs can be explored for human embryo reproductive competence assessment [65]. The acquisition of implantation competency for blastocysts involved the expression of molecules related to embryo–uterus crosstalk, such as the inflammatory molecule, to induce the attachment reaction. A recent report has demonstrated that the expression of inflammatory response genes in the human blastocyst stage is associated with open chromatin accessibility in their regulatory

regions [66]. How epigenetic regulation, such as chromatin accessibility and 3D chromatin organization, functions precisely during blastocyst dormancy and reactivation for implantation needs further exploration.

Epigenetic regulation of uterine preparation for uterine receptivity and attachment reaction

One of the most fascinating tissues in mammals is the uterus, whose major function is to accept implantation-competent blastocysts when the uteri were in a receptive state. In mice, the uterus on day 4 of pregnancy is in a state of receptivity, while 7–10 days after ovulation (the mid-secretory phase of the menstrual cycle) is defined as the uterine receptive stage in humans [2]. Increasing evidence has demonstrated that the acquisition of uterine receptivity is under the control of both transcription factors and epigenetic regulators, which might be responsible for the spatial–temporal dynamic changes of tissue morphology and gene expression in different endometrial cell types during the establishment of uterine receptivity [67].

DNA methylation and uterine receptivity

P4 and E2 are primary regulators of the cyclic changes of the uterus during the estrus cycles of animals and menstrual cycles of humans. Pregnancy is also a hormone-dominant process. The hormones during these physiological events are mainly ovarian E2 and P4, which function via their nuclear receptors E2 receptors (ER) and P4 receptors (PR), respectively. The expression of both ER and PR is accurately regulated in response to the fluctuation of their ligands. Aberrant DNA methylation of the CpG island in the promoter region in ER [68, 69] and PRB [70] has been reported in endometrial carcinoma, suggesting that the expression of ER and PR could be regulated by DNA methylation. It has also been demonstrated that DNA methylation is correlated with PR expression in normal endometrium [71], and in mouse uterus with constitutive Notch1 activation, PR expression was shut down as DNA methylation was significantly induced at the promoter region of Pgr (Fig. 2a) [72]. In addition, endocrine disruptor endosulfan or folate deficiency affected the methylation states of promoters or regulatory regions in ERα [73, 74], leading to altered expression of uterine ERα.

HOXA10, another critical transcription factor for implantation, is spatio-temporally expressed in the endometrium with expression peaks during the window of implantation both in mouse and human [75, 76]. Female mice with a targeted disruption of Hoxa10 are unable to support embryo implantation [77, 78], suggesting that HOXA10 is critical for uterine receptivity. It has been reported that HOXA10 expression is controlled by DNA methylation [79] and aberrant DNA methylation led to decreased expression of HOXA10 in the eutopic endometrium of patients with endometriosis, which caused infertility or subfertility in women (Fig. 2a) [80].

It has been reported that the loss of ER signalling triggered silencing of downstream targets by DNA methylation [81] and E2 can induce frequent methylation/demethylation on promoter CpG sites to regulate cyclic transcriptional activation of target genes [82] in breast cancer cells. This mechanism was also demonstrated to exist in endometrial cells, which are under the control of steroid hormones [83]. MUC1 is expressed in the endometrial epithelium and its important functions in endometrial receptivity and embryo attachment have been extensively studied [84, 85]. The CpG

