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Interaction of the conceptus and endometrium to establish pregnancy in mammals: role of interleukin 1 β

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Abstract

Implantation and the establishment of pregnancy in mammals involves an intricate interplay of hormones, cytokines, growth factors, proteins, lipids, ions and the extracellular matrix between the uterine epithelium, stroma, immune cells and the conceptus trophoctoderm. The divergent nature of implantation in the mouse, human and pig provides not only an interesting contrast in the establishment of pregnancy and early embryonic development but also intriguing similarities with regard to early endometrial-conceptus signaling. An interesting pro-inflammatory cytokine expressed in a number of mammalian species during the period of implantation is interleukin-1 β (IL1B). The presence of IL1B might be involved with immunotolerance at the maternal-placental interface and has been proposed as one of the mediators in placental viviparity. The production of IL1B and other proinflammatory cytokines might play a role in establishing pregnancy through modulation of the nuclear factor kappa-B (NFkB) system in a number of species. A model for the regulation of cellular progesterone receptor expression and NFkB activation for endometrial receptivity and conceptus attachment is continuing to evolve and is discussed in the present review.

Keywords

Endometrium; Conceptus; Pregnancy; Interleukin-1 β ; Nuclear factor kappa-B

Introduction

Implantation and the establishment of pregnancy in mammals is one of the most fascinating phenomena of reproductive biology. The intricate interplay of hormones, cytokines, growth

factors, proteins, lipids, ions and the extracellular matrix (ECM) between the uterine epithelium, stroma, immune cells and the conceptus trophoctoderm that establishes pregnancy is complex and distinct among species (Moffett and Loke 2006; Wang and Dey 2006; Bazer et al. 2010). The period of in vivo development of early cleaving embryos to blastocysts is less variable and can be mimicked outside the oviduct and uterus in vitro under proper culture conditions. Following hatching from the zona pellucida, the blastocyst is exposed to direct contact with the maternal uterine luminal (LE) and glandular (GE) epithelium and a milieu of endometrial secretions. The developing conceptus now initiates one of the most critical periods that is required for the maintenance of the pregnancy and implantation and that precedes placental transformation for nutrient exchange with the maternal system throughout pregnancy.

The opportunity for invasive implantation in rodents, primates and humans (the trophoblast erodes the uterine LE and basal matrix allowing migration into the underlying stroma and ECM of the lamina propria) or the non-invasive placental attachment to the uterine endometrial surface (trophoblast attachment to the uterine LE with no or limited erosion of the uterine surface epithelium) typical of large domestic farm species (cow, sheep, goat, horse and pig) is dependent upon the opening of the uterine “window of receptivity” (Dey et al. 2004; Fazleabas et al. 2004; Fazleabas 2007; Slayden and Keater 2007). A physical barrier to receptivity for uterine adhesion in a number of species, including the human, is the expression of high-molecular-weight mucin O-linked glycoproteins such as MUC1 by the uterine epithelia (Burghardt et al. 1997; Meseguer et al. 1998; Aplin 1999). In general, MUC1 on the surface of the uterine epithelia represents a non-adhesive state for blastocyst attachment in mice (Braga and Gendler 1993), baboons (Hild-Petito et al. 1996; Julian et al. 2005), sheep (Johnson et al. 2001) and pigs (Bowen et al. 1996) and is removed prior to the time of conceptus attachment. Removal of MUC1 permits conceptus attachment to the uterine LE through the expression of integrins and numerous possible adhesive molecules on the conceptus and uterine surface, as described in previous reviews (Burghardt et al. 2002; Carson 2002; Aplin and Kimber 2004; Spencer et al. 2004; Farach-Carson and Carson 2007; Singh and Aplin 2009; van Mourik et al. 2009).

The opening of the window of receptivity is regulated primarily by the pattern of ovarian estrogen and progesterone release and the expression of endometrial steroid receptors established during a normal estrous cycle of domestic farm species or menstrual cycle in humans. Although ovarian estrogen from the developing ovulatory follicle is critical for priming the endometrium, progesterone and the localization of its cellular receptor play an essential role in establishing the proper uterine environment for uterine attachment and early development of the conceptus (Spencer and Bazer 2002). Changes in the uterine LE and GE needed for opening the implantation window are controlled by the rapid and sustained increase in plasma progesterone following ovulation (Spencer and Bazer 2002; Spencer et al. 2004; Geisert et al. 2006). The role of progesterone in opening the window for implantation during early pregnancy is associated with cell-specific changes in the expression of the endometrial progesterone receptor (PGR). Progesterone is the ligand for two receptor isoforms, PGRA and PGRB, which are members of the nuclear receptor superfamily of transcription factors (Mulac-Jericevic and Conneely 2004). Endometrial expression of both receptors is involved with endometrial function but selective knockout

