Chapter 10
Implantation and Establishment of Pregnancy in Human and Nonhuman Primates

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Abstract Implantation and the establishment of pregnancy are critical for the propagation of the species, but yet remain the limiting steps in human and primate reproduction. Successful implantation requires a competent blastocyst and a receptive endometrium during a specific window of time during the menstrual cycle to initiate the bilateral communication required for the establishment of a successful pregnancy. This chapter provides an overview of these processes and discusses the molecular mechanisms associated with implantation of the blastocyst and decidualization of the uterus in primates.

10.1 Introduction

Reproduction is absolutely essential for the propagation of every species from generation to generation. In most mammalian species, a zygote is formed in vivo following fertilization of an egg by a sperm. After the egg is successfully fertilized in the fallopian tube, it travels through the fallopian tube toward the uterus, during which time the fertilized egg divides and develops into a multicellular structure termed a blastocyst. It then adheres itself to the endometrium, which is the initial step in the process of implantation (Wilcox et al. 1999).

Implantation and the establishment of pregnancy are critical for human reproduction. Implantation failure is responsible for significant pregnancy loss in the human (Koot and Macklon 2013; Koot et al. 2012; Norwitz et al. 2001). Understanding the mechanisms associated with the implantation process and other events during early pregnancy will significantly improve the success of assisted reproductive technologies (ART).

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10.2 Implantation

In humans, as well as other nonhuman primates, implantation is one of the most interesting biological events and marks the first biological interaction of the blastocyst with the uterus during the establishment of pregnancy. In humans, one in every six couples is subfertile, and 25 % of those are classified as unexplained infertility. ART offers many subfertile couples effective treatment, but implantation failure remains the rate-limiting step: only around 25 % of transferred blastocysts will successfully implant (Edwards 2006). Both a competent blastocyst and a receptive endometrium are key components required for successful implantation of the blastocyst (Cha et al. 2012).

10.2.1 Window of Implantation

Driven by estrogen and progesterone, the two primary steroid hormones produced by the ovaries, the human endometrium undergoes cyclic changes in morphology and function during the menstrual cycle (Cha et al. 2012). However, during the menstrual cycle, the uterus is only receptive to the blastocyst for implantation for a short window of time. In humans, implantation occurs during the mid-secretory phase, between cycle days (CD) 20 and 24, or 6–10 days after ovulation (Blesa et al. 2014; Donaghay and Lessey 2007; Psychoyos 1973), which is a temporally framed period called the window of implantation (WOI). During the WOI, the endometrium which has been primed by estrogen and progesterone is characterized by changes that are collectively termed endometrial receptivity (Lessey 2011). During the past decades, intensive morphological, histological, and molecular studies have defined the "signature" of the WOI in many species (Cheong et al. 2013; Diaz-Gimeno et al. 2014; Lessey 2011).

10.2.1.1 Morphological and Histological Characteristics

Histological dating of the endometrium has been performed for over 60 years following the Noyes criteria (Noyes et al. 1950). Using these established criteria, histological features of the receptive endometrium include the glands becoming more irregular with a papillary or sawtooth appearance, movement of vacuoles to a supranuclear position of epithelial cells with the possibility of the contents being visible within the uterine lumen, the uterine stroma becoming looser and more edematous, and decidualization of the uterine stroma (Diaz-Gimeno et al. 2013).

Pinopods or uterodomes are the hairlike microvilli of epithelial cells which transiently fuse to form a single flowerlike membrane projection which appears only on the luminal surface of endometrial epithelial cells during the WOI (Nikas 1999; Nikas and Aghajanova 2002). Pinopods found in human endometria are

proposed as a marker of uterine receptivity to implantation (Gordon 1975; Psychoyos 1986). Pinopods can be separated into developing pinopods, fully developed pinopods, and regressing pinopods according to their morphology (Nikas and Aghajanova 2002). Pinopods have also been observed in uteri of baboons (Nikas 1999). The association of pinopods with endometrial receptivity has been correlated with implantation outcomes in a clinical study: all patients with abundant pinopods (>50% of endometrial surface) became pregnant, while pregnancy rates were lower than 50 % in the patients with moderate numbers of pinopods group (20–50 %), and none of the patients with few pinopods (<20 %) were pregnant (Nikas and Aghajanova 2002). Other evidence that supports a correlation between numbers of pinopods and uterine receptivity to implantation is the expression of potential molecular markers of receptivity on the pinopods (Aplin et al. 1996; Nardo et al. 2003).

Epithelial plaques are an early endometrial response in primates to implantation of the blastocyst and the initiation of pregnancy. The epithelial plaque reaction is a morphological transformation of epithelia lining the uterine lumen and necks of the uterine glands characterized by the hypertrophy, hyperplasia, and rounded acinar multicellular pad (Enders 1991). The presence of epithelial plaques is common among primates, and it has been described in several Old and New World Monkeys such as rhesus monkeys (Enders 1991; Ramsey et al. 1976), baboons (Enders et al. 1997; Fazleabas et al. 1999b), green monkeys (Owiti et al. 1986), cynomolgus monkeys (Enders et al. 1996), and dusky leaf monkeys (Burton 1980), whereas this type of structural change has not been reported for humans and great apes. The epithelial plaque reaction of the endometrium has been observed as early as 1 day after implantation in primary implantation sites of rhesus monkeys and baboons (Enders et al. 1983; Tarara et al. 1987). The epithelial plaque reaction induced by chorionic gonadotropin affects the entire luminal surface of the endometrium in baboons compared to a reaction restricted to the site of implantation in pregnant baboons (Fazleabas et al. 1999a). Additionally, there are few reports of spontaneous epithelial plaque reactions in the secretory phase of the menstrual cycle in nonpregnant primates (Kaspareit et al. 2004). The absence of epithelial plaques is associated with infertility in the bonnet monkey (Rosario et al. 2005)

10.2.1.2 Molecular Characteristics

Steroid hormone nuclear receptors in humans and other primates, both estrogen (ESR1) and progesterone receptors (PGR), decline in uterine epithelial cells at the time of implantation while persisting in the stromal compartment of the uterus (Brenner et al. 1990). The mechanism responsible for this downregulation of PGR is progesterone dependent in the macaque (Dorofeyeva 1975).

