Review Article

Endometrial Receptivity to Implantation in Humans: Biochemical and Molecular Aspects

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Abstract

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The success rate of several advanced basic and clinical techniques in the field of mammalian biotechnology, including cloning, pre-implantation genetic diagnosis, and assisted reproductive techniques (ART) depends mainly on the success rate of pregnancy following in vitro fertilization-embryo transfer (IVF-ET). The techniques used in ART have advanced considerably since the first *in vitro* fertilization birth in 1978. However, despite these advances, pregnancy rates are still relatively low and have not increased significantly in the last decade. Based on the facts that embryo implantation is considered as the last barrier in ART and that inadequate endometrial receptivity is responsible for approximately two-thirds of implantation failures, intensive research work has been performed to understand the physiology, regulation, and the clinical assessments of the endometrial receptivity to improve the success rate of IVF-ET. This and the ongoing reviews tend to cover the different aspects of the endometrial receptivity mainly in human model. The present part of this series primarily concerns with biochemical and molecular events in the endometrium coordinated within its receptivity period termed as the window of implantation. Successive sections will deal with its ultrastructural changes, biomarkers, clinical assessments and regulators of endometrium within the window of implantation.

Keywords: Endometrial Receptivity, Adhesion Molecules, Anti-Adhesion Molecules, Decidua, Uterine Glands

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Introduction

Endometrial receptivity

A fertilized mammalian egg autonomously develops into a blastocyst, which must be successfully implanted in the endometrium to develop further into a fetus. The endometrium is unique as one of the few tissues into which an embryo will not attach and grow, except for a narrow period of endometrial receptivity in a self-limited time-frame period spanning between days 20 and 24 of a regular menstrual cycle (day LH+7 to LH+11), namely the window of implantation (WOI) (1-4). Considering the fact that up to 50% of embryos possess chromosomal errors such as aneuploidy, triploidy, translocations and other genetic disorders; receptive endometrial layers may provide a gating mechanism that help screen out impaired embryos (5). Receptivity, as originally conceived, is functionally defined: that state of uterine differentiation that is permissive for embryo attachment (6), a definition which has frustrated efforts to establish morphological and molecular correlates, particularly in the human, where ethical and moral constraints prohibit in vivo functional testing (7). Moreover, some mechanisms underlying embryo implantation in humans are likely unique to humans and data on embryo implantation which

depends heavily on animal experiments is not transposable to the human model. Generally, several physiological events are required for the development of a receptive endometrium. The first event is synthesis and secretion of histotroph by the endometrial glandular epithelium, which supports conceptus development (8). The second event is reorganization of the endometrial luminal epithelium to allow its intimate association with conceptus trophectoderm. Once trophectoderm has adhered to the uterine luminal epithelium, the inherently invasive nature of the conceptus must be restricted to a circumscribed region of the endometrium. Implantation and placentation then take place in an environment enriched in immune cells that protect against infectious pathogens and promote inflammatory cytokines for tissue remodeling while protecting the fetal-placental semiallograft from attack by the maternal immune system. The dominant features of the receptive phase endometrium can be categorized as: I) The plasma membrane transformation of luminal epithelium, II) Glandular secretion, III) Stromal decidualization and IV) The changes of the immune cell populations. In this review, the above-mentioned features of the receptive endometrium will be discussed from the basic point of view. However, determining molecular mechanisms of human embryo implantation is an extremely challenging task due to the limitation of materials and significant differences underlying this process among mammalian species.

I. Plasma membrane transformations of luminal epithelium during WOI

Unique among epithelia, all compartments of the plasma membrane of endometrial luminal epithelial cells are cyclically altered by ovarian hormones, which regulate its capacity to permit blastocyst implantation. These changes during WOI and early pregnancy are referred as "*the plasma membrane transformation*" (9, 10). A considerable body of evidence indicates that the plasma membrane transformation has many common aspects across species in an impressive variety of animals ranging from viviparous lizards to human beings regardless of the placental type which ultimately develops (11). Here, we describe the biochemical and the molecular changes of the endometrial luminal epithelium during WOI, mainly in the human model.

As the uterine epithelium is the first site of contact between maternal and embryonic tissue (12, 13), major changes in the adhesive properties of the uterine epithelium are necessary for implantation to occur. It involves a complex sequence of signaling events, consisting in the acquisition of adhesion ligands together with the loss of inhibitory components, which are crucial to the establishment of pregnancy. Consistently, apart from the purely morphological, the plasma membrane involves a major re-organization in membrane proteins of its domains, including adhesion and anti-adhesion molecules as well as its receptors to hormones, cytokines and growth factors.

I. A. Anti-adhesion molecules

The apical plasma membrane of surface epithelial cells seems to be non-adhesive unless specifically altered. This non-adhesive nature is attributed to some extent to the mucins, the major component of the glycocalyx, or anti-adhesion molecules found on the apical plasma membrane of endometrial epithelial cells (14-16). When a mammalian blastocyst enters the uterine cavity, anti-adhesive carbohydrates (mucins) are the first molecules a blastocyst encounters. Mucins are a family of highly glycosylated, high molecular weight glycoproteins that their expression pattern in the endometrium shows species to species variations. Among the 14 cloned human mucins, Mucin-1 (MUC-1), MUC-16, and to a lesser extent MUC-2, MUC-4, and MUC-6 have been found in the human endometrium (17-20). Generally, endometrial surfaces are covered by MUC-1. In the majority of cycling primate, a significant reduction or loss of MUC-1 is reported as the uterus transitioned to the receptive state (13). Humans appear to be a rare species in which MUC-1, the major transmembrane mucin in uteri of most species, does not seem to be reduced in luminal epithelia of the receptive uterus (21, 22). Surprisingly, human endometrial MUC-1 was found to be up-regulated during the peri-implantation period (17, 21, 23-25).

Indeed, both MUC-1 mRNA and protein show a several fold increase from the proliferative to the mid-secretory phase (17). Thus, it was suggested that humans require a locally acting mechanism for the removal of the MUC-1 barrier to the implanting embryo (26). Immunohistochemistry on human endometrium, using monoclonal antibodies against the MUC-1 ectodomain, could not detect noticeable variations in its localization on the apical surface of epithelial cells (17, 22). Nevertheless, scanning electron microscopy combined with immunohistochemistry has succeeded in precisely consigning the MUC-1 epitope only to ciliated cells. In contrast, MUC-1 was missing from the surface of non-ciliated cells and from uterine pinopodes (27). Indeed, human *in vitro* implantation models indicate that MUC-1 is lost at the site of embryo attachment (28, 29). It suggests that factors expressed on the blastocyst cell surface or secreted by the blastocyst itself trigger the local loss of MUC-1 (26). Interestingly, recently it has been indicated that MUC-16 contributes to the formation of a barrier to blastocyst adherence, and that the loss of MUC-16 from the pinopodes facilitates adherence in human luminal endometrial epithelium (20). The authors have reported that short interfering RNA (siRNA) knockdown of MUC16 in an endometrial epithelial cell line ECC-1 that, like uterine epithelium, expresses MUC-16 and MUC-1 allowed increased adherence of cells of a trophoblast cell line. In parallel experiments, siRNA knockdown of MUC-1 did not affect trophoblast cell adherence.

It has been suggested that MUC-1 can play a dual role in relation to cellular interactions. By virtue of high expression at the cell surface, density of glycosylation and extended conformation, it is capable of sterically hindering interaction with other cell surface adhesion molecules such as integrins and cadherins (30). On the other hand, some isoforms of MUC-1 are able to bind intracellular adhesion molecule (ICAM)-1 (via the exposed core protein) (31), and MUC-1 glycoforms carrying selectin ligands can be observed in the endometrium (32). Thus, the glycocalyx could act both as an adhesion substrate and a barrier.