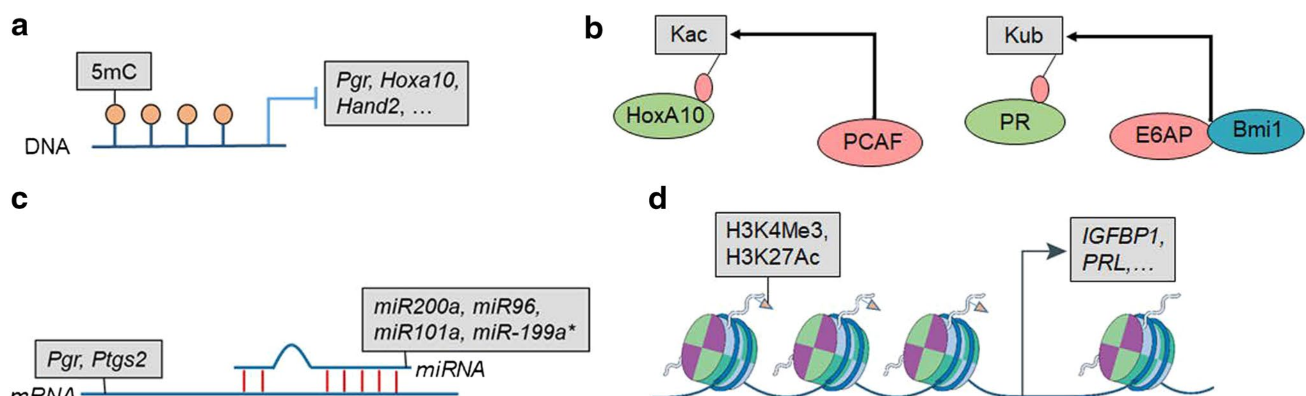

Fig. 2 Epigenetic regulation of critical molecule expression during implantation. **a** DNA methylation 5mC in the gene promoter or other regulatory region can negatively regulate the transcription target genes, such as *Pgr*, *Hoxa10*, and *Hand2*. **b** Nonclassical post-translational modification of critical molecules, such as HoxA10 and PR by epigenetic regulator can modulate the function or activity of these transcription factors, K Lysine residues, Ac acetylation, Ub ubiquitylation. **c** At post-transcriptional level, mRNAs of *Pgr* or *Ptgs2* (which encode the Cox2) is targeted by the miRNAs. **d** During decidualization, active chromatin modifications (such as H3K4me3 and H3K27Ac) in the gene regulatory region contribute to the highly expression of decidual marker gene *IGFBP1* and *PRL*

island of MUC1 was reported to be less methylated in the mid-secretory phase compared to the proliferative phase, which is strongly correlated with its increased gene expression in the mid-secretory phase [83].

Besides the regulation of specific gene by DNA methylation, DNA global methylation significantly decreases from the proliferative phase towards the secretory phase in glandular epithelial cells, but increases in the stromal cells of the endometrium by immunostaining [71]. Consistently, inhibition of DNA methylation by 5′-aza-2′-deoxycytidine (AZA) increased E-cadherin expression in uterine epithelial cells, in favour of establishing uterine receptivity in vitro [86]. Consistently, combined treatment with E2 and P4 significantly decreased the mRNA expression of DNMT3a and DNMT3b [87, 88]. However, DNMT1 mRNA expression was significantly higher in secretory-phase endometrium compared with proliferative endometrium and menstrual endometrium [89]. It was also reported that DNMT1 mRNA did not change over the menstrual cycle, while the transcription of DNMT3a and DNMT3b was significantly decreased in the secretory-phase endometrium [87]. The discrepancies may be due to the different methods of sample collection and the detection timepoints for in vitro experiments.

For the genome-wide change in DNA methylation during uterine receptivity establishment, the evidence is mainly from the research in human endometrium. Two research groups have reported that changes in DNA methylation were correlated with gene expression during the transition from the pre-receptive to the receptive phase in the endometrium [83, 90]. However, a recent report using the human endometrial stroma in vitro decidualization model, which mimics stroma cell differentiation during the establishment of uterine receptivity, has demonstrated stable DNA methylation status during decidualization, without a clear association between the differentially expressed genes and DNA methylation changes [91]. This discrepancy may be due to the difference between the in vivo and in vitro models. To further understand the role of DNA methylation during the establishment of uterine receptivity, a more sensitive and cell-type specific analysis of genome-wide DNA methylation is needed. Moreover, functional study utilizing the genetic mouse model will also provide critical cues.

