

Molecular determinants of uterine receptivity

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ABSTRACT Uterine receptivity is defined as a limited period when the uterine environment is conducive to blastocyst acceptance and implantation. Any disturbance of this early pregnancy event will compromise pregnancy success. In this review, we first briefly summarize uterine morphological coordination for the attainment of receptivity, then focus on elucidating the molecular complexity in establishing uterine receptivity and hence embryo implantation. A better understanding of the molecular basis governing uterine receptivity will help to improve the outcome of natural pregnancy and pregnancy conceived via assisted reproductive techniques.

KEY WORDS: *uterine receptivity, molecular determinants*

Introduction

Uterine receptivity is a condition in which the uterus is suitable for embryo implantation to occur and it lasts just for a limited time. The concept of a window of uterine receptivity or implantation was raised and established by studies employing the embryo transfer technique in the 1960s (Dickmann and Noyes, 1961, Psychoyos, 1966). While day 4 (day 1 = vaginal plug) preimplantation embryos showed severe damage 9 hour after transfer into a day 5 uterus in rats, day 5 blastocysts can implant normally after transfer to either day 4 or day 5 uteri, but not in the uteri beyond day 5 of pregnancy or pseudopregnancy in rats. These findings suggest that the uterus is not constantly receptive to blastocysts and embryo implantation can happen only in a limited period. This notion has been further confirmed in mouse studies employing both normal pregnant and delayed implantation models (Paria *et al.*, 1993b). On the basis of these previous findings, uterine sensitivity to implantation-competent blastocysts is classically divided into three 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 adverse to blastocyst survival (Wang and Dey, 2006). In mice, the uterus on days 1-3 of pregnancy is conventionally considered to be in the pre-receptive phase. On day 4 of pregnancy the uterus becomes fully receptive following

the priming actions of ovarian progesterone and preimplantation estrogen, whereas by late day 5 the uterus is refractory to initiate implantation. In humans, the first 7 days of the secretory phase is considered as the pre-receptive stage, 7-10 days after ovulation as the receptive stage and the rest of the secretory phase is defined as the non-receptive stage (Paria *et al.*, 1993b, Wang and Dey, 2006). In this review, we briefly summarize the uterine morphological coordination for the attainment of receptivity, with a focus on elucidating the involvement of steroid hormones, adhesion factors, growth factors, cytokines, lipid mediators and transcriptional factors in uterine receptivity, hoping to clarify the molecular complexity in establishing uterine receptivity and hence implantation for an improvement in pregnancy outcome.

Uterine morphological coordination for the status of receptivity

Pinopodes

Pinopodes are ultrastructural projections on the apical surface of the luminal epithelium, which appear only during the receptive phase. These bulbous cytoplasmic protrusions are the best studied ultrastructural marker of uterine receptivity that are believed to be helpful in the attachment of the blastocyst to the surface of

Abbreviations used in this paper: ER, estrogen receptor; PR, progesterone receptor; FKBP52, FK506 binding protein-4; LIF, leukemia inhibitory factor; COX, cyclooxygenase; Klf3, the Kruppel-like factors, Stat3, signal transducers and activators of transcription 3.

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luminal epithelium. This structure was first discovered in rats and mice by traditional electron microscopic methods and was named as a "pinopod" because of its pinocytotic function (Nilsson, 1958, Nilsson, 1966). In rats, the development of pinopods synchronizes with the window of uterine receptivity. Pinopod number increases on day 4 of pregnancy and becomes more abundant on day 5 when the uterus enters the receptive phase in rats (Psychoyos and Mandon, 1971). During the postimplantation period, pinopod number decreases rapidly (Singh *et al.*, 1996). This developmental change of pinopods in the uterus is highly progesterone dependent, while administration of high doses of estradiol abolishes the pinopod (Martel *et al.*, 1991), highlighting the similarity of hormonal conditioning for pinopod formation with the attainment of uterine receptivity. Therefore, the appearance of pinopods is a well-defined histological marker for uterine receptivity in rats and mice. However, it is still debatable whether human pinopods act the same as that observed in rodents, since human pinopods are structurally and functionally different from rodent pinopods (Quinn *et al.*, 2007).

