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Review article

A revised picture of extravillous trophoblast invasion

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ABSTRACT

Extravillous trophoblasts (EVTs) invade the decidual stroma (interstitial trophoblast) and thereby attach the placenta to the uterus. They also invade toward spiral arteries (endovascular trophoblast) for the establishment of the uteroplacental blood flow. The latter does not start before the end of the first trimester of pregnancy. A new type of extravillous trophoblast invading into uterine glands (endoglandular trophoblast) has been described recently opening uterine glands toward the intervillous space of the placenta to enable histiotrophic nutrition. This review gives an overview about the different subtypes of EVTs and presents novel peculiarities in the field of EVT invasion. EVTs invade more structures in the maternal decidua than previously assumed. Especially a proper invasion of uterine glands by endoglandular trophoblasts may have more impact on the outcome of pregnancy than assumed so far.

1. Introduction

So far the general opinion in placental research is that extravillous trophoblasts (EVTs) invade the decidual stroma (interstitial trophoblast) and thereby attach the placenta to the uterus, as well as invade toward spiral arteries (endovascular trophoblast) for the establishment of the uteroplacental blood flow.[1] The latter does not start before the end of the first trimester of pregnancy.[2] Recently, also a new type of extravillous trophoblast invading into uterine glands (endoglandular trophoblast) has been described opening uterine glands toward the intervillous space of the placenta to enable histiotrophic nutrition.[3]

EVTs can be found within the chorionic and basal plates, the chorion laeve and in the decidua basalis, the latter being the focus of this article. EVTs within the decidua basalis originate from cytotrophoblastic cell columns at the tips of anchoring villi. There – from proximal to distal – the cytotrophoblasts turn from a proliferative and non-invasive (HLA-G negative) to an invasive and non-proliferative (HLA-G positive) phenotype.[1] This also correlates with a switch in the expression of integrin subunits, members of a family of adhesion molecules.[4]

Invasive EVTs are characterized by a strong expression of HLA-G.[5–7] EVTs also show high expression of cytokeratin 7, while expression of cytokeratin 7 can also be found in the uterine epithelium as well as the glandular epithelium and thus is not a specific marker for EVTs in the decidua basalis.[8] The cytokeratin 7 expression of EVTs reflects their epithelial origin.

An extracellular matrix is secreted by EVTs (matrix-type fibrinoid[9]) and due to their location at the maternal-fetal interface this matrix is often associated with maternal components derived either from maternal blood (fibrin-type fibrinoid) or secretory products of decidual cells. These resulting peritrophoblastic accumulations of extracellular matrix are of mixed origin and referred to as "fibrinoid" in general.[1] It needs to be mentioned that a variety of antibodies such as the one directed against von Willebrand Factor (vWF) react with fibrinoid depositions, when assessing first trimester decidua basalis immunohistochemically. This review gives an overview about the different subtypes of EVTs and presents novel peculiarities in the field of EVT invasion.

2. Interstitial trophoblast

Interstitial trophoblasts originate from the distal ends of trophoblastic cell columns, in a histological section they are of variable appearance (Fig. 1). One phenotype is characterized by a small spindle-shaped cellular and nuclear appearance. These cells are mostly embedded in little fibrinoid matrix and express

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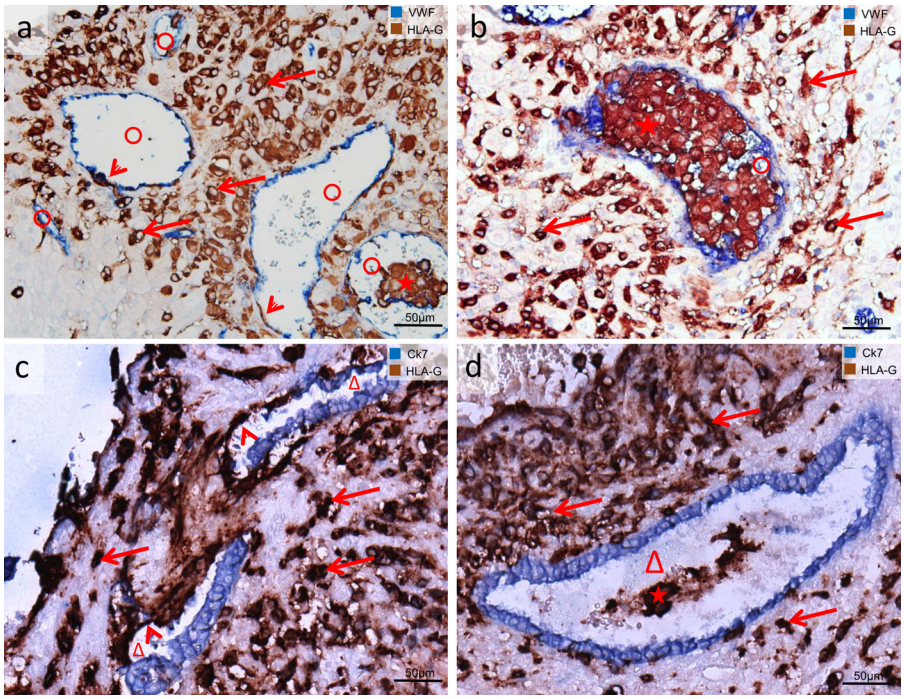