It is striking that several molecular systems that might potentially play a role in the epithelial phases of embryo implantation are predominantly localized to the lateral cell membranes of luminal epithelium between the embryo and luminal epithelium at implantation and it is entirely plausible that such signaling triggers a reorganization of the luminal epithelium surface with alteration of polarity and redistribution of components between membrane domains. It is noteworthy that when human embryos attach to primary human epithelial cells, transmission electron microscopic examination reveals direct membrane to membrane interactions between the trophectoderm and the lateral (not apical) surfaces of endometrial cells (33). This appears to occur after disruption of apical junctional complexes, with opening up of spaces between the lateral borders of epithelial cells, and intrusion of trophectodermal processes. There is sharing of apical junctional complexes and desmosomes between trophectoderm and luminal epithelium cells (34). Thus, the interaction between the embryo and the apical luminal epithelium surface is transient. The interactions occurring at the highly hydrated glycocalyx are difficult to visualize in electron microscopy because of dehydration artefacts arising at processing. The store of cell adhesion molecules in lateral luminal epithelium membranes may be called into action early in the epithelial phase of implantation, either following attachment to the glycocalyx or immediately after its clearance. Thus, the initial interaction locates the embryo within a specific area of the uterine surface. Short range signaling to maternal epithelial cells can then occur, leading to glycocalyx clearance. This is a test of viability for the embryo, and poor quality (e.g. monosomic) blastocysts may fail at this stage. At the same time, it places the state of receptivity in a new light: the ability of the epithelium to respond to embryo-derived signals (35). Moreover, strikingly numerous potential mediators of adhesion at implantation are located in the lateral rather than the apical surface of luminal epithelial cells, as shown in Figure 1 (36).

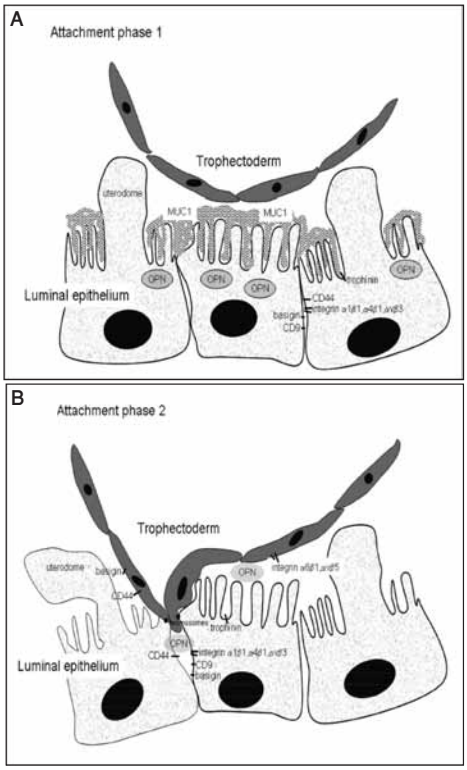

Fig 1: (A) Initial attachment is to the glycocalyx and may be mediated by a lectin-carbohydrate interaction. The lateral luminal epithelium (LE) membranes are rich in adhesion molecules. (B) Second phase attachment follows the clearance of apical glycocalyx in response to an embryonic signal. The lateral LE borders open and trophectodermal processes insert between the LE cells. MUC1: mucin 1; OPN: osteopontin. Adopted with permission from Aplin (36)

CD9 or motility-related protein 1 (MRP1)

CD9/MRP-1 is a member of the tetraspanin family, that is expressed on the endometrium epithelial cells in human and bovine (37-39). It can act as a receptor for the family of pregnancies specific glycoproteins, which are secreted hormones and are thought to act as immune modulators (40). Its distribution in the endometrium is mainly in the lateral membranes of the luminal epithelium epithelial cells. In the human placenta, the intensity of CD9 expression in the extravillous trophoblast cells (EVTs) differs between early pregnancy and term: expression in the EVTs invading the endometrium in early pregnancy is weak, but in the placental bed and chorionic leave of the term placenta (where EVTs have ceased invasion into the endometrium) expression is intense (41). Consistently, anti-CD9 monoclonal antibody has been reported to stimulate invasion of endometrial cancer cell lines *in vitro* (42) and CD9 was able to impair embryo invasion in mice *in vivo* (39).

I.B. Adhesion molecules

Morphological observations of human and monkey embryo implantation sites indicate that blastocyst trophectoderm cells that have adhered to the uterus proliferate and invade, whereas trophectoderm not in contact with the uterine epithelium remains a monolayer (43, 44). This finding suggests that the initial adhesion triggers activation of cells in trophectoderm. Adhesion molecules which are specifically up-regulated in the plasma membrane during early pregnancy are the subject of much interest because they may function as receptors for the blastocyst. The cell adhesion molecules (CAMs) family is mainly composed of four members known as integrins, cadherins, selectins and immunoglobulins.

Integrins

Most of the adhesive proteins share the tripeptide arginine-glycine-aspartic acid (RGD) sequence (45). The RGD sequences of these ligand proteins are recognized by one or several members of the family of structurally related receptors that are collectively called integrins (45). Integrins are a family of heterodimeric transmembrane glycoproteins, formed by the association of two different, non-covalently linked α and β subunits (46). These subunits contain extracellular, transmembranal and intracellular domains. The extracellular domain enables integrins to act as a receptor to extracellular matrix components, complement and other cells. The intracellular domain, however, is able to interact with the cytoskeleton. A large variety of integrins have been described within the luminal and glandular endometrial epithelium (47-50). Whereas the majority of the integrins are constitutively expressed throughout the entire menstrual cycle, others exhibit an interesting regulated pattern within the cycle (48-51). Integrins with increased expression in the mid-luteal phase were proposed as markers for the frame of the window of implantation (52, 53). Three cycle-specific integrins are co-expressed by the human endometrium defined histologically on days 20–24 of the human menstrual cycle: α1β1, α4β1 and αvβ3, but only the β3 mRNA subunit expression was shown to increase after day

19 and is not detected beforehand. αvβ3 integrin as well as its ligand osteopontin was positively detected by immunohistochemistry on the endometrial luminal epithelial surface, which first interacts with the trophoblast (54). The cycle-specific pattern of endometrial integrin expression is suggestive of hormonal regulation. Indeed, αvβ3 integrin expression is orchestrated in the human endometrium both by positive and negative factors (55, 56). During the proliferative phase, high estrogen levels act via the estrogen receptor-α to inhibit integrin expression. The luteal progesterone rise subsequently down-regulates the number of those receptors, thus indirectly suppressing the inhibitory effects of E_2 on integrins. Progesterone, probably, also acts positively by increasing paracrine stromal factors to induce epithelial β3 integrin expression that serves as the rate-limiting step in αvβ3 formation (57). However, there are some controversies in the *in vitro* assays (58). In regard to its expression pattern along with its epithelial localization, αvβ3 has been proposed as a potential receptor for embryonic attachment (57). Moreover, signalling through αvβ3 has been reported to be important to maintain a balance between cell proliferation and apoptosis, along with the modulation of inflammatory responses of decidual cells (59).

