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Review

Particular functions of estrogen and progesterone in establishment of uterine receptivity and embryo implantation

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Summary. The process of embryo implantation requires synchronized development of blastocyst and timely establishment of uterine receptivity. Establishment of uterine receptivity, preimplantation embryo development and embryo implantation events are mainly regulated by certain factors, including cytokines, chemokines, growth factors and steroid hormones. Recent studies suggest that steroid hormones, especially estrogen and progesterone, play important roles in supporting endometrial preparations to establish endometrial receptivity. Timely establishment of endometrial receptivity is a crucial process for providing successful embryo implantation. Although many investigations until now have been performed to precisely understand the effects of estrogen and progesterone on acquiring uterine receptivity and embryo implantation in humans and rodents, there are limited numbers of studies that largely focus on this subject. Therefore, in this article we discuss the studies associated with significant functions of estrogen and progesterone in establishing receptive endometrium and the process of embryo implantation in humans and rodents.

Key words: Estrogen, Progesterone, Uterine receptivity, Embryo implantation

Introduction

Successful embryo implantation requires synchronized development of the competent blastocyst and establishment of uterinal receptivity (Challis et al., 2005). As is known, the uterus, a specialized organ, does not have the capability to accept a healthy blastocyte at any time of the menstrual cycle. In humans and rodents, uterine sensitivity to embryo implantation is generally classified into three phases, named as; pre-receptive, receptive and non-receptive (refractory) phases (Carson et al., 2000; Paria et al., 2001). In fact, the uterus is unable to initiate blastocyte implantation during most of the menstrual cycle, coinciding with pre-receptive and non-receptive phases (Dominguez et al., 2009). The human endometrium undergoes two major phases, the proliferative (follicular) and secretory (luteal) phase, distinguished by histological and functional properties throughout the 28-day menstrual cycle. The endometrium is in pre-receptive state during the first ~5 days of secretory phase following ovulation. Then, it becomes receptive during the mid-secretory phase that spans 19-24 days. In the end, the human endometrium is considered as non-receptive for the rest of the secretory phase of the menstrual cycle (Kumar et al., 1998, 2001; Guffanti et al., 2008).

Mouse endometrium is in the pre-receptive phase on days 1-3 and acquires receptivity on day 4 of the cycle under actions of steroid hormones and other special factors. At the end, it enters into refractory phase on day 5 of the cycle (Wang and Dey, 2006) (Table 1). Uterine receptivity is briefly defined as the differentiated state of the uterus for a limited time, also termed as "window of implantation". When the uterus is in receptive state the endometrium allows a competent blastocyst to easily attach to the luminal epithelial cells and to invade the endometrial stroma (Sengupta and Ghosh, 2000; Challis et al., 2005). The window of implantation period is limited to days 19-24 of a typical 28-day reproductive cycle in human (Navot et al., 1991; Simon et al., 2003; Makrigiannakis et al., 2006). On the other hand, in some species, uterine receptivity ends in a short time, for example, it continues about 24-36 h in rats and mice. Finally, the receptive uterus enters into refractory phase, during which the uterus does not accept the competent

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blastocyst (Carson et al., 2000; Paria et al., 2001).

In establishing receptivity, uterine luminal epithelial cells exhibit functional and morphological changes to provide attachment of the trophoblast cells to the luminal epithelium. The alterations occurring in endometrial epithelial cells include loss of microvilli localized to apical sites of these cells, reduction in the thickness of the glycocalyx layer, changes of adhesion molecule levels and arising pinopodes from the cell membranes (Carson et al., 2000; Makrigiannakis et al., 2006). Adhesion molecules such as integrins, cadherins, selectins, galektins, heparan sulfate proteoglycans 1and trophinin-tastin-bystin complex display functional changes during the achievement of endometrial receptivity and embryo implantation process (Dey et al., 2004). Pinopodes on the endometrial surface (ectoplasmic projections) are smooth mushroom or balloon-like projections originated from apical surfaces of luminal epithelial cells in rodents and humans (Singh et al., 1996). The number of pinopodes demarcate the window of receptivity on day 4 and 5 of the pregnancy and specifically decrease on day 6, whereby they can be used as a reliable marker of endometrial receptivity in rats (Psychoyos, 1976; Quinn et al., 2007b). However, there is controversy about using pinopodes as a good marker of endometrial receptivity in humans and mice, because pinopodes have been detected out of receptive phase in these species, for example, the projections observed during the entire luteal phase in humans (Creus et al., 2002; Quinn et al., 2006, 2007a) (Table 1).

As is known, synchronized development of the embryo to the blastocyst and establishment of uterine receptivity are critical processes for successful implantation and the healthy progression of pregnancy. Both of these processes are strictly regulated by certain factors involving steroid hormones, growth factors, vasoactive factors, transcription factors, angiogenic factors, morphogens and cytokines (Carson et al., 2000). Secreted steroid hormones, especially estrogen and progesterone from the ovary play important roles in blastocyst activation, establishment of uterinal receptivity, and implantation of the blastocyte to receptive endometrium via binding to their specific nuclear receptors. Investigations showed that there is a remarkable difference in precise requirement of ovarian estrogen and progesterone between species (Ghosh et al., 1994; Paria et al., 2000). Ovarian estrogen is required for faithful embryo implantation in rodents, but some of the species, including pigs, guinea pigs, rabbits, humans (de Ziegler et al., 1992), rhesus monkeys (Ghosh et al., 1994) and hamsters do not require estrogen to succeed in the embryo implantation (Reese et al., 2008). In these species, progesterone (P4) alone is sufficient to provide successful implantation of the competent blastocyst to the receptive endometrium (Carson et al., 2000; Challis et al., 2005) (Table 1). Interestingly, in vitro studies showed that the blastocysts derived from the species involving pig, rabbit, and human have a steroid metabolizing enzyme system and secrete estrogen to the surrounding environment, but mouse preimplantation embryos do not have any estrogen metabolizing system (Sengupta and Ghosh, 2000; Paria et al., 2001). However, there is no clear information about the exact role of the blastocyst-derived estrogen in the embryo implantation process. As is known, human endometrium is also capable of producing estrogen using the steroid metabolic enzyme system (Bacallao et al., 2008). We believe that estrogen derived from the endometrium and blastocyte may function in uterinal preparations and blastocyst development via binding to its estrogen receptor (ER).

