4

Endometrial Receptivity to Embryo Implantation: Molecular Cues from Functional Genomics

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1. Introduction

The endometrium is the mucous lining the uterine cavity comprised of a basal and a functional layer being the latter the one that sheds during menses and regenerates from the basal portion. The main cell populations within the functional stratus are epithelial and stromal cells accompanied by a variable number of leukocytes. Epithelial cells are found covering the luminal surface and tubular glands in basal and functional layers. Endometrial stroma contains reticular connective tissue comprised mainly by uterine fibroblasts that rapidly differentiate into decidualized cells when stimulated by an implanting blastocyst. The stromal compartment contains also abundant lymphocytes, granulocytes and macrophages during luteal phase of the menstrual cycle. These cells along with epithelial and stromal fibroblasts are source and target of paracrine signals of proliferation and differentiation. Both components respond to ovarian steroid hormones and depend on each other for their structure, function and responsiveness to estrogen (E_2) and progesterone (P_4) (Tabibzadeh, 1998, review). During a normal menstrual cycles, human endometrium display unique features for an adult tissue: undergoes cyclic construction and sloughing. The outer layer of the endometrium is loss while the basal layer containing the deep glandular epithelium gets preserved. Later on, stem cells located in this layer will originate the various endometrial cell types in response to the appropriate hormonal stimulus, regenerating the whole endometrium (Padykula, 1991).

The endometrial cycle is driven by the ovarian steroidal hormones and can be divided in three phases: proliferative, secretory and menstrual. Proliferative phase lasts around 10 – 20 days averaging 14 days. During this phase, glands grow and become winding due to the active mitosis of the epithelial cells driven by rising levels of serum E_2 resulting in growing about 10 times the original thickness of the endometrium. Indeed, extensive DNA synthesis in epithelial cells and some in stromal cells is seen during this stage (Padykula, 1991). Once ovulation has taken place, the increase of circulating P_4 triggers the transition to the secretory phase. During this phase, mitotic activity is inhibited and a complex secretory activity is induced beginning with glycogen vesicles polarization in glandular epithelial cells, locating subnuclearly which is further transported by microfilaments to the apical region where glycogen is actively secreted to the lumen of glands. In addition, epithelial

cells initiate a complex secretory activity along with the establishment of an adequate environment for embryo implantation that take place only during a restricted time frame called 'window of implantation' (Psychoyos, 1986). During this period, morphological and molecular changes take place leading to a coordinated expression or repression of key molecules that ultimately enable the blastocyst to attach and invade the endometrial tissue. Such changes occur independently of the presence of a blastocyst; however the endometrium undergoes further biochemical and morphological changes induced by signals from the blastocyst and the following trophoblast invasion. With no embryo implantation, the endometrium undergoes a series of processes that end toward late secretory phase with sloughing and menses. When a successful embryo implantation takes place, luteolysis is prevented and the endometrium is not just maintained but differentiates to decidua and undergoes dramatic vascular changes at the implantation site. Therefore, gene expression in the human endometrium is likely to exhibit neat and distinct changes throughout the various stages of the menstrual cycle in accordance with the oscillations in estrogen and progesterone serum levels and their tissue receptor levels. Since these ovarian steroid hormones drive these processes eliciting an array of cellular and biochemical responses, mostly through genomic pathways (O'malley & Tsai, 1992), current thinking suggests that at the onset of receptivity, expression of some genes in given cell types of this tissue, is temporarily turned on or increased while some others are temporarily turned off or decreased (Tabibzadeh, 1998). Some of these changes are essential for establishing and maintaining pregnancy. Likewise, when implantation has occurred, another program of gene expression takes place in the endometrium, not only maintaining it, but also triggering further differentiation to decidua and facilitating and regulating trophoblast invasion and placenta development.