Selectins

Selectins are glycoproteins which belong to the CAMs family. They include P-selectin, L-selectin and E-selectin. Although previously it was thought that selectins are expressed only in the hematopoietic cells, L-selectin was found in human blastocysts (60). Furthermore, L-selectin ligand oligosaccharides were detected widely on luminal and glandular endometrial epithelia in the human uterus by immunohistochemistry using MECA-79 and HECA-452 antibodies, whose epitope structures are closely related to L-selectin ligand (61, 62). The expression of these ligands are up-regulated in human endometrium during the period receptive to embryo implantation and recently, the expression of L-selectin ligand MECA-79 has been considered as a predictive marker of human endometrial receptivity (63). Furthermore, it has been suggested that interactions between L-selectin on human blastocysts and oligosaccharide ligands on endometrial epithelia enables the initial adhesion of human embryo for implantation (60).

L-selectins are expressed on leukocytes and interact with their carbohydrate-based ligands on the endothelium. This interaction, termed tethering, allows the rolling of leukocytes on inflamed vascular endothelium before their firm adhesion and transmigration. A parallel can be made between the leukocytes' 'rolling' phenomenon and the blastocyst apposition to the endometrial epithelium (60, 64). The physiological importance of the interaction between L-selectin and its oligosaccharide ligands was investigated in the human endometrium and the selectin adhesion system is well established at the maternal-fetal interface (60). When the blastocyst enters through one of the fallopian ostia, 4 days after ovulation, it appears to move freely in the uterine cavity. Selectins were proposed to have an important role in this phase to ensure suitable rolling of the blastocyst. Since the human embryo is required to attach to the endometrium in a polarized way and because the embryo is looking for the best area in the endometrium for implantation, this 'rolling' phenomenon is strictly regulated to ensure that the blastocyst will eventually settle in the proper spot and in the correct orientation. To prevent the blastocyst from adhering to an area with poor chances of implantation, an important role is played by the repellent activity of MUC-1. As detailed above, MUC-1 is widely expressed throughout the endometrium and, surprisingly, even increases before implantation. This phenomenon seems to be crucial in preventing the embryo from adhering to the wrong location. Interestingly, it has been demonstrated that MUC-1 carries selectin ligands throughout the secretory phase of the menstrual cycle, including the mid-secretory (receptive) phase (65). Consequently, MUC-1 represents a potential ligand for selectins expressed by human blastocysts.

Cadherins

The cadherin family is made up of calcium-dependent cell adhesion molecules responsible for cell-to-cell recognition and

adhesion. Cadherin-mediated cell-cell interactions are dynamic processes, and cadherin function is tightly regulated in response to cellular context and signaling (66). They are divided into subclasses E-, P-, and N-cadherins that are distinct in immunological specificity and tissue distribution. Cadherin regulation is likely to reflect the interplay between a range of fundamental cellular processes, including surface organization of receptors, cytoskeletal organization and cell trafficking (66). They promote cell adhesion via a homophilic mechanism. In regard to implantation, E-cadherin represents the most studied subclass. E-cadherin is located in the adherens junctions that are specialized regions on the lateral side of the epithelial plasma membrane and is believed to be critical for the establishment and maintenance of these junctions in epithelial cells (67, 68). During WOI, a major re-organization take place in the membrane proteins of endometrial epithelium, which has been suggested to represent a loss of polarity in these cells and this thought has been extended to suggest further that an epithelial-mesenchymal transition may occur in the cells during this time (69).

Intracellular calcium is essential in the E-cadherin regulation. Indeed, a rise in its concentration activates key signaling pathways, which mediate cytoskeletal reorganization and disassembly of E-cadherin at the adherens junctions. Alterations in intracellular calcium concentrations affect epithelial cell adhesiveness and polarity by triggering CAMs redistribution (70). This phenomenon could be of importance in endometrial epithelial cells expressing E-cadherin. *In vitro* experiments on cultured Ishikawa cells demonstrated that a transient rise in intracellular calcium, triggered by calcitonin, suppresses E-cadherin expression at cellular contact sites (71). Interestingly, calcitonin expression is induced by progesterone in the human endometrial epithelium specifically during the mid-secretory phase of the menstrual cycle (72). Indeed, calcitonin is known to be a potential regulator and biomarker of endometrial receptivity (73, 74). Progesterone, probably via endometrial calcitonin induction leading to increased intracellular calcium, could regulate E-cadherin expression. Thus, it is possible that E-cadherin possesses a dual function. In the preliminary phases, its expression at the cell surface is required to ensure adhesiveness. In contrast, E-cadherin may be subsequently down-regulated to enable epithelial cells dissociation and blastocyst invasion. The upregulation of cadherin and catenin in the epithelial cells of peri-implantation uteri and the down regulation of cadherin, catenin and Ca^{2+} in invasive trophoblast appear to be associated with embryo-uterine interactions during early pregnancy (75). The suppression of E-cadherin expression at cellular contact sites is diagrammatically shown in figure 2.

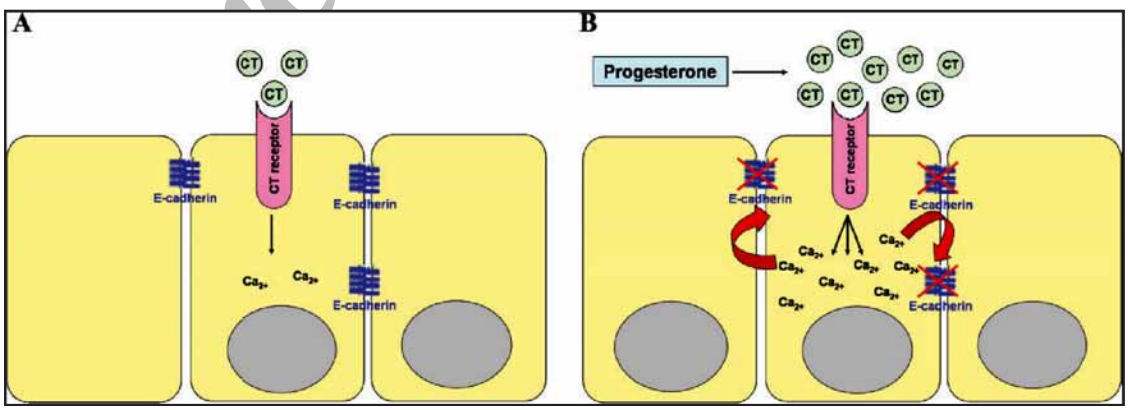

Fig 2: (A) Epithelial cell adhesiveness by E-cadherin is controlled by intracellular calcium. (B) Rising progesterone levels induce calcitonin (CT) expression and thus increase the concentration of intracellular calcium, which then suppresses E-cadherin expression at cellular contact sites. Adopted with permission from Achache (76)

Immunoglobulins

Among the CAMs, the immunoglobulins superfamily is the most extensive. Intercellular adhesion molecule-1 (ICAM-1 or CD54) is a transmembrane glycoprotein that belongs to the immunoglobulin superfamily and is constitutively expressed on the cell surface of a variety of cell types, such as fibroblasts, leukocytes, endothelial and epithelial cells. ICAM-1 adhesive interactions are essential for the transendothelial migration of leukocytes and for various immunological functions (77). It is well established that the endometrium, under ormal conditions, contains a wide population of leukocytes, which expresses ICAM-1 within the endometrium. Moreover, ICAM-1 was immunolocalized, throughout the menstrual cycle, to the apical surface of the glandular and luminal endometrial epithelial cells (EECs) as well as in the stroma. On the other hand, MUC1 that is expressed by early gestation trophoblasts is known to bind to ICAM-1 in other systems (78). In view of the fact that ICAM-1 is strongly expressed in both stromal and epithelial endometrial cells, it can be suggested that ICAM-1 may involve in the trophoblast adhesion o uterine endothelial cells and in trophoblast transendothelial migration (78).