studies in mice have indicated that PGRA is the essential form of the receptor for implantation and development (Fernandez-Valdivia et al. 2005). Epithelial PGR has been demonstrated to be a key regulator of uterine epithelial-stromal crosstalk crucial for uterine development and function in mice (Franco et al. 2011). A clear spatiotemporal association exists between the decline or removal of PGR from the endometrial LE and GE (stroma maintain PGR) and receptivity for conceptus implantation (Spencer et al. 2004; Geisert et al. 2006). The length of endometrial exposure to progesterone regulates the timing of PGR down-regulation in LE and GE of large domestic farm species. Administration of exogenous progesterone immediately following ovulation shortens the estrous cycle of sheep (Ottobre et al. 1980) and cattle (Garrett et al. 1988a), whereas the estrous cycle is lengthened in ewes treated with a PGR antagonist (Morgan et al. 1993). Treatment of pregnant pigs with a PGR antagonist following ovulation delays PGR down-regulation in the uterine LE and GE and alters the timing of uterine gene expression and conceptus survival (Mathew et al. 2011). Administration of progesterone following ovulation has been used to accelerate early conceptus growth in both sheep (Lawson and Cahill 1983; Satterfield et al. 2006) and cattle (Garrett et al. 1988b; Mann et al. 2006; Carter et al. 2008) and advance uterine receptivity for the transfer of asynchronous older embryos in cattle (Geisert et al. 1991). Advancement in uterine development with progesterone is consistent with accelerated down-regulation of epithelial PGR and accelerated release of uterine growth factors for the developing sheep conceptus (Satterfield et al. 2009). The down-regulation of PGR in endometrial epithelia (Fig. 1) is a conserved event among mammals associated with the opening of the implantation window in the mouse (Tan et al. 1999), pig (Geisert et al. 1994; Mathew et al. 2011), sheep (Spencer and Bazer 1995), cattle (Meikle et al. 2001), horse (Hart et al. 2005), baboon (Fazleabas et al. 1999) and human (Lessey et al. 1988, 1996; Critchley and Saunders 2009). A suitable uterine environment for the peri-implantation and activation of implantation is established through the loss of PGR from the epithelial cells but the maintenance of PGR in the stromal cell layer stimulates the expression and secretion of progestagens such as fibroblast growth factor 10 and hepatocyte growth factor (Spencer and Bazer 2002; Cunha et al. 2004), which activate multiple uterine genes involved with growth, morphogenesis, the synthesis of enzymes and enzyme inhibitors, the ECM and cell adhesion prior to trophoblast attachment to the uterine LE (Geisert et al. 2006; van Mourik et al. 2009; Bazer et al. 2009, 2010). Establishment of a receptive endometrium to conceptus attachment is thus regulated through progesterone induction of epithelial PGR loss allowing finely synchronized alterations in the ECM of the LE (exposing attachment factors) and balanced secretion of numerous cytokines, prostaglandins, growth factors, enzymes and their inhibitors (Spencer et al. 2004; Wang and Dey 2006; Bazer et al. 2010).

Although the rodent, human, pig and other domestic farm species provide contrasting models of implantation (invasive vs noninvasive) and placentation (hemochorial vs epitheliochorial), similarities exist in the uterine responses to estrogen (E_2) required for the establishment of pregnancy in the mouse and pig. Rodents have an invasive type of implantation and thus, have served as valuable models regarding uterine-conceptus interactions necessary for implantation in the human; however, distinct species differences do exist. Following initial priming with E_2 , endometrial receptivity for implantation of the human blastocyst requires only continuous progesterone stimulation rather than ovarian E_2

to induce uterine responsiveness as occurs in rodents (Simon et al. 2003; Wang and Dey 2006). As in humans, placental attachment to the uterine surface in the pig is regulated by progesterone. Although pig conceptuses are highly invasive when placed outside the luminal uterine environment (Samuel and Perry 1972), the pig has a diffuse central-type implantation leading to an epitheliochorial type of placentation because of endometrial secretion of multiple protease inhibitors that block invasion through the LE (Fazleabas et al. 1983; Geisert and Yelich 1997). Attachment of the trophoblast to the LE is preceded by conceptus secretion of E₂ to signal the establishment of the pregnancy (Geisert et al. 2006). The divergent nature of implantation in the mouse, human and pig provides not only an interesting contrast in the establishment of pregnancy and early embryonic development but also intriguing similarities with early endometrial-conceptus signaling; this will be the focus for the remainder of the review.

Conceptus signaling and development

Early development of porcine conceptuses is unique compared with that of other large domestic farm species (Bazer et al. 2009, 2010). Porcine conceptuses undergo rapid trophoblast differentiation and expansion between days 11 to 12 of gestation (Geisert et al. 1982a). Conceptuses develop from a 1- to 2-mm sphere into a 9- to 10-mm ovoid shape between days 10 to 12 and then a rapid transition occurs to tubular and filamentous forms by elongation at 30–40 mm/h to >100 mm in length in less than 1–2 h (Geisert et al. 2006). The elongating conceptuses produce E₂ that stimulates secretions from the uterine LE and GE; this is closely linked to the initiation of trophoblast attachment to the uterine LE (Burghardt et al. 1997; White et al. 2005; Bazer et al. 2010). Conceptus E₂ secretion acts through epithelial estrogen receptor 1 (ESR1) and directly stimulates uterine gene expression, release of uterine secretions (Geisert et al. 1993) and changes in the LE and GE needed for trophoblast attachment such as alteration in integrin expression (Burghardt et al. 2002) and endometrial GE secretion of osteopontin (Garlow et al. 2002; White et al. 2005; Johnson et al. 2003, 2009). Estrogen release might also have an autocrine effect on conceptus development, as ESR2 is expressed in early pre- and post-elongated day 12 conceptuses and then decreases significantly after rapid trophoblast elongation (Ying et al. 2000; Kowalski et al. 2002). Initial trophoblast elongation is followed by a continuation of placental growth until the conceptus reaches over a meter in length by day 16 (Perry and Rowlands 1962).

Porcine conceptus elongation is rapidly followed by attachment to the endometrial LE from days 13 to 18 of pregnancy (Burghardt et al. 1997). Conceptus E₂ release has been proposed as the pregnancy recognition signal that maintains the function of the corpora lutea (CL) by preventing development of the endometrial luteolytic mechanism (Bazer et al. 1984). Expression of ESR1 protein peaks in the endometrial LE and GE on day 12 of pregnancy but remains in the epithelia from days 13 to 18 of pregnancy, although at lower abundance (Geisert et al. 1993; Sukjumlong et al. 2003). In the pig, the acute (days 11 to 12) and chronic (days 15 to 20) synthesis and release of E₂ by the developing conceptuses provide the signal to maintain the CL throughout gestation (Geisert et al. 1987). The two phases of conceptus E₂ secretion alter the movement of endometrial prostaglandin F_{2α} (PGF_{2α}) release into the uterine lumen rather than toward the uterine vasculature as occurs during the estrous cycle (Bazer et al. 1984). During early pregnancy, a large accumulation of both

