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Review

Embryo implantation: Shedding light on the roles of ovarian hormones, cytokines and growth factors in the implantation process

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Implantation is a crucial step in mammalian reproduction, as it is a gateway to further embryonic development and successful pregnancy. Successful implantation requires coordinated interactions between the blastocyst and uterus. Uterine receptivity for embryo implantation is regulated by the ovarian hormones estrogen and progesterone. Some cytokines and growth factors play important roles in embryo implantation under the influence of ovarian hormones. Such molecules are involved in embryo-maternal interactions during the implantation process. This review describes the implantation process and highlights the potential roles of some cytokines and growth factors (such as leukemia inhibitory factor, interleukin-1, interleukin-6, interleukin-11, colony stimulating factor-1, epidermal growth factor family and insulin-like growth factor system) in the implantation process. Knowledge of the function of these molecules during implantation may help to address the reason of implantation failure and infertility.

Key words: Implantation, estrogen, progesterone, cytokines, growth factors.

INTRODUCTION

Implantation is a crucial step in mammalian reproduction, as it is a gateway to further embryonic development and successful pregnancy. Successful implantation requires an intricate succession of molecular and genetic interactions. These reciprocal interactions between the embryo and the uterus must be executed within a limited time (Psychoyos, 1986) known as the “window of implantation” or “window of receptivity”. Any breach in the communication between the endometrium and the embryo during this time leads to implantation failure. Implantation failure is an unsolved problem in reproductive medicine and is considered to be an important cause of infertility.

Implantation is a very complex process. The implantation process is controlled by number of molecules like ovarian hormones, cytokines, growth factors and their receptors. Knowledge of the function of these molecules during implantation will help to address the reason of implantation failure and infertility. This review sheds light on some molecules thought to be important for successful implantation.

IMPLANTATION PROCESS

Implantation is divided into three stages; apposition, adhesion (attachment) and invasion (Enders and Schlafke, 1967). In rodents and some primates, the embryo that enters the uterus attaches to the uterine epithelium immediately. After loss of the zona pellucida, closure of the uterine lumen brings the blastocyst into close apposition to the luminal epithelium (Parr and Parr, 1989). The blastocyst attaches to the anti-mesometrial side of the endometrium, and the inner cell mass is directed to the mesometrial side. The epithelial cells in contact with the blastocyst undergo apoptosis and are

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phagocytized by the polytene cells (that is, cells from the wall of the blastocyst), facilitating penetration of the epithelium. Rodents demonstrate rapid implantation, as apposition, attachment and invagination of the uterine epithelium occur within 6 h (Lee and DeMay, 2004).

In contrast to rodents and primates, domestic animals (such as cattle, horses, sheep, goats and pigs) have a prolonged pre-implantation period (the pre-receptive phase). This period is characterized by migration of the embryo, spacing of the embryos (as in pigs), secretions from the endometrial glands, and generation of the embryonic signal for maternal recognition of pregnancy (Bowen and Burghardt, 2000; Bazer et al., 2010).

Invasion or penetration varies with species (Bowen and Burghardt, 2000). In domestic animals (e.g., horses, cattle, sheep, goats and pigs), the trophoblast cells do not penetrate the uterine epithelium (no penetration). In rats, mice and some primates, the trophoblast cells displace the underlying uterine epithelium and penetrate the epithelial basal lamina and stroma. The trophoblast migrates into the endometrial stroma and penetrates the superficial endometrial vessels (displacement penetration) (Schlafke and Enders, 1975; Bowen and Burghardt, 2000). Fusion penetration occurs in rabbits; the trophoblast cells fuse with the uterine epithelium and subsequently penetrate the stroma. The fourth type of penetration is intrusion penetration, which is common in carnivores; the trophoblast cells migrate between the epithelial cells to the endometrial stroma.