Basigin, also known as CD147 or EMMPRIN, is a glycosylated membrane spanning immunoglobulin with multiple binding partners at the cell surface, which is known as an extracellular matrix metalloproteinases (MMPs) inducer or activator of their activity (79). Basigin is expressed most prominently at the lateral epithelial surface of endometrial epithelial cells in human and rodent. It is also expressed on pre-implantation embryos. The cyclic breakdown and subsequent regrowth of the endometrial layer of the uterus throughout each menstrual cycle are critical for maintenance of a functional endometrium. This extensive remodeling of the uterine lining requires precise regulation and activation of MMPs. Basigin regulates the production of MMP-1, -2, and -3 by uterine fibroblast cells (79). Implantation rates are severely compromised in animals lacking basigin (80, 81).

Trophinin

Trophinin is an intrinsic membrane protein with its amino terminal region localized in the cytoplasm and is directly responsible for homophilic cell adhesion. Identification of trophinin as unique apical cell adhesion molecule in human embryo implantation has been illustrated using a monoclonal antibody specific to human trophinin showing positive immunostaining in both trophoblast and maternal epithelia at embryo implantation sites in the human placenta (17, 82, 83). Trophinin expression was detected in the luteal-phase endometrium of both normal and infertile women, which peaked in the mid-luteal phase (82, 84). In comparison with normal women, infertile women with endometriosis or unexplained infertility had significantly weakened trophinin expression in the endometrium in the mid-luteal (85). There is evidence that human chorionic gonadotrophin can induce local expression of trophinin by maternal epithelial cells (86). Trophinins were detected in both trophoblasts and endometrial epithelium cells at the monkey blastocyst implantation site (87). In human endometrium, strong expression of trophinin is seen in a restricted region of the apical plasma membranes of the surface epithelium at the early secretory phase (87). Trophinin is not a typical membrane protein. Its amino terminal region, consisting of about 70 amino acids, is hydrophilic, and this region is predicted to be cytoplasmic because antibodies raised to this region do not recognize trophinin in cells unless they are permeabilized (82). The decapeptide repeats are assumed to be a key structural element for homophilic cell adhesion, but the structural basis for trophinin-trophinin binding is yet unknown (88, 89). It has been reported that trophinin, tastin, and bystin comprise a complex that mediates a unique adhesion between trophoblast and endometrial epithelial cells at their respective apical cell membranes (87). Tastin and bystin are soluble cytoplasmic proteins that associate with trophinin by presumably forming active adhesion machinery. It has been proposed that trophectoderm cells of human blastocyst

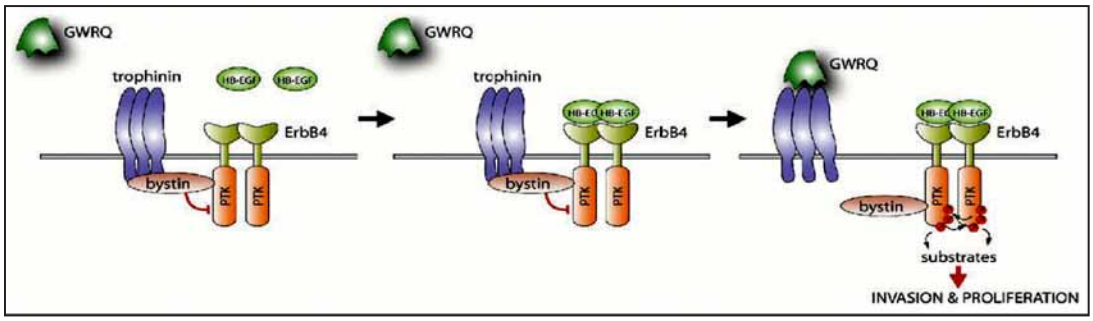

Fig 3: Interaction of trophinin, bystin, ErbB4 or tastin in HT-H cells before and after trophinin-mediated cell adhesion, which is mimicked by GWRQ peptide binding. (Left) Trophinin and bystin bound together in a cytoplasmic complex, which further interacts with ErbB4 and suppresses its tyrosine kinase activity. (Center) HB-EGF binds to ErbB4 but protein kinase activity is suppressed by trophinin/bystin. (Right) Trophinin-mediated cell adhesion is mimicked by binding of GWRQ peptide to trophinin on the cell surface, resulting in dissociation of trophinin from bystin, leading to activation of ErbB4. Adopted with permission from Fukuda (94)

remain silent as long as trophinin arrests ErbB4, a transmembrane receptor of heparin-binding epidermal growth factor (HB-EGF) (90). Upon trophinin-mediated cell adhesion, bystin is released from trophinin. This release allows the activation of ErbB4 protein tyrosine kinase (88). HB-EGF is a candidate molecule for facilitating endometrial receptivity and implantation and previous studies have implicated EGFR in mouse embryo implantation (91-93), where interaction between ErbB4 expressed on the trophectoderm and membrane-bound HB-EGF on the uterine epithelium mediates an initial adhesion. Interaction of trophinin, bystin, ErbB4 or tastin is summarized in figure 3.

Lectins

Lectins recognize and bind carbohydrates covalently linked to proteins and lipids on the cell surface and within the extracellular matrix, and they mediate many cellular functions ranging from cell adhesion to pathogen recognition. Carbohydrates surpass any other class of biomolecule in their capacity to store biological information (95). The emerging functionality of the sugar code via cell surface glycans and endogenous lectins ascribes pertinent roles in cell physiology to the carbohydrate signals of cellular glycoconjugates. To initiate monitoring of endogenous lectins in human endometrium, several studies focused on a family of growth/adhesion-regulatory lectins, i.e. galectins (96, 97). The galectins are a family of b-galactoside-binding animal lectins with a conserved carbohydrate recognition domain (CRD). They have a high affinity for small b-galactosides, but binding specificity for complex glycoconjugates varies considerably within the family. Several parallels in the function of galectins and the regulation of human endometrium suggest a role of galectins in the endometrium. First, several reports have shown that galectins-1 and -3 are important mediators of inflammation (98). As endometrial function and implantation inolve many inflammatory mediators, galectins might contribute to the modulation of the endometrial immune system. Second, galectins have been shown to play an important role in cell adhesion, migration and chemotaxis (98). As adequate endometrial function is dependent on leukocyte migration and as implantation is characterized by the accumulation of immune cells around the implantation site, galectins can be expected to play a role in the regulation of endometrial leukocytes. Third, galectins have been characterized as major players in the defense against invading micro-organisms (98). As the endometrial immune system is constantly challenged by bacteria ascending through the cervix, galectins might contribute to the protection of the endometrium against bacterial infection. Gray et al., (99) for the first time suggested galectins as cellular and molecular markers for the endometrial receptivity. Galectin-1 was present in the tissue compartments of the uterus except for the luminal and glandular epithelium. After implantation of the embryo, the endometrium including the decidualized stromal cells and the glandular epithelium showed immunohistochemical staining for

galectin-1. Galectin-3 expression was low in non-pregnant mice uteri and increased in the primary decidual zone and in the uterine epithelial cells adjacent to the implanting blastocyst immediately after implantation. A recent study extended the localization to human tissue, revealing a similar pattern of endometrial galectin expression with a strong presence of galectin-1 in decidualized stromal cells and of galectin-3 in secretory-phase epithelial glandular cells (100). Next, Popovici (96) identified galectin-9 as a new endometrial epithelial marker for the mid- and late-secretory and decidual phases, which exclusively expressed in the endometrial epithelial cells. Galectin-9 is one of the very few epithelial markers, such as glycodelin (PP14) that strictly regulated during the menstrual cycle, with a significantly increased expression during the mid-secretory phase (101). Because of anti-adhesive as well as pro-adhesive extracellular functions of galectins, they appear to be a novel class of adhesion-modulating proteins collectively known as matricellular proteins (102). Thus, the glandular expression of a lectin involved in adhesion, i.e. galectin-3, and the increasing expression of galectin-1 raises the question as to whether these galectins might be involved in adhesion events of implantation, as previously suggested for integrin and its ligand osteopontin.