Luminal closure

Luminal closure is defined as the closure of uterine lumen during embryo apposition prior to attachment, which is another morpho-

logical landmark of uterine receptivity. In rodents, a generalized stromal edema under the influence of ovarian steroid hormones leads to uterine luminal closure (Wang and Dey, 2006). This event supports a closer contact between the luminal epithelium and the blastocysts and is essential for appropriate blastocyst apposition and subsequent attachment. However, the occurrence of luminal closure does not require the presence of blastocysts, since this phenomenon can be observed both in pregnant and pseudopregnant uteri (Wang and Dey, 2006). Progesterone priming has been demonstrated to be essential for luminal closure. Uterine luminal closure fails to occur in mice missing FK506 binding protein-4 (FKBP52), a co-chaperone for full progesterone receptor (PR) function (Tranguch *et al.*, 2005a). Recent evidence shows that cystic fibrosis transmembrane conductance regulator (CFTR) and epithelial Na⁺ channel (ENaC) are the major gatekeepers regulating uterine fluid secretion and reabsorption (Salleh *et al.*, 2005). Activation of ENaC is required for prostaglandin synthesis and release, which has been proven to be critical for embryo implantation (Ruan *et al.*, 2012). Aberrant upregulation of CFTR or inhibition of uterine ENaC leads to abnormal uterine fluid accumulation and implantation failure. Progesterone has been shown to repress the expression of CFTR while stimulating uterine ENaC induction, which is con-