Implantation may also be divided into three categories based on the type of blastocyst–uterine cell interaction: centric, eccentric and interstitial (Wimsatt, 1975; Bazer et al., 2010). Centric implantation is non-invasive and occurs in domestic animals. The blastocyst in this type of implantation fuses with the luminal epithelium without penetrating through it. Implantation in mice, rats and hamsters is eccentric; the luminal epithelium forms an invagination to surround the trophoblast. Humans and guinea pigs have interstitial implantation; the trophoblast passes through the luminal epithelium to invade the endometrial stroma and become imbedded into the wall of the uterus (Wimsatt, 1975). The purpose of implantation, regardless of the mode of implantation, is to bring the maternal blood supply into contact with the developing embryonic blood vessels.

After the trophoblast invades the endometrial stroma, the stromal cells undergo extensive differentiation to form the decidua. Stromal decidualization is similar in all species regardless of the type of placentation, but the extent is variable and correlates with the depth of trophoblast invasion during implantation (Johnson et al., 2003). Decidualization in murines and humans occurs under the influence of steroid hormones, progesterone and estradiol. Decidualization is essential for a successful pregnancy, as the decidua plays various important roles (Robb et al., 1998); it encapsulates the developing embryo, facilitating nutrient transfer and limiting trophoblast invasion. Thus, decidualization is a prerequisite for implantation (Ramathal et al., 2010).

The first sign of implantation is the increase in uterine vascular permeability at the site of blastocyst apposition (Psychoyos, 1986). In mice and rats, an intravenous injection of macromolecular blue dye solution can show the implantation sites as blue bands along the uterus (Dey, 2003; Hamid et al. 2012). Increases in vascular permeability coincide with the attachment reaction between the blastocyst and uterine epithelium (Psychoyos, 1986; Dey, 2003).

OVARIAN HORMONES

Uterine receptivity is regulated by the ovarian hormones estrogen and progesterone. Progesterone is important for implantation and maintenance of pregnancy in all mammals, whereas the requirement for estrogen is species-specific (Wang and Dey, 2006). In pigs, guinea pigs, hamsters and rabbits, estrogen is not needed (Dey et al., 2004). In humans, an estrogen-primed endometrium develops under the control of progesterone (Jabbour et al., 2006). However, in rats (Canivenc et al., 1956), mice (Yoshinaga and Adams, 1966) and Mongolian gerbils (Norris and Adams, 1971), implantation requires both estrogen and progesterone. These hormones exert their effects on the endometrium via nuclear estrogen (ER) and progesterone (PR) receptors (Wang and Dey, 2006). In mice, spatial and temporal changes in the expression of ER and PR occur in the uterus during peri-implantation (Tan et al., 1999). ER is expressed in the uterine luminal epithelium and glandular epithelium on days 1 to 2; by days 3 to 4, ER is expressed in stroma and in the luminal and glandular epithelium. On day 5 after implantation, ER is expressed in the uterine luminal epithelium and glandular epithelium, but with lower expression in the stratum compactum stroma. On days 6 to 8, ER is expressed in undifferentiated stroma and in the secondary, but not the primary, decidual zone (Tan et al., 1999). PR is expressed in the luminal and glandular epithelium during days 1 and 2, with low levels of expression on day 1 and moderate levels on day 2. On days 3 to 4, PR is expressed in the luminal epithelium, glandular epithelium and stromal cells, but PR is absent from the luminal epithelium and restricted to stromal cells with abundant PR, particularly in the decidua, during days 5 to 8 (Tan et al., 1999). Each ER isoform (ERα and ERβ) and PR isoform (PRA and PRB) has specific functions in uterine biology and implantation. Their specific functions were confirmed by different studies on the effects of selective deletion on reproductive function. $ER\alpha^{-/-}$ mice have hypoplastic (underdeveloped) uteri that fail to support implantation (Lubahn et al., 1993), but implantation in $ER\beta^{-/-}$ mice occurs normally (Dey et al., 2004). While infertility due to defects in ovarian and uterine function

was observed in mice that lack both PR isoforms (Lydon et al., 1995), mice that are lack only PRB were normal. Thus, PRB modulates a subset of the reproductive functions of progesterone (Mulac-Jericevic et al., 2000).