PGF_{2α} and prostaglandin E (PGE) occurs in the uterine lumen (Geisert et al. 1982b). Elongating conceptuses induce an acute release of calcium and continued secretion of uterine proteins into the uterine lumen (Geisert et al. 1982b) and stimulate a local hyperemia surrounding the elongated conceptus (Keys et al. 1986). Early trophoblast expansion regulates and limits the final placental surface area in the epitheliochorial type of placentation in the pig. Uterine and conceptus factors involved with inducing rapid trophoblast elongation are of critical importance. Both embryonic and maternal endometrial syntheses of cytokines and growth factors are essential for providing the synergistic environment for the endocrinological and immunological signals needed for the establishment of pregnancy (Geisert and Yelich 1997; Spencer and Bazer 2004; Bazer et al. 2010), similar to that in other mammalian species (Wang and Dey 2006; Chaouat et al. 2007; Lea and Sandra 2007; Guzeloglu-Kayisli et al. 2009; Banerjee and Fazleabas 2010).

The rapid elongation of pig conceptuses on day 12 involves the expression of many conceptus genes (Ross et al. 2003a; Blomberg and Zuelke 2004; Degrelle et al. 2009; Blomberg et al. 2008; le Blomberg et al. 2010) and the presentation of adhesion factors on the endometrial LE to allow continuous adhesive attachment of the placenta throughout gestation (Bowen et al. 1996; Jaeger et al. 2001; Burghardt et al. 2002; Johnson et al. 2009). A number of endometrial growth factors and cytokines that are possible mediators of attachment and implantation at the conceptus-uterine interface of the mouse and human have been described (Carson et al. 2000; Wang and Dey 2006; Banerjee and Fazleabas 2010). In addition, induction of uterine PG synthesis via prostaglandin-endoperoxide synthase-2 (PTGS2) plays an essential role in the modulation of angiogenesis, cell proliferation and differentiation (Matsumoto et al. 2002). Development and attachment of the pig conceptus involves spatiotemporal expression of a similar cascade of paracrine and autocrine cytokines as described for mouse and human implantation. Uterine and/ or conceptus expression of insulin-like growth factors 1 and 2 (IGF1, IGF2; Green et al. 1995), IGF-binding proteins (Lee et al. 1998; Ashworth et al. 2005), epidermal growth factor (EGF; Vaughan et al. 1992; Kennedy et al. 1994), heparin-binding EGF (Kim et al. 1995), transforming growth factors (Massuto et al. 2010a, 2010b), leukemia inhibitory factor (LIF; Anegon et al. 1994; Modric et al. 2000), fibroblast growth factor-7 (Ka et al. 2000, 2007), interleukin-1β (IL1B; Tuo et al. 1996; Ross et al. 2003b), IL6 (Anegon et al. 1994; Modric et al. 2000), conceptus interferons (IFNτ and IFNγ; Cross and Roberts 1989; Lefevre and Boulay 1993) and PTGS2 (Wilson et al. 2002; Ashworth et al. 2006) have been studied during the critical period of conceptus attachment in the pig.

IL1B role in implantation

An intriguing pro-inflammatory cytokine expressed in a number of mammalian species during the period of implantation is IL1B (Simon et al. 1994a, 1997a; Takacs and Kauma 1996; Kruessel et al. 1997; Schäfer-Somi et al. 2008). The presence of IL1B might play a role in immunotolerance at the maternal-placental interface and has been proposed as one of the mediators in placental viviparity (Paulesu et al. 2008). IL1, previously termed leukocyte endogenous mediator, was first identified as a mediator of the acute-phase inflammatory response. The ability of IL1B to invoke inflammation is dependent on the expression of members of the IL1 system, which belongs to the IL1B/TLR superfamily. The IL1 system

consists in two agonists (IL1A and IL1B), two receptors, i.e., IL1R1 (functional) and IL1R2 (pseudo-receptor), converting enzymes, receptor accessory proteins and multiple isoforms of receptor antagonists (Mantovani et al. 1998). Early studies indicated an essential role of IL1B in implantation as repeated injections of IL1 receptor antagonist into pregnant mice prior to implantation caused implantation failure (Simon et al. 1994b, 1998). However, mice with a deficiency in either IL1B (Zheng et al. 1995) or caspase 1 (CASP1), which is involved with cleaving the pro-IL1B to release the bioactive form from cells (Li et al. 1995), are fertile. In addition, IL1R1 knockout mice (Abbondanzo et al. 1996) have only a slightly reduced litter size and IL1 receptor antagonist knockout mice only have growth retardation after weaning (Horai 2005). Although the essential need of IL1B expression at implantation has not been clearly resolved, its expression and stimulation of other factors involved with implantation have been established.

Habitual abortion in women is associated with a decrease in expression of IL1B and IL6 (von Wolff et al. 2000) suggesting a role for IL1B in the maintenance of pregnancy. Preimplantation human embryos express IL1B (Baraño et al. 1997) and IL1R1 is present in the uterine endometrium (Takacs and Kauma 1996). Human embryos selectively up-regulate $\beta 3$ integrin in endometrial epithelial cells during implantation; this is induced at least partially through IL1B (Simon et al. 1997b). IL1B has been demonstrated to induce endometrial expression of LIF (Sawai et al. 1997; Gonzalez et al. 2004), PTGS2 (Huang et al. 1998; Tamura et al. 2002) and leptin (Dimitriadis et al. 2005), to inhibit stromal cell differentiation (Frank et al. 1995) and to stimulate the release of placental metalloproteinase 9 (Librach et al. 1994), IL6 (Kauma et al. 1994), colony-stimulating factor-1 (Kauma 1993) and chorionic gonadotropin (Yagel et al. 1989; Seki et al. 1997) in the human.

