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Trophoblast Giant Cells, the Prime Suspects of Deficient Placentation Associated With Pregnancy Complications

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The placenta, as the indispensable intermediary organ between mother and fetus during pregnancy, assumes fetal nutrition for normal growth and development (1-3).

The embryonic portion of human placenta arises from the blastocyst and is mainly composed of chorionic villi, as its functional and structural units (2, 4).

Embryo implantation and invasion of the placenta into endometrium are mediated by extravillous trophoblast cells that, morphologically, are identifiable from other villous cells (4, 5). Extravillous trophoblast cells also are known as trophoblast giant cells (TGCs). The TGCs differentiate from the blastocyst trophectoderm layer during migration through the placental decidua (4, 6). These multinuclear cells have extensive cytoplasm, which contains necessary organelles for their endocrine functions (6).

The TGCs, using their specialized nature, convert the placenta to an endocrine organ that generates the hormones necessary for maintenance of pregnancy. These hormones work via induction of changes in the maternal physiology (3, 7). Transition of these factors to fetus circulation affects its development (7). Syncytiotrophoblast secretions, such as placental growth factor and a soluble receptor of vascular endothelial growth factor, are important to maintain the normal function and structure of maternal endothelial cells. Reports showed that this process is associated with pathogenesis of vascular disorders in pregnant women (3, 8).

During implantation, TGCs cooperate in uterine decidualization and remodeling of uterine spiral arteries in the decidua and uterine myometrium. These structural changes alter uterine vascularization, leading to increase in blood flow and decreased vascular resistance (4, 6). The TGCs protect the developing embryo by acting mother adaptability to pregnancy (6, 7). Therefore, normal development of TGCs is an essential process for the progression of blastocyst attachment to the uterine wall, adaptation of the maternal immune system and the required exchange between the mother and her fetus (3).

Regulation of TGCs development is dependent on various factors (6). The TGCs express oncogenes and molecules with adhesion properties that differ from other chorionic cells like c-erbB-2, integrins and other cell adhesion molecules (9, 10). These molecules, participate in the placentation by attaching the TGCs to extracellular matrix, matrix destruction and migration through the decidua. Increment of similar factors expressed in the decidua, in turn, regulates the trophoblastic invasion. Disorders in each of these elements could result in faulty trophoblastic invasion and embryo implantation (4, 5).

Players of defective placentation are premature detach, decidual confined invasion and disorder in vascularization and unfortunately decidual agents are responsible for leadership of this hostile orchestra (8).

According to previous studies, during pregnancy-complicating conditions, altered expression of several cellular factors in trophoblast and abnormality in the development and secretory function of TGCs are probably related to impaired placentation and maternal and/or fetal unpleasant fate (11). For example, investigations in pregnant patients with lupus erythematosus disease demonstrated that abnormal vascular remodeling is associated with defective placental attachment. These defects can cause critical effects on higher rate of pregnancy related complications, such as intrauterine growth restriction (IUGR), abortion, preeclampsia (PE) and preterm birth, in these women. One reason for this association might be the interaction of genetic background and lupus-related conditions and its effect on the histophysiology of the placenta (12).

Histological features of lupus placental samples confirm existence of vascularization defects in uterine and pla-

centa interface. These conditions also have been found in placental tissues of diabetic mothers and patients with PE during pregnancy (11). Stereological insight into placental changes during several diseases affecting pregnancy, such as lupus and placenta previa, in our previous studies, have showed that the disturbance of the normal structure of placenta might lead to perilous pregnancy for mother and afterward fetus (1, 2). In a similar way, insufficient placentation and impaired development of placenta could be corroborated in the pathogenesis of PE and IUGR (12).

Since the TGCs, due to their endocrine ability, tightly control uteroplacental vascularization, it is probable that these cells can be the main interventions of the pregnancy disorders (3, 8). All these findings indicate the probable involvement of TGCs in placental malfunctions that occur in IUGR, PE and other materno-fetal life-threatening conditions (4, 6).

Published reports assumed that the factors influencing the differentiation and function of TGCs might interfere with their invasion and affect pathogenesis of gestational complications, including pregnancy loss, IUGR, eclampsia, etc. (4). As it was demonstrated, disruption in TGCs development and their decidua-limited migration could be related to unsuccessful invasion or implantation of the embryo into the maternal uterine wall in PE and IUGR cases (4).

In-vitro examinations have shown that changes in gene expressions and the levels of required factors for TGCs differentiation might lead to altered counts of these giant cells. For example, products of Foxd3, Nodal and P53 genes led to increased number to TGCs in culture (6, 7). On the other hand, according previous studies, certain of these genes and their products are associated with increased incidence of several pregnancy complication. As an instance, reports showed that there is a disorder in the expression of P53 in lupus patients (13). These findings result in sparking the hypothesis that any factors including pregnancy-related disease affecting these genes could probably be able to control the number of TGCs population and eventually mode of placentation (6, 7).

Therefore, genetic and epigenetic investigation in patients with underlying disease like PE, lupus erythematosus, etc. around association of mentioned genes and factors with pregnancy disorders may be interesting for future researches.

Today it is accepted that the normal structure of the placenta could be changed due to gestational diseases, leading to defective placentation and, subsequently, fetal and maternal morbidity and mortality. However, the cellular and molecular bases of these changes are unknown clearly (1, 2).

Using newly entered techniques to medical sciences, including combination of stereology and immunohistochemistry and molecular assays may be helpful in determining the precise details of these changes and, probably, may lead to access new therapeutic strategies for increasing successfulness of pregnancies in the human populations.

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