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Review article

Regulation of trophoblast differentiation during embryo implantation and placentation: Implications in pregnancy complications

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ABSTRACT

A significant proportion of pregnancy related complications like preterm birth, preeclampsia, intrauterine growth restriction (IUGR) and spontaneous abortion may be due to defects at various stages of embryo implantation process, in particular, placentation. One of these defects is impaired syncytialization. This may also be responsible for low success rate of embryo implantation during Assisted Reproductive Technology (ART). As it is an early differentiation event of the trophectoderm, unveiling its elementary molecular network might help in understanding the cause behind such complications and even ameliorate the success rate of pregnancies. Therefore, the current review highlights the available information with respect to effector molecules such as syncytins, syndecan-1, CD98, connexin-43, proteases and protease convertase in trophoblast syncytialization. Promotion of syncytialization by EGF, hCG, IGFs, LIF etc. and its inhibition by TGF-β1 and TNF-α is also discussed. The signaling pathways, such as PKA-CREB, MAPK, STAT, Wnt/β-catenin etc. through which various factors modulate the process of syncytialization have also been presented. Post-transcriptional regulation via microRNAs has also been discussed. The information provided in this review will help in our understanding of the molecular mechanisms associated with syncytialization and their implications in pregnancy related complications.

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1. Introduction

The worldwide human population growth might point toward the virility of its reproductive potential; however, the efficiency of human reproduction is quite low. The average human monthly fecundity rate that represents the probability to get pregnant in one menstrual cycle, is only 20%. Nearly 15% of human couples suffer from one or the other kind of infertility. In addition to subfertility in humans, there is also a high percentage of pregnancy loss due to embryo wastage during preimplantation and at early stages of pregnancy.[1] Further the process of implantation is equally inefficient, as exemplified by ~25 to 35% success rate of implantation during Assisted Reproductive Technology (ART).[2]

In humans, rate of conception depends on the fertilization of the oocyte followed by implantation and its development till term. The success of each event depends on the success of the preceding event. Fertilization leads to zygote formation, which during its journey through the Fallopian tube divides several times leading to formation of a blastocyst. It has an inner cell mass that gives rise to the 'embryo proper' and the outer trophectodermal layer that contributes to the formation of 'placenta'. The blastocyst can implant on the receptive endometrium only during the "Window of Implantation", which lasts for a limited period.[3–7] This occurs in the mid-luteal phase of the female menstrual cycle, which is also accompanied by initiation of pre-decidualization of stromal cells around the terminal spiral arteries of the superficial endometrial layer. In the absence of fertilization, these cell disintegrate with the onset of menstruation mediated by fall in circulatory progesterone levels. However, in a conception cycle, stromal-decidual cell transition occurs in late lacunar, early villous stage of placentation ~3 to 4 days after trophoblast invasion of uterine epithelium ultimately involving the entire endometrium.[8,9] Implantation process is broadly classified into three stages: apposition, adhesion, and invasion. By this time the blastocyst trophectoderm has differentiated into an outer, multinucleated primitive or early syncytium and an inner mononuclear layer of early cytotrophoblasts. Apposition is the initial stage signifying loose connection of the blastocyst to the uterine wall. It is followed by strong and stable adhesion between the blastocyst and the uterine epithelium, involving an increased physical contact carried out by

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integrins, L-selectins, mucin-1 and heparin bound epidermal growth factor.[10] The last stage is the invasion process, which in several species including humans, starts with the penetration of the trophectodermal processes between the healthy luminal epithelial cells to the basal lamina and further extending to the uterine stroma, known as intrusive type of implantation, which is different from displacement type of implantation that is seen in rodents like mice, rats and hamsters where uterine epithelial cells are sloughed off from the underlying basal lamina, promoting blastocyst invasion.[10–13] After successful implantation inside the uterus, the trophoblast precursor cells give rise to mononucleated cytotrophoblasts which further undergo differentiation giving rise to two notable trophoblast lineages:

i) The invasive/extravillous lineage: Invasive capabilities developed by the cytotrophoblasts characterize them as undergoing extravillous differentiation. Their major role is to regulate feto-maternal blood flow by remodeling the uterine spiral arteries. They also help in anchoring the placenta to the uterus.[14] Altered invasiveness can lead to intra-uterine growth restriction (IUGR) or can lead to spontaneous abortion due to premature rise in oxygen level.[15]
ii) The syncytial/villous lineage: Syncytial differentiation is characterized by the proliferation and fusion of the villous cytotrophoblast cells at the basal membrane giving rise to the multinucleated overlying syncytiotrophoblast layer. This process is called syncytialization. Syncytiotrophoblast performs various functions, like feto-maternal exchange of nutrients, gases, and other factors, secretion of various growth factors and steroid or protein hormones which are crucial for fetal growth and/or pregnancy maintenance.[14] Dysregulation during syncytial development may lead to pregnancy complications like preeclampsia or even IUGR.[16]

Therefore, in normal physiological conditions, processes of trophoblast invasion and syncytialization are tightly regulated. This review will majorly focus on the underlying mechanisms associated with trophoblast differentiation and its implications on pregnancy outcome. The role of various transcription factors, proteins and signaling pathways involved in trophoblast fusion will be presented. The prospective role of microRNAs (miRNAs) will be briefly highlighted in modulating trophoblast fusion.