CYTOKINES AND GROWTH FACTORS

Numerous cytokines and growth factors are involved in embryo-maternal interactions during implantation. In this review, we will discuss the potential roles of leukemia inhibitory factor, interleukin-1, interleukin-6, interleukin-11, colony stimulating factor-1, epidermal growth factor family and insulin-like growth factor system in embryo implantation.

Leukemia inhibitory factor

Leukemia inhibitory factor (LIF) is a member of the interleukin-6 (IL-6) family and is a pleiotropic cytokine. LIF is important for implantation in murines and humans. In mice, LIF expression in the uterus increases on day 4 of pregnancy, coinciding with implantation. LIF is expressed first in the uterine glands on the morning of day 4. During attachment, LIF is expressed in the stromal cells that surround the blastocyst (Stewart et al., 1992; Song et al., 2000). This pattern indicates that LIF plays an important role during attachment as well as in preparing the uterus for implantation. In mice lacking LIF, the blastocysts fail to implant and remain dormant (Stewart et al., 1992; Song et al., 2000). These blastocysts can develop to term and implant after being transferred to wild-type pseudopregnant recipients (Stewart et al., 1992). Uterine LIF expression is also high at implantation in other species, including humans (Arici et al., 1995; Aghajanova, 2004), rabbits (Yang et al., 1994), and minks (Song et al., 1998). In infertile women, LIF expression is low during the receptive period (Aghajanova, 2004). A decreased concentration of LIF in uterine flushing is correlated with unexplained infertility (Laird et al., 1997; Mikolajczyk et al., 2007). Moreover, a recent study by Jasper et al. (2011) revealed that LIF regulates fucosyltransferase 2 (Fut2) expression, which is required for embryonic attachment and implantation. Interestingly, LIF expression is suppressed in stressed mice. Kondoh et al. (2009) found that exposure to stress reduced the number of implantation sites and suppressed LIF expression. All these factors together indicate to the pivotal role of LIF in implantation in mice and humans.

In ruminants, LIF expression is low at implantation compared with the levels after implantation and in mid-pregnancy (Vogiagis et al., 1997a; Oshima et al., 2003); immunization of ewes against LIF resulted in a reduced pregnancy rate (Vogiagis et al., 1997b). Therefore, LIF may not be obligatory for implantation in ruminants, but it is apparently important for the establishment of pregnancy. On the contrary, a recent study by Song et al. (2009) in ewes revealed that the mRNA and protein of both the LIF receptor (LIFR) and its co-receptor, IL6 signal transducer (IL6ST), are more abundant in pregnant than cyclic ewes, with high expression levels from 10 to 20 days of pregnancy. Moreover, LIFR and IL6ST were expressed in the conceptus trophectoderm on days 18 and 20. Expression of LIFR and IL6ST in the uterus and trophectoderm indicate that LIF may have roles in endometrial function, trophectoderm growth and differentiation during early pregnancy (Song et al., 2009).

Interleukin-1

Interleukin-1 (IL-1) is a cytokine that is assumed to have a role in implantation process, at least in mice and humans. IL-1 and the IL-1 type-I receptor are found in the mouse uterus around the implantation time (Simon et al., 1994). In humans, IL-1 was also detected in the endometrium during implantation (Kauma et al., 1990); however, the precise role of IL-1 in implantation is not clearly understood. Although IL-1 knockout-mice were shown to be fertile, intraperitoneal injection of IL-1 receptor antagonist (IL-1ra) can prevent implantation (Simon et al., 1994). In addition, the number of implantation sites and the litter size are reduced in the absence of IL-1 (Salamonsen et al., 2000).