Estrogen and progesterone are important factors for establishing receptive uterus

Uterus is composes of heterogeneous cell types which are able to respond to steroid hormones in different ways (Challis et al., 2005). Spatiotemporal secretions of ovarian estrogen and progesterone regulate proliferations and differentiations of definite uterinal cells, and following that the uterus enters into receptive state in rodents and humans (Carson et al., 2000; Paria et al., 2001). Although only estradiol (E2), the most active form of three naturally occurring estrogens, stimulates endometrial epithelial cell proliferation via binding its specific receptors in contrast to epithelial cells, stromal cells require both E_2 and P_4 activities (Carson et al., 2000). In addition, estrogen and progesterone are implicated in controlling locally produced growth factors, cytokines, homeobox transcription factors, morphogens, cyclooxygenase-derived prostaglandins and vasoactive factors through autocrine and paracrine pathways in the uterus (Challis et al., 2005; Bazer et al., 2009). Furthermore, estrogen functions by increasing the thickness of the glycosylation appearing in the endometrial epithelial cell plasma membranes (Fig. 1).

Estrogen and progesterone are expected to act for regulating pre-implantation embryo development apart from uterinal preparations. Bowman and McLaren (1970) showed that embryo number and number of cells per embryo dramatically decreased in the absence of progesterone and estrogen in mouse (Bowman and McLaren, 1970). Administration of estrogen and progesterone alleviate negative effects initially occurred in the absence of the steroid hormones (Roblero and Garavagno, 1979; Paria et al., 2001). In fact, there is no clear evidence to clarify how these hormones affect pre-implantation embryo development. Probably steroid hormones influence early embryo development via stimulating the secretions of growth and growth-inducing factors from the reproductive tract (Paria and Dey, 1990; Wen et al., 2009). Moreover, in vitro studies showed that pre-implantation embryos were able to secrete growth-promoting factors to the culture media (Paria et al., 2001). These factors may function in inducing the early embryo development process.

Experimental mice models have been formed to completely understand particular roles of estrogen and

progesterone during the implantation of the competent embryo. One of them is the delayed implantation model. In 1891, Lataste primarily found that natural suckling could be used to stimulate delayed implantation in mice and rats (Gidley-Baird, 1981; Paria et al., 2001). Nowadays, delayed embryo implantation models can be faithfully formed using ovariectomy techniques prior to pre-implantation estrogen secretion on day 4 of the pregnancy in mice. Thus, the blastocyst remains in dormant phase within the uterine lumen. Dormancy condition can be extended by daily P4 treatment that maintains the uterus in pre-receptive phase (Paria et al., 2000; Challis et al., 2005). Following estrogen administration, the uterus enters into receptive phase and then embryo implantation occurs. Interestingly, blastocyst dormancy is not observed in some species involving rabbits, hamsters, guinea pigs and pigs (Lessey et al., 2002a,b; Paria et al., 2002). However, there is no information on whether delayed implantation appears in humans (Table 1). In fact, dormant blastocysts are different from normal blastocyte in some aspects containing certain gene expressions, morphological and metabolic features. Expressional levels of epidermal growth factor receptor (EGF-R), cyclooxygenase-2 (Cox-2) and histamine receptor type 2 (H_2-R) are higher in normal blastocysts than dormant blastocysts. However, cannabinoid receptor (CB1) expression is vice versa (Fig. 1). Each of these genes transcribed by certain uterinal cell types has crucial functions in embryo implantation processes (Challis et al., 2005). In addition to the blastocyte, some of the genes, such as COX-2, are also expressed in human endometrial luminal epithelium and perivascular cells, where blastocyst invasion occurs (Marions and Danielsson, 1999). An *in vitro* study showed that secreted prostaglandins catalyzed by cyclooxygenase play critical roles in mouse blastocyst hatching and early embryo development (Pakrasi and Jain, 2007). Paria et al. (1995) firstly demonstrated the presence of the CB1 mRNA from four-cell to the blastocyte stages using reverse transcription-coupled PCR in mouse (Paria et al., 1995). The accumulation of CB1 mRNA during the embryonic genome activation may be associated with regulating genomic activation. Histamine is a biogenic amine produced from L-histidine by histidine decarboxylase enzyme and plays roles in implantation and decidualization processes in mouse uterus (Joseph et al., 1990; Paria et al., 1998a). Zhao et al. (2000) observed that histamine peaked on day 4 of the pregnancy, produced by uterine epithelia cells to mediate interactions between blastocyte and endometrium during the implantation process in mouse. In this study, they also found that secreted histamine was capable of binding to the histamine receptor type 2 synthesized by the blastocyte in a paracrine fashion to initiate the attachment reactions and blastocyst zona hatching (Zhao et al., 2000). Indeed, binding of histamine to histamine receptor type 2 leads to increasing intracellular cAMP levels, so releasing calcium ions from the intracellular stores may trigger essential activities related to attachment reaction and zona hatching (Schwartz et al., 1991). Blastocyte derived epidermal growth factor receptor (EGF-R) is localized to the cell-surface and stimulated via binding of the specific ligands, such as epidermal growth factor and transforming growth factor α (TGFα) (Dreux et al., 2006). Wiley et al. (1992) primarily detected that EGF-R was distributed at the apical sites of mature oocyte, blastomeres of cleavage stage embryo and trophectoderm cells of the blastocyst in mouse (Wiley et al., 1992; Paria et al., 1993). Similar results associated

