Implantation: Mutual Activity of Sex Steroid Hormones and the Immune System Guarantee the Maternal–Embryo Interaction

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Abstract

Implantation is strictly dependent on the mutual interaction between a receptive endometrium and the blastocyst. Hence, synchronization between blastocyst development and the acquisition of endometrial receptivity is a prerequisite for the success of this process. This review depicts the cellular and molecular events that coordinate these complex activities. Specifically, the involvement of the sex steroid hormones, estrogen and progesterone, as well as components of the immune system, such as cytokines and specific blood cells, is elaborated.

Keywords

- endometrium
- immune cells
- estrogen
- progesterone
- cytokines

Implantation of the embryo in the uterus is essential for successful pregnancy. This multistage event consists of the attachment and adherence of the blastocyst to the endometrium, followed by its invasion through the luminal epithelium into the stroma, where it generates the placenta that in turn, nourishes the developing fetus throughout pregnancy. This intricate crosstalk, between the blastocyst and the receptive endometrium is mediated by different cytokines, and opens the gateway for further embryonic development. The endometrium is receptive during a limited period known as the window of implantation (WOI) that extends, in human, between days 19 and 23 of the menstrual cycle. The synchronization between the preparation of the endometrium and early embryonic development is therefore fundamental for successful implantation. It is the regulation of the ovarian sex steroid hormones, estrogen (E_2) and progesterone (P_4), which allows follicular development, ovulation, and blastocyst formation to synchronize with the development of a receptive endometrium.

Development of a Receptive Endometrium

The preparation of the endometrium is hormone dependent. The pituitary gonadotropins follicle-stimulating hormone and luteinizing hormone stimulate the ovary to secrete the sex steroids E_2 and P_4. Proliferation of the endometrial cells is induced by E_2, which is mainly secreted during the first half of the menstrual cycle, referred to as the proliferative phase. The predominant sex steroid in the second half of the cycle, known as the secretory phase, is P_4, which induces the differentiation of the endometrial cells. This phase of the cycle is characterized by the formation of glands that secrete large amounts of cytokines and growth factors, vascularization, infiltration of the endometrium by a variety of immune cells from the blood, edema of the tissue caused by a localized increase in vascular permeability, and decidualization of the stromal cells.[1] It is important to note that in humans, decidualization (differentiation of the stromal cells) begins spontaneously during the secretory phase, unlike rodents, in which decidualization requires embryo implantation or another local mechanical stimulation.

Regulation of Endometrial Receptivity by E_2 and P_4

The ovarian steroid hormones, E_2 and P_4, are key regulators of endometrial function. Binding of these hormones to their receptors in the uterus drives the proliferation and differentiation of the endometrial tissue, preparing it for the implanting blastocyst. Activation of downstream genes by E_2 and P_4 stimulates a crosstalk between the endometrial stroma and epithelium that is crucial for the development of a receptive