Interleukin-6

Interleukin-6 (IL-6) is a pleiotropic cytokine that shares the signal transducer gp130 with LIF. In mice, IL-6 expression increases on day 5 and day 6 of pregnancy (De et al., 1993). In humans, both IL-6 and IL-6 receptor are maximally expressed in the endometrium during the window of implantation (Sharkey et al., 1995; Tabibzadeh et al., 1995). Women who experience spontaneous abortion have reduced levels of IL-6 in plasma compared to those with normal pregnancies (Koumantaki et al., 2001). Although expression of IL-6 receptor in the blastocyst and endometrium (Sharkey et al., 1995) suggests a paracrine/autocrine role for IL-6 at implantation time, mice lacking IL-6 have shown normal implantation (Kopf et al., 1994); nevertheless, the development of blastocyst is compromised (Salamonsen et al., 2000), and the number of implantation sites and the litter size are decreased. Thus, IL-6 may play an important, but not essential, role during implantation.

Interleukin-11

Interleukin-11 (IL-11) is a cytokine that has pleiotropic functions in different tissues and cells. IL-11 and its receptor (IL-11Ra) are found in the endometrium. The

expression of IL-11 has been characterized in murine and humans (Robb et al., 1998; Karpovich et al., 2005). In mice, IL-11 is maximally expressed at decidualization time, 5.5 to 7.5 days post-coitus, with strong IL-11 expression in the developing decidual cells (Robb et al., 1998) and low expression in the cycling uterus. However, no changes were observed in the IL-11Rα expression in gravid and cycling uteri (Robb et al., 1998). Female mice lacking IL-11 receptor α are infertile due to defective decidualization. Thus, IL-11 in mice is crucial for implantation (Dimitriadis et al., 2010).

IL-11 expression in the human endometrium is also crucial during decidualization (Karpovich et al., 2005). An *in vitro* study by Marwood et al. (2009) revealed that both LIF and IL-11 regulate endometrial epithelial cell adhesion. In clinical studies, plasma IL-11 decreased in women with unexplained first trimester abortions (Koumantaki et al., 2001) compared to women with normal pregnancies. In addition, IL-11 and IL-11Rα protein, during peri-implantation, are present at lower levels in the endometrial epithelium in women with recurrent miscarriage compared to normal women (Linjawi et al., 2004). Interestingly, although low production of endometrial IL-11 is associated with primary infertility, levels of IL-11Rα in stromal cells derived from the fertile and infertile women are similar (Karpovich et al., 2005). Thus, the emerging roles of leukemia inhibitory factor and interleukin-11 in implantation and establishment of pregnancy imply that they are critical for successful pregnancy (Dimitriadis et al., 2010).

Colony stimulating factor-1

Colony stimulating factor (CSF-1) or macrophage-colony stimulating factor is a mononuclear phagocyte lineage-specific hemopoietic growth factor. It modulates proliferation, differentiation and survival of mononuclear phagocytes and their precursors (Stanley et al., 1983). In mice, CSF-1 expression in the endometrium starts on day 3 post-coitus and increases throughout pregnancy. CSF-1 expression peaks 14 to 15 days post-coitus (Arceci et al., 1989).

In pigs, CSF-1 shows a similar pattern. Tuo et al. (1995) reported that pig CSF-1 expression was observed from day 10 to 112 of pregnancy. Maximal expression of CSF-1 occurred at 20 to 30 days of pregnancy and the high levels were maintained to term. In bovines, CSF-1 expression changes dramatically between days 14 and 17, indicating that CSF-1 is implicated in earliest step of implantation in bovine, as this period is approximately the time of maternal recognition of pregnancy (Lee et al., 2003).

CSF-1 is expressed in the human endometrium during normal cycling. In the luteal phase, CSF-1 levels are higher than in the proliferative phase. Further, CSF-1 levels are higher in first trimester decidual tissue than in non-pregnant tissue (Kauma et al., 1991). Moreover, abnormal CSF-1 expression is associated with infertility (Lee and DeMayo, 2004).