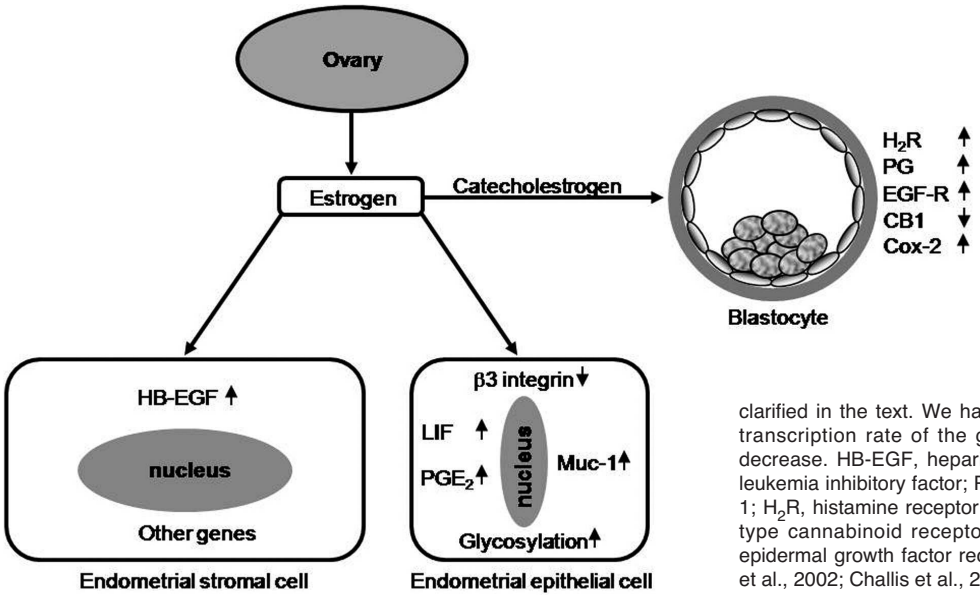

Fig. 1. This figure summarizes certain gene expressions that undergo control of estrogen in stromal and epithelial cells of the endometrium during the menstrual cycle. Also, expression levels of the genes regulated by catecholestrogen are indicated on the right of the blastocyst. Functional importance of the genes near the blastocyte is clarified in the text. We have noted the effect of the estrogen on transcription rate of the gene as using ↑ for increase, ↓ for decrease. HB-EGF, heparin-binding EGF-like growth factor; LIF, leukemia inhibitory factor; PGE_2, prostaglandin E_2; MUC-1, mucin-1; H_2R, histamine receptor type 2; PG, prostaglandin; CB1, brain-type cannabinoid receptor; Cox-2, cyclooxygenase-2; EGF-R, epidermal growth factor receptor (Paria et al., 2000, 2001; Cheng et al., 2002; Challis et al., 2005).

with EGF-R expression pattern were also obtained from human oocyte and cleavage stage embryos (Antczak and Van Blerkom, 1999). Binding of the TGF-α temporally produced in the luminal epithelium of the uterus to the EGF-R present on the trophectoderm layer of the blastocyte may be implicated in initiating embryo implantation process (Chen et al., 2001). As a result, differential expression levels of the genes displayed on the right site of the blastocyte contribute to implantation of the competent embryo to the receptive endometrium (Fig. 1).

Preimplantational mouse embryos, apart from estrogen secretion, accomplish expression of certain proteins involving ER-α (estrogen receptor-α), ER-ß (estrogen receptor-ß) and EFP (estrogen responsive finger protein) mRNAs (Hiroi et al., 1999). Furthermore, human pre-implantation embryos are capable of synthesizing human chorionic hormone (hCG) at 8-cell stage (Fishel et al., 1984; Casan et al., 1999), gonadotropin releasing hormone (GnRH) and the receptors of TGFα, EGF, PGE2, IGF and LIF in different early embryonic stages (Smotrich et al., 1996; Chen et al., 1999; Sengupta and Ghosh, 2000; Lessey, 2003; Challis et al., 2005).

LIF expression in early embryos may be indirectly regulated by steroid hormones via controlling production of cytokines and growth factors (Arici et al., 1995; Carson et al., 2000; Chen et al., 2000; Cheng et al., 2002). Charnock-Jones et al. (1994) demonstrated that human blastocysts transcribed LIF receptor mRNAs, and this finding interpreted as the blastocyst may be received LIF-mediated uterinal signal (Charnock-Jones et al., 1994). As is known, LIF is intensively secreted by endometrial glands on day 1 of the pregnancy in mice, but LIF production decreases by day 3 of gestation and then a significant amount of LIF expression occurs in glands on day 4 of gestation (Bhatt et al., 1991; Carson et al., 2000) (Figs. 1, 2). Following embryo implantation on day 4 of pregnancy LIF secretion attenuates and remains at very low level for the rest of gestation. When the LIF gene is ablated in mice, the males have a normal reproduction system, but the females are infertile. In fact, preimplantation embryonic development and some of the uterinal preparations take place normally in LIF knockout mice. Additionally, the uterus of these mice could not respond to signals required for inducing the decidual reactions, even though a competent blastocyte existed in the uterine lumen (Chen et al., 2000, 2002).

Particular functions of estrogen in the establishment of uterine receptivity and embryo implantation

During the menstrual cycle, estradiol blood level increases in two different phases in humans. One of them is in proliferative stage (6-14 days of human menstrual cycle) in which growing follicles secrete an excessive amount of estradiol that peaks approximately 48 hours before ovulation (Groothuis et al., 2007). Granulose cells of the follicles use aromatase and p450 enzymes to synthesize estrogen under control of follicle stimulating hormone (FSH). The second phase is the mid-luteal phase, during which corpus luteum produces a high level of estradiol, in addition to progesterone (Laven and Fauser, 2006; Kulendran et al., 2009).