Tissue transglutaminase (tTG)

tTG is a unique member of the transglutaminase family, as it is both a transamidating enzyme and a GTPase (103). Moreover, tTG is localized mostly in the cytosol, however it is also found in the nucleus, the extracellular matrix (ECM), and is associated with the plasma membrane (104, 105). The complex of tTG and integrins is formed in the cytoplasm and accumulates on the cell surface and focal adhesions (FAs) (106). Human endometrial tTG exhibits a regulated development and a 10-fold higher activity in the luteal phase than in the follicular phase (107), which implies that progesterone regulates the expression of tTG *in vivo* (108) and suggests its potential role in endometrial receptivity. Furthermore, the importance of tTG expression during decidualization in human endometrial stromal cells (109) has been already confirmed. Kabir-Salmani et al. (110) demonstrated the expression of tTG on human uterodomes and suggested that tTG actively participates in adhesion events at the embryo-maternal interface through its interaction with FN at least in part, by activating integrin-signaling pathways. Apparently, tTG lacks a transmembrane domain that activates the intracellular signaling pathways directly (111). Then, considering the fact that integrins span the cell membrane and are physically and functionally associated with tTG (106), it is tempting to hypothesize that an integrin-tTG-FN axis exists in these cells. Accordingly, two models are suggested for the ternary adhesion complexes concerning these interactions (Fig 4). In this model, tTG as a bridge between integrin and FN could strengthen these adhesion complexes firstly through its higher affinity for FN and by simultaneously providing the second integrin molecule with the RGD site of the same FN chain.

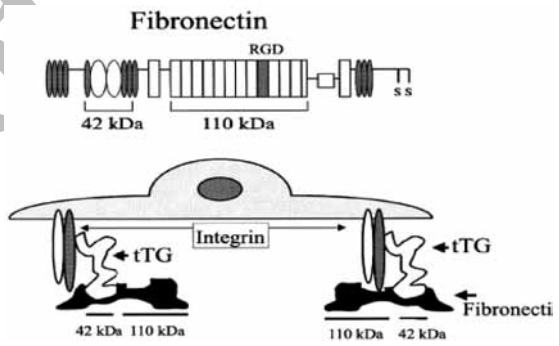

Fig 4: Model proposed by Akimov et al., to show schematically the possibilities of the involvement of tTG in conjunction with integrins during the processes of cell adhesion or spreading. Panel (A) shows a scheme of the molecular structure of the FN and 42-kDa and 110-kDa FN fragments. In panel (B), the possibilities of the associations of integrins with tTG are illustrated. Tissue TG stimulates cell adhesion and spreading due to its either acting as a bridge between integrins and FN (left side) or mediating the formation of stable ternary complexes with FN and the βsubunit of integrins (right side).

Heparan sulphate proteoglycans (HSPGs)

HSPGs reside on the plasma membrane of all animal cells studied so far and are a major component of extracellular matrices (112, 113). Numerous functions of HSPGs are mediated through interactions between their heparan sulfate glycosaminoglycan chains and extracellular ligands. Cell adhesion is one of the processes requiring the presence of proteoglycans on the cell surface (114,

115). The syndecans are proteoglycans, i.e. they consist of a core protein to which long, unbranched carbohydrate polymers, called glycosaminoglycans, are covalently attached. They are called the syndecans (from Greek syndein, to bind together), because of their ability to bind extracellular matrix components and growth factors (116, 117). All syndecans were expressed within human endometrium. Syndecan-1 and -4 proved to be significantly up-regulated in whole endometrium during the secretory phase (2.73-fold and 2.85-fold, respectively).

II. Glandular epithelium and secretion during WOI

Two principal pathways have evolved to transfer nutrients from the mother to her fetus. These are termed histiotrophic and hemotrophic, respectively (118). Histiotroph is an extracellular material derived from the endometrium and the uterine glands that accumulates in the space between the maternal and fetal tissues. It is phagocytosed initially by the trophectoderm of the blastocyst, and later by the trophoblast of the placenta or the endoderm of the yolk sac. By contrast, hemotrophic nutrition is the exchange of blood-borne materials between the maternal and fetal circulations. This is facilitated by the extensive and intimate apposition of the maternal and fetal tissues that occurs within the placenta. All mammalian uteri contain endometrial glands that secrete histotroph, which includes enzymes, growth factors, cytokines, lymphokines, hormones, transport proteins, and other substances (119-121). Histotroph plays a role in conceptus nourishment, production of pregnancy recognition signals, immunoprotection, attachment, implantation, and placentation (121, 122). The interstitial form of implantation displayed by the human blastocyst is generally associated with early onset of the maternal blood flow to the developing placenta, and hence hemotrophic exchange. However, the recent finding that the maternal intraplacental circulation is not fully established until the third month of gestation suggests that human fetal nutrition may be initially histiotrophic (8). Uterine secretions may also perform an important role in feto-placental development besides acting as a source of nutrients. There is increasing evidence that they contain a number of cytokines, such as tumor necrosis factor (TNF-α) (97), uteroglobin (123), epidermal growth factor (EGF), colony stimulating factor (CSF), and vascular endothelial growth factor (VEGF). These are powerful regulators of trophoblast proliferation and migration *in vitro* (124, 125), and so may exert a profound influence on remodeling the uteroplacental arteries and in defining the ultimate form and extent of the villous tree. In addition, glycodelin that is the major progesterone-regulated glycoprotein secreted into the uterine luminal cavity by the secretory/decidualized endometrial glands is known to have many immunosuppressive properties and so could be an important factor in the maternal tolerance of the placenta (126, 127).

II. B. Biochemical and molecular aspects of glandular epithelium during WOI

Osteopontin (OPN)

OPN (phosphoprotein-1) is an acidic member of the small integrin-binding ligand *N*-linked glycoprotein (SIBLING) family of proteins that undergoes extensive posttranslational modifications believed to be important to its function (128, 129). OPN is an extracellular matrix molecule and cytokine hypothesized to influence the uterine environment as 1. a component of histotroph required for adhesion and signal transduction at the uterine-placental interface, 2. a gene product expressed by uterine stroma as it decidualizes in response to conceptus invasion, and 3. a product of resident placental and uterine immune cells that regulates their behavior and cytokine production (128, 129). Uterine OPN and its integrin receptors have become the focus of studies concerning conceptus adhesion for implantation in a number of species, including humans, in which OPN expression is increased by progesterone during the menstrual cycle, starting on Days 16-17, and secretory glandular epithelium (GE) appears to be a source of OPN localized on the apical LE surface.

Integrins

Like luminal epithelium, there are several integrins that are preferentially expressed by the glandular eplithelium, including $\alpha_1\beta_1$,

$\alpha_2\beta_1$, and $\alpha_4\beta_1$ (130). Integrins $\alpha_v\beta_3$ and $\alpha_4\beta_1$ are co-expressed on the glandular epithelium only during a 3 to 4 day interval correspond to the WOI. Finding of increased integrin expression only during the maximal endometrial receptivity suggests that integrins play a role in glandular epithelium during implantation.

