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QUESTION:

Write a short note on *IMPLANTATION.*

Answer:

Implantation is the stage of pregnancy at which the embryo adheres to the wall of the uterus. At this stage of prenatal development the conceptus is called a blastocyst. It is by this adhesion that the embryo receives oxygen and nutrients from the mother to be able to grow.

In humans, implantation of a fertilized ovum is most likely to occur around nine days after ovulation; however, this can range between six and 12 days.

During fertilization, the sperm and egg unite in one of the fallopian tubes to form a zygote. Then the zygote travels down the fallopian tube, where it becomes a morula. Once it reaches the uterus, the morula becomes a blastocyst. The blastocyst then burrows into the uterine wall.

Once the embryo reaches the blastocyst stage, approximately five to six days after fertilization, it hatches out of its zona pellucida and begins the process of implantation in the uterus.

In nature, 50 percent of all fertilized eggs are lost before a woman's missed menses. In the in vitro fertilization (IVF) process as well, an embryo may begin to develop but not make it to the blastocyst stage — the first stage at which those cells destined to become the fetus separate from those that will become the placenta. The blastocyst may implant but not grow, or the blastocyst may grow but stop developing before the two week time at which a pregnancy can be detected. The receptivity of the uterus and the health of the embryo are important for the implantation process.

1. Preconditions for implantation

To achieve successful implantation, the uterus should undergo structural and functional remodeling. Estrogen and progesterone are the master hormones mediating these changes. Estrogen and progesterone bind to their respective nuclear receptors. The progesterone receptor exists in two isoforms, PR-A and PR-B, and the estrogen receptor also exists in two isoforms, as ERα and ERβ .In recent years, and genetically engineered mouse models have provided information to understand the roles of ovarian steroid hormones during embryo implantation. PR-A is essential for implantation as mice lacking both PR-A and PR-B are infertile, whereas mice lacking only PR-B have normal. Likewise, ERα is the primary mediator of estrogen action because the uterus of ERα knockout mouse is hypoplastic and they are, while ERβ knockout mice are fertile. Progesterone plays a pivotal role in implantation that allows the uterus to support the development of the embryo. The advent of advanced omics technologies provides unique insight of embryo implantation using targeted proteomics by identifying endometrial epithelial cellular and secreted protein changes in response to ovarian steroid hormones. The proliferative (follicular) phase is under the influence of rising estrogen levels due to growing ovarian follicles, leading to proliferation of the epithelium, stroma, and vascular endothelium to cause regeneration of the endometrium). Rising estrogen levels are observed before the receptive phase but it remains to be determined whether this mid-luteal phase estrogen is necessary for implantation in humans or non-human primates Although estrogen can induce uterine receptivity, the window of implantation remains open for an extended period at lower estrogen levels but rapidly closes at higher levels in the mouse model Uterine receptivity is improved when estrogen levels are decreased during the pre-implantation period in patients undergoing *In Vitro* Fertilization and Embryo Transfer (IVF-ET).

Progesterone induces the formation of pinopodes, epithelial cells that lose their polarity and microvilli through down regulation of cell-cell adhesion and develop smooth protrusions along the apical surface. The most important feature of pinopodes is removal of the cell surface glycoprotein mucin 1 (MUC1) which inhibits cell to cell adhesion during the window of implantation. However, the validity of pinopodes as a marker of uterine receptivity is controversial as pinopodes are detected throughout the luteal phase of the menstrual cycle and in human pregnancy.

The early embryo enters the uterine cavity as a morula and becomes a 32 to 256-cell blastocyst before implantation. Implantation begins with the loss of the zona pellucida known as hatching about 1-3 days after the morula enters the uterine cavity in preparation for attachment. The active blastocyst undergoes structure changes such that a more irregular surface with more microvilli is observed with accumulation of glycogen granules in the cytoplasm. In conclusion, the window for successful implantation could be defined as a limited time span when the activated stage of the blastocyst is superimposed on the receptive state of the uterus.

Implantation consists of three stages:

(a) The blastocyst contacts the implantation site of the endometrium (apposition);

(b) Trophoblast cells of the blastocyst attach to the receptive endometrial epithelium (adhesion); and

(c) Invasive trophoblast cells cross the endometrial epithelial basement membrane and invade the endometrial stroma (invasion).