Histone modification and uterine receptivity

In the early 1970s, it was found that treatment with estradiol led to increased histone acetylation in the uterus of rat and mouse [92–94], suggesting that the ovarian steroid hormones might act through chromatin alterations to effect gene transcription. In fact, co-treatment with E2 and P4 increased the levels of acetylated histone H3 and H4, and this increase was enhanced by co-treatment with the HDAC inhibitor TSA [95]. Likewise, it has been shown that HDAC inhibitors treatment can enhance the proliferative actions of E2 in mice [96]. Moreover, HDAC inhibitor was able to induce morphological and molecular changes comparable to treatment with E2 and P4 in human endometrial cells [97]. Consistently, during E2- and P4-induced stroma decidualization, many epigenetic regulators have been reported to be dynamically expressed [98]. These findings suggest that epigenetic regulation is involved in uterine events controlled by E2 or/and P4.

During the menstrual cycle, the endometrium undergoes morphological and functional changes, which are essential for the establishment of uterine receptivity and are also under the regulation of histone modification. Glycodelin, a secretory protein, is highly expressed at 10 days after ovulation (within the implantation window) in the human endometrium, and treatment with HDAC inhibitor upregulated the expression of glycodelin [99]. As we previously mentioned, HOXA10 is a transcription factor critical for endometrial receptivity. It has been demonstrated that acetylation of HOXA10 by PCAF downregulated HOXA10-mediated β3-integrin (ITGB3) expression and diminished HOXA10-mediated embryo adhesiveness (Fig. 2b) [100]. These data suggest that the acetylated modification of receptivity-related genes is essential for the achievement of endometrial receptivity. Moreover, BMI1, a key component of the Polycomb repressive complex-1 (PRC1), interacts with the PR as well as the E3 ligase E6AP in a polycomb complex-independent manner and regulates the PR ubiquitination that is essential for normal P4 responsiveness during the acquisition of uterine receptivity (Fig. 2b) [101]. In addition, uterine glands are essential for embryo implantation and pregnancy, as demonstrated by implantation or pregnancy failure in several gene mutation mouse models [102, 103]. The histone H4K20me1 methyltransferase Pr-set7 has been reported to regulate gland development and thus female fertility [104].

A number of transcription factors have been demonstrated to be critical for uterine receptivity establishment, such as Hand2 and Msx1/2. Hand2 is specifically expressed in uterine stroma cells and induced by P4 signalling through PR. Hand2 mediated one of the PR's critical functions, inhibiting uterine ER signalling and epithelium proliferation, mainly through repressing the expression of the stroma-derived growth factors [105]. However, how Hand2 inhibits target gene expression in uterus is still unclear, and it was reported that Hand2 could repress target gene expression through the distal enhancer [106]. Msx1 and Msx2 are another example of transcription factors, whose function is reported to repress Wnt5a to regulate the cell polarity of luminal epithelium for blastocyst attachment [107]. In myoblast cells, Msx1 could interact with the repressive PRC2 complex to inhibit target gene expression by upregulating the H3K27Me3 [108], and

whether these histone modification regulators are involved in uterine cells requires further exploration.

Non-coding RNA for uterine receptivity

Several miRNAs have been recently identified both in the human and mouse endometrium using next-generation sequencing [109–112]. A study using mid-secretory endometrial samples from women with repeated implantation failure discovered that miRNAs with altered expression are likely to contribute to defective endometrial receptivity in humans [113]. Moreover, Altmae et al. found that the expression of miR-30b, miR-30d, and miR-494 was closely related to human endometrial receptivity [43]. Overexpression of miR-30d in human endometrial epithelial cells demonstrates that miR-30d participates in the maintenance of DNA methylation, supporting an epigenetic role for miR-30d [114]. Ponsuksili et al. further revealed that differential expression of miRNAs and their target mRNAs in the endometrium is associated with endometrial receptivity [115]. In addition, microRNA-31 is significantly elevated in both human endometrium and serum during the window of implantation, and might act as a potential biomarker for optimum receptivity [116]. Several miRNAs, including miR-96, have been demonstrated to regulate epithelial PGR expression during the establishment of uterine receptivity in rhesus monkeys and humans (Fig. 2c), but not in rodents [117]. Cox-2, an attachment reaction marker encoded by prostaglandin endoperoxide synthase 2 (PTGS2) and expressed around the implanted blastocyst, was reported to be regulated by miR-101a and miR-199a* at the post-transcriptional level (Fig. 2c) [112]. Moreover, miRNAs secreted within the exosome by the embryo or/and uterine epithelial cells are reported to be involved not only in the interaction between the embryo and uterus during implantation [118], but also in the potential crosstalk between the ICM and TE for coordinating the trophoblast cell migration during implantation [119]. For more detailed knowledge about miRNAs during implantation, one can refer to several recent reviews [120–122].