Mice lacking CSF-1 showed many reproductive abnormalities, including low ovulation rates and reduced implantation and fetal survival rates (Pollard et al., 1991). Even treatment of these mice with human recombinant CSF-1 failed to rescue the reproductive phenotype, highlighting the significance of local synthesis of CSF-1 for uterine function (Wiktor-Jedrzejczak et al., 1991). Surprisingly, mating osteopetrotic (op/op) females to heterozygote males partially rescued the fertility (Pollard et al., 1991), suggesting that +/op fetus or +/op seminal fluid CSF-1 or CSF-1-induced factor can compensate for the absence of maternal CSF-1. The concentration of CSF-1 in the uterus is regulated by the synergistic action of estradiol-17 beta and progesterone (Pollard et al., 1987). These findings indicate that maternal CSF-1 plays a role, under the influence of sex hormones, in the implantation process.

Epidermal growth factor family

The epidermal growth factor family includes epidermal growth factor (EGF), amphiregulin (AR), heparin-binding epidermal growth factor (HB-EGF) and transforming growth factor alpha (TGFα). A preponderance of evidence indicates that the epidermal growth factor family plays an important role in implantation in a variety of species. The EGF members signal through a set of tyrosine kinases receptors known as the ErbB family that are composed of four distinct receptors: EGFR/ErbB-1, HER2/ErbB-2, HER3/ErbB-3 and HER4/ErbB-4 (Ullrich and Schlessinger, 1990). EGF family members regulate diverse cellular functions, that is, cell proliferation, survival, adhesion, migration and differentiation (Yarden, 2001).

In mice, TGFα, HB-EGF and AR are expressed in the uterus at implantation (Das et al., 1997); in particular, HB-EGF appears to be highly relevant to implantation (Das et al., 1994). It is considered as an early molecular marker of embryo-uterine crosstalk. HB-EGF is induced in the luminal epithelium surrounding the blastocyst 6 to 7 h before attachment begins (Das et al., 1994). In cases of delayed implantation, HB-EGF is not induced at the site of blastocyst attachment but is immediately induced after termination of delayed implantation by estrogen. Thus, the cells that expressed HB-EGF adhere only to active (not dormant) blastocysts (Raab et al., 1996). This pattern indicates that the blastocyst signals the luminal epithelial cells at the site of attachment to express HB-EGF.

In rats, EGF, HB-EGF, TGF-α and AR are expressed in the rat uterus around the time of implantation (Vertes et al., 2000; Byun et al., 2008). EGF and its receptor (EGF-

R) mRNA levels peak at implantation, after which their expressions gradually decrease. Transforming growth factor-α (TGF-α) and heparin-binding EGF (HB-EGF) show modest expression on days 4 and 3 of pregnancy, respectively. Amphiregulin (AR) is strongly expressed around the time of implantation (Byun et al., 2008). The expression levels of all of these growth factor genes are blocked in pregnant rats that have been treated with RU486, suggesting that the activities of the EGF family members in the uteri of pregnant rats are controlled by progesterone (Byun et al., 2008).In rhesus monkeys, the highest expression levels of EGF, TGFα, HB-EGF, AR and EGF receptor (EGF-R) were detected on days 9 and 11 (Yue et al., 2000), localized in the luminal and glandular epithelium; these findings indicate that these growth factors have role(s) in monkey implantation.

HB-EGF is expressed in the human endometrium during the secretory phase of the menstrual cycle, with highest expression occurring immediately prior to the window of implantation. HB-EGF is thought to play a role in both attachment and penetration during implantation in humans (Yoo et al., 1997; Lessey et al., 2002; Stavreus-Evers et al., 2002). In the mid-secretory phase, lower expression of HB-EGF was observed in the endometrium in cases of unexplained infertility compared to normal endometria (Aghajanova, 2008).

In bovine endometrium, the expression of EGF, TGFα and EGF-R were detected on day 13 of pregnancy (Kliem et al., 1998). All of these findings confirm that EGF-family members are important for the implantation process in mammals.