Leukemia Inhibitory Factor (LIF)

LIF is a member of the interleukin (IL)-6 family, which the timing of its expression in the human endometrial suggests its potential role in implantation (131). In the human, LIF is secreted by the endometrial epithelium, CD16–CD56^{bright} natural killer cells (NKs) and type 2 T-helper (Th2) cells (132, 133). Immunolocalization of gp130 and the LIF receptor showed that the glandular epithelium and endothelial cells was target for LIF (134). LIF, which is also locally produced by decidual cells, can augment cell viability in certain activated endometrial stromal cells in autocrine or paracrine manner (135). In humans, LIF mRNA and protein are expressed in the endometrial glands during the luteal phase of the menstrual cycle when implantation would occur (136). The regulation of LIF plays an important role in the physiological processes of human reproduction and impaired endometrial LIF production, and secretion may be the cause of infertility.

Glycodelin

Glycodelin, also known as progesterone-dependent endometrial protein (PAEP), placental protein 14 (PP14) or placental α2-macroglobulin (137) is a glycoprotein with immunosuppressive properties, having similar temporal characteristics as β_3 integrin. Its isoforms are abundant in amniotic fluid (glycodelin-A), seminal plasma (glycodelin-S) and follicular fluid (glycodelin-F) (138). Glycodelin-A is abundant in the secretory endometrium and is the major progesterone-regulated glycoprotein secreted into the uterine luminal cavity by secretory/ decidualized endometrial glands (138-140), and is highly upregulated in the endometrium at implantation (141). Further, it has been demonstrated that glycodelin is present in pinopodes of receptive-phase human endometrium and is associated with down-regulation of progesterone receptorβ (142). It is essentially undetectable in proliferative phase endometrium and usually appears in the glands on the fifth post-ovulatory day (143). It is the first endogenous glycoprotein found to inhibit spermatozoa-zona pellucida binding (144, 145) and its absence in the endometrium in the periovulatory period may be related to the opening of a fertilization window (138). A possible role of endometrial glycodelin in local inhibition of natural killer activity and immune tolerance of the conceptus during implantation process has also been proposed (146).

III. Stromal decidualization during WOI

In the late luteal phase of the menstrual cycle, the endometrium undergoes a profound morphological and biochemical alteration process called decidualization. This process starts around the day 23 in stromal cells adjacent to the spiral arteries and occurs independently of the presence of a blastocyst. The decidua regulates the invasion of the trophoblast and facilitates the anchoring of the pregnancy, recruiting immune cells that promote the survival of the fetal allograft, angiogenesis, and maintaining a pathogen-free, free radical-free environment (147). As the conceptus implants, decidual cells and vasculature undergo a transformation called “the decidual reaction”. Many decidual cells degenerate near the chorionic sac in the region of the syncytiotrophoblast and, together with maternal blood and uterine secretions, provide a rich source of nutrition for the embryo. Under the control of steroid hormones, the decidual cells of the endometrium fulfill paracrine, nutritional, immunoregulatory, and embryo-regulatory functions throughout pregnancy (15).

The primary function of deciduas is to provide an immunologically privileged site for the conceptus. The formation of the decidua in the stromal bed surrounding the implanting embryo is an important event during implantation and the protection of the embryo from the maternal adverse environment during early pregnancy is considered to be achieved by the establishment of a transitory permeability barrier created by decidual cells immediately surrounding the implanting

embryo. It is speculated that the acquisition of epithelial-like properties by decidual cells under the influence of the embryo is a possible means of regaining epithelial-like barrier functions at the implantation site after the loss of the luminal epithelium surrounding the implanting embryo. Further, to protect the mother from the attack of invasive trophoblasts migrating towards the uterine spiral arteries, endometrial stromal cells undergo transformation into a dense cellular matrix known as the deciduas (148). The decidua obstructs the movement of the trophoblast by forming a physical barrier to cell penetration and by generating a local cytokine environment that promotes trophoblast attachment rather than invasion (149). The decidualization reaction is initiated around the blood vessels and spreads throughout the stroma of the late luteal phase and pregnant endometrium (150). Because of this association with blood vessels, it is likely that decidual cells also play a key role in gating leukocyte entry and haemostasis (151). A recent work suggests that the trophoblast acts to alter the local immune environment of the decidua to facilitate the process of implantation and ensure an enriched cytokine/chemokine environment while limiting the mitotic activity of the stromal cells during the invasive phase of implantation (152). Besides cellular changes, decidualization creates an ECM composition of utmost importance. This matrix is composed mainly of laminin, heparan sulphate proteoglycans and type IV collagens (reviewed by: Ferenczy (153). The decidua secretes products (e.g. fibronectin and insulin-like growth factor binding protein-1, IGFBP1) that bind to trophoblast-specific integrins and modulate trophoblast migration, invasion, or both in in vitro models (154).

III.B. Biochemical and molecular aspects of the decidua during WOI

Decidualization involves changes in the expression of a large number of genes (15, 155) and is marked by a rapid increase in vascular permeability with resulting oedema in the stroma around the implantation site (156). Decidualization is defined as the differentiation of the elongated fibroblast-like mesenchymal cells in the endometrium to the large, round decidual cells and the coordinated expression of numerous new cellular products of the ECM (e.g. tissue inhibitors of MMP (TIMPs), cytokines, hormones such as the prolactin, and various other peptides such as insulin-like growth factor binding-protein-1 (157-158) and the influx of specific leukocyctes (159). Decidual cells are particularly characterized by their secretory products such as prolactin (PRL) and insulin-like growth factor binding protein-1 (IGFBP-1) and their pavement like morphology (159, 160). Decidualization of the endometrium itself has features in common with an inflammatory response (161). At the time of decidualization, increased cytokine production leads to the migration of immune cells into the endometrium, of which the most important are monocytes and uterine natural killer (NK) cells (162). Progesterone is the main physiological inducer of decidualization in women, and decidualization of human endometrial stromal cells (HESC) can be induced *in vitro* by the addition of progesterone or cyclic (c) AMP to cultures treated with E2 (163-165). The initiation of the decidual process requires elevated intracellular cAMP levels and sustained activation of the protein kinase A (PKA) pathway (163). *In vitro* decidualization can also be initiated by prostaglandin E2 (PGE2), the gonadotrophins luteinizing hormone (LH), and the follicle stimulating factor (FSH) (166), as well as by relaxin (164). The Beads soaked in soluble heparin binding-epidermal growth factor (sol-HB-EGF) placed in the uterus of pseudopregnant mice elicited local decidual responses that mimic those induced by the blastocyst (155), indicating that HB-EGF secreted locally at the site of implantation may have some function in the decidualization process. Many paracrine factors that are expressed throughout the cycle, including prostaglandins (167), IL-11 (168), the corticotropin-releasing hormone (CRH) (169), activin A (170) and relaxin (171, 172) promote decidualization. Recently, it has been demonstrated that ghrelin, the endogenous ligand for the growth hormone secretagogue receptor (GHS-R) (173), both increased and accelerated the secretion of prolactin and IGFBP-1 during progesterone-induced decidualization, suggesting a role in

the progression of decidualization possibly by synergizing with progesterone (173). IGFBP-1 is the major secretory product of the human and baboon decidualized endometrium (174, 175) and prolactin (176), the pregnancy-associated plasma protein A (177), placental protein 12 (175), and a 32-kiodalton protein (178) are gene products released by cultured decidua. Some of these procesures have been summerized in figure 5.

