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Redefining Endometrial Receptivity

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Endometrial receptivity is conditional, requiring an escape mechanism sensitive to maternal and embryonic status. Several decision points are identified in early pregnancy at which cooperative progression or conservative failure may be negotiated between the maternal and embryonic systems. Different endometrial and decidual cell populations play various roles depending on the timing and location of the respective interactions they mediate.

The action of the steroid hormones estrogen and progesterone on receptors in endometrial cells is classically situated at the top of a cascade of events that leads to the endometrium becoming receptive to an implanting embryo (1). Beneath the master transcriptional regulators ER and PR lie numerous subsidiary transcription factors, including androgen receptor (AR), C/EBPβ, COMP-TF2*, FKBP52*, FKHR*, HoxA10, HoxA11, Hmx3, KLF9/BTEB, NCOA1/SRC1*, NCOA2/SRC2*, PPARγ, PPARδ and snail (2, 3). Some of these (*) associate with the progesterone receptor to form a larger transcriptional complex, while others appear to act independently (3). The AR activates a subset of genes that is smaller than, and quite distinct from, PR gene targets (4). A large number of diffusible components including hormones, growth factors, cytokines and chemokines are activated by transcription factors to coincide with the timing of implantation; of these, only a small subset has been functionally verified (2).

However, the notion of receptivity as a static state in which the tissue is poised, frozen in time, awaiting the arrival of an adequately developed embryo, is naïve. An integrative definition of receptivity must embrace communication between maternal and embryonic tissues. At receptivity, the endometrium has reached a point at which negotiation can begin that may or may not lead to successful implantation, placentation, development and growth of a viable conceptus.

Global transcriptomic comparison of receptive and non-receptive endometrium has undergone refinement to identify signalling pathways that may operate in different cell compartments (5). The Wnt pathway is operative at several stages of implantation including blastocyst activation, juxtacrine signalling at the epithelial stages and later interaction with deciduas (6). Chemokine pathways are implicated (7) as are prostaglandins (8), cannabinoids (9), lysophosphatidic acid (10), HB-EGF (11) and others.

The idea that the initial interaction between trophectoderm and apical uterine epithelium might either mediate or impede a molecular cascade leading to implantation (12-16) came from observations suggesting that embryos would attach freely to stromal cells or extracellular matrix (17), but not to epithelial cells outside the receptive phase, and led to a hypothesis that the luminal epithelium resists attachment until the mid-secretory phase.

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Luminal epithelium has a transcriptome and other phenotypic features that are distinct from the glandular epithelium (18-21). The effort to establish the molecular basis of adhesion is an active current area of research (2, 14, 22). Based on animal models and in vitro studies of human embryos, MUC-1 in the apical glycocalyx appears to be cleared from the epithelium at the time of attachment, though the mechanism differs between species (13, 22). In human, epithelial cells cocultured with embryos show enhanced levels of MUC-1 in the presence of developmentally arresting embryos. At attachment sites local MUC1 clearance occurs, apparently as a result of signalling from the embryo (23). MUC16, another transmembrane mucin with anti-adhesive properties, is cleared under maternal control from apical protrusions known as uterodomes in the mid secretory phase (24).

The epithelial glycocalyx might offer an initial attachment site, but it also poses a barrier to implantation progression such that a fraction of embryos is excluded (25, 26). Chromosomally abnormal blastocysts attach efficiently to cultured endometrial stromal cells (27), but their capacity to adhere in vitro to epithelial cells is untested. If indeed selection occurs at the epithelial stage, it is at best an inefficient process – monosomic embryos, though they may develop to form blastocysts (28) are not observed post-implantation, but many trisomic and mosaic embryos progress, only to fail in the following few weeks. Similarly, in sycp3-/- mice which produce over half aneuploid embryos, most pregnancy losses occur after implantation in the postgastrulation period (E7-E8). Conceptuses that survive to day 12.5 are uniformly normal (27).