Mucin 1 (MUC1) is a highly glycosylated polymorphic mucin-like protein. In the human endometrium, MUC1 is produced and secreted by the epithelium as a large and extended transmembrane glycoprotein, which continues to be expressed

in the luteal phase and peri-implantation period of pregnancy in a progesterone-dependent manner (Hey et al. 1994). In baboons, however, MUC1 displayed strong surface expression on days 5–8 postovulation or following treatment with estrogen and progesterone, and its expression decreases in the late secretory phase (Hild-Petito et al. 1996).

Integrins are transmembrane glycoproteins with alpha and beta subunits which mediate cell-to-cell and cell-to-extracellular matrix (ECM) adhesion as heterodimers. Three integrins were discovered that have unique expression patterns which correlate with the WOI in women: α1β1, α4β1, and αvβ3 (Lessey 2002). The localization of αvβ3 on the pinopods on the apical surface of the luminal epithelium at the time of uterine receptivity suggests a role for this integrin in initializing implantation (Aplin et al. 1996; Lessey 2002).

Osteopontin (OPN, also known as secreted phosphoprotein 1, SPP1) is a glycoprotein produced by endometrial epithelia and secreted into the uterine lumen at the time of implantation where it binds to the αvβ3 integrin present on the surface of uterine luminal epithelia (Apparao et al. 2001). OPN is also the only common differentially expressed gene from five microarray studies that identified the genomic signature of endometrial receptivity to implantation of the blastocyst (Mirkin et al. 2005).

Heparin-binding epidermal growth factor-like growth factor (HB-EGF) is expressed in a cycle-dependent manner by luminal epithelial cells of the human endometrium in response to both estrogen and progesterone (Lessey et al. 2002). HB-EGF is expressed by the uterine luminal epithelium when fully developed pinopods are localized to the surface of pinopods during the menstrual cycle which suggests its role in the ability of the endometrium to interact with the blastocyst during implantation (Stavreus-Evers et al. 2002).

Transcriptomics signature Since the beginning of the twenty-first century, a number of studies have been performed to identify the global transcriptomic signature of the endometrium during the WOI of natural menstrual cycles (Borthwick et al. 2003; Carson et al. 2002; Kao et al. 2002; Mirkin et al. 2005; Riesewijk et al. 2003) and controlled ovarian stimulated menstrual cycles (Horcajadas et al. 2005; Mirkin et al. 2004). The results offer an opportunity to develop a database of endometrial genes expressed uniquely during the WOI, even though there are significant variations among the studies due to differences in experimental design, sample collection, data analyses, and statistical methods (Horcajadas et al. 2007). Based on the transcriptomic signature elucidated from these studies, a customized endometrial receptivity array (ERA) that contains 238 endometrial receptivity-related genes was created as a genome-based diagnostic tool for assessing human endometrial receptivity to implantation (Diaz-Gimeno et al. 2011). This ERA is superior in accuracy and reproducibility to the traditional histological dating method as a diagnostic tool for endometrial receptivity (Diaz-Gimeno et al. 2013) and offers a chance for clinicians to personalize the time of transfer of a blastocyst(s) during ART procedures (Diaz-Gimeno et al. 2014).

10.2.2 Process of Implantation

Histological examination of human uteri during early pregnancy revealed distinct patterns of blastocyst adherence to the endometrial surface and underlying stroma: the process of implantation could be classified into three stages: apposition, adhesion, and invasion (Hertig et al. 1956; Lindenberg 1991).

10.2.2.1 Apposition and Attachment

Apposition is the very first connection between the blastocyst and the endometrium, during which the human blastocyst finds a location at which to implant, guided by the maternal endometrium. At this stage the blastocyst is able to be dislodged from the uterine surface by flushing the uterine lumen without damage to the blastocyst (Bischof and Campana 1996; Sharma and Kumar 2012). The attachment phase is much stronger and initiates a physical connection between the blastocyst and the endometrium. During attachment, direct contact occurs between the endometrial epithelium and the trophoblast, and the blastocyst cannot be dislodged (Bischof and Campana 1996; Sharma and Kumar 2012; Valles and Dominguez 2006).

The apposition and attachment of the trophoblast to the endometrial epithelium is unique in that it occurs via respective apical cell membranes of the endometrium (Lindenberg 1991). On the blastocyst, the inner cell mass (ICM) usually faces the endometrium. Nevertheless, the area of the blastocyst at which apposition occurs is not dependent on the orientation of the ICM. Instead, the ICM migrates along the inside face of the trophoblast to align itself to the side of apposition. In short, the entire surface of the blastocyst has the potential to form the apposition and attachment site to the endometrium (Sharma and Kumar 2012; Vinatier and Monnier 1990).

There is significant communication between the blastocyst and the endometrium during apposition and attachment phases of implantation which is mediated by receptor-ligand interactions. For example, L-selectin is a protein expressed on the surface of trophoblast cells, and an in vitro model of implantation provided evidence to support the hypothesis that L-selectin mediates apposition of the blastocyst to the uterine epithelium by interacting with its carbohydrate ligands (Genbacev et al. 2003). MUC1 was later identified as a major scaffold for L-selectin to bind to the surface of the endometrium (Carson et al. 2006). Another example of receptor-ligand pairing that mediates blastocyst-endometrial communication is integrin αvβ3 and its ligand OPN which are both spatially and temporally expressed on the surface of endometrial epithelium when attachment occurs (Apparao et al. 2001; Lessey 2002). The integrin heterodimer αvβ3 is also present on the surface of human trophoblast cells; therefore, it is likely that integrin αvβ3 and its ligand OPN participate in trophoblast endometrial recognition during attachment (Reddy and Mangale 2003).