Fig. 1. Interstitial, endovascular and endoglandular trophoblast. Immunohistochemical double staining of paraffin sections from first trimester decidua basalis (gestational age 9–11 weeks). First row is stained for HLA-G (brown, extravillous trophoblasts) and von Willebrand Factor (vWF, blue, vascular endothelium), second row is stained for HLA-G (brown, extravillous trophoblasts) and cytokeratin 7 (Ck7, blue, glandular epithelium). Arrows show examples for interstitial trophoblasts situated in the decidual stroma. (a and b) Endovascular trophoblasts are replacing the vascular endothelium (arrow heads) and agglomerate to trophoblast plugs (stars) in the vascular lumen (circles). (c and d) Endoglandular trophoblasts replace the glandular epithelium (arrow head) and are also situated in the glandular lumen (endoglandular trophoblast, star; lumen, triangle). No nuclear counterstain.

integrins such as α5β1, αvβ3/5.[10] Another phenotype, which is very prominent in the decidua basalis is characterized by a large polygonal cellular and nuclear appearance. These cells secrete large amounts of matrix-type fibrinoid and can be identified due to their size. They express integrins such as α6β4, α5β1.[10]

The two cellular phenotypes differ in their frequency of appearance in the first and third trimester of pregnancy. The small spindle-shaped cells are more prominent early in gestation while the large polygonal cells are very prominent at term.[1,10] In uncomplicated pregnancies invasion of interstitial EVTs stops at the inner third of the myometrium. In compromised pregnancies (*e.g.* placenta accrete, placenta percreta, placenta increta) the invasion does not stop at this point but may reach into the muscle wall of the bladder.[1,11]

In the last years, there is accumulating evidence that the maternal decidua plays an active role during encapsulation of the early conceptus as well as interstitial trophoblast invasion than assumed. Factors secreted by decidual cells (*e.g.* protease inhibitors) may inhibit and/or control the invasiveness of EVTs.[12] Besides, it was demonstrated that human endometrial stromal cells also display a migratory and invasive capacity and thereby contribute to the intense tissue remodeling associated with embryo implantation, trophoblast invasion and endometrial regeneration.[12] Weimar et al. showed that endometrial stromal cells of fertile women discriminate between high- and low-quality embryos whereas endometrial stromal cells from women suffering from recurrent miscarriage fail to do so.[13] There is increasing evidence that implantation failure and recurrent miscarriage involves abnormal migratory responses of decidualizing endometrial stromal cells and trophoblast signals. The migration of decidualizing endometrial stromal cells also serves to support blastocyst implantation and embryo selection depending on embryo quality.[14]

3. Endovascular trophoblast

By the current state of scientific knowledge perfusion of the intervillous space of the placenta with maternal blood is only fully established at the end of the first trimester. This was clearly depicted by blood flow measurements which show no maternal blood in the intervillous space prior to 10–12 weeks of pregnancy.[2,15–18]

During the first trimester of pregnancy, decidual spiral arteries are transformed from narrow, muscular vessels into expanded stiff tubes. This is accompanied by loss of vascular smooth muscle cells and endothelial cells.[19] Finally, EVTs invade through the vessel media and reach and replace the endothelium, now lining the vessel lumen. Already in 1967 this process was termed "physiological change" by Brosens et al.[20] Until recently the remodeling of spiral arteries was believed to begin dependent on extravillous trophoblast invasion.[21,22] Smith et al. demonstrated that vascular remodeling occurs prior to trophoblast invasion in trophoblast-independent stages.[19]

Endovascular trophoblasts massively infiltrate uterine spiral arteries, some of them line and remodel the vessel, while a large number of trophoblasts accumulates in the lumen of spiral arteries and forms trophoblast plugs (Fig. 1a and b). These plugs are responsible for blocking of blood flow from the mother toward the placenta during early pregnancy, only blood plasma is seeping through the plugs toward the intervillous space.[2] Toward the end of the first trimester the trophoblast plugs start to disintegrate and this marks the onset of the utero-placental blood flow. This process is correlated with a rise in oxygen concentration within the placenta and has been reviewed by Huppertz et al.[23] Very recent data provide evidence that endovascular trophoblasts are also situated in uterine veins (unpublished data).