Prolactin (PRL)

PRL is one of the major proteins synthesized and secreted by human decidualized endometrial stromal cells (179, 180). In the nonpregnant uterus, prolactin synthesis is detected between the mid-secretory phase and menses and coincides with the first histological signs of decidualization (181). Prolactin expression is controlled most effectively in the decidualized endometrium by progesterone. In the presence of progesterone, decidualized endometrium secretes prolactin at increasing concentrations and in its absence prolactin secretion ceases within 2-3 days (182). The temporal pattern of expression of prolactin receptors throughout the menstrual cycle indicates that prolactin plays a differentiative rather than a mitogenic role in the glandular epithelial cells. Prolactin influences the expression of a number of adhesion and proteolytic molecules (reviewed in Yu-Lee, (183). In early pregnancy, the placental development and the establishment of maternofetal circulation is tightly controlled through the expression of angiogenic and anti-angiogenic factors. Prolactin stimulates and inhibits angiogenesis: the intact prolactin molecule is angiogenic and its N-terminal 16 kDa fragment is anti-angiogenic (184). Furthermore, a role for prolactin in immune regulation is well documented (reviewed in Yu-Lee) (183).

Insulin-like growth factor binding protein-1 (IGFBP-1)

IGFBP-1, which is a major constituent of human amniotic fluid and the most important decidual secretory product together with insulin-like growth factors (IGF-I and IGF-II) and their receptors (IGF-Rs) play important roles at the embryo-maternal interface in the regulation of placental development, embryo implantation and fetal growth. IGFBP-1 undergoes some forms of post-translational modifications, which regulate its biological functions (185, 186). The IGFBP-1 protein competes with endometrial membrane receptors for binding insulin-like growth factor (187) and binds to the $\alpha_5\beta_1$ integrin on the cytotrophoblast membrane (188).

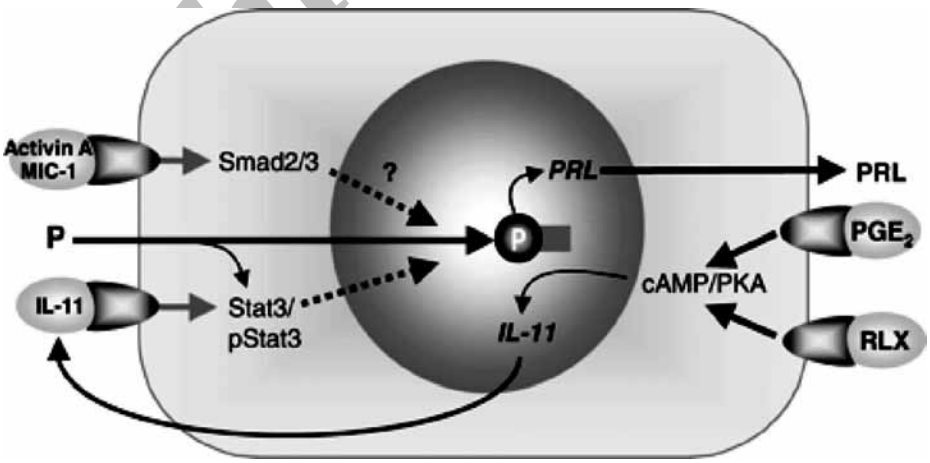

Fig 5: The figure shows as an example, the potential complex interrelationships between progesterone, prostaglandin (PG) estradiol (E_2), relaxin (RLX), interleukin-11 (IL-11), activin A and macrophage inhibitory protein-1 (MIC-1) in stimulating decidualization of human endometrial stromal cells. Prolactin is a marker of decidualization. Progesterone is necessary for decidualization, and its effects can be enhanced in vitro by PG E_2 or relaxin, both of which act via cAMP (exogenous cAMP can also drive the process in vitro). Effects of both relaxin and PG E_2 are via stimulation of IL-11 production. Progesterone attenuates IL-11 expression. IL-11 enhances P-induced decidualization via phosphorylation of signal transducer and activator of transcription (STAT3). Both Activin A and MIC-1 also stimulate decidualization via activation of Smads. ligand; receptor. Adopted with permission from Dimitriadis (171)

Superoxide dismutase (SOD)

Decidualization stimulates production of many bioactive substances such as growth factors, cytokines and adhesion molecules. This increase in metabolism stimulates generation of superoxide radicals in the mitochondria because superoxide radicals are normally generated during normal metabolic activities (189, 190). The elevated oxygen radicals have detrimental effects including DNA and protein damage and lipid peroxidation, which primarily affect membrane structure and function (191-193). Intracellular sources of reactive oxygen species include the mitochondrial electron transport system, endoplasmic reticulum, nuclear membrane electron transport systems, and plasma membranes (189). The human endometrium has specific superoxide radicals, which scavenge toxic reactive oxygen species, specific metallo-enzymes: copper-zinc superoxide dismutase (Cu, Zn-SOD), located in the cytosol, and manganese SOD (Mn-SOD), located in the mitochondria (194). The mechanism of SOD induction by decidualization is unclear. It has been shown that Cu, Zn-SOD and Mn-SOD expression in human endometrial stromal cells was induced by progesterone and oestradiol (195). Moreover, it is well known that prolactin and its receptor are detected in the endometrial stromal cell after the late secretory phase (196-197) and produced concomitantly with the onset of in-vitro decidualization (164, 198, 199). Since it has recently been found that prolactin induces both Cu, Zn-SOD and Mn-SOD expressions in luteal cells (200), it is possible that the SOD induction in the endometrial stromal cell by decidualization may be mediated by prolactin in an autocrine or paracrine fashion.

Tissue inhibitors of matrix metalloproteinases (TIMPs)

Cyclic remodeling and breakdown of the extracellular matrix (ECM), a unique feature of the human endometrium, depends on matrix metalloproteinases (MMPs). These enzymes are globally controlled by estradiol and progesterone or their with drawal, and their physiological tissue inhibitors (TIMPs) (201). Cytotrophoblastic cells are constitutively invasive and produce MMPs. The tissue inhibitors of metalloproteinases inhibit cytotrophoblastic invasion in vitro, indicating that MMPs are causally related to trophoblast invasion in the endometrium (202). TIMPs are expected to be largely expressed during the nonmenstrual phases to prevent inappropriate lysis of the tissue. In particular, TIMP-3 is thought to limit the invasion of the decidualized mucosa by trophoblast at implantation (203). Moreover, the high levels of TIMP-3 during the implantation window are in support of its proposed key role at this early stage of embryonic development (204, 205).

Corticotropin-releasing hormone (CRH)

The hypothalamic neuropeptide corticotropin-releasing hormone (CRH), as well as its receptors, has been identified in several reproductive organs, including the endometrial glands, the decidualized endometrial stroma and the placental trophoblast, synctiotrophoblast and deciduas (159, 206). CRH induces the decidualization of endometrial stroma (207, 208) and potentiates the decidualizing effect of progesterone. The concentration of CRH is significantly higher in the luteal phase, associating endometrial CRH with the intrauterine phenomena of the luteal phase of the menstrual cycle, such as decidualization and implantation (209). Further, it has been shown that intrauterine CRH may participate in local immune phenomena associated with embryo implantation.

Heparan sulphate proteoglycans (HSPs)

The change in the phenotype of decidual cells from mesenchymal to more epithelioid may also be regulated in part by the heparan sulphate proteoglycans that is secreted into the external lamina to interact with other matrix components. It has been reported that decidual cells synthesize heparan sulphate proteoglycans and that one component of the major human decidual cell secretory granule is HSPs (210). Since proteoglycans also function in the retention of water and subsequent production of swelling pressure in tissues (211). This results in a resistance to compression by load within the tissue. The developing placenta and fetus undoubtedly place a heavy load on the uterine wall, which

would be compensated by the increased swelling pressure in the uterus.