10.2.2.2 Invasion

Invasion of the uterine endometrium by the blastocyst is a process during which trophoblast cells penetrate the endometrial epithelium and invade into the endometrial stroma to reach maternal blood vessels. In humans and nonhuman primates, as attachment is established, trophoblast cells penetrate the endometrial epithelium and reach the matrix layer under the epithelial cells, known as the basement membrane (BM), via intercellular gaps between neighboring endometrial epithelial cells without destroying them (Carson et al. 2000). This is defined as interstitial implantation (Bischof and Campana 1996).

The formation of invadopodia, the thin folds of trophoblast cells between the adjacent endometrial epithelial cells, leads to degradation of the basement membrane and extracellular matrix (ECM), allowing trophoblast cells to reach the endometrial stromal compartment (Giudice 1999). The activated gelatinases (metalloproteinases, MMPs) play a primary role in degrading matrices during this process, and different types of integrins guide the invading trophoblast through different layers of cells and matrices within the endometrium (Bischof and Campana 1996).

The process of invasion in humans and nonhuman primates is followed by syncytialization, during which the protrusions of trophoblast cells that migrate into the endometrium continue to proliferate, differentiate, and fuse to become a new type of cell: syncytiotrophoblasts (STB). The rest of the trophoblast cells, surrounding the inner cell mass, are referred to as cytotrophoblasts (CTB). STB cells invade the endometrium to guide the entire blastocyst as it invades into the endometrium. In humans, the blastocyst is completely embedded within the endometrial stroma at 8 days after ovulation and the entry site is covered by fibrin, over which the endometrial epithelial cells grow and embed the blastocyst in the endometrium (Bischof and Campana 1996). In nonhuman primates such as gibbons, gorillas, and chimpanzees, implantation is also invasive, like humans, whereas in baboons and macaques, implantation is superficial (Carter and Pijnenborg 2011; Houston 1969).

In STB, fluid-filled spaces, known as lacunae, separated by trabeculae appear, transforming the STB into a spongelike material (Bischof and Campana 1996). Eventually, the STBs come into contact with maternal blood vessels, and maternal blood is trapped within the lacunae, forming a basic oxygen and nutrition transfer unit for the developing conceptus (embryo/fetus and placenta). The CTBs grow into the trabeculae of STB to form the primary chorionic villi which are considered to represent the initiation of placentation (Dockery et al. 2000).

10.3 Decidualization

10.3.1 Decidua

The word decidua is from the Latin “de” which means down and “cadere” which means to fall and is so named since the uterine decidua is shed after parturition. The decidua is classified into three different types in the human uterus during pregnancy relative to the developing conceptus: the region of the decidua directly beneath the site of implantation

forms the decidua basalis; the region that overlies the developing conceptus and separates it from the uterine cavity is the decidua capsularis; and the rest of decidua is the decidua vera or decidua parietalis (Pritchard et al. 1985). Both the decidua basalis and the decidua capsularis can be invaded by trophoblast cells and chorionic villi of the conceptus, but only the decidua basalis supports the formation of the discoid placenta in middle and late pregnancy while the rest of the tissue undergoes degeneration later in pregnancy (Pritchard et al. 1985). The decidua in great apes resembles that of humans, whereas Old World monkeys such as baboons and macaques do not have the decidua capsularis due to their superficial implantation (Carter and Pijnenborg 2011).

10.3.2 Functions of Decidua

The main cell type of the decidua is decidualized endometrial stromal cells, which can provide nutritional support for the implanting blastocyst. Apart from the decidual stromal cell, other cell types within the decidual tissue include hematopoietic cells, macrophages, an abundance of uterine natural killer (uNK) cells, and monocytes (Dunn et al. 2003). Associated with these cells are uterine glands and small blood vessels, including spiral arteries, which support the maternal blood supply to the growing conceptus. Functionally the decidua plays a central role in the establishment and maintenance of pregnancy.

10.3.2.1 Controlled Trophoblast Invasion

Implantation and placentation in the human involves deep invasion of trophoblast cells into the maternal uterine architecture. The decidua is the compartment of the uterus with which trophoblast cells interact with during invasion. The decidua forms a dense cellular matrix that, on the one hand, generates a local microenvironment to promote trophoblast attachment and invasion and, on the other hand, limits the extent of aggressive invasion of trophoblast cells (Gellersen et al. 2007; Gellersen and Brosens 2014).

The extracellular matrix formed by decidual cells is the target of trophoblast invasion. Recent studies showed that decidual cells actively engage in the process of invasion by encapsulating the blastocyst (Gellersen and Brosens 2014). Trophoblast invasion requires proteolytic degradation and remodeling of the decidual extracellular matrix. Matrix metalloproteinases (MMPs) secreted by trophoblast cells are able to degrade the extracellular matrix of the decidua (Librach et al. 1991; Shimonovitz et al. 1994). Based on recent studies, decidualized stromal cells also produce MMPs, and the capacity of MMP secretion of these cells is comparable to that of trophoblast cells (Anacker et al. 2011; Weimar et al. 2013). In in vitro culture models, decidualized human endometrial stromal cells (HESCs) surrounding the blastocyst migrate away to accommodate the outgrowth of the trophoblast (Grewal et al. 2010; Grewal et al. 2008). Furthermore, elastin microfibril interfacer 1, a connective tissue glycoprotein produced by the decidua, can attract migrating extravillous trophoblast cells (Spessotto et al. 2006).