One previous work was conducted to identify specific miRNAs involved in hormonal regulation of normal human endometrium by E2 and P4 and revealed that miRNAs down-regulate the expression of some cell cycle genes in the endometrial epithelium during the secretory phase, thereby suppressing cell proliferation [110]. Another finding revealed that the microRNA-200a locally attenuates P4 signalling in the cervix by downregulating the PR protein level and upregulating P4 inactivating enzyme (20α-HSD), leading to a different response to P4 between the cervix and uterus (Fig. 2c) [123]. These findings demonstrated that the functions of E2 and P4 are mediated or affiliated by epigenetic regulators.

Several lncRNAs were reported to be actively transcribed in the uterus during embryo implantation, such as HOXA11-AS [124], Scx-AS [125], FGF2-AS [126], and EMX2-OS [127], which are naturally occurring antisense RNAs and supposed to mediate transcriptional activation or transcriptional silencing of their respective host genes. Moreover, the steroid receptor RNA activator (SRA) gene, an intergenic ncRNA and steroid receptor co-activator, was also detected in the uterus [128]. Recently, Sigurgeirsson et al. performed comprehensive RNA sequencing of healthy human endometrium at the proliferative stage and mid-secretory stage (receptive phase), and found that 516 lncRNAs were significantly differentially expressed in the endometrium [129]. Another group also explored RNA-Seq to compare the transcriptome of the endometrium between LH + 2 (pre-receptive phase) and LH + 7 (receptive phase) and identified 2372 differentially expressed genes [130]. Using similar method, different expressed lncRNA transcripts were identified during the implantation window both in the mouse and porcine [131, 132]. Although these findings have shown that lncRNAs are associated with the acquisition of uterine receptivity, the functions, and the molecular mechanism of these lncRNAs during uterine receptivity establishment need further investigation. On the other hand, lncRNA H19, one of the first genes found to be transcribed into long non-coding RNAs, was decreased in repeated implantation failure [133]. Feng et al. reported that six lncRNAs were significantly elevated in the endometrium of RIF or recurrent miscarriage patients [134]. These data suggest that lncRNAs may be prospective biomarkers for predicting endometrial receptivity.

Moreover, circRNA-9119 was demonstrated to regulate the expression of prostaglandin endoperoxide synthase 2 (PTGS2), which is involved in the regulation of some markers of endometrial receptivity, by sponging miR-26a in ovine endometrial epithelial cells [135], suggesting that circRNAs might participate in embryo implantation. Indeed, altered circular RNA expression has been reported to be associated with repeated implantation failure in humans [136].

Epigenetic control of stromal–decidual transformation after implantation

In mice, the embryo attachment to the uterine luminal epithelium would initiate the stroma differentiation program, known as decidualization. Decidual cells in the endometrium provide nutrients to the fetus before the establishment of maternal–fetal circulation, inhibit trophoblast cells from invading too deeply inside the uterine wall, and are involved in the immunotolerance of the allogeneic fetus. Therefore, decidualization is a pivotal step for normal embryo implantation, placental development, and successful completion of pregnancy to term. While decidualization in women occurs during the secretory phase of each menstrual cycle as well

as in pregnancy, this event only occurs during pregnancy in rodents [7]. Gene expression undergoes dramatic changes in human endometrial stromal cells (HESCs) during decidualization. These changes in gene expression are associated with changes in chromatin structure, which are partially regulated by epigenetic factors. Since the finding that histone phosphorylation and acetylation were increased upon decidualization in the mouse uterus approximately 40 years ago [92], there is increasing evidence that the epigenetic mechanisms regulate gene expression during decidualization in the endometrium.