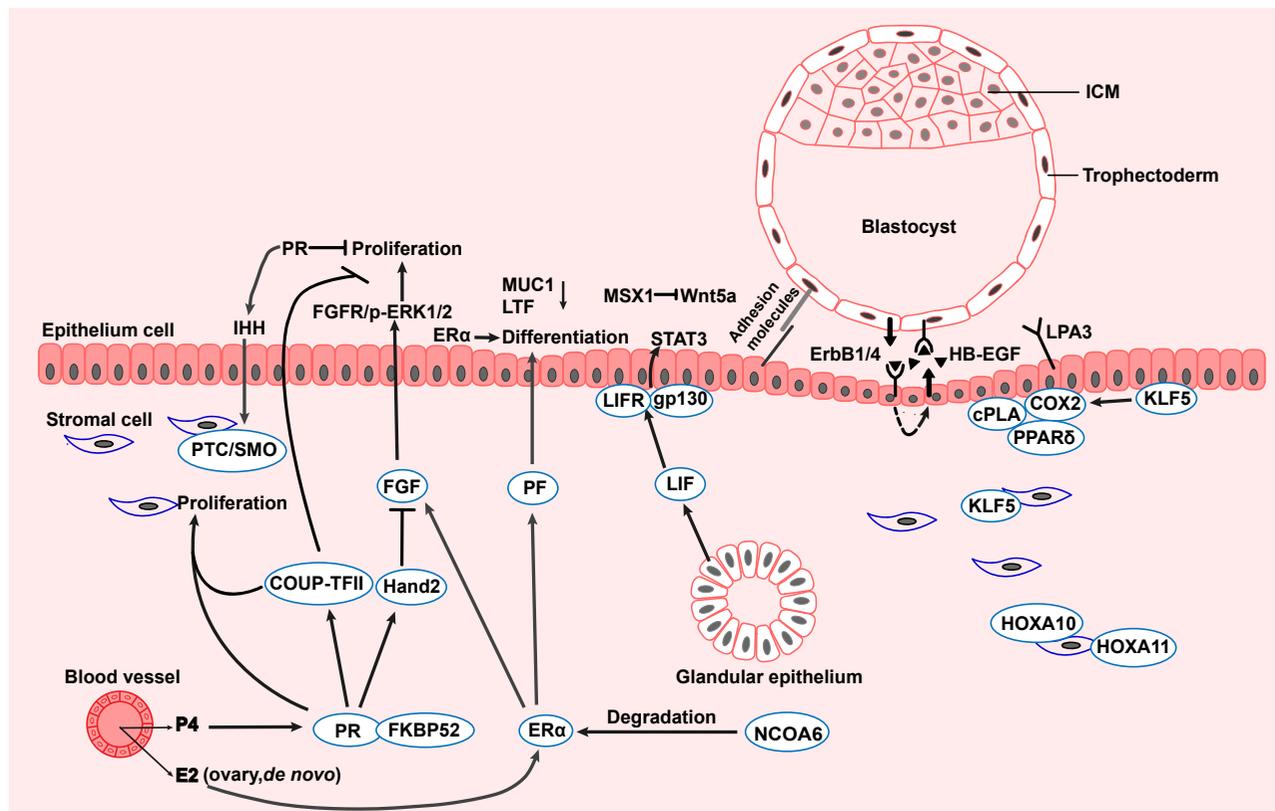


Fig. 1. Hormonal and molecular basis of uterine receptivity. Ovarian steroid hormones in cooperation with a wide range of signaling molecules confer uterine receptivity. cPLA2 α , cytosolic phospholipase A2 α ; COUP-TFII, chicken ovalbumin upstream promoter transcription factor-2; COX-2, cyclooxygenase-2; E2, 17 β -estradiol; ER, estrogen receptor; PR, progesterone receptor; Hand2, Heart and neural crest derivatives-expressed protein 2; ErbB1/4, epidermal growth factor receptor 1/4; ERK1/2, extracellular signal-regulated kinase 1/2; FGF, fibroblast growth factor; Hoxa10/11, homeobox A10/11; ICM, inner cell mass; LIF, leukemia inhibitory factor; LIFR, LIF receptor; gp130, glycoprotein 130; LPA3, lysophosphatidic acid receptor 3; PG, prostaglandin; PPAR δ , peroxisome proliferator-activating receptor δ ; STAT3, signal transducers and activators of transcription 3; HB-EGF, heparin-binding epidermal growth factor-like growth factor; MSX1, Muscle segment homeobox 1; Wnt5a, Wingless-Type MMTV integration site family members 5a; KLF5, Kruppel-like factor 5; FKBP52, FK506-binding protein 52; NCOA6, nuclear receptor coactivator-6; IHH, Indian hedgehog; Ptc, Patched-1.

cive to embryo implantation (Nobuzane *et al.*, 2008, Zheng *et al.*, 2004). Moreover, it has been shown that serum and glucocorticoid inducible kinase-1 (SGK1), a key regulator of sodium transport in mammalian epithelia (Fejes-Toth *et al.*, 2008), can enhance ENaC expression via inhibiting the ubiquitin ligase, neural precursor cell expressed developmentally down-regulated protein (NEDD) 4–2 (Lang *et al.*, 2006). Its overexpression induces increased ENaC expression and abolishes normal implantation (Salker *et al.*, 2011). Therefore, it is conceivable that a tightly regulated balance between the uterine fluid secretion and reabsorption is required for timely luminal closure, and hence the attainment of uterine receptivity.

Molecular basis of uterine receptivity

Estrogen and progesterone signaling

The conversion of the uterus to competence for embryo implantation is regulated primarily by ovarian steroid hormones, estrogen and progesterone (Dey *et al.*, 2004). Progesterone is necessary for implantation in almost all mammalian species and estrogen is essential for uterine receptivity in the rat and mouse. Maternal estrogen is not required for implantation in some species such as rabbit, hamster, pig and guinea pig; and blastocysts in these species, notably the hamster, pig and rabbit, have the capacity to synthesize estrogen, which may contribute to activation of the implantation process. In other species, including nonhuman primates and the human, estrogen's function in implantation remains inconclusive (Paria *et al.*, 2001b).