2. Hormonal regulation of the endometrial cycle

The endometrial cycle depends mainly on the steroidal ovarian hormones, acting though cytoplasmic receptors that on its inactive form are found forming a complex with chaperone proteins (O'malley & Tsai, 1992). Upon binding of the steroidal hormone with its cognate receptor, the chaperone-receptor complex dissociates and the new hormone-receptor complex translocates to the nucleus, binding to specific elements of DNA in target genes. As a result from this binding and the recruitment of co-activator and co-repressor proteins, the transcription rate to mRNA is modified. This process ultimately increases or decreases the mRNA transcribed from target genes, which is transported to the cytoplasm where is translated to peptides or proteins. Steroid hormones can also elicit rapid actions on target cells independently of its genomic regulatory effects. Such actions occur in a time scale from seconds to minutes and have been commonly denoted as non-genomic actions so they can be distinguished from their direct actions over nuclear gene expression (Gellersen et al., 2009).

Cytoplasmic expression of receptors for estrogen (ER) and progesterone (PR) in the endometrium is mainly regulated by the own steroidal hormones. ER expression increases in response to rising levels of E_2 during follicular phase of the menstrual cycle, peaking during proliferative phase (Bergeron et al., 1988; Lessey et al., 1988). After ovulation, ER decrease by P_4 influence. The highest expression of PR occur at the time of ovulation driven by circulating E_2 and are more abundant in glandular epithelium than stroma, disappearing

almost completely toward mid secretory phase by effect of the own P_4 action. However, stromal cells exhibit moderately high PR expression during proliferative and secretory phases (Lessey et al., 1988).

Although E_2 and P_4 have long been believed to be essential for endometrial development, it is now evident that these effects are further mediated and modulated by peptide hormones and peptide growth factors secreted by a variety of cell types within the uterine endometrium. Cooke et al. (Cooke et al., 1997) using mice model ER deficient showed that the proliferative effects of E_2 on endometrial epithelium was mediated by stromal ER through a paracrine mechanism. The paracrine messenger appears to be insulin growth factor (IGF)-1 (Pierro et al., 2001). Several cytokines have bee also described as part of endometrial signaling networks such as interleukin (IL)-1, transforming growth factor (TGF)-β, vascular-endothelial growth factor (VEGF) and colony stimulating factor (CSF)-1 (Salamonsen et al., 2000, review).

The endometrial basal layer which is adjacent to the myometrium, undergoes few changes during the menstrual cycle; whereas the functional layer is very sensitive to E_2 and P_4. Estrogens induce proliferation and growth of the endometrial tissue during the proliferative phase while post-ovulatory rising levels of circulating P_4 from the *corpus luteum* inhibits proliferation and induces the secretory phenotype. This latter hormone has been shown to be critical for endometrial receptivity (Baulieu, 1989) regulating the expression of several cytokines and growth factors, as well as morphological and molecular changes of the endometrial epithelial cells lining the uterine lumen (Giudice, 1999; Lessey, 2003). In addition induces the influx of distinct immune cells and subsequently triggers the differentiation of the fibroblast from the stromal compartment, a process termed decidualization (Irving & Giudice, 1999) characterized by vascular remodeling and extensive secretion of prolactin, insulin-like growth factor binding protein (IGFBP)-1 and tissue factor (Tseng & Mazella, 1999; Christian et al., 2001).

3. Endometrial receptivity and embryo implantation

Experimental evidence that showed embryo and endometrial development synchronicity as a critical factor for successful pregnancy, has underpinned the importance of determinants for uterine receptivity to further improve implantation rates in couples under assisted reproductive technologies (ART) such as *in vitro* fertilization. The concept of endometrial receptivity is referred to the ability of the endometrium to allow embryo implantation, which is the process whereby the blastocyst gets fixed to the uterine epithelium and penetrates though it. During this process, complexand synchronized interactions between the endometrial and the embryonic cells take place and it has been divided in three consecutive stages. The first one is the apposition or the orientation of the blastocyst embryonic pole toward the uterine epithelium. During the second stage of implantation or adhesion phase, the embryonic throphoectodermal cells attach to the endometrial epithelium a firm adhesion is established. Thereafter the invasion phase occurs where blastocyst braches the endometrial epithelium and invades the entire endometrium reaching the inner third of the myometrium and remodeling the uterine vasculature.