IL1 system during implantation in the primate

In the human and primate, implantation has been characterized as an inflammatory type response. A number of cytokines have been identified at the implantation site and many of these molecules are of embryonic origin (Tabibzadeh and Sun 1992; Tabibzadeh 1994). IL1 was identified as one such paracrine factor that modulates the communication between the maternal endometrium and embryo (Simon et al. 1994a, 1994b; Krussel et al. 2003; Paulesu et al. 2008). IL1 is a key regulator of the inflammatory response and is currently recognized as a cytokine capable of a wide spectrum of effects on numerous cell types (Bankers-Fulbright et al. 1996). The two forms of IL1 agonists (IL1A and IL1B) bind to the same IL1R1 and, therefore, also show similar, if not identical, biological activities.

In human endometrium, both ligands have a ubiquitous presence in epithelium, stroma and endothelial cells (Tabibzadeh 1994). Purified cytotrophoblasts in culture release IL1B in the manner that parallels their invasive potential (Librach et al. 1994). The cytotrophoblasts isolated from first trimester placentae produce approximately four times more IL1B than those isolated from second and third trimester placentae (Librach et al. 1994). Successful implantation after in vitro fertilization has been correlated to high concentrations of both IL1A and IL1B in the culture medium of human embryos (Karagouni et al. 1998). However, the role of IL1A in the human or non-human primate endometrium has not been as clearly established as IL1B (Simon et al. 1994b; Krussel et al. 2003). IL1 is produced by

macrophages, stromal cells and trophoblast cells (Kauma 2000). The expression of IL1R1 throughout the human menstrual cycle follows a triphasic pattern, both in epithelial and in stromal cells. Protein expression is low in the proliferative phase, moderate during the peri-ovulatory and the implantation phases and intense at the end of the cycle (Bigonnesse et al. 2001). In early human implantation sites, immunostaining for IL1R1 has been reported for syncytiotrophoblast and hyperplastic endometrial glands in the maternal decidua, with only weak staining in stromal cells (Hu et al. 1992; Simon et al. 1994a). The expression of the IL1 system in single blastomeres of preimplantation human embryos has also been documented and the selective release of IL1 from human embryo is observed only when embryos are co-cultured with human endometrial epithelial cells (Krussel et al. 1998; De los Santos et al. 1996). The third member of the IL1 ligand family is the natural IL-1 receptor antagonist (IL1RN). IL1RN can block the binding of IL1A and IL1B to its receptor and its binding to the receptor does not result in signal transduction (Bankers-Fulbright et al. 1996). As has been reported, IL1RN prevents embryonic implantation through a direct effect on the transformation of the epithelial plasma membrane at the time of implantation as a result of the down-regulation of integrins α_4 , α_v and β_3 (Simon and Dominguez 2004). Although these data suggest an important role for the IL1 system during implantation (Krussel et al. 2003), as previously discussed, the targeted deletion of IL1R1 and IL1 do not prevent the ability of these animals to reproduce (Abbondanzo et al. 1996; Zheng et al. 1995).

To determine whether IL1 plays a physiological role in vivo, Strakova et al. (2005) investigated the synergistic effect of human chorionic gonadotrophin (hCG) and IL1B on endometrial function by using a baboon model of simulated pregnancy. Infusion both of hCG and of hCG plus IL1B induced marked differences in the distribution of α -smooth muscle actin, proliferation marker Ki67, decidualization marker IGFBP1 and PTGS1. The most marked effect of IL1B was the induction of IGFBP1 protein in stromal cells close to the apical surface, whereas PTGS1 was down-regulated in the glandular epithelium. Protein arrays of uterine flushings showed significant suppression of death receptors, Fas and tumor necrosis factor (TNF) receptor 1, in the groups treated with hCG alone or with hCG plus IL1B, suggesting an inhibition of apoptosis. Subsequent studies have confirmed that hCG inhibits endometrial apoptosis, both in vivo and in vitro (Lovely et al. 2005; Jasinska et al. 2006). Additionally, cytotoxic T lymphocyte antigen-4, matrix metalloproteinase-3 (MMP-3) and IL4 were suppressed in treated animals compared with controls (Strakova et al. 2005). However, no differences were observed in the cytokine profile between baboons treated with hCG alone or with hCG plus IL1B. The study of Strakova et al. (2005) confirmed that, in preparation for pregnancy, functional changes modulated by hCG and IL1B lead to the inhibition of apoptosis and the development of an immunotolerant environment. Furthermore, the results suggest distinct functions associated with IL1B. The presence of IL1B specifically regulates decidualization (as evidenced by IGFBP1 expression) and PTGS1 protein regulation, which represent functional changes associated with the presence of the conceptus during early pregnancy and is in agreement with in vitro studies on both baboon and human stromal fibroblasts (Strakova et al. 2000; Tarantino et al. 1992; Kim et al. 1999a, 1999b).

During implantation, trophoblast migration and invasion is modulated by several factors, including IGFBP1, which is the major secretory product of the primate decidua (Irving and

Lala 1995; Hamilton et al. 1998; Rutanen et al. 1988). Decidualization is a major change that occurs in the endometrium after conception and involves the differentiation of stromal fibroblasts into decidual cells (Kearns and Lala 1983; Kliman 2000; Brosens and Gellersen 2010). The decidualization response is characterized by local edema, influx of immune cells and the transformation of stromal fibroblasts into secretory decidual cells (Gellersen et al. 2007) and defects in this process lead to multiple reproductive pathologies associated with pregnancy (Karpovich et al. 2005; Klemmt et al. 2006; Brosens and Gellersen 2010). However, the exact molecular mechanisms regulating this complex process of stromal cell transformation are still unknown.