1) Apposition and adhesion

Implantation begins with apposition of the blastocyst at the uterine epithelium, generally about 2-4 days after the morula enters the uterine cavity. The implantation site in the human uterus is usually in the upper and posterior wall in the midsagittal plane. Implantation is considered a pro-inflammatory reaction in which endometrial vascular permeability is markedly increased at the attachment site, mediated by Cyclooxygenase (Cox)-derived prostaglandins. Prostaglandin E_2 is increased in the luminal epithelium and the underlying stroma at the both of mice and human implantation site, thus indicating its role in attachment and localized endometrial vascular permeability Prostaglandin E_2 is considered as one of the important regulators of human trophoblast invasion, which activates other signaling proteins. During apposition process, the blastocyst differentiates into an inner cell mass (embryo) and trophectoderm (placenta). Stromal cells surrounding the implanting blastocyst differentiate into a specialized cell type called decidual cells, via a process known as decidualization.

Cytokines are regulatory peptides or glycoproteins. Unlike hormones, cytokines usually act as paracrine or autocrine signals in local tissue, and only occasionally, they have more distant

effects as endocrine mediators. Leukemia-inhibitory factor (LIF) is a member of the interleukin-6 family of cytokines, which is a major mediator of estrogen action. Knock-out of *Lif* gene in mice results in infertility, characterized by a defect in implantation and decidualization that can be rescued by administering recombinant LIF. *Lif* expression is higher around the time of implantation in fertile women as opposed to lower levels in infertile women. LIF mediates a shift from a proliferative state of luminal epithelium to a differentiated state through down-regulation of cell-cell junctional molecules acting as a barrier to embryo invasion. LIF also drives stromal proliferation through regulation of the epidermal growth factor (EGF) signaling pathway. Mice with an inactivating mutation in the colony-stimulating factor-1 (CSF-1) gene are infertile due to lower rates of implantation and fetal viability. Both the embryo and endometrium express CSF-1 receptor mRNA, and it has been suggested that cross-talk of endometrial epithelial CSF-1 with trophectodermal CSF-1 receptor enhances attachment. Interleukin-1 (IL-1) is considerably involved in implantation and the pre-implantation development of the embryo. IL-1 stimulates vascular endothelial growth factor (VEGF) expression and regulates Matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs) Dominguez et al. observed that Interleukin-6 (IL-6) displayed the highest protein concentration in the endometrial epithelial cell coculture system. Protein microarrays offer a unique platform for the evaluation and identification of multiple protein targets. Upon further assessment of IL-6 using an ELISA-based assay, viable blastocysts were shown to display an in uptake of IL-6 compared with blastocysts that failed to result in a pregnancy, suggesting a potential role for IL-6 in blastocyst development and implantation. Heparin-binding epidermal growth factor-like growth factor (HB-EGF) is a crucial molecule in the interactions between the uterus and the embryo during the attachment reaction. It is expressed exclusively in the luminal epithelium surrounding the blastocyst 6-7 hours before the attachment process in rodents. Its expression is maximal in the receptive epithelium and is concurrent with pinopodes. HB-EGF is synthesized as a transmembrane protein that can be processed to release the soluble growth factor, and both forms influence the blastocyst through the EGF family of receptors expressed on the blastocyst surface as a juxtacrine adhesion factor. HB-EGF also promotes blastocyst growth and zona-hatching.

Cell adhesion of the blastocyst trophectoderm and endometrial luminal epithelial cells of the uterus is mediated by cell adhesion molecules, including integrins, cadherins, selectins, and immunoglobulin. Cell adhesion molecules are expressed on the surface of invasive trophoblast,