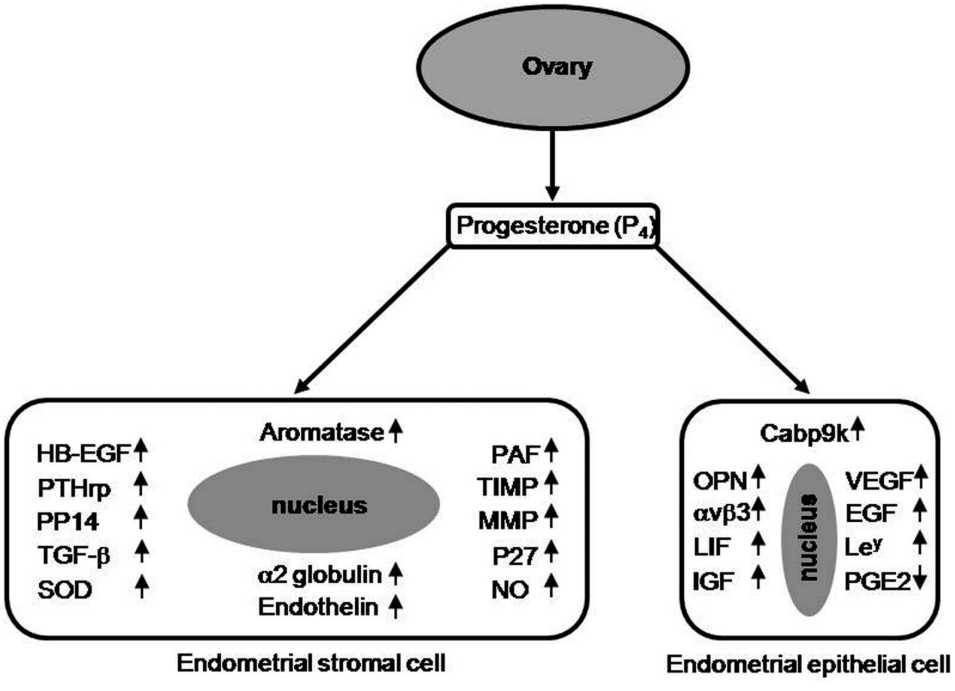

Fig. 2. The figure outlines progesterone-regulated gene expression in stromal and endometrial epithelial cells of the endometrium throughout the reproductive cycle. We have noted the effect of the progesterone on transcription rate of the gene as using ↑ for increase, ↓ for decrease. HB-EGF, heparin-binding EGF-like growth factor; PTHrp, parathyroid hormone related peptide; placental protein-14; TGF-ß, transforming growth factor; SOD, superoxide dismutase; PAF, plasminogen activator; TIMP, tissue inhibitor of metalloproteinase; MMP, matrix metalloproteinase; NO, nitric oxide; OPN, osteopontin; LIF, leukemia inhibitory factor; IGF, insulin-like growth factor; VEGF, vascular endothelial growth factor; EGF, epidermal growth factor; Le^y, Lewis antigen; PGE_2, prostaglandin E_2 (Paria et al., 2000; Sengupta and Ghosh, 2000; Cheng et al., 2002; Lessey, 2003; Franco et al., 2008).

However, the rise of estrogen level in mid-luteal phase, which coincides with the time when the uterus becomes receptive, is not required for successful embryo implantation in human (Ghosh et al., 1994; Groothuis et al., 2007). In fact, peaked estrogen concentration prior to the ovulation plays important roles in foundational events involving endometrial regeneration, uterinal growth and responses of uterinal cells to progesterone. Preovulatory ovary-derived estrogen induces uterinal epithelial cell proliferations, intensively appearing on days 1 and 2 of pregnancy in adult mice (Ferenczy et al., 1979; Paria et al., 2001; Franco et al., 2008). Then, epithelial cells cease proliferation and start to differentiate on day 4 of pregnancy under the control of both estrogen and progesterone in mice (Carson et al., 2000; Paria et al., 2000; Challis et al., 2005). Furthermore, both of these steroid hormones secreted by the ovary on day 4 of pregnancy participate in proliferation of the uterine stromal cells in mouse. In this day of pregnancy, the uterus enters into a receptive state that permits crosstalk with the blastocyst to initiate attachment and invasion events (Carson et al., 2000).

E_2 profoundly suppresses the apoptotic process by up-regulating transcription of the anti-apoptotic genes and simultaneously decreases the expression of the pro-apoptotic genes in the human endometrium (Choi et al., 2001; Havelka et al., 2005; Zubor et al., 2009). In parallel, estrogen down-regulates the expression of cell cycle inhibitors to stimulate endometrial cell proliferation without activating cell division stimulators (Hewitt et al., 2005; Groothuis et al., 2007). Another crucial role of estrogen is that elevated E_2 concentration on day 3.5 promotes secretion of leukemia inhibitory factor (LIF) from uterinal gland cells, which aids establishing endometrial receptivity in mice (Stewart et al., 1992; Franco et al., 2008). In addition, ovarian estrogen is capable of raising endometrial capillary permeability by stimulating expressions of certain genes related to vascular alterations in the uterus where the embryo implantation occurs. Wen et al. (2009) recently found that estrogen and progesterone could potentially stimulate the production of VEGF (vascular endothelial growth factor) from Ishikawa endometrial epithelial cells. Secretion of high level VEGF increase subendometrial vascularity and blood flow to supply adequate blood to the receptive endometrium (Wen et al., 2009). Also, E_2 mediates activation of estrogen and progesterone receptor transcriptions in stromal cells and uterinal glands during the follicular phase in humans (Makrigiannakis et al., 2006; Mylonas et al., 2009).

Secreted estrogen from ovary uses two types of nuclear receptors (ER-α and ER-ß), which belong to the steroid receptor super family. These receptors are encoded by separate genes localized to the different chromosomes. ER molecules form dimers after they enter the nuclear compartment and bind to the response element of the target gene (Childs et al., 2001).The levels of ER receptor mRNA and protein that change throughout the menstrual cycle are regulated by various physiological factors, such as estradiol. Estradiol controls up- and down-regulation of the endometrial estrogen receptor gene expression using a posttranscriptional mechanism in adult rodents (Lubahn et al., 1993; Nephew et al., 2000; Mylonas et al., 2009). ER expression is at a high level during the proliferative phase (particularly the late proliferative phase) and peaks at the time of ovulation in human endometrium. ER concentration dramatically decreases in the secretory phase and there is very weak expression of ER in late secretory phase (Bayard et al., 1978; Moutsatsou and Sekeris, 1997).