Estrogen and progesterone act mainly through nuclear receptors, estrogen receptor (ER) and progesterone receptor (PR), respectively. ER α and ER β are two ER isoforms encoded by different genes, while PRA and PRB are generated from the same gene by transcription at different promoters. ER α is the dominant isoform expressed in mouse uteri (Tan *et al.*, 1999). Previous studies have demonstrated that ER α is the major mediator in the uterus, while ER β plays a minor role in mice (Krege *et al.*, 1998, Lubahn *et al.*, 1993). PRA is the predominant functional isoform in the mouse uterus, since only PRA, but not PRB null mice reproduce PRKO mouse phenotypes in the uterus (Lydon *et al.*, 1995). Both ER and PR are ligand-dependent nuclear transcription factors and have a complex crosstalk with other signaling pathways.

During the preimplantation period, the uterus undergoes dynamic remodeling (Zhang *et al.*, 2013b). In mice, estrogen promotes uterine water imbibition and increased epithelial cell proliferation during the first two days of pregnancy. After day 3, progesterone derived from newly formed corpora lutea shifts cellular proliferation from the epithelial layer to the stromal bed. On day 4 of pregnancy, stromal cell proliferation is further elevated by increased preimplantation secretion of ovarian estrogen. It has been shown that estrogen promotes epithelial proliferation through the stromal ER α (Cooke *et al.*, 1997). However, both stromal and epithelial ER α are essential for epithelial differentiation and the attainment of uterine receptivity. Ablation of preimplantation estrogen secretion or its action inhibits embryo attachment (Paria *et al.*, 1993b). Under these conditions, embryos will transform into a diapause state, and the uterus enters a neutral phase. This delayed implantation can be maintained for a few weeks by daily progesterone supplementation, whereas a single injection of estrogen can reactivate the embryo and confer uterine receptivity for implantation. Previous studies from the Dey Laboratory have employed this physiologically relevant delayed

implantation model to demonstrate that estrogen, within a very narrow dose range, determines the duration of uterine receptivity. For example, at suboptimal doses estrogen fails to confer uterine receptivity, whereas at appropriate estrogen levels the window of uterine receptivity remains open for an extended period, but rapidly closes at higher estrogen levels accompanied by aberrant uterine expression of implantation-related genes (Ma *et al.*, 2003). Therefore, tightly regulated estrogen-ER activity together with progesterone is essential for normal uterine receptivity (as indicated in Fig. 1).

In mice, progesterone can either facilitate or antagonize estrogen action in the context of uterine function. While progesterone inhibits estrogen-induced epithelial proliferation, it cooperates with estrogen to promote stromal cell proliferation. Previous studies employing tissue recombination techniques and uterine conditional PR knockout mouse models have demonstrated that both stromal and epithelial PR are required to antagonize estrogen function in the epithelium (Franco *et al.*, 2012, Kurita *et al.*, 1998, Lydon *et al.*, 1995). In mice lacking the PR co-chaperone, FKBP52, uterine receptivity is disrupted due to exaggerated estrogen activity, which resulted from reduced progesterone activity and failure of uterine epithelial differentiation (Tranguch *et al.*, 2005b). Moreover, a conditional knockout of SRC2, a nuclear receptor coactivator in the uterus, also results in implantation failure (Mukherjee *et al.*, 2006). In addition, null mutations of SRC3 or SRC1 can reduce uterine estrogen responsiveness compromising pregnancy success (Xu *et al.*, 2000, Xu *et al.*, 1998). Uterine-specific deletion of NCOA6 (also known as SRC6), which can accelerate ER α degradation via ubiquitination, also disrupts uterine receptivity and is characterized by increased uterine sensitivity to estrogen and aberrant expression of progesterone-responsive genes (Kawagoe *et al.*, 2012). These findings indicate the complexity and precision of ER and PR signaling that is required for normal uterine receptivity.