DNA methylation and decidualization

DNA methylation is high in the proliferative phase, with a significant decline towards the end of the secretory phase (corresponding to the stage of decidualization) [71]. Consistently, the methylation inhibitor 5-Aza-2′-deoxycytidine (AZA) induced some decidualization-like changes in endometrial stromal cells possibly via the cytoskeletal reorganization pathway, even though this decidualization was different from that induced by hormones [137]. Although it has also been demonstrated that no obvious changes in global DNA methylation are observed after decidualization is induced in humans [98], the DNMT inhibitor 5-AZA-Dc has negative effects on decidualization in mice [138, 139], suggesting that gene locus-specific changes in DNA methylation or DNA methylation maintenance play an important role during decidual development. The expression of DNMT1, DNMT3a, and DNMT3b in the endometrium fluctuates during the cycle and in differentiating HESCs [87–89, 98, 140]. Even though there is considerable discrepancy between these investigations due to different treatment recipes, cell sources, and other experimental variations, these findings further support the notion that active changes in DNA methylation are essential for the expression of decidual genes. Recently, using mice with different genetic backgrounds, decidual caps with widely and apparently randomly disturbed DNA methylation were demonstrated to be responsible for the pregnancy failure in the CBA/J X DBA/2 spontaneous abortion mouse model [141]. Combining the DNA methylation analysis and RNA-Seq in decidua tissue from women with normal pregnancy and recurrent pregnancy loss, Yu et al. identified 539 differentially methylated regions (DMRs) that are significantly correlated with gene expression [142]. Moreover, hypermethylation at the promoter region of FOXP3, which is extremely important for the development and function of Treg cells, down-regulates FOXP3 expression, resulting in a broken immune balance at the maternal–fetal interface and pregnancy failure [143]. Hand2, another critical molecule for embryo implantation and decidualization, is reported to be silenced in endometrial cancer through DNA methylation at its promotor [144].

Histone modification and decidualization

Recent studies confirmed dynamic regulation of histone marks during the menstrual cycle in vivo [67] and upon decidualization of HESCs in culture. It has been demonstrated that trichostatin A, an inhibitor of histone deacetylation, enhanced estradiol and progestin-induced decidualization of primary HESCs, suggesting that histone acetylation is involved in uterine decidualization [95]. Treating HESCs with TSA was also reported to increase the expression of TIMP-1 and TIMP-3 by acetylating histones in their promoters, and inhibit trophoblast invasion during implantation [145]. Retinoblastoma-binding protein 7 (Rbbp7), a core component of many histone modifications and chromatin remodelling complexes, has been demonstrated to be a potentially functional player regulating normal histone acetylation and cyclin D3 expression during decidual development [146]. Moreover, it has been shown that C/EBPβ regulates the expression of IGFBP-1 and PRL by altering the histone acetylation status of their promoters during HESC decidualization [147]. Recently, the increases of H3K27ac and H3K4me3 in both the proximal and distal regulatory regions have been found to be the main changes of histone modifications accompanying uterine decidualization, which are tightly associated the upregulated gene expression (Fig. 2d) [148]. For example, increased H3K27ac levels in the distal upstream region of IGFBP1 can significantly stimulate IGFBP1 expression in endometrial stromal cells during decidualization [149]. In addition, the down-regulation of the histone methyltransferase EZH2 was reported to contribute to epigenetic programming during the decidualization of HESCs [150].

In mouse decidual differentiation, the H3K27me3-mediated silencing of inflammatory chemokine genes can limit T cell access to the fetal–maternal interface for the establishment of immune tolerance during pregnancy [151]. An additional study demonstrated the dynamic changes of H3K27Me3 during the whole pregnancy: transcriptional silence of target genes related to parturition-inducing signals through H3K27Me3 to ensure uterine quiescence during early pregnancy; then, genome-wide demethylation occurs to derepress these genes for labor [152]. A recent report uncovered that uterus-specific deletion of Ezh2 derail post-implantation decidualization [153]. Cbx4/Ring1B-containing PRC1, which is responsible for the ubiquitination of histone-H2A at lysine-119, was found to control decidualization through the regulation of extracellular matrix remodelling genes [154]. These findings demonstrate that different histone modifications are involved in the regulation of decidualization.