Alternatively, decidual cells and their microenvironment play a role to limit over-invasion of the trophoblast to protect the endometrium from invasive damage. Conditioned medium from human decidual cells inhibits growth of cultured BeWo choriocarcinoma cells as well as invasion of trophoblast cells (Graham and Lala 1991; Lewis et al. 1993). The actions of MMPs are inhibited by tissue inhibitors of metalloproteinase (TIMPs). In humans, TIMPs abolish trophoblast invasion (Librach et al. 1991). *TIMP-3* mRNA expression is upregulated in decidualized endometrial stromal cells by progesterone treatment both in vivo and in vitro (Higuchi et al. 1995), whereas endometrial *TIMP-1* and *TIMP-2* mRNA expression is not dependent on the stage of the menstrual cycle. Additionally, decidual cells secrete transforming growth factor-β (TGF-β) to inhibit the production of MMPs by trophoblast cells (Graham et al. 1992).

10.3.2.2 Protection of the Conceptus from Maternal Immune Rejection

The decidua also plays an integral role in ensuring immune tolerance toward the semi-allogeneic fetal-placental unit and protects the conceptus from the mother's immune system. The physiological mechanisms are mediated by immune cells, particularly uterine natural killer (uNK) cells and regulatory T cells (Tregs), which increase in their numbers during early pregnancy (Fu et al. 2013; Tilburgs et al. 2008; Xiong et al. 2010).

The uterine NK cells are often considered to be cytotoxic, killing virally infected cells and cancer cells (Biron 2010). However, this killing function is lost in the uterus during pregnancy: the uNK cells play a supportive role. Differentiating resident stromal cells, but not trophoblast cells, have been demonstrated to play a critical role in the recruitment of $CD56^{bright}/CD16^{-}$ uNK cells at the maternal-conceptus interface (Rieger et al. 2004; Vassiliadou and Bulmer 1998). uNK cells promote immune tolerance and successful pregnancy by dampening inflammatory Th17 cells via IFN-γ (Fu et al. 2013). The uNK cells can also inhibit the function of T cells by expressing immunomodulatory molecules such as galectin-1 and glycodelin A (Koopman et al. 2003). Galectin-1 is known as an inhibitor of T-cell proliferation and survival, and it promotes apoptosis of activated T cells in the decidua (Kopcow et al. 2008). Glycodelin A inhibits T-cell activation through its ability to interact with the tyrosine phosphatase receptor CD45 on the T-cell surface (Rachmilewitz et al. 2003; SundarRaj et al. 2008). The uNK cell-mediated T-cell regulatory response is lost in patients who experience recurrent spontaneous abortions (RSA) due to extensive local inflammation (Fu et al. 2013).

Tregs are $CD4^{+}CD25^{+}$ T cells, which suppress the activity of other immune cell types and are involved in downregulating immune responses (Campbell and Koch 2011). Tregs produce immunosuppressive cytokines such as IL-10 for exerting immune tolerance (Hara et al. 2001). Tregs are essential for the maintenance of pregnancy. The decrease in these cells and its product IL-10 in the decidua is associated with RSA which involves an inflammatory response and is accompanied by an increase in Th17 cells (Plevyak et al. 2002; Sasaki et al. 2004). Since IL-10 signaling

in Tregs is required for suppression of Th17 cell-mediated inflammation (Chaudhry et al. 2011), it is plausible that Tregs regulate immune tolerance in decidua during early pregnancy by suppressing Th17 cell-mediated inflammation via its product IL-10.

Besides immune cells, decidualized stromal cells are able to induce apoptosis of activated T cells by inducing expression of Fas ligand (FasL) (Kayisli et al. 2003). Thus, the decidua acts as a gatekeeper that controls immune tolerance during pregnancy by blocking T cells that would otherwise attack the developing conceptus.

10.3.3 Decidualization

Decidualization is the differentiation of elongated fibroblast-like mesenchymal cells in the uterine stroma to rounded epithelioid-like cells during the menstrual cycle and pregnancy. This process is one of the most critical and remarkable events that occurs within the endometrium of human and nonhuman primates during pregnancy (Kim et al. 1999a). This morphological change in humans is initiated in the luteal phase and begins with stromal cells surrounding the spiral arteries in the upper two-thirds of the endometrium regardless of the presence or absence of a conceptus (Ramathal et al. 2010). This initial change is referred to as predecidualization.

Once implantation of the blastocyst occurs, the reaction persists and spreads beyond the perivascular regions and becomes the decidua of pregnancy. The decidual reaction continues throughout pregnancy. Not only do the decidual cells increase in size throughout pregnancy, but the percentage of stromal cells in the decidua increases progressively from 9.8 % in early pregnancy to 57.8 % at term (Wewer et al. 1985). In contrast, baboons and macaques do not undergo a predecidual reaction during the menstrual cycle (Enders 1991; Kim et al. 1999a; Ramsey et al. 1976). However, the stromal cells undergo extensive modification following the establishment of pregnancy to form the decidua in baboons and macaques (Enders 1991). This decidualization process is slower in the baboon compared to the human, but earlier than that seen in the macaque (Carter et al. 2015). Decidualization of HESCs as well as baboon uterine stromal cells can be induced in vitro in the presence of hormones and cyclic adenosine monophosphate (cAMP) (Kim et al. 1998). Additionally, human uterine fibroblast (HuF) cells obtained from full-term decidua (maternal side of placenta) are able to differentiate morphologically and biochemically in vitro (Richards et al. 1995). HuF cells are used extensively to study decidual function due to the fact that these cells are readily available in larger numbers than those from endometrial biopsies (Afshar et al. 2012; Richards et al. 1995; Strakova et al. 2000).