Binding of endogenous estrogen to the ER-α in the endometrium leads to increased PR expression, secretion of IGF-1 and uterinal cell proliferation in mice (Couse and Korach, 1999; Zhu and Pollard, 2007). Hewitt et al. (2002) showed that functional estrogen receptor-α was an essential factor to support successful embryo implantation in mice (Hewitt et al., 2002). However, the functional property of ER-ß is not clearly explained, probably it plays a role in the control of EGF receptor expression in mouse uterus (Wada-Hiraike et al., 2006). Some investigators also suggest that ER-ß may participate in modulation of ER-ß roles (Koehler et al., 2005; Makrigiannakis et al., 2006). Both ER-α and ER-ß are expressed in glandular epithelial and stromal cells in the functional layer of the human endometrium during the normal menstrual cycle. Interestingly, the expression level of ER-α in glands and stroma is reduced during the secretory phase, but there is no ER-α expression in the endothelium and uterine natural killer cells in human endometrium. On the other hand, ER-ß expression is observed in glands, stroma, endothelium and uterine natural killer cells and, similar to ER-α, ER-ß expression also declines during the secretory phase (Critchley et al., 2001; Critchley and Saunders, 2009). ER-ß probably mediates the direct effects of estrogen on endometrial vessels, involving angiogenic activity and vessel permeability (Critchley et al., 2001; Lecce et al., 2001).

ER-α knockout mice models were formed to accurately understand significant functions of ER-α in uterinal changes appearing during the menstrual cycles. Knockout investigations demonstrated that when the ER-α gene was ablated, male and female mice were able to develop to adult state with normal external phenotypes (Lubahn et al., 1993; Tranguch et al., 2005; Franco et al., 2008). However, there were certain abnormalities in female mice, including hypoplastic uteri and hyperemic ovaries which lacked corpora lutea. Although ER knockout female mice were infertile (Lubahn et al., 1993; Hewitt et al., 2002), decidual reaction could be induced by artificial P4 treatment (Challis et al., 2005; Makrigiannakis et al., 2006). As expected, these mice were unable to stimulate luminal epithelial cell proliferation and specific gene expressions, normally taking place under control of estrogen. No faithful embryo implantation was detected in these mice, but only a few embryos implanted to the endometrium were immediately reabsorbed (Hewitt et al., 2002). On the

other hand, ER-ß knockout female mice solely exhibited subfertility and apparent defects in hypothalamic-pituitary-gonadal axis. Also, complete genomic response to estrogen retained in the ER-ß (-/-) mice models (Challis et al., 2005). Consequently, these results indicate that ER-, has minimal effect in responding to ovarian estrogen in mouse uterus. When both ER-α and ER-ß were knocked out at the same time, apparent infertility was observed in these mice (Makrigiannakis et al., 2006).

When performing a study to determine estrogen effects on endometrial receptivity, we should use the appropriate estrogen concentration to prevent harmful activities of this hormone. Wen-ge (2003) formed a delayed implantation mice model to investigate the effect of several estrogen levels on duration of implantation window (Wen-ge, 2003). Prior to blastocyst transfer, they injected 1.5, 3, 10 and 25 ng E_2 to the ovariectomized mice daily treated with P4 injection at day seven of pseudopregnancy. When examining implantation sites, Wen-ge (2003) found that optimal exogen estrogen level to promote embryo implantation was between 3 and 25 ng. In the second set of experiments of the same study, 3 ng E_2 administrated secondly on day eight in addition to the first dose applications to detect the effects of different estrogen treatments on the duration of uterine receptivity. The second experiment showed that the mice which first received 1.5 and 3 ng E_2 doses accomplished blastocyst implantation faithfully. However, the uterus of the mice first treated with high dose estrogen (10 or 25 ng) became refractory in a short time. As a consequence, Wen-ge (2003) displayed that if the estrogen dose treated first was low (3 ng), the uterus remained in receptive state for at least four days in most of the mice. However, when the first estrogen dose was high (25 ng), the uterus rapidly became refractory within 24 h and maintained this state for the next 72 h (Wen-ge, 2003). Probably, high dose estrogen administration abolishes the implantation related gene expressions such as Hoxa10, Dtr, Areg, LIF, Ptsg1 and Ptsg2 in uterinal cells, therefore duration of receptivity was abbreviated in those mice treated with high dose estrogen (Simon et al., 2003; Wen-ge, 2003). The minimal required estrogen level to maintain the window of uterine receptivity open for an extended period is in the range of 1.5-3 ng (Milligan et al., 1995; Ma et al., 2003; Simon et al., 2003; Groothuis et al., 2007).

As is known, ovarian stimulation frequently used by in vitro fertilization (IVF) centers may lead to increasing E_2 level of the patients' serum. Presumably, an increase in the estradiol concentration in these patients may cause impairments in expression of certain genes related to the establishment of uterine receptivity and embryo implantation (Makrigiannakis et al., 2006). Furthermore, in vitro models showed that an E_2 concentration higher than 10^{-6} M may decrease adhesive activities of the competent blastocyte to the endometrial luminal epithelium (Valbuena et al., 2001; Simon et al., 2003; Challis et al., 2005). However, in human the negative effect of supraphysiological concentration of serum estradiol level on uterine receptivity is controversial (Valbuena et al., 2001; Simon et al., 2003).

Estrogen is transformed into different molecules that have critical roles in early embryo activation. One of them is catecholestrogen (also known as 4-hydroxy-estradiol-17ß (4-OH-E_2)) which plays important roles in blastocyst activation in a paracrine manner. Catecholestrogen is a metabolite of estradiol and is secreted by human and mouse endometrium (Paria and Dey, 1990; Lepine et al., 2004; Tsuchiya et al., 2004). It is produced by aromatic hydroxylation from phenolic estrogens, catalyzed by CYP1B1 (P-450-linked enzymes) or peroxidase enzyme system. CYP1B1 enzyme is specifically expressed throughout the implantation site of mouse uterus on day 4 and dramatically disappears on day 5 of the pregnancy (Paria et al., 2000; Challis et al., 2005). When the dormant blastocysts cultured in the presence of 4-OH-E_2 *in vitro*, these blastocysts activated and successfully implanted to receptive mouse uterus (Paria et al., 1998b). Interestingly, only catecholestrogen except other forms of estrogen enables to stimulate secretion of the prostaglandins known to mediate activation of the dormant blastocysts (Paria et al., 2001; Makrigiannakis et al., 2006). ICI-182, 780 an antagonist of estradiol used to determine the role of ER-α signaling in dormant blastocyst activation, findings showed that estrogen receptor signaling was not required in blastocyst activation. Consequently, catecholestrogen activates dormant blastocysts regardless of using ER receptor α signaling pathway (Challis et al., 2005; Makrigiannakis et al., 2006).