Since IL1 has been identified as one modulator of the communication between human maternal endometrium and the embryo (Simon and Dominguez 2004), investigations have indicated the possible involvement of IL1B in decidualization. IL1B induces PTGS2 expression, PGE₂ synthesis and in the presence of steroid hormones, IGFBP1 expression in human and baboon stromal fibroblasts (Strakova et al. 2000). Dissociation of filamentous actin is essential for IGFBP1 expression during decidualization (Kim et al. 1999a, 1999b). Forces of tension generated within the cytoskeleton by actin and myosin determine the organization of the cytoskeleton (Elson 1988). Cytoskeletal changes can also be induced from the outside of the cells by disruption of their ECM, which serves as external scaffold for the cells (Huang and Ingber 1999). Degradation of ECM by MMPs in stromal cells can result in intracellular cytoskeleton changes. IL1B induces mRNA expression and synthesis of proMMP-3 protein in baboon stromal fibroblasts (Strakova et al. 2000) in agreement with results from a previous study of human stromal fibroblasts (Rawdanowicz et al. 1994). Results also indicate that IL1B stimulates the phosphorylation of extracellular-signal-regulated kinase (ERK) and p38 mitogen-activated kinases in a time-dependent manner (Strakova et al. 2000). The results with specific inhibitors suggest that ERK and p38 pathways are involved in the IL1B-induced proMMP-3 synthesis (Strakova et al. 2003). Recent data on the role of IL1B in the decidualization process point to a central role in the remodeling of the cytoskeleton, a process that is critical for the inhibition of apoptosis and the initiation of differentiation (Kim et al. 1999a, 1999b; Jasinska et al. 2006). Destabilization of the cytoskeleton by inhibitors of myosin light chain kinase or myosin II ATPase accelerates the decidualization induced by cAMP but inhibits the decidualization induced by IL1B (Ihnatovych et al. 2007). Changes in actin dynamics, specifically the stabilization of filamentous actin, negatively impact decidualization and prevent the translocation of the actin-binding protein cofilin to the nucleus, an essential response to permit stromal cell differentiation (Ihnatovych et al. 2009). Furthermore, cofilin-mediated actin reorganization in uterine epithelial cells might also be important in preparation for blastocyst implantation, since dysregulation of this reorganization is evident in baboons with endometriosis and might lead to the decreased fertility associated with this disease (Braundmeier and Fazleabas 2009; Morris et al. 2011). Paracrine stimulation by IL1B secreted by decidualized stromal cells enhances trophoblast migration and impaired IL1B leads to fetal death further emphasizing the importance of this cytokine in the establishment of pregnancy (Ashley et al. 2010; Gonzalez et al. 2011).

In summary, the transformation of stromal cells into fully differentiated decidual cells is a complex process. Results of both in vivo and in vitro studies suggest that IL1B contributes to

this process by reorganizing the actin cytoskeleton and indirectly increasing intracellular cAMP concentrations by up-regulating PTGS2 and PGE₂. Inhibition of this process, either by disrupting or stabilizing the cytoskeleton, results in impaired decidualization and induction of apoptosis, both of which lead to impaired fertility.

IL1 system during implantation in the pig

Porcine conceptus IL1B gene expression and release of IL1B protein into the uterine lumen is temporally and spatially associated with rapid trophoblast elongation between days 11 and 12 of pregnancy (Ross et al. 2003a, 2003b). IL1B, an inducer of phospholipase A2 (Kol et al. 2002), might regulate the release of arachidonic acid from the phospholipid bilayer allowing an increase in membrane fluidity necessary for remodeling of the trophoblast during elongation and its conversion to prostaglandins, which are needed for placental attachment during the establishment of pregnancy. Filamentous (day 12) porcine conceptuses express *PTGS2* mRNA (Wilson et al. 2002), which is temporally associated with IL1B expression. Therefore, conceptus IL1B secretion possibly has an autocrine effect by inducing the rapid morphological transformation of the conceptuses on day 12 of pregnancy. Indeed, conceptus *IL1B* mRNA expression is rapidly increased during trophoblast elongation but decreases over 2000-fold immediately following the completion of the elongation process (Ross et al. 2003b). Because pro-IL1B lacks a signal sequence, its activation and secretion require cleavage by an intracellular cysteine protease (Fantuzzi and Dinarello 1999). IL1B-converting enzyme, also known as caspase-1 (CASP1), transforms IL1B to its biologically active form. Conceptus expression of CASP1 occurs coincidentally with IL1B secretion on days 12 and 13 of pregnancy (G.L. Morgan, J.W. Ross and R.D. Geisert, unpublished). Analyses of genome sequences and expressed sequence tags (EST) of the domestic pig (*Sus scrofa domestica*) indicate that two forms of *IL1B* are expressed in the pig. The close proximity of both of the genes on chromosome 3 suggests a gene duplication event resulting in a porcine embryonic form of *IL1B*. The classical *IL1B* is expressed in macrophages and endometrial tissue, whereas the embryonic form of *IL1B* has only been detected in the early elongating porcine conceptus prior to attachment to the uterine LE (C.K. Tuggle, Iowa State University, personal communication). The two predicted protein sequences are 86% identical and are least homologous near the N-terminus, as CASP1 cleaves this portion of the peptide resulting in a functional protein (D.J. Mathew, M.C. Lucy and R.D. Geisert, unpublished). Interestingly, in the case of embryonic IL1B, a proline is inserted just two amino acids away from the predicted CASP1 cleavage site. Porcine embryonic IL1B is secreted only within a brief window associated with conceptus elongation on day 12 of pregnancy. The specific roles of conceptus secretion of IL1B in trophoblast elongation and uterine receptivity have not been determined.

The pig conceptus isoform of IL1B signaling could be critical not only for trophoblast elongation in the pig but also for the initiation of events essential to implantation and placentation for the establishment and maintenance of pregnancy. The pig endometrium expresses IL1R1, accessory protein and antagonist, which are involved in stimulating a pro-inflammatory response (Ross et al. 2003b). Secretion of IL1B and E₂ by pig conceptuses might establish immunological interactions between the endometrium and conceptus during placental attachment and maintenance of the CL function. Endometrial expression of

PTGES1 and PGE₂ are increased by IL1B in vitro (Franczak et al. 2010); this might play a role in blocking luteolysis and provide immunotolerance during pregnancy.