Ultrastructural studies of human decidual cells indicate characteristics of epithelioid cells: progressive enlargement, rounding of the nucleus, increased number and complexity of nucleoli, expansion of the rough endoplasmic reticulum and Golgi complex, cytoplasmic accumulation of glycogen and lipid droplets, and dense membrane-bound secretory granules (Wynn 1974). In between these cells, adherens junctions, but

not true desmosomes, are found and the arrangement of gap junctions in these cells may be helpful for trophoblast invasion (Lawn et al. 1971). Extracellular matrix (ECM) proteins produced by decidualized stromal cells include decorin, laminin, type IV collagen, fibronectin, and heparin sulfate proteoglycans (Gellersen et al. 2007).

The characteristics of decidual cells described previously are also characteristics of secretory cells (Kim et al. 1999a). The major secretory products of decidual cells are prolactin (PRL) and insulin-like growth factor binding protein-1 (IGFBP1), which have been used widely as marker genes for decidualization (Gellersen et al. 2007). Other secretory molecules from decidual cells include interleukin-11 (IL-11), epidermal growth factor (EGF), heparin-binding epidermal growth factor (HB-EGF), LEFTY2, activin A, and neuropeptides (Dimitriadis et al. 2005). In the past decades, microarray studies have been used to identify transcriptional changes during differentiation of stromal cells to decidual cells. Based on results of those studies, decidualization has been described as a process of sequential reprogramming of functionally related changes including ECM organization, cell adhesion, cytoskeletal organization, signal transduction, metabolism, stress responses, cell cycle progression, differentiation, and apoptosis (Gellersen et al. 2007).

10.3.4 Molecular Mechanisms

The decidualization process encompasses changes that commence in response to the actions of progesterone. Circulating concentrations of progesterone increase during the secretory phase of the menstrual cycle and remain elevated during pregnancy. Progesterone acts by binding and activating its nuclear receptor, PGR. In the stromal compartment of the human endometrium, PGR-A is the dominant isoform (Chen et al. 2009). It is highly expressed in stromal cells throughout the menstrual cycle and in pregnancy, whereas its expression in epithelial cells decreases after ovulation (Chen et al. 2009). Progesterone regulates the expression of IGFBP1 and decidual PRL via PGR-A (Christian et al. 2002a; Gao et al. 2000). Silencing of downstream progesterone-regulated genes and PGR co-regulators such as *HOXO10*, *KLF9*, and *FKBP52* leads to decrease in expression of markers of decidualization, *PRL* and *IGFBP1*, in HESC cells (Lu et al. 2008; Pabona et al. 2010; Yang et al. 2012). However, decidualization of the superficial layer of the endometrium is only apparent in vivo approximately 10 days after the increase in circulating concentrations of progesterone (de Ziegler et al. 1998). The induction of decidualization of HESC in vitro with progesterone or progesterone and estradiol is relatively slow (Brar et al. 1997). The addition of cAMP rapidly accelerates decidualization of HSEC cells (Brosens et al. 1999).

The concentration of cAMP is higher in endometrial biopsies taken during the secretory phase compared with proliferative phase of the menstrual cycle (Bergamini et al. 1985) and reaches a peak in the late-secretory phase in response of prostaglandin E2 (PGE2) (Tanaka et al. 1993). In pregnancy, human chorionic gonadotropin (hCG) further enhances concentrations of cAMP and decidualization of endometrial stromal cells (Tang and Gurpide 1993). In cultured HESCs, cAMP alone increases the expression of *PRL*, but for only a few days (Brosens et al. 1999).

Further induction and stabilization of PRL, a decidualization marker requires the presence of both cAMP and progesterone (Brosens et al. 1999). The effect of cAMP during in vitro decidualization can be blocked with a PKA inhibitor (Brar et al. 1997). Thus, cooperation of progesterone and cAMP is necessary and sufficient for decidualization. Progesterone, via PGR-A, together with cAMP and genes under regulation of progesterone/cAMP, such as *HOXO10*, *FOXO1*, *BMP2,* and *WNT4,* comprise a critical network for decidualization of endometrial stromal cells (Li et al. 2007, 2013; Lu et al. 2008; Takano et al. 2007; Vasquez et al. 2015).

Based on in vivo studies in the baboon, the process of decidualization can be separated into two distinct phases. The first phase is manifested by the expression of alpha smooth muscle actin (α-SMA) in the differentiation of endometrial stromal cells, which is regulated by chorionic gonadotropin (CG) and progesterone (Christensen et al. 1995). This change in cytoskeletal reorganization is associated with binding of decidual integrins to the ECM, which also undergoes extensive remodeling in response to CG (Fazleabas et al. 1997a). The second phase of decidualization requires the presence of a conceptus and is manifested by the downregulation of expression of α-SMA and the induction of IGFBP1 (Kim et al. 1999a).

Results from high-throughput analysis revealed that genes and proteins involved with the cell cycle, apoptosis, transcription and translation, metabolism, inflammatory response, cell structure remodeling, and paracrine signaling are differently regulated during decidualization of human endometrial cells (Brar et al. 2001; Popovici et al. 2000). MicroRNAs also play a role during decidualization (Estella et al. 2012; Qian et al. 2009). As a result of differentiation, decidual cells acquire unique biochemical and cellular properties that enable them to support implantation of the blastocyst. Therefore, the decidualization of stromal fibroblasts within the human endometrium is a requirement for successful pregnancy.

10.4 Endometrial Response to Blastocyst/Conceptus Signals

In humans, the presence of a blastocyst/conceptus alters the endometrial phenotype compared to the normal menstrual cycle in the mid-secretory phase. This altered phenotype of endometrium during the cycle of conception includes the persistent increase of stromal edema, predecidual formation, and the absence of leukocytic infiltration compared to the normal menstrual cycle (Hertig 1964; Karow et al. 1971; Wentz et al. 1986). These observations suggest the importance of embryonic signals for the development of uterine receptivity to facilitate implantation.