Since ER and PR are the primary upstream transcription factors regulating uterine function, increasing evidence has been paid to elucidate the downstream estrogen/progesterone-responsive regulatory molecules and potential coupled signaling cascades. In this respect, C/EBP β , a transcription factor that is responsive to estrogen and progesterone in the uterus has been shown to be essential for normal uterine epithelial and stromal proliferation during implantation (Mantena *et al.*, 2006). Moreover, Hand2 is a progesterone-targeting transcription factor expressed in the uterine stroma and a functional mediator of progesterone in antagonizing estrogen-stimulated epithelial proliferation (Li *et al.*, 2011). Another transcription factor, COUP-TFII, which is mainly expressed in uterine stromal cells, is also required for normal progesterone function. Conditional knockout of COUP-TFII in the mouse uterus leads to implantation failure with disrupted uterine receptivity associated with high estrogen activity (Kurihara *et al.*, 2007). The ER inhibitor ICI182780 treatment can restore normal implantation and decidualization in uterine-COUP-TFII knockouts (Lee *et al.*, 2010). Besides estrogen/progesterone-targeted transcription factors, Indian hedgehog (Ihh) and its signaling cascade contribute to the regulatory circuit directed by progesterone in the uterus. Ihh and its transmembrane receptor (Ptc1) show a complementary expression pattern in the receptive mouse uterus with the ligand in the epithelium and the receptor in the underlying stroma, respectively (Matsumoto *et al.*, 2002). Uterine conditional depletion of Ihh results in implantation failure (Lee *et al.*, 2006), further suggesting that

the progesterone-primed Lhh-Ptc1 signaling pathway is critical for normal stromal-epithelial interaction during implantation.

Adhesion molecules

Integrins

The integrin family of cell adhesion molecules is a major class of receptors for the ECM and participates in cell-cell and cell-substratum interactions. They have many functions in cellular processes including differentiation, apoptosis and cell survival, motility and attachment (Desgrosellier and Cheresh, 2010). Previous studies have demonstrated that integrins exhibit distinctive expression patterns in different phases of uterine receptivity in the mouse and human. $\alpha 4\beta 1$ and $\alpha v\beta 3$ integrins are both present in the mouse uterus at the time of implantation and intrauterine inhibition of these two molecules results in defective implantation (Basak *et al.*, 2002, Illera *et al.*, 2000). $\alpha 1\beta 1$, $\alpha 4\beta 1$, and $\alpha v\beta 3$ integrins are co-expressed in the endometrial epithelium only during the window of implantation in the human (Lessey, 1994). Moreover, decreased expression of $\alpha v\beta 3$ is often associated with unexplained infertility (Lessey *et al.*, 1995).

Selectins

Selectins, including L-selectin, E-selectin and P-selectin, are another group of cell adhesion molecules, which can bind to carbohydrates. In the human, selectin oligosaccharide-based ligands are upregulated in uterine epithelial cells during the window of receptivity, while L-selectin is expressed in trophoblasts. More interestingly, trophoblasts can bind to selectin ligand-coated beads and to selectin ligand-expressing uterine luminal epithelial cells. These findings demonstrate a functional L-selectin ligand-receptor system in the embryo-uterine dialog during implantation in the human (Genbacev *et al.*, 2003).

Mucins

Mucins are large molecular weight O-linked glycoproteins present on the apical surface of polarized secretory epithelial cells. They can be divided into secreted and transmembrane forms (Surveyor *et al.*, 1995). Muc1 is one of the transmembrane forms. Due to its anti-adhesive nature, Muc1 is an effective barrier preventing embryo attachment to the uterine epithelium. Thus, diminishing Muc1 expression in the uterus facilitates uterine receptivity in many species. In mice, uterine Muc1 expression declines to undetectable levels prior to blastocyst attachment, reinforcing the notion that loss of Muc1 contributes to the establishment of a receptive uterus (Surveyor *et al.*, 1995).