Particular functions of progesterone (P4) in establishment of uterine receptivity and embryo implantation

Progesterone is conventionally known as mammalian "pregnancy hormone". This hormone performs physiological effects via binding to its specific progesterone receptor localized in the cell nucleus. Progesterone has critical roles in establishment of endometrial receptivity through regulation of stromal and epithelial cell proliferations and differentiations. Also, progesterone functions in coordinating expression of many genes transcribed by endometrial cells, using endocrine or paracrine pathways (Lydon et al., 1995; Qian et al., 2005). For example, Le^y (Lewis-Y) antigen production in endometrial glandular cells is tightly controlled by progesterone in mouse and in rhesus monkey (Zhu et al., 1995; Sengupta and Ghosh, 2000). Secreted Le^y antigen from endometrial glands contains α1-3-fucosylated type 2 chain and is implicated in recognition of blastocyst by endometrial epithelial cells. The importance of Le^y for the embryo implantation process was obtained from inhibition of this antigen by administration of mifepristone, a modulator of

progesterone receptor (Fenderson et al., 1990; Ghosh et al., 1998; Sengupta and Ghosh, 2000). In addition to Le^y, placental protein 14 (PP14) which participates in the preparation of endometrium for blastocyst implantation, is also under control of progesterone in humans (Seppala and Tiitinen, 1995; Lalitkumar et al., 1998) (Fig. 2). PP14 is a glycoprotein and is expressed by human endometrial glandular epithelial cells during the late secretory phase and gestational decidua (Borri et al., 1998). Suggestion related to role of PP14 in implantation process is that; PP14 may mediate immunomodulatory effects in the endometrium throughout the blastocyte implantation in humans (Julkunen et al., 1990; Okamoto et al., 1991).

Expression of LIF, PTHrp, TGF-ß, aromatase, PAF, MMP, α_2-globulin, TIMP and endothelin increases in the progesterone-dominated phase of the reproductive cycles in rhesus monkey (Sengupta and Ghosh, 2000) (Fig. 2). Other P4 targeted genes involving Indian hedgehog (Ihh), bone morphogenetic protein 2 (Bmp2) and homeobox A10 (Hoxa10) were identified in human and mouse uterus (Franco et al., 2008). The expression of Ihh in the uterinal luminal epithelium and glandular epithelial cells peaks on the fourth day and interestingly declines shortly after implantation on the fifth day of pregnancy in mice. Ihh is probably implicated in crosstalk between endometrial epithelium and stromal cells in the endometria (Wakitani et al., 2008). Furthermore, C/EBP, (CCAAT/enhancer binding protein beta), amphiregulin, HB-EGF (heparin-binding EGF-like growth factor) and cell cycle regulators (p27 and p53) are regulated by ovary derived progesterone (Franco et al., 2008) (Fig. 2). HB-EGF up-regulates the integrin alphanubeta3 expression in preimplantation embryos and outgrowing blastocysts to contribute to the process of embryo implantation in mouse (Lim et al., 2006). Besides progesterone, estrogen also regulates ß3 integrin productions by increasing HB-EGF secretion. As is known, ß3 integrin plays a major role in adhesive interactions between trophoblast and uterinal lumen epithelia (Carson et al., 2000; Lessey et al., 2002b; Lessey, 2003) (Fig. 1). Peptide hormone calcitonin (CT) included in calcium homeostasis could be induced by progesterone in receptive human and rat endometrium (Kumar et al., 1998). However, E2 inhibits P4-induced calcitonin production to bring into balance of its level. This peptide hormone is transiently expressed in rat and human receptive endometrial epithelia within the window of implantation (Zhu et al., 1998; Carson et al., 2000; Li et al., 2002). Binding of CT to its cell surface receptor in the epithelial cells leads to temporarily increasing intracellular calcium concentration. A rise in intracellular calcium levels represses production of calcium dependent cell adhesion molecules such as E-cadherin, which mediates the remodeling of the adherens junctions between the epithelial cells to facilitate blastocyte implantation (Li et al., 2002).

Investigations showed that TGFß-1 expression is promoted by both progesterone and estrogen in stromal cells (Arici et al., 1996; Sengupta and Ghosh, 2000), but only progesterone regulates tumor necrosis factor (TNF-α) (Hunt et al., 1992; Laird et al., 1996) and superoxide dismutase (SOD) (Sugino et al., 1996) expressions in human endometrium (Fig. 2). SOD is produced in high levels by endometrial cells during the mid-secretory phase to protect the embryo and endometrium from superoxide radical damages (Narimoto et al., 1990; Sengupta and Ghosh, 2000). Notably, osteopontin, a ligand of $\alpha v ß3$ integrin also undergoes control of ovarian progesterone (Lessey, 2003). Osteopontin secreted by glandular epithelial cells during receptive phase may function in embryo-uterine interactions in humans and rats (Kao et al., 2002). In addition, adhesion molecules such as trophinin (Fukuda et al., 1995) and cadherin-11 (Getsios et al., 1998) expressed by endometrial epithelial and stromal cells are strictly regulated with progesterone in humans (Lessey, 2003).