10.4.1 Endometrial Response to Chorionic Gonadotropin (CG)

Chorionic gonadotropin (CG), the major embryonic signal in the primate, is a glycoprotein hormone synthesized and secreted by the trophoblast cells. The CGβ mRNA is detected as early as the 6–8 cell stage of the human embryo, but measureable levels of CG protein are present in culture medium of the late blastocyst

(Srisuparp et al. 2001). In vivo, CG is first detectable in maternal serum during the window of implantation and increases rapidly along with the establishment and progress of early pregnancy (Alfthan and Stenman 1996). In primates, CG acts as a luteinizing hormone (LH) superagonist, extending the lifespan of the corpus luteum to sustain progesterone production to support the pregnancy. In baboons, pregnancy-associated serum CG activity is detectable by day 15 of gestation, peaks at day 27, and returned to baseline values by day 51. Lower levels of CG are associated with spontaneous abortion (Fortman et al. 1993). Besides the ovarian response to CG, the endometrium also responds to embryonic CG, since LH/CG receptor is expressed in the primate endometrium (Reshef et al. 1990; Cameo et al. 2006). In vivo studies in the baboon from our laboratory showed that CG alters the morphology and biochemical activity of the endometrium (Banerjee and Fazleabas 2011; Fazleabas et al. 1999a; Hausermann et al. 1998). Transcriptomics analysis identified genes influenced by CG in the baboon and identified pathways that are involved in embryo attachment, extracellular matrix remodeling, and modulation of the immune response around the implanting blastocyst (Banerjee and Fazleabas 2010; Sherwin et al. 2007).

10.4.1.1 Epithelial Response

Our laboratory has utilized the baboon as a nonhuman primate model to investigate endometrial responses to embryonic CG. CG was infused into the uterine cavity of cycling baboons from day 6 to day 10 postovulation to mimic normal blastocyst transit (Fazleabas et al. 1999a; Jones and Fazleabas 2001). As a result of CG treatment, an epithelial plaque reaction was observed in the luminal epithelium (Fig. 10.1) (Fazleabas et al. 1999a; Jones and Fazleabas 2001). Endometrial glandular structures in response to CG infusion resemble those observed in the pregnant baboon at the same age of gestation. Glandular secretions including glycodelin, a major secretory protein of uterine glands during the secretory phase and pregnancy, also increase in response to CG (Fig. 10.1) (Fazleabas et al. 1997a, b; Hausermann et al. 1998).

Several in vitro studies also support the role of CG in inducing changes in endometrial epithelial cells in the baboon and human. Prostaglandin E2 (PGE2) induces cAMP in endometrial stromal cells to promote their predecidualization response during the secretory phase (Tanaka et al. 1993). According to results from our and other laboratories, treatment of both human and baboon endometrial epithelial cells with CG induces expression of cyclooxigenase-2 (COX2, coded by *PTGS2*) and prostaglandin E synthase (PGES), two enzymes that control the synthesis of PGE2 (Banerjee et al. 2009; Zhou et al. 1999), as well as the production of PGE2 (Srisuparp et al. 2003). The response of endometrial epithelial cells to CG and the downstream PGE2 production occurs through the CG receptor LHCGR, a seven transmembrane G protein-coupled receptor, and the inositol phosphate-dependent mitogen-activated protein kinases (MAPK) pathway (Banerjee et al. 2009). Interestingly, treatment with CG failed to induce production of cAMP in endometrial epithelial cells, but

leads to a release of PGE2 which induces cAMP production in stromal cells (Srisuparp et al. 2003; Tanaka et al. 1993), suggesting the role of epithelial cells mediating the stromal response to embryonic CG. The mechanism by which this response is initiated is summarized in Fig. 10.1a. Furthermore, CG downregulates expression of its receptor in baboon endometrial epithelium, but upregulates LHCGR in stromal cells surrounding spiral arteries (Cameo et al. 2006), indicating a shift in the endometrial response to CG from epithelium to stroma which is driven by CG itself.

10.4.1.2 Stromal Response

In the baboon model, the first detectable molecular response to CG in uterine stromal cells is an increase in the expression of α-SMA in the subepithelial region in early gestation after implantation and after CG infusion, indicating that remodeling of the stromal cell cytoskeleton is necessary for decidualization of endometrial stromal cells (Fazleabas et al. 1999a; Jones and Fazleabas 2001; Strakova et al. 2005). This stimulation has been attributed to binding of ECM proteins to integrin heterodimers on stromal cells (Fazleabas et al. 1997a). The remodeling of the cytoskeleton of stromal cells is essential for their differentiation. In vivo, in the absence of α-SMA, endometrial stromal cells in baboons are not able to predecidualize until induced by CG signaling from the implanting blastocyst or infusion of CG