Growth factors

During the course of revealing the molecular basis governing the blastocyst-uterine dialog during implantation, the Dey Laboratory and collaborators have conducted a robust body of work to address the role of EGF family growth factors in implantation. Several members of the EGF family of growth factors and their receptor subtypes exhibit spatiotemporal expression patterns in the peri-implantation uterus. For example, EGFR is detected in the stroma and myometrium while ERBB2 and ERBB3 are predominantly located in epithelial cells (Lim *et al.*, 1997a). In contrast, ERBB4 is detected in a subpopulation of stromal cells (Lim *et al.*, 1998). Moreover, ERBB1 and ERBB4 receptors are highly expressed

in the implantation-competent blastocyst trophectoderm (Paria *et al.*, 1993a, Paria *et al.*, 1999). Among the ligands, HB-EGF is specifically expressed in the luminal epithelium surrounding the blastocyst a few hours prior to the attachment reaction (Das *et al.*, 1994). Local release of HB-EGF via Affi-gel beads can induce the expression of implantation-related genes, including its own transcripts, in the receptive uterus (Hamatani *et al.*, 2004, Paria *et al.*, 2001a). More interestingly, implantation-competent blastocysts express high levels of HB-EGF, highlighting the notion that HB-EGF senses the blastocyst-uterine dialog during implantation via an auto-induction loop. Indeed, HB-EGF null mice also show a deferral of on-time implantation, reinforcing the critical role of HB-EGF in implantation (Xie *et al.*, 2007).

Cytokines

Cytokines are small multifunctional glycoproteins and act as potent intercellular signals regulating uterine function, particularly leukemia inhibitory factor (LIF). In mice, LIF shows a biphasic expression pattern. It is distinctly expressed in the glandular epithelium on day 4 of pregnancy, and with the initiation of embryo implantation, LIF is also expressed in the sub-luminal stroma cells surrounding the implanting embryo (Song *et al.*, 2000). LIF is indispensable for the establishment of uterine receptivity, since LIF null mutant mice exhibit a complete implantation failure with suspended blastocysts within the uterine horn (Chen *et al.*, 2000, Song *et al.*, 2000, Stewart *et al.*, 1992). LIF binds to its receptor LIFR/gp130 and specifically activates Stat3. This signaling pathway, including Stat3 nuclear translocation in the luminal and glandular epithelium, is attenuated in LIF null mutant uteri (Cheng *et al.*, 2001). Recent studies further demonstrate that uterine conditional deletion of Stat3 also induces implantation failure (Lee *et al.*, 2013, Pawar *et al.*, 2013, Sun *et al.*, 2013). In the human, a low level of LIF is associated with unexplained recurrent abortion and infertility (Hambartsumian, 1998, Piccinni *et al.*, 1998). These findings collectively indicate that the LIF-LIFR/gp130-Stat3 axis is essential for normal embryo implantation.

Lipid mediators

The Dey Laboratory has performed pioneering research in elucidating the pathophysiologic significance of endocannabinoid signaling in early pregnancy. Their studies have demonstrated that this lipid signaling pathway is essential for synchronizing embryo development and uterine receptivity for implantation (Wang and Dey, 2006). Anandamide is one of the primary endogenous endocannabinoids. Its levels are lower in the receptive uterus and at implantation sites than in the nonreceptive uterus and at interimplantation sites (Guo *et al.*, 2005, Schmid *et al.*, 1997), suggesting that the lower level of anandamide confers uterine receptivity. Furthermore, expression of the brain-type cannabinoid receptor, CB1, in the implantation-competent blastocysts is also down-regulated during the uterine receptive stage (Guo *et al.*, 2005, Paria *et al.*, 2001c). In fact, anandamide, within a very narrow concentration range, regulates blastocyst function and implantation by differentially modulating mitogen-activated protein kinase (MAPK) signaling and Ca^{2+} channel activity via CB1 receptors (Wang *et al.*, 2003). For example, anandamide at a low concentration induces the activation of MAPK signaling, while anandamide at a higher concentration inhibits Ca^{2+} channel activity and blastocyst competency for implantation without influencing MAPK signaling.