2. Human placental development

Humans have hemochorial placentation where the placenta directly bathes in maternal blood. A.A.W. Hubrecht in the 19th Century gave the name ‘trophoblast’ to the blastocyst cells that fulfill embryo’s nutritional needs and forms the placenta.[17] The early syncytium, formed by blastocyst trophoblast differentiation, produces various enzymes and apoptotic factors that help in extracellular matrix (ECM) degradation and enable blastocyst to embed inside the endometrial stroma.[11] Following implantation, the villous stage of placental development commences and the blastocyst trophectodermal cells are now called cytotrophoblasts.[18] By 10th to 12th week of pregnancy, the placental villous tree like structure becomes apparent with maternal blood filled in its inter-villous spaces surrounded by floating and anchoring villi. These villi have an outer layer of multinucleated syncytiotrophoblast covering a layer of mononucleated cytotrophoblasts. An anchoring villous contains two types of cytotrophoblasts: the villous cytotrophoblast and the extravillous or intermediate cytotrophoblast. The villous cytotrophoblast cells (VCT) are polar immotile cells that differentiate and fuse to form syncytia, whereas the extravillous cytotrophoblast (EVT) are non-polar invasive cells. Anchoring villous is formed when a floating villous comes in contact with the decidua, there is breach in the syncytial layer and the cytotrophoblast cells proliferate to form a cell column anchoring the villous to the decidua. Toward the proximal end i.e. toward villous basement membrane side, the cell column consists of actively proliferating EVT whereas toward the distal end these cells cease to divide and acquire invasive mesenchymal cell like properties. These are further classified into ‘interstitial’ (iCTB) and ‘endovascular’ (eCTB) cytotrophoblasts. The iCTB mimic endometrial fibroblasts and invade the decidua and the one-thirds of the myometrium where they form multinucleated giant cells and thus control the extent of invasion. The eCTB are phenocopies of the endothelial cells of the uterine spiral arteries and replaces them, resisting high velocities of maternal blood flow.[18] A brief account of placental development has been depicted in Fig. 1 following blastocyst implantation.

3. Consequences of impaired placental development

Defect in trophoblast development at blastocyst stage or at later stages of differentiation especially during the first trimester into either syncytial or invasive pathways may lead to pregnancy associated complications like unexplained miscarriages, pre-eclampsia or IUGR (Fig. 2).[16,19] Early pregnancy loss and first trimester miscarriages might be due to chromosomal anomalies or might be due to reduced trophoblast invasion and inadequate maternal arteriole plugging. This can lead to premature entry of maternal blood into intervillous spaces, causing oxidative stress in the placental tissue which might be the primary cause of early pregnancy loss even in the absence of abnormal karyotype. Furthermore, excessive local placental inflammation due to dysregulated expression of inflammatory factors in Hofbauer cells and syncytiotrophoblast may also lead to early pregnancy loss.[19] As first trimester placental development is highly vulnerable to any intrinsic or extrinsic insult, expression of genes that are involved during this period were found to include genes associated with immune tolerance, cell cycle progression, regulation of apoptosis, development, epithelial-mesenchymal transition and transport proteins.[20] Dysregulation in genes involved in immune responses, antigen processing, angiogenesis, transport processes etc. were found to be associated with preeclampsia.[19] Preeclampsia is one of the most common cause of maternal mortality and is prevalent in 5–7% of pregnancies worldwide. It is associated with maternal hypertension and proteinuria at 20 weeks of pregnancy onwards in women with prior normal blood pressure. It can be further divided as early onset (before 34 weeks of gestation) and late onset (after 34 weeks of gestation) preeclampsia. Majority of cases are late onset preeclampsia, where there is no effect on the growth of the fetus and uterine spiral arteries are normal having unaltered blood flow pattern and is often associated with increased placental mass. Whereas the etiology of early onset preeclampsia is very similar with that of IUGR, that includes restricted fetal growth, inadequate invasion of the uterine spiral arteries, abnormal feto-maternal blood flow with increased resistance of the placental vessels. Latest hypothesis of the origin of preeclampsia states that any impairment or insult in the development of blastocyst trophoblast or early cytotrophoblast can result in severe outcomes starting from a combination of preeclampsia or IUGR or even spontaneous abortion. Any insult in the differentiation of EVT results in IUGR with abnormal uterine spiral artery remodeling and restricted endovascular trophoblast invasion resulting in oxidative damage of the villous tissue due to increased flow velocity of maternal blood in the intervillous space. Whereas, defect in VCT differentiation results in preeclampsia associated with the release of syncytiotrophoblast membrane fragments (STBM). Impaired syncytial fusion may lead to dysregulation in syncytiotrophoblast turnover, that is improper balance between

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