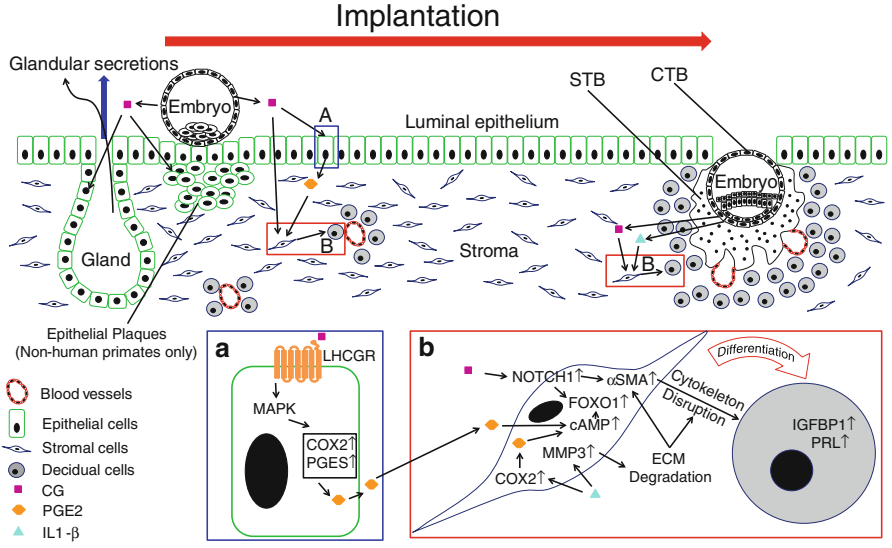

Fig. 10.1 Endometrial responses to the embryonic signal in primates. Epithelial and stromal cells respond to chorionic gonadotropin (*CG*) and interleukin 1 β (*IL-1β*) during the establishment of pregnancy in the primates. Inserts *A* and *B* reflect the changes in epithelial and stromal cell responses which are described in detail in expanded form in Panels (**a**) and (**b**)

into the uterine lumen (Enders 1991; Kim et al. 1999a; Ramsey et al. 1976). However, these stromal cells can be induced to decidualize by cAMP and steroid hormones since they induce expression of α-SMA during in vitro culture (Kim et al. 1998). Furthermore, disruption of actin filaments by cytochalasin D sensitizes the cultured baboon endometrial stromal cells response to inducers of decidualization characterized by expression of IGFBP1 within 24 h after treatment (Kim et al. 1999b) compared to 6 days under standard conditions (Kim et al. 1998). Stromal cells isolated from the endometrium primed by embryonic or infused CG in vivo exhibit the decidualization response in vitro as rapidly as cytochalasin D-sensitized stromal cells (Kim et al. 1999b), indicating the importance of CG to initiate decidualization of endometrial stromal cells. Expression of the decidualization marker IGFBP1 is also regulated by the conceptus and CG (Fazleabas et al. 1997b). In early gestation (day 28), LHCGR is expressed by stromal cells around spiral arteries where decidualization is initiated, indicating that those cells are a direct target of CG to induce initiation of decidualization (Cameo et al. 2006). Responses of endometrial stromal cells to CG during decidualization are summarized in Fig. 10.1b.

Full differentiation of endometrial stromal cells requires a decrease in abundance of α-SMA to allow for an increase in the expression of IGFBP1. In vivo, α-SMA disappears between days 32 and 40 of pregnancy, which is the time when expression of IGFBP1 is detectable (Christensen et al. 1995; Strakova et al. 2005; Tarantino et al. 1992). In vitro, an increase in IGFBP1 is associated with the decrease in expression of α-SMA (Kim et al. 1998, 1999b). This decrease in α-SMA is also associated with a decrease in expression of LHCGR in later stages of gestation (days 40–50) and at the completion of in vitro decidualization (Cameo et al. 2006). Collectively, the embryonic signal CG first induces expression of α-SMA to promote remodeling of the cytoskeleton of stromal cells and differentiation of endometrial stromal cells around spiral arteries via its membrane receptor. Subsequently the decrease in CG signaling appears to be necessary for the completion of decidualization. Our recent studies demonstrated that NOTCH1, a membrane receptor of Notch signaling, may mediate CG-regulated decidualization (Afshar et al. 2012; Su et al. 2015).

10.4.2 NOTCH1 Acts Downstream of Chorionic Gonadotropin (CG)

CG is believed to rescue the endometrium from its apoptosis cascade, which usually occurs at the end of each menstrual cycle, and direct it toward a decidualization response. CG inhibits this apoptotic fate of endometrial cells (Lovely et al. 2005) and, with ovarian hormones, differentiates them into the decidualized phenotype (Jasinska et al. 2006). CG prevents apoptosis by inducing anti-apoptosis genes like BCL-2 (Jasinska et al. 2006).

Notch signaling is a highly conserved pathway across most multicellular organisms. It plays an important role in cell-cell communication and mediates cell fates such as proliferation, differentiation, and apoptosis (Rizzo et al. 2008). Notch signaling is associated with four transmembrane receptors (Notch 1–4) and five transmembrane ligands of the jagged/delta-like families (Afshar et al. 2012). Activation of Notch signaling is generally initiated by interactions between adjacent cells expressing receptor and ligand. This results in a series of receptor-mediated cleavage events and the release of the Notch intracellular domain (NICD) which translocates to the nucleus where it binds and activates the Notch family transcription factor, recombination signal binding protein Jκ (RBP-Jκ). RBP-Jκ then initiates the expression of Notch target genes, such as the "hairy enhancer of split" (Hes) and Hes-related (Hey) transcription factor families (Su et al. 2015).

Notch signaling mediates cellular processes that are essential for successful decidualization. Expression of NOTCH1 and its target α-SMA are both induced by CG in baboon endometrial stromal cells in vivo. Silencing of NOTCH1 in human uterine fibroblast (HuF) cells cultured in vitro leads to the impairment of decidualization, suggesting that NOTCH1-α-SMA mediates CG function in rescuing endometrial stromal cells from apoptosis and differentiating them to decidual cells (Afshar et al. 2012). In vivo CG infusion upregulates expression of both NOTCH1 and α-SMA in human endometrium, which further supports our findings from studies of the baboon model (M.R. Strug and A.T. Fazleabas, unpublished data). Furthermore, activation of Notch signaling is regulated by progesterone which indicates a significant interaction between the CG-Notch pathway and progesterone signaling during decidualization (Afshar et al. 2012). Additional studies have shown that silencing NOTCH1 in HuF cells inhibits decidualization only during the initiation of the differentiation process. To inhibit decidualization of HuF cells in vitro, NOTCH1 must be silenced before the induction of decidualization, whereas silencing NOTCH1 three days after induction of decidualization does not inhibit the expression of decidualization markers (Su et al. 2015). Furthermore, comparative microarray analysis indicated that Forkhead box protein O1 (FOXO1) is a downstream target of NOTCH1 during in vitro decidualization, since FOXO1 and its specific target genes are downregulated when NOTCH1 is silenced during in vitro decidualization (Su et al. 2015). FOXO1 is one of the earliest genes induced during decidualization (Brar et al. 2001; Christian et al. 2002b). A number of in vitro experiments conclusively demonstrated the importance of FOXO1 for the induction of decidualization (Buzzio et al. 2006; Grinius et al. 2006; Labied et al. 2006). Overexpression of FOXO1 in human endometrial stromal cells can induce expression of IGFBP1 and PRL independent of cAMP and hormones induced in vitro decidualization (Buzzio et al. 2006; Christian et al. 2002b; Kim et al. 2005; Takano et al. 2007). A recent study demonstrated that FOXO1 is functionally required for the binding of PGR to genomic targets during decidualization (Vasquez et al. 2015). These results demonstrate that NOTCH1 acts downstream of CG and plays a critical role during the decidualization response of endometrial stromal cells by regulating the expression of its targets, α-SMA and FOXO1 (Fig. 10.1b).