Endometrial receptivity is not permanent, if fact the uterus does not allow embryo implantation during most of the endometrial cycle. This particular feature was first

described in the rat and in the mice was described the existence of a 'window of implantation', which is controlled by the ovarian steroidal hormones: a narrow time frame in which the endometrium allows blastocyst implantation (Mclaren, 1956; Psychoyos, 1986). These studies showed that depending on the hormonal stimulus used, the endometrium can be driven to a neutral, receptive or non-receptive (or refractory) state to embryo implantation. Since such window was found to be present in other species (Psychoyos, 1973; Psychoyos & Casimiri, 1980) it was postulated this mechanism could be operating also in humans. In this regard, Hertig *et al.* (Hertig et al., 1956) proposed that human embryo implantation occurs 5-6 days after ovulation by examination of uterine samples in women attempting pregnancy before hysterectomy. They observed free floating embryos within the uterine lumen before days 19-20 of the menstrual cycle, whereas from day 21 blastocysts were found already implanted. These data have been corroborated in oocyte donation cycles in which fertilized oocytes are transferred to the uterus of recipient women during spontaneous and induced cycles with exogenous steroids (Navot et al., 1986; Navot et al., 1991; Bergh & Navot, 1992), leading to the conclusion that the window of implantation in humans lasts for 4-6 days during the secretory phase coinciding with peak P_4 plasmatic levels. It should be noted that unlike the situation in rodents, in humans could not operate the switch from the receptive to the non-receptive state. Insufficient release of human chorionic gonadotrophin to maternal systemic circulation may lead to failure to rescue the *corpus luteum*. As a consequence, serum P_4 will decline leading to menstruation and conceptus loss. Embryo-uterine interactions that allow implantation can only occur when embryo development is synchronized with the endometrial receptivity period since lack of coordination between both events lead to implantation failure (Pope, 1988).

4. Cellular and molecular changes associated to endometrial receptivity

Cowel (Cowell, 1969) found that removing the uterine luminal epithelium in the rat, blastocyst implants regardless of any hormonal control suggesting that endometrial refractoriness lies on the endometrial epithelial cells. Recent data from IVF cycles (Huang et al., 2011) seems to support this fact in humans. In animal experiments and *in vitro* models for human implantation have revealed that the endometrial surface undergoes significant changes in its adhesive properties. In the pre-receptive state, the endometrium displays a structural and functionally polarized epithelium with differentiated basal-lateral and apical domains. During the endometrial receptive state, a reduction of the glycocalyx thickness and electrostatic charge has been seen in the surface of epithelial cells (Murphy & Rogers, 1981; Morris & Potter, 1984). In addition, the long and abundant epithelial microvilli retract, creating multiple flat areas in the surface (Schlafke & Enders, 1975; Murphy, 1993). This process could be related to the destabilization of the actin cytoskeletal network observed in these structures (Luxford & Murphy, 1989; Luxford & Murphy, 1992). On the other hand during the receptivity period it has been reported biosynthesis and expression of a different repertoire of surface proteins in the apical (Aplin, 1997; Lessey, 1998; Kirn-Safran & Carson, 1999) and basal-lateral domains (Rogers & Murphy, 1992; Albers et al., 1995; Murphy, 1995; Nikas, 1999). Considering the above mentioned evidence, the acquisition of adhesive properties by the epithelium may occur by disruption of the polarized apical-basolateral phenotype (Denker, 1983; Denker, 1994). Although it is not well understood yet the relation between the epithelial polarity loss and the initiation of the adhesion stage of implantation, it is speculated that facilitates close apposition between the endometrial epithelium and the blastocyst.