Many of the biological events during conceptus implantation in the pig resemble an acute phase pro-inflammatory response (Geisert et al. 2003). IL1B secreted by the conceptus has been implicated in inducing the inflammatory response during implantation in other species (Martin et al. 2002; Simon et al. 1995). The expression of IL1B increases prior to the initiation of blastocyst implantation in the mouse (Takacs and Kauma 1996; Kruessel et al. 1997) and might be an initiator of conceptus-uterine cross-talk during pregnancy in the human (Lindhard et al. 2002). IL1B induces *PTGS2* gene expression in human endometrial stromal cells (Huang et al. 1998). Activation of *PTGS2* expression in the endometrium and conceptus might be regulated through NFKB activation stimulated by IL1B (Kniss et al. 2001). An increase occurs in endometrial *IL1R1* and *IL1RAP* gene expression on day 12 of pregnancy in the pig (Ross et al. 2003b). Interestingly, *IL1R1* and *IL1R2* are also molecular markers for uterine receptivity in mice (Reese et al. 2001). Conceptus secretion of IL1B induces a pregnancy-specific increase of salivary lipocalin (SAL1) from the GE only during the period of porcine conceptus elongation on day 12 (Seo et al. 2011). Lipocalins belong to a family of extracellular proteins that bind hydrophobic molecules and act as lipid transporters. Uterine secretion of SAL1 possibly serves as a scavenger for toxic products during the period of rapid conceptus elongation, which involves alterations in lipid movement. IL1B-stimulated endometrial GE expression of *Sal1* and E₂-induced stanniocalcin expressed in the LE (Song et al. 2009) are markers of implantation in the pig.

Implantation and the NFKB pathway

The NFKB family of transcription factors regulates the tissue immune function and inflammatory and acute phase responses (Ghosh and Hayden 2008; Hayden and Ghosh 2011). NFKB is regulated through receptor activation by a variety of stimuli such as the bacterial endotoxin lipopolysaccharide, oxidative stress, radiation exposure and specific cytokines, particularly, IL1B and TNFA. NFKB is a cytoplasmic heterodimer composed of various Rel family proteins (Ghosh et al. 1998). The heterodimer of p50 and p65 is the most abundant form of NFKB in eukaryotes. NFKB is sequestered in an inactive form within the cytoplasm through binding by inhibitors of NFKB, known as IκBs (Ali and Mann 2004). IL1B and TNFA receptor activation stimulates the classical pathway for the phosphorylation of two serines in IκB by IκB kinase composed of two catalytic units, IKKα and IKKβ and the regulatory subunit IKKγ. Phosphorylation of IκB results in its release from the NFKB complex and degradation by polyubiquitination in the 26S proteasome (Ghosh et al. 1998). Release of IκB allows the nuclear translocation of NFKB (p65:p50 dimer) for binding to specific κB-sites in the promoter region of target genes to activate transcription. Activation of nuclear κB sites also stimulates IκB to bind NFKB and translocate as an inactive complex back to the cytoplasm (negative feedback loop). Activation of NFKB targets a variety of genes, including those for cell adhesion molecules, cytokines, growth factors, anti-apoptotic factors and immunoreceptors. Genes containing κB sites that are transcriptionally regulated by NFKB include those for many cytokines (TNFα, IL1, IL2, IL6, IL12, LIF and GMCSF), chemokines (IL8 and RANTES) and enzymes such as *PTGS2* (Ali and Mann 2004).

IL1B possibly invokes an endometrial NFkB-stimulated inflammatory response through the induction of *PTGS2* gene expression and prostaglandin secretion, which is a required maternal signaling component for the establishment of a successful pregnancy in a number of species. Establishment of pregnancy in mice has been shown to involve the NFkB system. Not only does the activation of NFkB during the implantation window in mice occur (Nakamura et al. 2004b) but it has also been shown to be required for uterine receptivity through its effects on LIF expression, as LIF administration restores normal implantation during pregnancy when NFkB function is compromised (Nakamura et al. 2004a). Activation of NFkB in the human endometrium has been shown to regulate IL6 and LIF production (Laird et al. 2000) and is associated with implantation (Page et al. 2002; King et al. 2010). Interestingly, peak LIF secretion by the pig uterus occurs on day 12 of the estrous cycle (Anegon et al. 1994), as does the up-regulation of uterine *PTGS2* (Ashworth et al. 2006), an NFkB-regulated gene (Kniss et al. 2001). Endometrial gene expression of p65 and p50 increases between days 5 to 12 of the estrous cycle and pregnancy in the pig suggesting that NFkB is involved in regulating uterine function (Ross et al. 2010). Endometrial NFkB translocation to the nucleus (activation) during pregnancy (Fig. 2) is specifically localized only to uterine LE adjacent to the overlying IL1B-secreting elongating pig conceptuses (Mathew et al. 2011).

Endometrial activation of NFkB provides a unique model to explain the coordinate down-regulation of epithelial PGR and concomitant induction of many cytokines involved with early conceptus development and implantation. The available evidence indicates that an interaction between NFkB and PGR can occur (Kalkhoven et al. 1996) which might explain the timing of endometrial cytokine and *PTGS2* expression being under uterine control. Progesterone exerts an inhibitory effect on pro-inflammatory chemokine and *PTGS2* synthesis by blocking the NFkB pathway (McKay and Cidlowski 1999), whereas loss of endometrial progesterone stimulation is associated with enhanced in vivo chemokine release in women (Jones et al. 1997). Knockout mice lacking PGR have a strong uterine inflammatory response (Lydon et al. 1995). Mutual repression between PGR and NFkB activation has been reported (Kalkhoven et al. 1996; McKay and Cidlowski 1998) and this mechanism might control the timing of cytokine release for the establishment and maintenance of pregnancy. Progesterone has been proposed to inhibit NFkB activation through its receptor by directly interfering with NFkB binding to its consensus DNA response element, inhibiting transcription of ligands and receptors that activate NFkB, or increasing expression of binding proteins that inhibit NFkB activity (Davies et al. 2004). Davies et al. (2004) have indicated that liganded PGR inhibits NFkB activation. Therefore, the presence of PGR in cells might inhibit NFkB activation until either (1) the withdrawal of progesterone as would be the case during the end of the estrous cycle or parturition, or (2) PGR is down-regulated in progesterone-sensitive epithelial cells.