Aberrant anandamide signaling also leads to miscarriage in women (Habayeb *et al.*, 2008, Maccarrone *et al.*, 2000).

Prostaglandins (PG) have been shown to play a critical role in increasing vascular permeability, a hallmark of embryo implantation. The Dey Laboratory has provided comprehensive physiological and genetic evidence showing that the cPLA2 α -COX2-PG signaling axis is essential for successful embryo implantation (Lim *et al.*, 1997b, Song *et al.*, 2002a, Wang *et al.*, 2007, Zhang *et al.*, 2013a). Cytoplasmic phospholipase A2 α (cPLA2 α) selectively releases arachidonic acid, which can be further converted into PGH2 by the rate-limiting cyclooxygenase (COX) enzymes, COX-1 and COX-2 (Smith and Dewitt, 1996). In the absence of cPLA2 α , the normal window of implantation is altered accompanied by disruptions in embryo spacing, eventually leading to defective post-implantation development of embryos (Song *et al.*, 2002b). These observations introduced the novel concept that the quality of embryo implantation determines term pregnancy success. Moreover, mice with a null mutation for COX-2 show multiple female reproductive deficiencies that span ovulation, fertilization, implantation and decidualization (Lim *et al.*, 1997b). The reproductive defects of COX-2 deficient female mice on a CD1 background are less severe due to COX-1 compensation (Wang *et al.*, 2004). Collectively, these findings highlight the physiological significance of the PG signaling axis on implantation. Among various PGs, COX-2 derived prostacyclin is the primary PG produced at the implantation site (Lim *et al.*, 1999a). In mice deficient in the prostacyclin nuclear receptor, peroxisome proliferator activated receptor δ , the window of embryo implantation becomes deferred, reinforcing the necessity of PGs for on-time implantation (Wang *et al.*, 2007). Interestingly, on-time implantation is also linked to the actions of another lipid mediator, lysophospholipids (LP), which signal through the lysophosphatidic acid receptor, LPA3. LPA3 null mutant females phenotypically mimic the defects observed in cPLA2 α deficient mice showing deferral of the implantation window, embryo crowding, and decreased COX-2 expression (Ye *et al.*, 2005). It is conceivable that LPA3-signaling may function through COX-PG signaling during embryo implantation.

Transcription factors

Hox family genes

Homeobox-containing transcription factors are highly conserved regulators during tissue and organ development, as well as in early pregnancy events. In mice, Hoxa10 is expressed in both uterine epithelial and stromal cells with an increased expression during the window of implantation (Satokata *et al.*, 1995). Hoxa10 mutant females show implantation failure (Satokata *et al.*, 1995), with a reduced response to progesterone and estrogen induced stromal cell proliferation (Lim *et al.*, 1999b). Although estrogen stimulated uterine epithelial cell proliferation is unaltered in Hoxa10 deficiency, uterine pinopod number decreases dramatically in the Hoxa10 deficient model (Bagot *et al.*, 2001), suggesting that Hoxa10 is important for epithelial pinopod development and the attainment of uterine receptivity.

Hoxa11, another member of Hox family, is highly expressed in stromal cells of both human and mice, with peak expression at the time of implantation (Gendron *et al.*, 1997, Taylor *et al.*, 1997). Loss of Hoxa11 in mice leads to infertility (Hsieh-Li *et al.*, 1995). Hoxa11 null mutant females exhibit defective glandular differentiation with an absence of LIF expression and stromal cell proliferation

in response to ovarian steroids (Gendron *et al.*, 1997). Therefore, Hoxa11 is critical for normal uterine function during implantation.