Several molecules contributing to trophoectoderm adhesion to endometrial epithelium have been proposed. During the window of implantation, there is an up-regulation of oligosaccharides ligands for selectin in uterine epithelial cells while human trophoectoderm express L-selectin, establishing a ligand-receptor system since it promotes binding between both cellular types (Genbacev et al., 2003). Other glycoproteins, oligosaccharides chains and their receptors found in the endometrial luminal epithelium have been proposed as mediators of the blastocyst adhesion. Amongst them is heparan sulphate proteoglycan and heparan sulphate binding proteins (Carson et al., 1998; Fukuda & Nozawa, 1999), H type-1 carbohydrate antigen (Fukuda & Nozawa, 1999). In addition the cell surface mucin with antiadhesive properties MUC1 has been involved in endometrial receptivity (Surveyor et al., 1995). MUC1 is expressed at the luminal endometrial surface in the mid-secretory phase (Aplin et al., 1998; Aplin, 1999) and *in vitro* evidence has shown a local cleavage from endometrial epithelial cells at the site of blastocyst attachment (Meseguer et al., 2001). Amongst the most studied adhesion molecules is the integrin family, which act as extracellular matrix elements receptors mediating adhesion events and signal transduction between cells. Some of these glycoproteins display a cycle-dependent endometrial expression (Lessey et al., 1992; Tabibzadeh, 1992; Lessey et al., 1994). At least three integrins seem to be flanking the opening and closure of human window of implantation, which are expressed in glandular epithelium only between days 20-24 of the menstrual cycle (Lessey et al., 1992). These integrins are $\alpha_v\beta_3$, $\alpha_v\beta_5$ y $\alpha_5\beta_1$ and recognize the RGD peptide motif. The best characterized integrin in endometrial receptivity is integrin $\alpha_v\beta_3$ (Lessey & Castelbaum, 2002, review). Intrauterine injection of an antibody against integrin $\alpha_v\beta_3$ before implantation has taken place reduces the number of implantation sites y mice and rabbits (Illera et al., 2000). However the precise role of integrins in the implantation process is not known yet.

The transmembrane protein trophinin mediated the hemophilic adhesion between cells along with the cytoplasmic proteins tastin and bystin forming a complex with cytoskeletal elements (Suzuki et al., 1998). These three proteins have been detected in both trophoblast and decidual cells at the embryo-maternal interphase (Suzuki et al., 1999) suggesting a potential role in the implantation process.

Temporal-spatial expression of Epidermal Growth Factor (EGF) family members and their receptors (ErbBs) in the embryo and endometrium during the peri-implantation period, suggest these growth factors may be mediating the interaction between them (Das et al., 1997). Members of the EGF family expressed in mice uterus at the moment of implantation are the own EGF, the transforming growth factor (TGF)-α, heparin-binding EGF (HB-EGF), amphiregulin (Ar), β-cellulin (BTC), epiregulin (Er) and Herregulin (HRG) (Das et al., 1997). HB-EGF is expressed in humans during the window of implantation (Leach et al., 1999), and also stimulates the development of human embryos generated in IVF cycles (Martin et al., 1998). The relative importance of the other members from the EGF-family in the implantation process has not been determined; however the expression of multiple ligands and receptors of such family may assure an adequate embryo development and further, a successful implantation.

The expression of the leukemia inhibitory factor (LIF) cytokine increases in mice endometrial glands prior to implantation and this regulation is under maternal control (Bhatt et al., 1991). LIF is essential for embryo implantation in mice (Stewart et al., 1992). In human endometrium, LIF is expressed in glandular and luminal epithelium (Cullinan et al.,

1996; Vogiagis et al., 1996). Although its biological functions are not well understood, the intrauterine injection of a monoclonal anti-leukemia inhibitory factor antibody inhibits blastocyst implantation in the rhesus monkey (Sengupta et al., 2006), suggesting a potential role in human embryo implantation.