Currently available data suggest that the onset of receptivity in human endometrium may be controlled by adhesion systems in the luminal epithelium, but that other cell compartments are at least as important in the spectrum of pregnancy loss. Given the high rates of aneuploidy and post-implantation demise in human, the concept remains attractive that quality control is exerted on embryos by means of a dialogue with the endometrium at implantation and during early placental development (25). Evidence that gene expression in the pregnant endometrium is influenced by embryonic phenotype has been gathered from gene array studies comparing endometrial signatures in pregnancies with cloned bovine conceptuses from single cell nuclear transfer [associated with high rates of placental abnormality (29)] and those with embryos conceived after fertilisation in vitro or by donor insemination. Differences observed in signalling and immune pathways implicate the endometrium as a sensor of developmental potential (30, 31). In vitro models of human implantation comparing the phenotype of endometrial cells exposed to normally developing or arresting embryos also show differences consistent with this function (23, 32).

Adverse maternal systemic influences on placentation can include nutrition (33), immune and complement-mediated effects such as antiphospholipid antibody toxicity (34, 35), the pre-eclampsia-like effects of autoantibodies to the angiotensin receptor AT1 (36, 37) and possibly antibodies to placental transglutaminase (38, 39) in celiac disease (40). Until recently relatively little was known of the influence of the local uterine environment on placental development and pregnancy outcome (41). However, it is now becoming possible to inquire what roles the various cell populations of the endometrium play in sensing and quality control. Stromal decidualisation and the attendant vascular remodelling clearly have an important influence on placental development in both mouse and man (41, 42). The maternal LIF-null mouse, in which implantation fails apparently as a result of a decidualisation disorder (43, 44), has been an influential paradigm. In human, chorionic gonadotrophin derived from trophoblast stimulates decidual prokineticin 1 which in turn increases LIF production (45). Downstream of the LIF receptor,

stat-3 phosphorylation is a key signalling event in stromal decidualisation in mouse, is important in implantation, and is a potential contraceptive target (46-48). Evidence has been obtained using genetically altered mice (49, 50) that an interferon-regulated gene, Isg15, is upregulated in antimesometrial but not mesometrial decidual tissue as a result of stimulation by adjacent trophoblast giant cells.

Before blood circulation is established in the labyrinth (mouse) or the intervillous space (human), placental development requires deciduochorial histiotrophic support. Insulin-like growth factors are important for normal growth of the conceptus (51), and both maternally- and placentally-derived IGFs are capable of enhancing early placental growth (52-54). The IGF binding protein IGFBP-1, which restricts the bioavailability of IGF by competing with its receptor, is a decidual secretory product whose overexpression in mouse leads to altered placental morphogenesis with changed allocations of cells to various trophoblast lineages, and reduced fetal growth (55). In turn IGFBP-1 may be broken down by local MMP-3 and MMP-9 or protected by association with α2-macroglobulin (56, 57).

In human, vascular remodelling begins with subtle morphological changes that occur independent of the presence of a conceptus (58). In early pregnancy, maternal uNK cells and macrophages invade the arterial walls in advance of the infiltration of trophoblast, but this only occurs if a conceptus is present, suggesting a possible chemoattractant of placental origin. In a paradigmatic example of cooperation, this is followed by the migration of trophoblast into the vessel walls and full physiological transformation (59). This process is specific to the pregnant uterine vascular bed; human trophoblasts introduced experimentally into post-menopausal spiral arteries, or vessels from other tissue beds, do not infiltrate the media (60). There is also emerging evidence that lymphangiogenesis in the maternal environment is stimulated by trophoblast (61). In mice, uNK and dendritic cells are crucial for development of the decidual vascular bed (62, 63), and regulatory T cells are required to suppress an allogeneic response to the fetus (64). The motility and phenotypic plasticity of the major decidual leukocyte populations as well as the presence on uNK cells of polymorphic KIR receptors that bind HLA C, which is expressed on extravillous trophoblast, implicate these cells in a dialogue that might lead either to a successful outcome or to spontaneous pregnancy loss (65).

In conclusion, it is becoming clear that a series of checkpoints exists for pregnancy viability. Cooperation between maternal and embryonic systems is required either for progression towards the delivery of healthy offspring at term, or alternatively for conservative failure – the loss of a non-viable conceptus with minimal adverse consequences for the mother. The earlier this can be achieved, the smaller the maternal resource wastage.

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