Conceptus expression of IL1B would be consistent with the continued activation of NFkB, whereas the synchronous E₂ secretion by pig conceptuses would provide a negative effect to prevent a full inflammatory reaction that would be detrimental to conceptus survival. In the pig, conceptus secretion of E₂ mirrors the increase and decrease of uterine luminal IL1B between days 12 and 15 of pregnancy (Ross et al. 2003b). The pig endometrial expression of ESR1 during conceptus trophoblast elongation (Geisert et al. 1993; Sukjumlong et al. 2003)

might regulate the uterine inflammatory response during the conceptus release of IL1B. Negative reciprocal cross-talk between the activation of ESR and NFKB has been described in other tissues (Evans et al. 2001; Quaedackers et al. 2007). Thus, conceptus E₂ secretion might play an important role in modulating the inflammatory response induced by the implanting conceptus. However, recent information has indicated that E₂ and IL1B have an additive stimulation on PGE₂ production through the up-regulation of prostaglandin E synthetase in human endometrial cells (King et al. 2010). This is consistent with the increase in PGE synthesis and secretion induced by IL1B in the pig endometrium (Franczak et al. 2010).

In the pig, conceptus IL1B gene expression and secretion declines dramatically by day 15 of pregnancy together with a decrease in E₂ production (Ross et al. 2003b). However, a second sustained phase of estrogen secretion by conceptuses occurs that is necessary to maintain CL function beyond 28 days of gestation (Geisert et al. 1987). The second sustained increase of conceptus estrogen secretion is temporally associated with a pregnancy-specific increase in endometrial *CASP1* mRNA on days 15 and 18 of gestation (Ashworth et al. 2010). The increase in endometrial *CASP1* is not associated with the endometrial release of IL1B for which the uterine luminal content is decreased on days 15 and 18 of pregnancy, suggesting the involvement of an alternate substrate. Pro-IL18, which has structural similarities to pro-IL1B and is involved with the modulation of the immune system through the induction of interferon- γ , is another substrate for *CASP1* (Fantuzzi and Dinarello 1999). Although similar to IL1B, IL18 binds to a unique IL18 receptor and therefore does not function through the NFKB pathway (Lee et al. 2004). IL18 is expressed by the human endometrial epithelia and is suggested to regulate maternal-embryo interplay during the establishment of pregnancy (Yoshino et al. 2001). Porcine endometrial *IL18* mRNA expression increases from day 10 to 15 of the estrous cycle with mRNA expression increasing by 10-fold on day 18 of pregnancy (Ashworth et al. 2010). However, the uterine luminal content of IL18 increases on days 15 and 18 of pregnancy in contrast to no change during the estrous cycle because of the increase in *CASP1* induced by the developing conceptuses. The conceptus factor that stimulates the increase in *CASP1* in the uterine epithelium is unknown. The increased endometrial expression of *CASP1* and the release of IL18 into the uterine lumen might induce the secretion of interferon- γ by conceptuses (Cencic and La Bonnardiere 2002) to modulate the maternal immune system through STAT1 at the interface between trophoctoderm and uterine LE (Joyce et al. 2007). The loss of IL1B stimulation and switch to endometrial IL18 production during placental attachment in the pig would decrease the potential pro-inflammatory stimulation of the conceptuses following trophoblast elongation. Repression of the NFKB activation following attachment might be important for controlling cytokine and immune function following implantation (Hadfield et al. 2011).

Concluding remarks

A model for the regulation of cellular PGR expression and NFKB activation for endometrial receptivity and conceptus attachment is continuing to evolve. Clearly, the loss of the PGR from the uterine LE initiates the period of conceptus implantation and early development following blastocyst hatching from the zona pellucida. The down-regulation of the uterine epithelial PGR during the estrous cycle permits the activation of the NFKB system, possibly

through Toll-like receptors (Ross et al. 2010). The loss of epithelial PGR shifts progesterone stimulation of uterine function to the stroma, which retains PGR (Bazer et al. 2010). Stromal progestagens and other regulatory factors stimulate gene activation of multiple cytokines, growth factors and prostaglandin for conceptus growth. Removal of MUC1 from the LE surface permits adhesion between the conceptus trophoblast and uterine LE surface receptors. The NF κ B system is activated during the period of implantation in the pig (Mathew et al. 2011), mouse (Nakamura et al. 2004b) and human (Page et al. 2002). Production of IL1B can localize the activation of NF κ B to enhance the LE expression of LIF together with leptin in the human to induce implantation (Gonzalez et al. 2004). Moreover, IL1B increases LE expression of integrin β 3 in the human (Simon et al. 1997b); this will aid conceptus attachment to the uterine surface, activation of PTGS2 for implantation and secretion of cytokines, growth factors and proteases for conceptus development and uterine remodeling (van Mourik et al. 2009). Estrogen might serve to control the pro-inflammatory response induced by IL1B activation of NF κ B. Once the initial stimulation of the pro-inflammatory response of IL1B on the endometrium has occurred, maternal activation of IL18 takes place through an increase in endometrial CASP1 activity. Both the pig and mouse have an active IL18 system following conceptus attachment and initiation of implantation (Croy et al. 2003; Ashworth et al. 2010). Endometrial secretion of IL18 regulates the immune response via stimulating interferon- γ through either uterine immune cells (Laird et al. 2006) or, in the case of the pig, conceptus trophoblast (Joyce et al. 2007). The current model obviously cannot mirror the process of implantation in all mammalian species but does present similarities in the interplay between the conceptus-uterine-immune systems for the establishment of pregnancy.