5. Morphological and molecular assessment of the endometrium

Histomorphological changes of the endometrium throughout the menstrual cycle have been described over half a century ago by Noyes (Noyes et al., 1950) where particular features of the endometrial histology were correlated to specific days of the menstrual cycle allowing the dating of endometrial specimens. Since then, the Noyes criteria remained as the gold standard for endometrial evaluation. However the usefulness of endometrial dating for couples with infertility has been questioned since histological delay in endometrial maturation fails to discriminate between fertile and infertile couples (Coutifaris et al., 2004).In addition, other studies (Murray et al., 2004; Dietrich et al., 2007) have shown that endometrial histological features failed to reliably distinguish specific menstrual cycle days or narrow intervals of days, leading to the conclusion that histological dating has neither the accuracy nor the precision to be useful in clinical management. Another approach used to assess the endometrial status based on its morphological features was the use of scanning electron microscopy. Through the use of this technique, it was revealed the cyclic appearance of bulging structures from the apical pole of luminal epithelial cells during mid-secretory phase termed pinopodes (Nikas et al., 1995) or uterodomes (Murphy, 2000), becoming a candidate for endometrial receptivity marker. Although its involvement in embryo implantation has not been demonstrated, it is speculated that since they extend beyond cilia, they may be the first structure contacting the embryo. The molecular structure of pinopodes remains unknown so an adhesive role has yet to be determined. *In vitro* evidence has shown blastocyst attachment to endometrial epithelial cells displaying pinopode-like structures (Bentin-Ley et al., 1999). However, recent studies have failed to show a reliable pattern for the appearance of these structures in human endometrium (Acosta et al., 2000; Usadi et al., 2003; Quinn & Casper, 2009), rising controversy about its usefulness as an endometrial receptivity marker. In addition, morphological features seldom provides information regarding the molecular mechanisms taking place in the tissue throughout the menstrual cycle, which may allow a better understanding of the physiological status of the endometrium.

Molecular changes associated with the acquisition of the endometrial receptive phenotype in natural spontaneous cycles and pathological and pharmacological models in which endometrial function is compromised rendering it refractory to embryo implantation, have been used in search for molecular markers for endometrial receptivity. A number of candidate molecules have been proposed including members of the integrin family (Lessey et al., 1995; Thomas et al., 2003), glycodelin (Chryssikopoulos et al., 1996), Hb-EGF (Yoo et al., 1997), LIF (Ledee-Bataille et al., 2004) and CSF-1 (Kauma et al., 1991). Although much effort has been put on identifying endometrial receptivity markers to date no single one has been proved to be sensitive and specific enough in predicting pregnancy (Hoozemans et al., 2004; Strowitzki et al., 2006).

6. Wide genomic analysis of human endometrial function

The search for reliable molecular predictors for embryo implantation in the endometrium has been mainly focused on the one-by-one approach. With the development of functional genomics analysis tools more than 10 years ago, was possible to identify endometrial gene expression profiles under different conditions of receptivity or pregnancy, using DNA microarrays technology (Horcajadas et al., 2007). Through this technique it is possible to measure the level of expression in a collection of cells for thousands of genes, allows discovering genes or pathways likely to be involved in a biological process, even when there is no hint regarding their identity (Schena et al., 1995).

The global gene expression assessment has been used to characterize in a broader way the molecular bases of endometrial function in the women, determining the corresponding transcript profile to each endometrial phase during the menstrual cycle (Ponnampalam et al., 2004; Punyadeera et al., 2005; Talbi et al., 2006). In addition, this approach has been used to specifically investigate the particular gene signatures that allow acquisition of endometrial receptivity to embryo implantation during spontaneous cycles (Carson et al., 2002; Kao et al., 2002; Borthwick et al., 2003; Riesewijk et al., 2003; Mirkin et al., 2005). Since acquisition of endometrial receptivity is mainly driven by P_4 (Conneely et al., 2002; Spencer & Bazer, 2002), two strategies based on this feature have been used for gene discovery during spontaneous menstrual cycles: comparing gene expression profiles of the endometrium under peak P_4 circulating levels (days 19-23, window of implantation) and under absent (days 8-11, proliferative phase) (Kao et al., 2002; Borthwick et al., 2003) or low (days 15-17, early secretory phase) (Carson et al., 2002; Riesewijk et al., 2003; Mirkin et al., 2005; Haouzi et al., 2009; Haouzi et al., 2009) serum P_4. Several other strategies have been used to determine the repertoire of genes related to endometrial receptivity using animal, *in vitro*, pharmacological and pathological models which are discussed elsewhere in a comprehensive review (Horcajadas et al., 2007).