MUC-1 intensively studied intrinsic transmembrane mucin is strongly controlled by steroid hormones in many species involving mice and human (Carson et al., 2000) (Fig. 1). MUC-1, known as an anti-adhesive component contains a stretch of long carbohydrate branches and localizes to the apical surfaces of uterine luminal and glandular epithelial cells (Surveyor et al., 1995; Burghardt et al., 2009). In mouse, the purpose of MUC-1 expression in endometrial epithelium is to prevent unfavorable interactions between trophoblast cells of the blastocyte and luminal epithelium before commencing the implantation process. The abundance of MUC-1 on uterine epithelium is reduced during peri-implantation period by stimulating the cell surface protease (Surveyor et al., 1995; Carson et al., 2000; Bazer et al., 2009). Reduction of MUC-1 in endometrial epithelium during the window of implantation facilitates attachment reaction of blastocyt to endometrial lumen epithelial in rodents and humans (Meseguer et al., 2001; Shiozawa et al., 2003; Dey et al., 2004; Quezada et al., 2006). Interestingly, progesterone-activated MUC-1 highly expressed throughout the window of implantation in human endometrium may play role in selecting healthy embryos (Surveyor et al., 1995; Brayman et al., 2004). Another P_4-regulated gene is calcium binding D-9K (Cabp9k) detected in mouse uterus, control the intracytoplasmic calcium concentration and transfer of free calciums. Progesterone participates in the control of Cabp9k gene transcription in endometrial luminal and glandular epithelial cells during embryo implantation. However, on day 5 of pregnancy Cabp9k is solely detected in luminal epithelium in mouse uterus (Tatsumi et al., 1999). Furthermore, progesterone plays important roles in the regulation of OPN (osteopontin), $\alpha v ß3$ integrin, IGF, VEGF, and PGE_2 in human endometrial epithelium (Kotani et al., 2005; Qu et al., 2008; Wen et al., 2009) (Fig. 2).

Progesterone influences uterinal physiology via binding to its specific receptors localized to the nuclear compartment of the cells. Three isoforms (PR-A, PR-B and PR-C) of progesterone receptor (PR) transcribed

from the same gene with alternative splicing mechanisms have been determined. Progesterone receptor is composed of multiple domains involving activation domain-1 (AF-1), DNA binding domain, and ligand binding domain which also contains additional activation domain-2 (AF-2) (Takimoto et al., 1992; Lessey, 2003; Franco et al., 2008). Conserved DNA binding domain of PR motif locates close to the center of the protein and includes zinc finger domains that enhance binding of the receptor to target genes. Also, ligand binding domain has moderately conversed amino acid sequences and place in the carboxy-terminal of the PR. The amino-terminal region of the PR receptor is the most variable site and functions especially in transcriptional activation of certain genes (Lydon et al., 1995). However, PR-B is little different from PR-A and PR-C because it includes third activation domain (AF-3) in N-terminal region that consists of 164 amino acids (Lessey, 2003; Franco et al., 2008). AF3 probably plays a role in binding of PR-B to various coactivator proteins. PR-C, a recently found isoform of progesterone receptor may function in regulating desidual cell activities during late pregnancy (Giangrande et al., 2000; Moutsatsou and Sekeris, 2003).

There are two known mechanisms operating PR actions: ligand-dependent and ligand-independent mechanisms. If there is no ligand around the progesterone receptor, heat shock proteins and immunophilins bind PR to inactive its ligand based activity. Binding of the ligand to the complex causes dissociations of the heat shock proteins and immunophilins from progesterone receptor. Then, formed progesterone-PR dimer interacts with the progesterone response element site of the target gene. Subsequently, PR recruits coactivators such as p160/SRC family, CBP/p300, and ASC-2 to increase transcriptional rate of the target gene. In the ligand independent mechanism, PR action is stimulated using other intracellular signaling pathways. Eventually, use of these mechanisms results in activation of progesterone-regulated gene expressions (Franco et al., 2008).

Similar to estrogen receptor expression pattern, PR levels rise in proliferative phase and peak at ovulation and then gradually decrease in the secretory phase of human endometrium (Press et al., 1988; Moutsatsou and Sekeris, 1997). Progesterone receptor is expressed by glands and stromal cells in the functional layer of the endometrium throughout the reproductive cycle, but there is no transcription of PR receptor in the endothelium and uterine natural killer cells (Critchley and Saunders, 2009). Secreted estrogen throughout the follicular phase increases expression of progesterone receptor that allows the uterus to respond to progesterone produced during the luteal phase of the human menstrual cycle (Critchley and Saunders, 2009). Therefore, expression level of PR in normal proliferative human endometrium is higher than mid-secretory phase of normal menstrual cycle due to high concentration of estrogen (Kreitmann et al., 1979; Tseng and Zhu, 1997). PR-A, dominant type progesterone receptor is produced in stromal cells close to the uterine vasculature during the secretory phase and early pregnancy. However, both PR-A and PR-B subtypes significantly decrease in glands throughout the secretory phase in human endometrium (Perrot-Applanat et al., 1994; Wang et al., 1998).

As accomplishing crucial functions, both estrogen and progesterone receptors require regulator factors, including coactivators and repressors, which interact with these receptors in a ligand-dependent fashion. Binding of coactivators to the receptor-complex leads to expression of target genes controlled by these steroid hormones. However, corepressors implicate in suppression of the target gene transcriptions to balance their expressional levels. Coactivators such as steroid receptor coactivator-1 (SRC-1) and p300/CREB-binding protein (p300/CBP) and corepressors involving nuclear receptor corepressor and silencing mediator for retinoid and thyroid hormone receptors have critical roles in regulating steroid receptor actions. Quezada et al. (2006) characterized expression patterns and cellular localizations of coactivators, corepressors and steroid receptors in human endometrium during the menstrual cycle. Although binding of SRC-1 to ER was only demonstrated in the proliferative phase, p300/CBP-ER interaction was demonstrated in proliferative and secretory phases of the endometrium. Complex composed of p300/CBP and PR was only detected in secretory endometrium, although there was no complex formation between SRC-1 and PR in either of the endometrial phases in human (Shiozawa et al., 2003; Quezada et al., 2006). Progesterone receptor also uses additional contributive factors, including FK506 binding proteins (FKBPs), basic transcription element binding protein (Bteb1), the p160/SRC family of coactivators and Src kinase. These factors mediate ligand-independent PR activities. As stated above, heat shock proteins and immunophilins bind to progesterone receptor in the absence of ligand to regulate ligand-independent progesterone action. FKBP4 (FKBP52) and FKBP5 (FKBP51) members of immunophilins family interact with PR and ablation of FKBP4 gene causes infertility in adult male and female mice (Tranguch et al., 2005; Franco et al., 2008). In addition, PR establishes a relation with the Src kinase pathway to carry out its certain effects. Subluminal stroma, luminal and glandular epithelium produce the active form of Src on day 4.5 of pregnancy. Concordantly, Src knockout female mice were infertile and failed to successfully stimulate the uterinal desidual reactions (Shimizu et al., 2005; Franco et al., 2008). New investigations associated with the effect mechanisms of coactivators, corepressors and contributor factors of progesterone receptor on the establishment of endometrial receptivity and embryo implantation should be performed to completely understand the roles of these factors. Understanding functional properties of these factors may provide new approaches in relation to reproductive problems in

humans.