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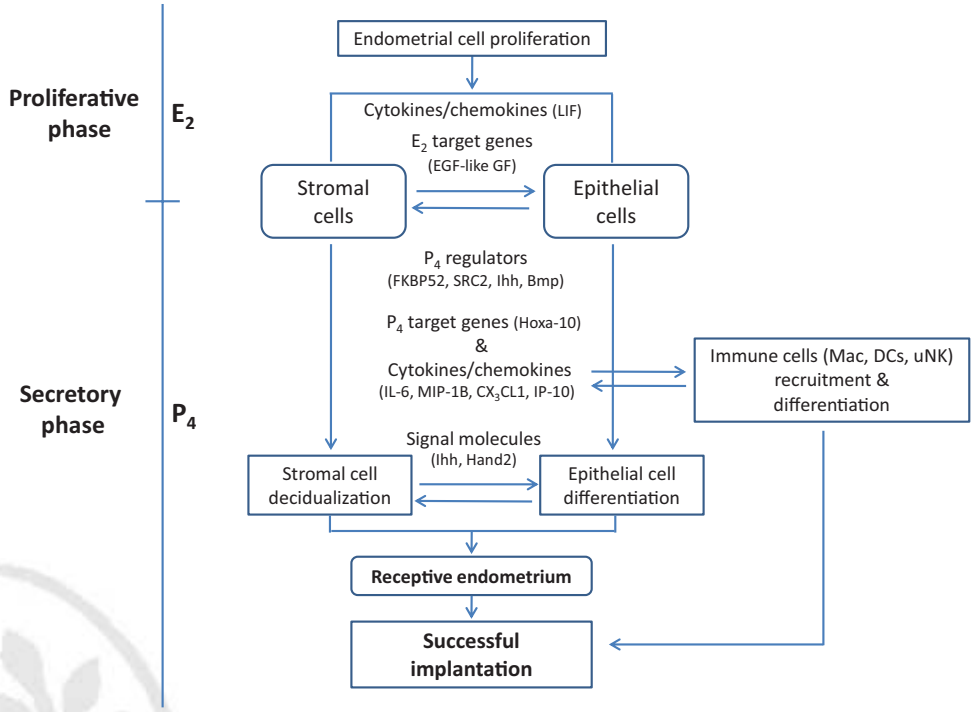

Figure 1 Molecular and cellular events that lead to the development of a receptive endometrium. Estrogen (E_2), secreted during the proliferative phase induces proliferation of endometrial cells and up-regulates the expression of different cytokines and other target genes that promote stromal cell decidualization. This activity is mediated mainly by LIF and its downstream EGF-like growth factors. Progesterone (P_4) acts during the secretory phase to induce the differentiation of the E_2-primed endometrial cells. The effect of P_4 is directly elicited via *Hox* gene family and indirectly by inducing molecular crosstalk between the stromal and epithelial cells. Its activity is regulated by several key molecules such as FKBP52, SRC2, Ihh, and Bmp that modulate its interaction with its receptor. The P_4-induced, endometrial cytokine/chemokine secretion recruits specific immune cells, macrophages (Mac), dendritic cells (DC), and natural killer (NK) cells, from the circulation. These immune cells directly affect remodeling, growth, and differentiation of the endometrial tissue, facilitating the transition of the endometrium from its nonreceptive to its receptive state. In addition to their role in the preparation of the endometrium for implantation, Mac, DC, and NK are directly involved in the implantation process. EGF, epidermal growth factor; LIF, leukemia inhibitory factor.

uterus. Different studies, most of which employed mouse experimental models, showed that of the two E_2 receptors, ERα and ERβ, the ERα is the predominant mediator of the activity of this hormone in the endometrium. Mice that are *Erα*$^{-/-}$ exhibited hypoplastic uteri that could not support implantation, whereas in *Erβ*$^{-/-}$ mice, implantation was normal.[2] Specifically, epithelial cell directed deletion of ERα caused a decrease in the synthesis of epithelial lactoferrin, an E_2-regulated secretory protein, and led to apoptosis (►**Fig. 1**).[3]

A predominant mediator of E_2 action in rodents is leukemia inhibitory factor (LIF), a member of the interleukin (IL)-6 cytokine family. Endometrial expression of LIF in mice is indispensable for implantation.[4,5] Upon its secretion, LIF binds to its specific receptor, LIFR, in the luminal epithelium, and through gp130, activates the januse kinase (JAK)-signal transducer and activator of transcription (STAT) JAK-STAT pathway that leads to acquisition of endometrial receptivity.[6] Using a model of endometrial epithelium specific, conditional *Stat3* knockout, Pawar et al demonstrated that LIF-induced STAT3 activation triggers reorganization of the uterine epithelium by modulating different specific components of the junctional complex, such as E-cadherin, α and β-catenin, and claudins.[7] Moreover, epithelial STAT3 regulates proliferation and differentiation of stromal cells during decidualization. This paracrine effect of the epithelium on the stroma is mediated by the epidermal growth factor (EGF)–like growth factors, *Egf*, *Hbegf*, and *Areg*, that are produced downstream to the LIF-STAT3 signaling.[7] Although LIF is a vital player in the mouse endometrium, its role in the human is still inconclusive. This cytokine reaches its peak level in human epithelium in the mid-secretory phase, the WOI, which is the receptive phase of the cycle.[8] Some clinical studies indicate that low levels of LIF as well as its receptor are associated with unexplained infertility and with endometriosis,[9–12] whereas other studies could not demonstrate such correlation.[13] Furthermore, it was reported that LIF administration to in vitro fertilization (IVF) patients did not improve pregnancy outcome.[14]