We studied the endometrial gene expression signatures from women with implantation failure using the oocyte donation model (Tapia et al., 2008). In an oocyte donation cycle, the endometrium from the embryo recipient woman is prepared with exogenous hormones in order to synchronize conceptus and endometrial development (De Ziegler et al., 1994; Younis et al., 1996), providing a better uterine environment than controlled ovarian hyperstimulation for embryo implantation to take place. In this sense, oocyte donation allows a unique opportunity for investigating endometrial factors involved in human blastocyst nidation (Damario et al., 2001). In our study, three groups of subjects were recruited: women who had previously participated as recipients in oocyte donation cycles and repeatedly exhibited implantation failure (Group A, study group) or had at least one successful cycle (Group B, control group); and spontaneously fertile women (Group C, normal fertility group). All were treated with exogenous E_2 and P_4 to induce an oocyte donation mock cycle as recipients. An endometrial biopsy was taken during the window of implantation (*i.e.* the seventh day of P_4 administration) and RNA from each sample was analyzed by cDNA microarrays to identify differentially expressed genes between groups. We found sixty three transcripts differentially expressed (≥ 2-fold) between Groups A and B, of which 16 were subjected to real time RT-PCR validation. Eleven of these were significantly decreased in Group A with regard to Groups B and C. In addition to those genes whose transcript levels was confirmed by real time RT-PCR, we integrated and cross-

validated a less stringent and larger data set that was constructed with other data sets about endometrial gene expression profiles publicly available obtained by other groups. Using this strategy we could increase the confidence in gene discovery for endometrial receptivity for many more genes than is tractable with classical validation (Kemmeren et al., 2002; Rhodes et al., 2002). For that we constructed a database with the reported transcript level changes from non-receptive to receptive endometrial phenotype at the time the study was made (Carson et al., 2002; Kao et al., 2002; Borthwick et al., 2003; Riesewijk et al., 2003; Mirkin et al., 2005) and 14 coincident genes were identified. Interestingly, five genes out of the 14 coincident genes were also dysregulated in eutopic endometrium from women with endometriosis. These genes are: Complement component 4 binding protein, alpha (C4BPA), Glycodelin (PAEP, glycodelin), RAP1 GTPase activating protein 1 (RAP1GA1), Endothelin receptor type B (EDNRB) and Ankyrin 3, node of Ranvier [ankyrin G] (ANK3). Interestingly, a detailed analysis of the functions associated to the 14 genes whose transcripts were significantly decreased in endometria without manifest abnormalities showed that 4 of them were related to the regulation of the immune function. This suggest that implantation failure in women from group A could be related to molecules from the immune system, whose function in the endometrium is to destroy infectious agents and foreign bodies, display an exaggerated response in presence of an implanting embryo (Damario et al., 2001).