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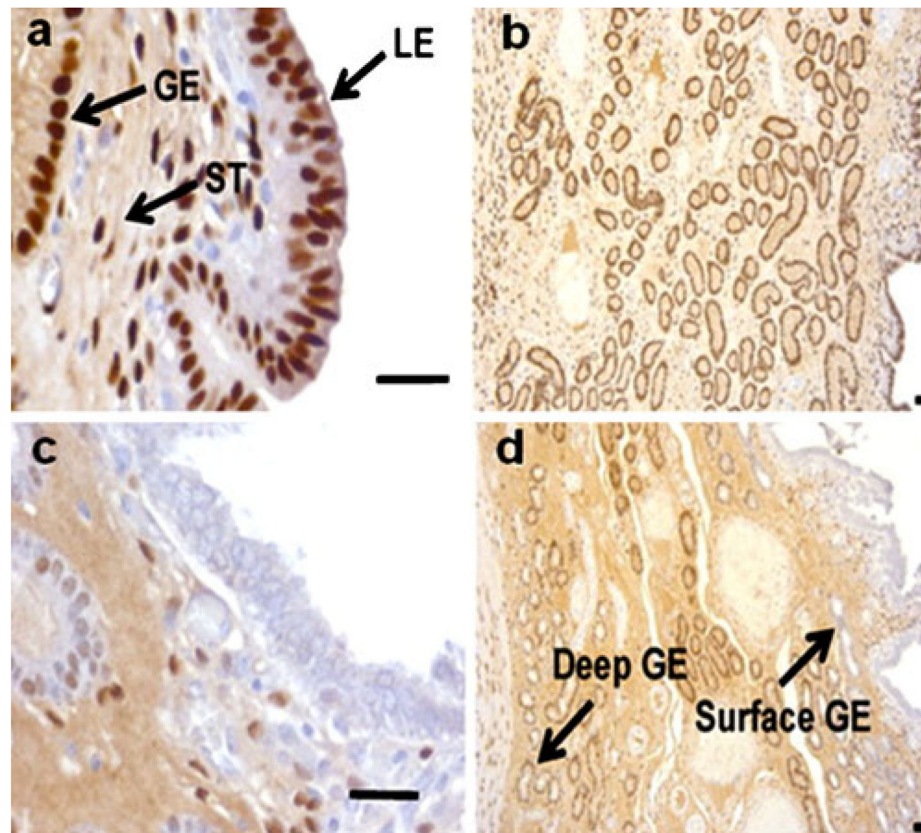


Fig. 1. Immunohistochemistry for progesterone receptor B (PGRB) in the endometrium on days 8 (a, b) and 12 (c, d) of pregnancy in the pig. Note the loss of PGRB in the luminal epithelium (LE) and surface glandular epithelium (GE) on day 12 when the pig conceptuses would initiate attachment to the uterine surface (ST stroma). Bars 50 μm (from Mathew et al. 2011)

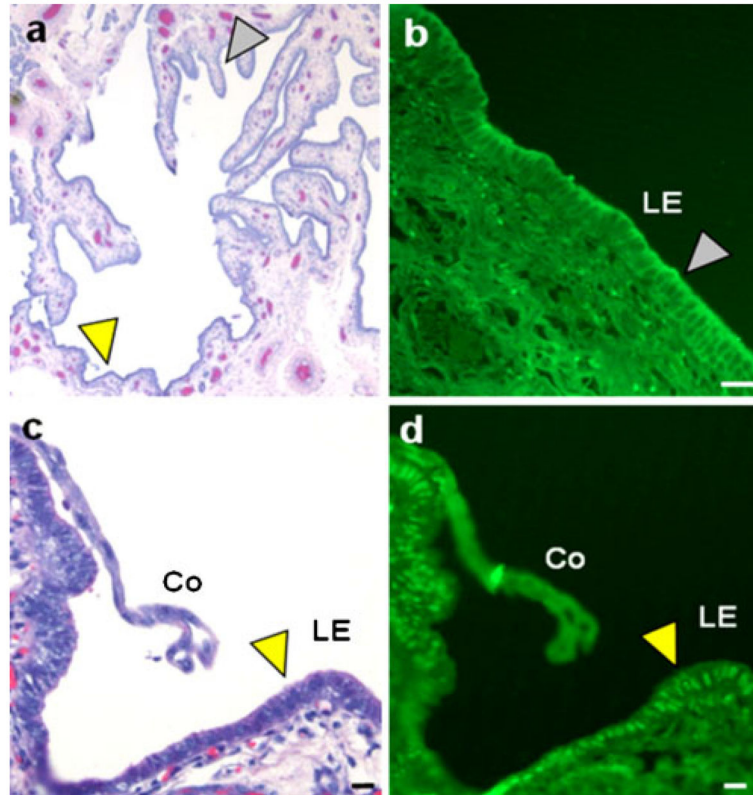


Fig. 2. Image of a hematoxylin-stained cross-section of uterine lumen from a day-12 pregnant pig (**a**) indicating the location of a conceptus attaching to the uterine luminal epithelium (**c, d**). **b** Immunofluorescence for NFKB is localized in the cytoplasm of the luminal epithelium (*LE*) distal to the conceptus (*white arrowhead* in **a, b**). **c** Enlarged image of a hematoxylin-stained conceptus (*Co*) attaching to the uterine luminal epithelium on day 12 of pregnancy (*yellow arrowhead* in **a, c**). **d** Immunofluorescence for NFKB has migrated to the nuclei of the *LE* (*yellow arrowhead*) near the elongating conceptus indicating that NFKB activation is locally induced by the conceptuses. Bars 50 μm (from Mathew et al. 2011)