The predominant hormone during the receptive phase of the human endometrial cycle is P_4, secreted by the corpus luteum that stimulates endometrial cell differentiation following E_2 priming. In fact, P_4 regulation is crucial for the transition of the endometrium from its nonreceptive to its receptive phase. This hormone modulates the expression of implantation-associated genes in the endometrium and is a key regulator of the transformation of the stromal cells to decidual cells, known as decidualization.[15] Like E_2, the activity of P_4 is exerted through its binding to two receptors, PRA and PRB, that function in a tissue-specific manner. The

P_4-induced reproductive functions, necessary for female fertility, are mediated by PRA, while PRB is required to elicit P_4-induced proliferation and differentiation of the mammary gland.[16,17] The signaling via PR depends on its interaction with molecular chaperones, such as immunophilins. Immunophilin FKBP52 (also called FKBP4) is one of the main regulators of the uterine P_4 function. Its elimination in mice leads to implantation failure due to impaired endometrial responsiveness to P_4.[18] In human, lower expression of FKBP52 is associated with endometriosis.[19] It was suggested that FKBP52 is critical for decidualization.[20] Decidualization, induced by P_4, is mediated by the homeobox transcription factors in the *Hox* gene family. Lack of murine endometrial Hoxa-10 impairs the responsiveness of stromal cells to P_4 that lead to an aberrant decidualization.[21] This reduced responsiveness to P_4 is attributed to the direct effect of Hoxa-10 on FKBP52 expression.[20] The *Hox* gene family is also involved in embryogenesis.[22,23] Mutation of Hoxa-10 in female mice caused implantation failure due to abnormal embryo development as well as impaired decidualization.[24]

Other molecules that regulate/mediate P_4 activity are the steroid receptor coactivator 2 (SRC2), Indian hedgehog (IHH/Ihh) and bone morphogenetic protein (Bmp). Deletion of murine SRC2 leads to implantation failure due to impaired P_4-induced decidualization.[25] The IHH/Ihh is an example of the P_4-induced crosstalk between the epithelium and the stroma, during acquisition of uterine receptivity. It is expressed in the epithelium in response to P_4 and acts as a paracrine signal upon binding to its specific receptors on the stromal cells, inducing their proliferation. Deletion of *Ihh* gene, negatively affects uterine receptivity, leading to implantation failure.[2] In the human, expression of IHH increases during the secretory phase of the cycle in response to the P_4 receptor modulator CDB-2914.[26] It was further shown that chicken ovalbumin upstream promoter-transcription factor II, a downstream target of IHH, is responsible for keeping balance between ER and PR activities.[2,27] Unlike IHH, the P_4-induced transcription factor, Hand2 is expressed in the stroma and suppresses the E_2-induced fibroblast growth factor (FGF) production. Deficiency in uterine Hand2 results in implantation failure that is associated with high estrogenic activity and epithelial cell proliferation, suggesting that Hand2 mediates the antiproliferative activity of P_4 and by that allows epithelial differentiation, facilitating the acquisition of uterine receptivity.[28] Conditional ablation of the Bmp-2 leads to a complete infertility, due to impaired decidualization. Microarray analysis in vivo and in vitro identified FKBPs and WNT ligands as Bmp-2 downstream targets.[29,30] Taken together, these studies suggest that the balance between uterine E_2 and P_4 activities is crucial for normal receptivity and that this balance is regulated by stromal-epithelial communication.