Non-coding RNA and decidualization

During the cAMP and medroxyP4 acetate induced in vitro human uterine stromal decidualization, some of the miRNAs were found to be significantly differentially expressed [155, 156]. However, siRNA-mediated knockdown of Dicer displayed no obvious defect in decidualization marker expression, and further evidence suggested microRNA resistance in decidual cells due to the limited level of miRNA processing enzyme Ago1/2 [156]. It has also been reported that individual miRNAs regulate the stroma decidualization [157, 158]. Therefore, more specific studies are needed to explore the function of miRNAs during decidualization.

The different manners of epigenetic modification do not function independently. Different epigenetic modifiers interact with one another. In detail, the establishment of histone modifications and DNA methylation is interdependent. They not only interplay with each other, but also with regulatory proteins and non-coding RNAs [159–164]. Specifically, the crosstalk between DNA methylation and histone modifications is established by MBD proteins, which contain a methyl-CpG binding domain. MBDs specifically recognize and bind to methylated CpGs, and subsequently recruit histone deacetylases (HDACs), which remove acetyl groups from the lysine of histone tails, leading to chromatin condensation and transcriptional inactivation [159, 160]. The expression of DNMT1 and MBD2 was increased significantly by treatment with E2 in combination with P4, suggesting that the interactions between different epigenetic modifications may also exist in the endometrium.

Epigenetic control of infertility-related uterine disease

Increasing evidence demonstrates that uterine diseases, such as endometriosis and endometritis, are closely related to subfertility or infertility [165–167]. The occurrence of these diseases and disease-induced infertility are associated with disturbed epigenetic regulation.

As mentioned above, HOXA10 has an important function in regulating endometrial development and in establishing conditions necessary for implantation. It has been reported that HOXA10 expression was decreased in the endometrium of women with endometriosis [168]. In endometriosis models established in both mouse and baboon, DNA hypermethylation of Hoxa10/HOXA10 promoters was demonstrated in eutopic endometrium [169, 170]. In humans, the HOXA10 promoter was also hypermethylated in the endometrium of women with endometriosis [80, 171]. Moreover, the overexpression of DNMT1, DNMT3A, and DNMT3B was revealed in ectopic endometrium compared with normal controls [172], further suggesting that DNA methylation might be one of the possible mechanisms underlying endometriosis. A hypermethylated promoter of PRB is also observed in endometriosis with decreased PRB expression, which might account for P4 resistance in endometriosis since P4 functions through its receptors PRB [173]. In addition, the positive regulators for endometriosis, such as aromatase and ERβ, are both with hypomethylated promotors and display aberrant upregulation [174, 175]. In addition to DNA methylation, histone modification is also involved in the underlying mechanism of endometriosis. HDAC1 and HDAC2 are reported to be differentially expressed in endometriosis [176]. Hypoacetylation at H3K4, H3K9, and H4K16, and hypermethylation at H3K4, H3K9, and H3K27 were found in endometriosis tissues [177, 178], suggesting a possible role of histone modification in regulating gene expression in endometriosis.

In addition to endometriosis, several other common gynecologic disease, such as hydrosalpinges, polyps, and submucosal myomas, are associated with implantation defects [179]. CpG sites within the HOXA10 promotor were highly methylated [180], which is responsible for the defective HOXA10 expression [181] in these diseases. E-cadherin, the major cadherin molecule expressed in epithelial cells, is known to act as an invasion suppressor in cancer cells. It has been shown that hypermethylation in the promoter region of E-cadherin is associated with dedifferentiation and myometrial invasion of endometrial carcinoma [182]. Moreover, several studies have demonstrated that circRNAs are involved in uterine dysfunction, such as in repeated implantation failure [136].