On the other hand, Threadgill et al. (1995) reported that epidermal growth factor receptor (EGFR) plays a crucial role in inner cell mass (ICM) formation. EGFR deficiency in the CF-1 strain results in peri-implantation death due to degeneration of inner cell mass. Interestingly, the consequences of EGFR deficiency in mice depend on genetic background (Threadgill et al., 1995). Although EGFR deficiency in the CF-1 strain leads to peri-implantation death, EGFR deficiency in the 129/Sv strain results in fetal death in mid-gestation due to defects in the placenta, whereas EGFR deficiency in the CD-1 strain does not lead to embryonic death but does result in abnormalities in the skin, brain, kidney, liver and gastrointestinal tract. Threadgill and his co-workers (1995) reported the death of mice with abnormalities up to 3 weeks after birth.

ErbB4 is expressed in the trophectoderm in human blastocysts during peri-implantation (Chobotova et al., 2002). The expression of EGF receptor (s) in the blastocysts at implantation provides strong evidence for the important role of EGF-family members in embryo-maternal interactions during implantation.

Insulin-like growth factor system

The insulin-like growth factor (IGF) system comprises an increasingly complex network of ligands (IGF-I and IGF-II), receptors (IGF-IR and IGF-IIR), and high-affinity binding proteins (IGFBP1 to -6), as well as specific proteases affecting their activity. IGFs are polypeptides that promote growth before and after birth. They affect the metabolism, mitogenesis and differentiation of a variety of cell types by binding to IGF receptors. IGFBPs modulate the bioavailability and effects of the IGFs (Rajaram et al., 1997; Sferruzzi-Perri et al., 2011). IGFs regulate cell growth and differentiation.

IGFs are widely expressed in the female reproductive tract, particularly in the oviduct when the embryo is in transit (Watson et al., 1999). Moreover, many studies have described temporal and spatial expression patterns of IGF-system components at peri-implantation in the uteri of humans (Zhou and Bondy, 1992; Strowitzki et al., 1996), mice (Markoff et al., 1995), rats (Tamura et al., 2004) cows and sheep (Simmons et al., 2009), pigs (Hofig et al., 1991) and rhesus monkeys (Dhara et al., 2001), indicating their crucial role in the implantation process. IGFs have been detected in pre-implantation embryo of different mammalian species, including mice, cattle and water buffalo (Prelle et al., 2001).

Insulin-like growth factor-I (IGF-I) is produced by the reproductive tract to induce early embryonic development at the morula and blastocyst stages through the IGF-IR. Deficiency in IGF-I or its receptors results in blastocyst cell deaths (Spanos et al., 2000). In humans, the IGF-system has a role in early embryonic development and low expression of certain IGF-system members may be one of the causes of unexplained infertility in women (Wu and Zhou, 2004).

Simmons et al. (2009) reported that both IGFBP1 and IGFBP3 are expressed in the ewe endometrium during the period of conceptus elongation; only IGFBP1 is expressed in cow endometrium at conceptus elongation time. IGFBP1 mRNA levels, in the ewe endometrium, increase between days 12 and 16 of pregnancy by 5 to 29 fold compared with the estrous cycle. In cows, IGFBP1 has higher expression in the uterus on day 16 of pregnancy compared to a non-pregnant cow. Thus, IGFBP1 in sheep and cows mostly regulates conceptus by stimulating migration and attachment of the trophectoderm (Simmons et al., 2009). A recent study by Matsumoto et al. (2008) revealed that IGFBP-1 has a biological role in endometrial stromal cell decidualization that is independent of its binding to IGF-I. Collectively, IGF system members are critical for successful implantation.

CONCLUSION

Implantation is a complex process that involves numerous signaling pathways. The signaling molecules that produced by the maternal tissue (such as cytokines, growth factors and ovarian hormones) can be used to specify the uterine receptivity (Wang and Dey, 2006).

On the basis of the studies described here, it can be concluded that cytokines (that is, LIF, IL-1, IL-6, IL-11 and CSF-1) and growth factors (that is, EGF family and IGF system) play important roles in embryo-maternal interactions during the implantation process; however, it is still unclear whether they work dependently or independently. Therefore, efforts should continue so as to elucidate the relationships among these molecules during the implantation process. Achieving this goal will help to better understand the implantation process and address the reason of implantation failure and infertility.

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