Other Genes that Are Involved in the Development of a Receptive Endometrium

One of the genes that is up-regulated during the WOI is proprotein convertase 6 (PC6), localized mainly at the site of implantation. In vivo ablation of the PC6 in mouse endometrium completely inhibited implantation.[31] This protein is crucial for decidualization in mice and humans.[31,32] Knockdown experiments in human endometrial epithelial cells demonstrated its critical role in blastocyst adhesion.[33]

It has been suggested that normal implantation takes place in an inflammatory environment provided by the receptive endometrium.[34,35] In this context, prostaglandins (PGs) were demonstrated to be crucial for successful embryo implantation. Uterine depletion of cytosolic phospholipase A_2, cyclooxygenase-2 (COX-2), and lysophosphatidic acid receptor LPA_3, which have a central role in PG synthesis, leads to implantation failure in the mouse.[36–38] In human, defective PG synthesis correlates with repeated implantation failure in patients undergoing IVF treatment.[39] It was suggested that the levels of PGE_2 and $PGF_{2\alpha}$ in the uterine fluid, 24 hours before embryo transfer, could predict pregnancy outcome. In vitro experiments demonstrated that embryo adhesion to the epithelium is significantly reduced in epithelial cells pretreated with inhibitors of PG synthesis.[39]

Involvement of the Immune System in Acquisition of Endometrial Receptivity

In contrast to its classical role in protecting the organism from invading foreign antigens, the endometrial immune system supports invasion and maintenance of the fetal semiallograft.[40] This paradoxical immune activity is a result of specific E_2 and P_4-regulated cytokines and chemokines which serve to recruit specific leukocyte populations into the endometrium and regulate their differentiation. Leukocytes in human endometrium comprise different subpopulations, including uterine natural killer (uNK) cells, macrophages (Mac), and dendritic cells (DCs). The uNK cells, the abundance of which increases at the WOI and early pregnancy, compose approximately 70% of the decidual leukocyte population, and their role in stromal decidualization has been suggested.[41] Circulating NK cells in the peripheral blood are cytotoxic, however, upon their infiltration into the endometrium, they undergo differentiation into uNK cells, losing their killing activity.[42] The cytokine IL-15, secreted by DCs and endometrial cells, as well as transforming growth factor beta (TGF-β)1, secreted by Mac, are essential for this process.[41,43–45] Mac and DCs are the major antigen presenting cells in the endometrium. They are present in the endometrium throughout the menstrual cycle and demonstrate increased abundance during the WOI and early pregnancy.[46–48]

Accumulating evidence suggests that, in addition to their classical role in mediating immune response, DCs and Mac have a pivotal role in implantation. Transient deletion of DCs resulted in a faulty decidualization characterized by reduced proliferation, differentiation, and delayed angiogenesis.[49,50] Supporting their role in implantation, therapy by DCs administration significantly decreases the rate of spontaneous resorption of embryos in the mouse uterus.[51] As initially reported by us, and later by others, endometrial biopsy substantially increases implantation and clinical pregnancy rates in IVF patients with repeated implantation failure.[52–58] This increase in pregnancy rate was associated with elevation of DCs and Mac abundance.[59] Endometrial Mac and DCs

secrete both proinflammatory and anti-inflammatory cytokines, by which they may affect Th1/Th2 cytokine balance as well as tissue remodeling and growth,[60–62] thus inducing endometrial regeneration. Based on in vitro experiments, we suggested that endometrial biopsy-induced tumor necrosis factor (TNF)α mediates the injury-induced secretion of macrophage inflammatory protein (MIP)-1B, growth-regulated protein (GRO)α, IL-15 by the endometrial tissue.[59] Other studies showed that TNFα induces secretion of IL-11 and LIF, cytokines that are essential for decidualization,[63,64] further supporting the contribution of inflammation to the development of receptive endometrium.