and these molecules interact with ligands expressed by the extra-cellular matrix of the decidua in a temporal and spatial way. Integrins are a family of transmembrane glycoproteins that act as cell surface receptors formed by various combinations of two different, non-covalently linked α and β subunits. Menstrual cycle-specific integrins are up-regulated in the mid-luteal phase of human endometrium and have been considered as markers of the window of implantation. It has been suggested that a lack of integrin expression during the window of implantation can contribute to unexplained infertile women. The trophoblast also expresses integrins at the time of implantation and at a site of outgrowing trophoblast cells. Cadherins are a family of glycoproteins involved in the Ca^{2+}-dependent cell-cell adhesion mechanism. In mice, E(epithelial)- cadherin was detected in embryonic cells during the peri-implantation period, and it is also detected in the uterine epithelium. The presence of E-cadherin in both the trophoblasts and endometrial epithelium indicates that E-cadherin may play an important role in the initial attachment process. Selectins are a group of carbohydrate-binding proteins. Although L-selectin was previously thought to be expressed only in hematopoietic cells, human trophoblasts also express L-selectin and its oligosaccharides are expressed in pinopodes. Interaction between L-selectin on human blastocysts and oligosaccharide ligands on the endometrial epithelium has been proposed as an initial step in implantation. Blocking L-selectin with specific antibodies leads to impaired adhesion of trophoblasts to the endometrial epithelium. CD98, a component of tetraspanin-enriched microdomians, is a multifunctional type II glycoprotein involved in amino acid transport and cell fusion. CD98 expression in human endometrium is strictly restricted to the implantation window, and its subcellular localization at the apical surface of endometrial epithelial cells is consistent with a role in blastocyst adhesion.

*2) **Invasion***

The process of implantation allows fetal trophoblast cells to invade and migrate into the maternal decidua. By this time, the trophoblasts at the implantation site have formed masses of cytotrophoblasts and syncytiotrophoblasts. Eventually, trophoblast cells destroy the wall of the maternal spiral arteries, converting them from muscular vessels into flaccid sinusoidal sacs lined with endovascular trophoblast. The aim of invasion is to reconstruct the maternal spiral arteries, which will maintain a high blood flow between the fetus and the mother, replacing small, high-resistance vessels with large, low-resistance vessels. The extent of trophoblastic invasion

determines later placental efficiency and fetal viability in late gestation. Deficiencies in trophoblastic invasion give rise to adverse pregnancy outcomes such as intrauterine growth restriction (IUGR) and preeclampsia. Formation of placental villi is associated with remodeling of the extra-cellular matrix through tissue degradation and revision by various proteinases including serine proteases, matrix metalloproteinases (MMPs) and collagenases. Serine proteases, including urokinase-type plasminogen activator (uPA) and tissue-type plasminogen activator (tPA) can catalyse the conversion of plasminogen to plasmin for proteolytic degradation of the ECM. Trophoblast cells express plasminogen activator receptors. Invasion and migration of mouse trophoblastic cells are closely related to their PA activity. The zinc-dependent family of MMPs is a key player in matrix degradation during trophoblastic invasion. The MMP family is classified into three groups, including collagenases, gelatinases, and stromelysins based on the specificity of substrate. Type IV collagen is a fundamental component of the basal membrane and it is one of the major structures of the uterine ECM. The invasive capacity of human trophoblastic cells has been shown to correlate with increased production of type IV collagenase (MMP-2 and MMP-9). During early pregnancy, fetal trophoblast cells invade the uterus and penetrate the basement membrane, a property that is characteristic of malignant cells. However, unlike tumor invasion, trophoblast invasion of the uterus should be under strict control confining the placenta and within the time constraint of a pregnancy. Limitation of trophoblastic invasion is attributed to the balance of activating and inhibiting growth factors, cytokines, and enzymes. Decidual cells produce plasminogen activator inhibitor-1 (PAI-1) which is the major inhibitor of uPA. The tissue inhibitors of MMPs (TIMPs) tightly regulate the activities of MMPs. Decidual transforming growth factor (TGF)-β plays a major regulatory role in limitation of human trophoblast invasion by up-regulating both TIMPs and PAI-1. In addition, TGF-β provides antiproliferative signals to differentiate from invasive and proliferative cytotrophoblasts into non-invasive and multinucleated syncytiotrophoblasts at the human fetal-maternal interface. Decorin, a decidua-derived TGF-β binding proteoglycan, negatively regulates proliferation, migration, and invasiveness of human extra villous trophoblast cells in a TGFβ-independent manner.