On the other hand, NOTCH1 is downregulated at the completion of decidualization (Afshar et al. 2012) similar to α-SMA and LHCGR expression, which is necessary for the induction of IGFBP1 (Cameo et al. 2006; Kim et al. 1998). Results of our most recent studies indicated that constitutively active Notch signaling by overexpressing the NOTCH1 intracellular domain (N1ICD) prevents HuF cells from undergoing decidualization (R. Su and A.T. Fazleabas, unpublished data). The necessity for the decrease in NOTCH1 expression for the completion of decidualization may be because decidualization depends on cAMP stimulation, sustained PKA activity, and CREB activation (Gellersen and Brosens 2014; Kusama et al. 2014), but N1ICD sequesters nuclear CREB and inhibits cAMP/PKA mediated signaling (Hallaq et al. 2015).

In summary, NOTCH1 initially mediates a survival signal in the uterine endometrium in response to CG from the implanting blastocyst together with progesterone, so that menstrual sloughing is averted. Subsequently, NOTCH1 downregulation may be critical for the complete transition of stromal fibroblasts to decidual cells, which is essential for the establishment of a successful pregnancy.

10.4.3 Endometrial Response to Interleukin-1β

Implantation has been characterized as an inflammatory response, and IL-1β is a key regulator of this response (Fazleabas et al. 2004). Cytotrophoblast cells isolated from first trimester placentae release more IL-1β then those from second and third trimester in culture (Librach et al. 1994), and co-culture of cytotrophoblast cells with HuF cells induces them to decidualize (Jasinska et al. 2004). Numerous studies have provided evidence of the importance of IL-1β as an embryonic signal that affects endometrial responses in primates.

Our laboratory previously reported that IL-1β induces expression of COX2 and PGE2 synthesis in human and baboon endometrial stromal cells (Strakova et al. 2000), which is believed to subsequently increase cAMP in stromal cells and induce decidualization (Fazleabas et al. 2004). Indeed, induced expression of the decidualization marker IGFBP1 by IL-1β in the presence of steroid hormones is blocked by COX-2 inhibitor in human and baboon endometrial stromal cells (Strakova et al. 2000). Induction of IGFBP1 expression by cAMP with steroid hormones is not affected by inhibition of COX-2 which supports the inference that cAMP acts downstream of IL-1β-COX2-PGE2 signaling during decidualization. Interestingly, cAMP prevents decidualization induced by IL-1β which suggests a negative crosstalk between IL-β- and cAMP-induced decidualization responses (Strakova et al. 2000, 2002).

The remodeling of the cytoskeleton of stromal cells is essential to the differentiation of stromal cells (Kim et al. 1998). Cytoskeleton changes can be induced by the disruption of the ECM (Fazleabas et al. 1997a). In baboon endometrial stromal cells, IL-1β induces expression and synthesis of MMP3, which can degrade the ECM (Strakova et al. 2003). This induction of MMP3 is regulated via the MAPK

pathway and is critical for decidualization. Inhibition of MMP3, using doxycycline or specific MMP-3 inhibitor N-isobutyl-N-(4-methoxyphenylsulfonyl) glycyl hydroxamic acid (NNGE), suppresses the induction of decidualization by IL-1β and hormones (relaxin, estradiol-17β, and medroxyprogesterone acetate) (Strakova et al. 2003). The expression of MMP3 and degradation of ECM may contribute to the decrease in expression of the cytoskeleton protein α-SMA that is induced by IL-1β and hormones during decidualization (Strakova et al. 2000). Additionally, expression of IGFBP1 can be induced in stromal cells close to the apical surface by in vivo infusion of IL-1β in the presence of CG which further supports a role for IL-1β from the blastocyst in regulating decidualization of endometrial stromal cells during implantation (Strakova et al. 2005). The postulated roles of IL-1β during decidualization are summarized in Fig. 10.1.

10.5 Summary

Successful implantation and decidualization are necessary for providing required maternal support and protection of the developing conceptus. Human reproduction is highly inefficient compared to other primates. In women the average chance of pregnancy is only 15 % per cycle during their reproductive lifespan (Hjollund et al. 2000). In ART, only around 25 % of transferred embryos will successfully implant (Edwards 2006). Understanding the processes and mechanisms required for implantation and the establishment of pregnancy can help improve outcomes of ART. In support of results of studies on the role of CG in modulating the receptive endometrium as discussed in Sect. 10.4, intrauterine injection of CG before embryo transfer significantly improves implantation and pregnancy rates following ART (Mansour et al. 2011). Thus, an understanding of endometrial response to embryonic cells in primates may provide insight into improving pregnancy rates in women who are infertile.

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