It is important to note that during the menstrual cycle, the steroid hormones, E_2 and P_4, modulate the production of different proinflammatory cytokines such as IP-10 and MIP-1B.[65,66] Interestingly, E_2 synthesis is reciprocally regulated by the proinflammatory cytokine IL-6. This cytokine acts synergistically with TNFα to increase aromatase, 17-β-hydroxysteroid dehydrogenase and estrone sulfatase activity, enhancing local E_2 biosynthesis.[67] In this context, local injury of the endometrium during the proliferative phase substantially increases endometrial ER expression in the following secretory phase.[68] Previous experiments in mice revealed that endometrial niche cells expressing ERα directly respond to E_2 by transmission of proliferative signals to neighboring endometrial stem/progenitor cells.[69,70] Taken together, it seems that in IVF patients undergoing endometrial biopsy, stem cells that are present in the endometrium[71] may respond to the injury by proliferation in an E_2-dependent manner.[72] Therefore, in IVF patients with recurrent implantation failures, when steroid hormones are apparently insufficient in provoking endometrial receptivity, mechanical intervention by endometrial biopsy may elicit the inflammatory response required for successful implantation.

Implantation

Embryo implantation is divided into three sequential stages: apposition, adhesion, and invasion.

Apposition

Apposition is a dynamic process, during which the free-floating blastocyst and the receptive endometrium initially interact. Having tethering and rolling over, "scanning" the uterine surface, the embryo spots the specific site of implantation and attaches the endometrium. A similarity between the rolling blastocyst in the uterus and the leukocyte migration on the endothelial wall has been suggested.[73] In both processes, interaction is established by binding of the L-selectin molecule expressed on the leukocytes as well as on the trophoblast cells, to its oligosaccharide ligands, localized on the endothelial wall and on the luminal epithelium, respectively.[74] Surprisingly, L-selectin-deficient mice are fertile.[75] However, in human, elevated level of the L-selectin ligand, MECA-79, is associated with improved implantation, while decreased expression of sulfotransferase, GlcNAc6ST-2, which is involved in the generation of functional L-selectin ligands in the endometrial cells, was associated with infertility.[76,77] It has been further shown that reduced expression of endometrial fucosyltransferase, FUT7, generating fucosylated L-selectin ligands, reduces the embryo–endometrium interaction, while overexpression of FUT7 has a positive effect on implantation in vitro and in vivo in the mouse.[78,79] Attempts to localize the L-selectin ligand, MECA-79, in human endometrium detected a high abundance of this ligand on the pinopods,[80] emphasizing the importance of development of these organelles for the initial interaction of the human embryo with the receptive endometrium.