In contrast to the constitutive contributions of Hoxa10 and Hoxa11, Msx1 (also known as Hox7.1) is distinctly and transiently expressed in the epithelium prior to implantation. With approaching implantation, Msx1 expression decreases on day 4 evening and remains undetectable thereafter. This temporal decrease in Msx1 expression could be essential for conferring uterine receptivity. For example, implantation failure observed in the LIF null mutant uterus is associated with sustained uterine Msx1 expression (Daikoku T, 2004). Conditional deletion of Msx1 in the uterus leads to subfertility due to impaired implantation, whereas deletion of both Msx1 and Msx2 results in infertility due to altered uterine luminal epithelium cell polarity and integrity (Daikoku *et al.*, 2011). This genetic evidence further supports the importance of the timing of Msx1 expression for normal uterine receptivity. Similar to observations in the mouse, Msx1 is also down-regulated in the receptive endometrium in human (Tapia *et al.*, 2011).

The Kruppel-like factors

The Kruppel-like factors (Klfs) are zinc finger-containing transcription factors implicated in diverse cellular processes, including proliferation, differentiation, apoptosis and development. Among them, Kruppel-like factor 5 (Klf5) is essential for conferring uterine receptivity (Cha *et al.*, 2012). In mouse uteri, Klf5 is spatiotemporally expressed during peri-implantation. On days 1-4 of pregnancy, Klf5 expression is limited to luminal and glandular epithelium. With the initiation of attachment, Klf5 expression shifts to proliferating stromal cells accompanied by a simultaneous decrease in epithelial Klf5 expression. Uterine depletion of Klf5 leads to female infertility due to implantation failure. In Klf5 null mice, the luminal epithelium surrounding the blastocyst remains intact with no signs of apoptotic death, resulting in the retention of the epithelial barrier past the normal window of implantation and impairing blastocyst implantation growth (Sun *et al.*, 2012). These findings demonstrate the importance of Klf5 for embryo implantation.

Klf9, another Kruppel-like transcription factor has been identified as a PR cofactor that can functionally interact with PRA and PRB in regulating progesterone-responsive gene expression in endometrial epithelial cells (Zhang *et al.*, 2003). Loss of Klf9 in female mice results in reduced fertility due to defective implantation. In Klf9 null females, the expression of Klf13, a highly related family member is upregulated in the uterus, suggesting Klf13 is compensating for the loss of Klf9 during implantation (Simmen *et al.*, 2004). Klf13 null female mice have normal fertility. However, again there is evidence for compensation. Nuclear levels of Klf9 are higher in Klf13 null uteri (Heard *et al.*, 2012). These observations indicate a potential requirement for Klf9 and/or Klf13 in normal uterine function during early pregnancy.

Concluding remarks

Uterine receptivity involves complex interactions between the different uterine cell types, including the stroma, luminal and glandular epithelium coordinated by a wide range of regulatory molecules and signaling pathways as illustrated in Fig. 1. Ovarian steroid hormones, estrogen and progesterone, act as the commander directing a series of uterine events, such as luminal closure, pinopod formation, as well as coordinated uterine epithelial and stromal cell

proliferation and differentiation. For example, progesterone via PR receptors with the aid of the co-chaperone protein, FKBP52, induces the expression of transcription factors, such as Hand2, Hoxa10 and COUP-TFII to confer uterine receptivity (Li *et al.*, 2011, Tranguch *et al.*, 2005b). This transcriptional regulatory circuit is further modulated by various signaling cascades, which are driven by lipids, cytokines, and growth factors, resulting in the construction of a complex, but precisely controlled regulatory network ensuring the success of implantation. These key regulators of implantation have been primarily generated from genetic mouse models. More effort should be directed to the translational aspects of this research, including the development of appropriate molecular markers for endometrial receptivity in human clinical practice.

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