PR inhibitors such as mifepristone (RU486) have been used to determine the effects of inhibition of progesterone receptor-dependent signalization. Single dose administration of mifepristone precludes blastocyst implantation without changing the serum steroid hormone concentrations in primate (Sengupta and Ghosh, 2000). Treatment of mifepristone in the luteal phase caused increases in apoptosis, degeneration, and an increase of gene expression levels of ER and PR in glands. Furthermore, mifepristone leads to increased mitotic index, leukocyte accumulations, and matrix metalloproteinase levels in the uterinal stroma (Carson et al., 2000; Sengupta and Ghosh, 2000). Besides antagonist experiments, PR knockout mice models are created to exactly clarify the physiological functions of the progesterone receptor and to depict distinctions between PR and ER responses. Lydon et al. (1995) showed that male and female embryos, homozygous mutant for the PR gene normally developed to adulthood state. Also, homozygous and heterozygous mutant male mice were fertile as wild type siblings. However, adult female mice ablated for PR gene exhibited considerably significant abnormalities associated with the reproductive system. Existing defects were listed as: impairment of ovulation, hyperplasia in uterus, insufficient development of mammary glands, intensive inflammation, and sexual behavioral disorders (Lydon et al., 1995). Moreover, PR-A and PR-B knockout mice models were separately formed to determine important impacts of these isoforms on the reproductive system and other organs. Although PR-A knockout female and male mice normally developed to adult state, the females were infertile. Furthermore, decidualization reaction was not observed in these female mice even though artificially induced. As expected, expressions of P_4-dependent genes that play crucial roles in establishment of uterine receptivity were down-regulated in the uteri of PR null mice (Mulac-Jericevic et al., 2003; Franco et al., 2008). On the other hand, PR-B (-/-) knockout mice showed mild reproductive failures such as reduced mammary gland morphogenesis. Fertility, ovarian and uterinal responds to progesterone normally occurred in the absence of PR-B (Mulac-Jericevic et al., 2000, 2003). When both PR-A and PR-B were knocked out simultaneously, major abnormalities, including infertility, impaired decidualization and ovulation impairments were signed (Paria et al., 2001; Challis et al., 2005; Makrigiannakis et al., 2006). These results show that PR-A is the more significant isoform in correctly preparing the uterus for competent embryo implantation.

Conclusion and future remarks

In this review article, we discussed functional properties of ovary-derived estrogen and progesterone on the establishment of uterinal receptivity and the embryo implantation process. Both estrogen and progesterone generally play crucial roles in controlling endometrial cell proliferation and differentiation processes by regulating certain gene expressions. As is known, estrogen and progesterone bind to their specific nuclear receptors in endometrial cells to strictly regulate transcription of certain genes associated with acquiring uterine receptivity. The significance of these steroid hormones in uterinal preparations for embryo implantation revealed from the experimental knockout models formed by ablation of the estrogen and progesterone receptor genes.

Unfortunately, distinct results were found in some of the studies related to the effects of steroid hormones on endometrial receptivity, despite using the same experimental models and techniques. To resolve these controversies between investigations, the studies should be performed in multicenter collaborations to reduce the effects of biological and different technical applications. Generally, most of the laboratories use rodent models to understand the functional properties of ovarian steroid hormones in human reproductive physiology. However, apparent differences exist between reproductive physiological features of human and rodent: a) hormonal

Table 1.

Properties	Humans	Mice
Pre-receptive days	Secretory phase (-14-18 days)	1-3 days
Receptive days	Mid-secretory phase (19-24 days)	4th day
Non-receptive days	Rest of secretory phase (25-28 days)	5th day
Estrogen requierement for implantation	No	Yes
Progesterone requierement for implantation	Yes	Yes
Estrogen secretion from early embryo	Yes	No
Occurrence of blastocyte dormancy	?	Yes
Use of pinopodes as a marker of uterine receptivity	-	-

In this table, certain properties, including uterine sensitivity to embryo implantation, estrogen and progesterone requirement for implantation and other significant features have been compared between human and mice (Gidley-Baird, 1981; de Ziegler et al., 1992; Carson et al., 2000; Paria et al., 2001; Paria et al., 2002; Challis et al., 2005; Makrigiannakis et al., 2006; Wang and Dey, 2006). ? is used to state that no information is available about the property.

regulation of the uterine receptivity; the window of implantation opens with presence of progesterone after E_2 priming in human, but it is vice versa in rodents b) genomic responses to uterine receptivity; LIF and Ptgs2 expressions are critical proteins for embryo implantation in mice. By contrast, when these genes were investigated in global gene expression analysis, they were not detected in the human uterus (Kao et al., 2002; Simon et al., 2003). Other important differences between mice and human have been documented in the Table 1.

Up to now, whole functions and effect mechanisms of estrogen and progesterone in the establishment of uterine receptivity and embryo implantation process are not clearly clarified. When the effect mechanisms and intracellular signalization pathways of these steroid hormones in the endometrial cells are completely documented, some reproductive failures associated with steroid hormones may be treated by utilizing new technologies. Also, the impacts of the factors secreted by pre-implantation embryos to the uterinal environment should be investigated, using in vitro and in vivo experimental models to determine contributions of these molecules in achieving endometrial receptivity and early embryo development.

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