Another protein that was suggested to mediate the initial embryo–endometrium interaction is heparin-binding EGF (HB-EGF)–like growth factor.[81] The highest expression of HB-EGF was found at the WOI in both human and mouse endometrium. In the mouse, HB-EGF is localized in the luminal epithelium surrounding the blastocysts.[82] In human, it is expressed at the WOI in the epithelium and stroma.[83,84] In the luminal epithelium, its localization was associated with the fully developed pinopodes.[85] The receptors for HB-EGF (ErbBs) are expressed on the blastocyst surface.[86] Deletion of HB-EGF from the uterus in the mouse resulted in a reduced litter size.[87] Further evidence for the HB-EGF-ErbB4–mediated attachment of the human blastocyst was generated using in vitro experimental models.[88] It was also suggested that HB-EGF promotes blastocyst growth, zona-hatching, and trophoblast outgrowth followed by its differentiation to its adhesive state.[82,89] As previously reported, cytokines/chemokines secreted by the endometrial cells as well as by the infiltrated immune cells are essential for endometrial receptivity and implantation. Chemokines, secreted by the endometrial cells during the WOI, create a gradient that attracts the blastocyst to the implantation site.[90] In vitro experiments indeed demonstrated that IL-6, MIP-1B, CX3CL1, and IP-10 are effective chemoattractants of the human trophoblast cells.[91–93] Furthermore, a positive correlation between endometrial levels of MIP-1B and IP-10 and successful implantation in IVF patients was demonstrated by us and by others.[59,94] The role of IP-10 in regulation of blastocyst migration, apposition, and initial adhesion has been confirmed in vivo in the mouse as well.[95] Attachment of the blastocyst at the precise implantation site is ensured by mucins (MUC), O-glycosylated proteins that cover the luminal epithelium surface thus preventing an undesirable embryo–uterine interaction at the incorrect site. One of the most studied mucins in the endometrium is MUC1. Its removal is necessary for successful implantation in many species.[96] In humans, expression of endometrial MUC1 is increased during the receptive phase under the regulation of P_4 and different proinflammatory cytokines.[96–100] In vitro experiments suggest that MUC1 is locally down-regulated by the implanting blastocyst.[96,97] It was proposed that a disintegrin and the metalloproteinase (MMP)-17 (ADAM17) as well as the membrane type 1 matrix MMP (MT-MMP1), secreted by the blastocyst shed the MUC1 molecules from the epithelial cells, allowing its attachment to the uterine line.[101,102] Down-regulation of MUC16, another member of the mucin family, was also demonstrated as a critical event for trophoblast cells adhesion to the epithelium.[103]

Adhesion

Embryo–endometrium interaction is stabilized by adhesion molecules such as troponin, cadherins, and integrins (ITGs).[104] ITGs that are expressed by both, the endometrium and the blastocyst, bind to several ECM Arg-Gly-Asp (RGD) containing ligands such as fibronectin, vitronectin, thrombospondin, and osteopontin (OPN). This binding serves as a bridge between the luminal uterine epithelium and the blastocyst.[104] It was suggested that OPN, the expression of which increases in the endometrium during its receptive phase, plays a crucial role in establishing the embryo–endometrium interaction.[59,105] Interestingly, although OPN KO mice are fertile, functional blocking of endometrial OPN with specific antibodies, significantly reduced the number of implantation sites.[106] Moreover, it has been shown that OPN increases blastocyst adhesiveness by binding to its surface receptors, CD44 and/or ITGs. This binding initiates focal adhesion kinase and PI3K/AKT signaling pathways that induce the formation of functional ITG adhesion complexes.[107] ITG αvβ3 is a well-characterized OPN receptor in human endometrium, the production of which is elevated at the WOI. In vivo studies in mice showed that ITGβ3 – deficient mice are infertile, and that functional blocking of endometrial ITGαvβ3, by intrauterine injection of specific antibodies, significantly reduces the number of implantation sites.[106,108] Similar to these results, blastocysts failed to attach to epithelial cells pretreated with ITGβ3 siRNA in vitro.[109] Nevertheless, the correlation between endometrial ITGβ3 levels and infertility is still inconclusive.[13,110–116] The expression of this ITG is regulated by P_4 and mediated by EGF, HB-EGF, and Hoxa-10.[84,117–119] Simón et al[120] demonstrated that human endometrial epithelial cells induce the secretion of the cytokines IL-1α and IL-1β by the blastocyst, and these in turn, increase ITG expression by the epithelial cells. A bidirectional crosstalk between the blastocyst and the endometrium is also suggested by a recent demonstration that factors released to the medium by human blastocysts that successfully implanted following embryo transfer, alter messenger RNA levels of several genes in the epithelial cells, in vitro, facilitating their adhesive properties.[121]