Chemokines

CXC chemokine (or α-chemokine) (CXC) ligand1 (*CXCL1)/*(*GRO1*), interleukin-6 (*IL-6),* radical S-adenosyl methionine domain containing 2) *(RSAD2),* CC chemokine (or β-chemokine) ligand8 (*CCL8),* pentraxin 3 (*PTX3), IL-8*, prostaglandin E synthase *(PTGES)*, intercellular cell adhesion molecule1 (*ICAM1)*, and a variety of interferon (IFN)-responsive and related genes are among the most highly upregulated genes in decidual endometrial stromal cells in response to trophoblast-secreted products (152).

IV. Changes of the immune system during WOI

An important discovery in the recent years is that immune components are an integral part of pregnancy. This discovery stems from the research initially aiming at the resolution of 'Medawar's paradox' (Medawar, 1953) of "Nature's semiallograft" (212). Trophoblast, a unique lineage without counterpart in adult tissues, is in direct contact with maternal blood and tissue. The major graft rejection-promoting molecules, human leukocyte antigens (HLAs), are tightly regulated in these cells, with none of HLA-A, HLA-B, or HLA class II antigens, including HLA-E, HLA-F, and HLA-G expressed (213). It is possible that HLA-G production by preimplantation embryos may be involved in the mechanisms that lead to their ability to establish adequate cross-talk with the endometrium and to achieve embryo implantation. In addition, soluble HLA-G from alternative origins and detectable in the maternal blood, even before ovulation, are also likely to influence human embryo implantation, presumably by promoting endometrial receptivity. The mechanisms involved in this process remain unclear, in particular because eutopic endometrial tissue has been shown to fail to express HLA-G. Studying 65 IVF patients, these investigators observed that the women achieving intact pregnancy after IVF displayed significantly higher plasma HLA-G levels during early pregnancy than did the women who experienced early abortion or the healthy control subjects. The most striking of the study findings was that soluble HLA-G levels were higher in the women achieving successful pregnancies even before ovulation. This indicates that maternal soluble HLA-G molecules may foster embryo implantation, irrespective of the inherent embryo HLA-G production. Additional investigation focusing on soluble HLA-G levels in the maternal blood and their relationship with uterine receptivity to embryo implantation remains necessary to confirm these preliminary data. Embryonic trophoblast and maternal decidua cells, i.e., the cells located in the interface between the fetal placenta and the maternal endometrium, produce CRH and express Fas ligand (FasL) (169). The Fas receptor and its ligand play an important role in the regulation of immune tolerance (214). CRH may play a crucial role in the implantation and the anti-rejection process that protects the fetus from the maternal immune system, primarily by killing activated T cells through the Fas-FasL interaction (169). Furthermore, the expression of FasL by fetal extravillous trophoblast cells can induce apoptosis of activated T lymphocytes expressing the Fas receptor (215).

On the other hand, during the secretory phase, changes in the immune cell populations are initiated in the preparation for nidation. The role of the immune system at this stage is adapting the immune environment in the endometrium for the potential arrival of the immunologically "foreign" or " semiallograft" conceptus (216). Maternal tolerance against fetal antigens is still one of the unsolved questions in pregnancy. Implantation and placentation present an immune challenge because of the semi-allogeneic nature of the conceptus. Endometrial tissue is characterized by a sensitive network of inflammatory mediators, allowing the accumulation of a spectrum of immune cells in the secretory phase (217) and migration of immune cells to the implantation site (218). Focusing on the various subsets of immune cells playing in concert with the human immune system, tolerance induction is nowadays often accredited to a specialized group of immune cells, the antigen-presenting cells (APC) (219). At least three populations of APC, the

macrophages, dendritic cells and immature, monocyte-derived APC, could be found in the deciduas (219). APCs are scattered throughout human decidualized endometrium during all the stages of pregnancy (220). These powerful, multi-functional leukocytes reside in close proximity to uterine glandular epithelium, uterine blood vessels, and HLA-G-producing invasive cytotrophoblast cells.

Human decidual antigen presenting cells (DAPCs) exposed to fetal cells *in vitro* induce generation of suppressor T cells among a population of peripheral blood lymphocytes (221). The major immune cell types in secretory endometrium are T cells, the uterine natural killer (uNK) cells and macrophages. T cells comprise approximately 45% of leukocytes in proliferative endometrium and their number remains constant throughout the secretory phase and into pregnancy (222). However, their relative numbers decrease because of a large increase in uNK cells during the secretory phase and early pregnancy. The secretory phase is marked by an increase in the number of uNK cells (162). The uNK cells in the endometrium function primarily as a source of cytokines important in implantation, including leukemia inhibitory factor (LIF), tumor necrosis factor (TNF)-a, interferon (IFN)-c, granulocyte macrophage-colony stimulating factor (GM-CSF), and IL-10 (132, 223, 224). During implantation, uNK cells comprise 70–80% of the total leukocyte population in the endometrium, and their increased numbers are attributable to proliferation *in situ* (225, 226) and also to influx from the peripheral circulation (227).

A comprehensive review of the different aspects of the immune system changes during WOI is rather diverse and out of the scale of this review. We will discuss in this regards in our future publications.

Conclusion

The endometrial epithelium, which is surprisingly hostile towards the embryo implantation and thus, the first barrier during implantation, acquires functional status supportive to blastocyst acceptance during a limited period of the menstrual cycle, termed as the 'window of implantation'. Endometrial receptivity now appears to be the bottleneck of the embryo implantation. Inadequate uterine receptivity is responsible for approximately two-thirds of the implantation failures, whereas the embryo itself is responsible for only one-third of these failures (228, 229). Receptive endometrium is the results of a well-orchestrated sequence of events in which various factors come into play one after the other, yet remaining in close collaboration. In all eutherian mammal species, several physiological events are required for the development of a receptive endometrium. The first event is synthesis and secretion of histotroph by the endometrial glandular epithelium, which supports conceptus development (8). The second event is the reorganization of the endometrial luminal epithelium to allow its intimate association with conceptus trophectoderm. Once trophectoderm has adhered to the uterine luminal epithelium, the inherently invasive nature of the conceptus must be restricted to a circumscribed region of the endometrium. Implantation and placentation then take place in an environment enriched in immune cells that protect against infectious pathogens and promote inflammatory cytokines for tissue remodeling while protecting the fetal-placental semiallograft from attack by the maternal immune system.

Embryo implantation is unique to mammals and differs significantly among different species (122). Some mechanisms underlying human embryo implantation are likely unique to humans. Thus, the endometrial biopsy samples can be used to identify molecules associated with uterine receptivity to obtain a better insight into human implantation. In addition, development of functional *in vitro* systems to study embryo-uterine interactions will lead to better define the interactions existing between the molecules involved in this process. Up to date, only a few modalities have been employed to treat the failures of conception, despite the repeated transfer of apparently good-quality embryos. Future research, therefore, must be directed towards deciphering the functional, rather than the morphological, characteristics of endometrial receptivity. The knowledge, acquired from this line of research, will surely assist investigators in the development of

specific therapeutics measures that will optimize embryo implantation, and also may lead to the development of new and improved contraceptive methods.

Competing interests

To the authors' best knowledge, no competing interests of any nature arise from the current publication.

Authors' contributions

The three authors have drafted the article, revised it critically and gave final approval of the version to be published. All authors read and approved the final manuscript.

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