Other strategy we have used is the integration and cross-validation of all available data sets about endometrial gene expression profiles produced by different groups (Tapia et al., 2011)to determine the up- and down-regulated genes that together orchestrate the acquisition of the receptive phenotype of the endometrium for embryo implantation. We considered studies that had used microarrays technology to determine the gene expression profiles that identify different phases of the endometrial cycle in spontaneous menstrual cycles (Ponnampalam et al., 2004; Punyadeera et al., 2005; Talbi et al., 2006). In addition we included those that also had used this technology during the acquisition of endometrial receptivity to embryo implantation (Carson et al., 2002; Kao et al., 2002; Borthwick et al., 2003; Riesewijk et al., 2003; Mirkin et al., 2005). In two studies the proliferative phase was compared with the 'window of implantation' time (Kao et al., 2002; Borthwick et al., 2003) and in another three studies gene expression differences between the early secretory phase (2–4 days after the luteinizing hormone (LH) surge) and the receptive phase (7–9 days after the LH surge) were included (Carson et al., 2002; Riesewijk et al., 2003; Mirkin et al., 2005). The intersection of lists with regulated genes reported in these studies showed a rather small number of coincident transcripts. We identified 40 up-regulated genes in at least four of seven reports and 21 down-regulated genes present in at least three of six studies considered. We denominated this set of coincident genes the consensus endometrial receptivity transcript list (CERTL) (Tapia et al., 2011). The most consistent up-regulated genes were C4BPA, SPP1, APOD, CD55, CFD, CLDN4, DKK1, ID4, IL15 and MAP3K5; whereas OLFM1, CCNB1, CRABP2, EDN3, FGFR1, MSX1 and MSX2 were the most consistently down-regulated in endometrial tissue for the acquisition of receptivity to embryo implantation.

7. Future perspectives in the clinic

One of the main objectives in reproductive medicine especially in the context of IVF has been the search for markers predictive of endometrial receptivity. Even though great efforts

have been made to predict embryo implantation for improving live-births, no successful endometrial evaluation has been clinically validated so far. Moreover, attempts to improve IVF pregnancy rates treating infertile patients with factors thought to be essential for implantation process have turned out to achieve the opposite (Brinsden et al., 2009). Nevertheless gene expression profiling of endometrial biopsies during the window of implantation is one of the most promising strategies for gene discovery related to uterine receptivity. In fact, a genomic tool composed of a customized microarray and a bioinformatic predictor for endometrial dating and detection of endometrial pathologies has been recently described (Diaz-Gimeno et al., 2011). This tool denominated Endometrial Receptivity Array (ERA) assesses the transcriptomic signature defined by 134 genes related to endometrial receptivity, becoming specific for uterine function evaluation. Other study recently published (Tseng et al., 2010), analyzing gene expression profiles of endometrial biopsies and using hierarchical cluster analysis described a 123-gene model for endometrial function with transcripts up-regulated at mid-secretory phase, moderately expressed at late-secretary phase, and down-regulated at late-secretory phase.

The role of the proteins encoded by the transcripts contained in CERTL, ERA and the '123-gene model' in the acquisition of endometrial receptivity and embryo implantation; as well as the prognostic value for each transcript profiling as a marker for endometrial receptivity has yet to be determined. Although is highly possible that a combination of these three approaches may allow defining the actual transcriptomic signature of human endometrial receptivity.

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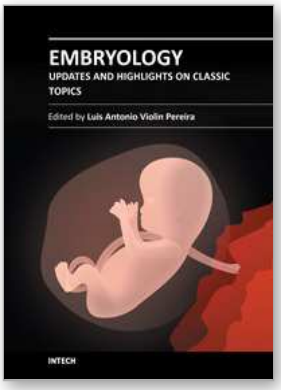

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Embryology is a branch of science concerned with the morphological aspects of organismal development. The genomic and molecular revolution of the second half of the 20th century, together with the classic descriptive aspects of this science have allowed greater integration in our understanding of many developmental events. Through such integration, modern embryology seeks to provide practical knowledge that can be applied to assisted reproduction, stem cell therapy, birth defects, fetal surgery and other fields. This book focuses on human embryology and aims to provide an up-to-date source of information on a variety of selected topics. The book consists of nine chapters organized into three sections, namely: 1) gametes and infertility, 2) implantation, placentation and early development, and 3) perspectives in embryology. The contents of this book should be of interest to biology and medical students, clinical embryologists, laboratory researchers, obstetricians and urologists, developmental biologists, molecular geneticists and anyone who wishes to know more about recent advances in human development.

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