Conclusion

At present, although an increasing number of epigenetic factors and their expressions, as well as the regulations have been reported during the peri-implantation stage (summarized in Table 1), the systemic exploration of their physiological function and the underlying mechanism is still a major challenge in this field. Genetic mouse models, especially temporal induced genetic manipulation models in different uterine compartments, and other in vivo/ex vivo approaches combined with the newly developed genome-wide strategy must be utilized to uncover the mystery of the genetic regulation network during embryo implantation. Moreover, some epigenetic regulators such as miRNA and circRNAs, which can be stably detected in the serum and other body fluids, might act as biomarkers for the diagnosis and targets for potential treatment of embryo implantation defects [183]. In addition, both the internal environment such as uterus aging [184, 185], and external environment, such as malnutrition and endocrine disruptors [74, 186–188], have been reported to influence embryo implantation and lead to an adverse pregnancy

Table 1 Represent epigenetic regulators for embryo implantation in the mouse and human

Epigenetic regulator	Function	References
Let-7a	Regulate the blastocyst implantation potential via its action on β3-Integrin and Dicer	[63, 64]
miR-30d	Upregulated during the acquisition of receptivity in the endometrium	[43]
	Overexpression induced gene expression changes at transcriptome and proteomics changes in the epithelium	[114]
	Involved in interaction between embryo and uterus as secreted by uteri and taken up by the embryo	[118]
miR-31	Elevated in both human endometrium and serum during the implantation window	[116]
miR-96	Modulate PGR expression during the establishment of uterine receptivity in rhesus monkey and human, but not in rodents	[117]
miR-101a/miR-199a*	Regulate the attachment reaction marker Cox2 expression at the post-transcriptional level	[189]
miR-200a	Locally attenuates progesterone signalling in the cervix through downregulating the PR protein level and upregulation of progesterone inactivating enzyme (20α-HSD)	[123]
DNMT	Regulate the expression of implantation- and pregnancy maintenance- related genes, such as E-cadherin, Hoxa10, Muc1, FoxP3 and Hand2 were influenced through the DNA methylation	[79, 86, 143, 144]
	DNA methylation changes in endometrium were correlated with gene expression during the transition from pre-receptive to receptive phase in human	[83, 90]
	DNMT inhibitor 5-AZA-Dc inhibits decidualization in mice	[138, 139]
	Disturbed DNA methylation of decidual tissue in spontaneous abortion mouse model	[141]
	PR down-regulation through DNA methylation in Notch1 constitutive activation mouse uterus	[72]
	Altered DNA methylation states of promotors and expressions of ERα in endocrine disruptor endosulfan or folate deficiency mouse uterus	[73, 74]
	Hypomethylated region near CREB5 recruited transcription factors binding, such as P53 and SP1, and in turn upregulated CREB5 in recurrent pregnancy loss, which induced compromised trophoblast cell migration and apoptosis	[142]
circRNA-9119	Regulate the expression of Cox2, by sponging miR-26a in endometrial epithelial cells	[135]
Histone acetylation	HDAC inhibitors upregulated the glycodelin expression, which induced LIF expression in glandular epithelial and enhanced implantation	[99]
	Acetylation of HOXA10 diminished its transcription activity on β3-integrin promotor	[100]
	TSA treatment enhanced the estradiol and progestin-induced decidualization	[95]
	Rbbp7, a core component of histone acetylation, regulate the mouse decidualization	[146]
	Upregulation of decidualization marker IGFBP-1 and PRL was associated with increased histone acetylation status in their promoters	[147]
	Increased H3K27ac and H3K4me3 levels in both the proximal and distal promoter regions of decidual upregulated genes	[148]
Histone methylation	Down-regulation of Ezh2 during the human stroma cell decidualization	[150]
	H3K27me3 mediate silence of inflammatory chemokine genes in mouse decidualization	[151]
	Dynamic H3K27me3 fluctuation for pregnancy maintenance and labor	[152]
	H4K20Me1 methyltransferase Pr-set7 is indispensable for uterine gland development	[104]
Histone mono- ubiquitination	PR ubiquitination regulated by Bmi1 independent of PRC1 complex is essential for normal progesterone responsiveness in endometrium	[101]
	Cbx4/Ring1B-containing PRC1 control decidualization through the regulation of extracellular matrix remodelling gene	[154]

outcome. However, the underlying mechanism, especially from the epigenetic aspect, must be first addressed before the potential management for these disturbances.

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