Invasion

Invasion is the final step of implantation, during which the trophoblast fractures the epithelial lining of the uterus and penetrates into the endometrial stroma. Decidualized stromal cell and uNK cells secrete factors that stimulate trophoblast invasion by altering expression of key regulators such as, ITGs, MMPs, and their tissue inhibitors of metalloproteases (TIMPS).[41,122–124] They also induce vascular growth and remodeling by secretion of large amount of angiogenic factors, MMP-2 and MMP-9.[92,125] Moreover, uNK cells secrete factors that trigger endometrial stromal cells to produce cytokines/chemokines, such as IL-15, which in turn supports uNK differentiation, while others, IL-8, CCL8, and CXCL1, act synergistically with uNK-secreted chemokines to induce trophoblast migration.[126]

Regulation of endometrial remodeling and clearance of apoptotic trophoblast cells during trophoblast invasion is attributed to Mac.[127,128] The invading trophoblast secretes chemokines, such as CXCL16 and CXCL12 that recruit and activate immune cells to the deciduas.[129–131] Monocytes that are recruited and "educated" by the trophoblasts cells, positively affect trophoblast development and function, by both secretion of cytokines such as IL-6, IL-8, MCP-1, and GROα and stimulating trophoblast to secrete cytokines that in an autocrine manner facilitate their own growth, survival, and invasion.[130]

Proteases pave the way for the invading trophoblast by digesting the extracellular matrix. The human *MMP* gene family includes 23 members,[132] of which MMP-2 and -9 were mostly studied. Almost all MMPs are produced by the trophoblast, decidual stromal cells, and uNK cells,[133] and their expression is tightly regulated by hormones, cytokines, and growth factors as well as by the TIMPs. It was demonstrated that EGF and cytokines, such as IL-6, IL-1β, TNFα, and IL-8, stimulate trophoblast invasion by increasing levels of trophoblast MMP-2 and -9.[134–138] Activation of STAT3 by LIF was shown to regulate trophoblast invasiveness by TIMP-1 down-regulation.[124] However, TGF-α1 inhibits the proteolytic activity of cytotrophoblast cells by up-regulating TIMP-1 and 2.[138,139] Another negative regulator of MMP activity in the trophoblast cells is P_4 that inhibits the expression of MMP-2, MMP-3, MMP-7, and MMP-9 and increases the expression of TIMP-3, thus restraining trophoblast invasion.[15] In addition to MMPs, the invasive trophoblast expresses various members of a disintegrin and MMPs (ADAMs), such as ADAM8, -12, -19, and -28.[140] In contrast to the secreted forms of MMPs, most of the ADAM family members are membrane proteins. It was suggested that ADAM family members regulate trophoblast invasion by proteolytic shedding of the membrane anchoring ectodomains, thus activating variety of chemokines, cytokines, growth factors, receptors, and their ligands.[141]

Epilogue

Although protocols for infertility treatments are being constantly improved, implantation remains the rate-limiting step for their success. In IVF patients, who generate high-quality embryos but fail to conceive, it is apparently inadequate uterine receptivity that is responsible for implantation failure. Many efforts have been invested in identifying endometrial biomarkers that can predict implantation competence. The studies discussed in this review suggest different implantation-associated genes/proteins as promising candidates. Using the "omics" approach (transcriptomics, proteomics, and secretomics) in endometrial biopsies/uterine aspiration, groups of genes/proteins that characterize a receptive endometrium were proposed.[142] A new assay defined as endometrial receptivity array (see article "Endometrium and Implantation Clinical Management of Endometrial Receptivity" by Blesa and Ruiz-Alonso in this issue) seems to provide accurate and consistent parameters for the evaluation of uterine receptivity.[143–146] Evaluating uterine receptivity using the appropriate biomarkers could provide a potential tool for assessing the success of infertility

treatments. Furthermore, high probability of implantation argues in favor of the transfer of a single embryo in IVF treatment, avoiding the subsequent severe complications of multiple pregnancies.

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