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REVIEW ARTICLES

Apoptosis and its role in the trophoblast

Berthold Huppertz, PhD,[a] Mamed Kadyrov, MD,[a] John C. P. Kingdom, MD[b]

Department of Anatomy II, University Hospital RWTH,[a] Aachen, Germany; Department of Obstetrics and Gynecology, Samuel Lunenfeld Research Institute, Mount Sinai Hospital, University of Toronto,[b] Toronto, Canada

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During early placentation the trophoblast of the human placenta differentiates to the villous and extravillous types of trophoblast. Villous trophoblast provides the epithelial cover of the placental villous trees in direct contact to maternal blood. Extravillous trophoblast invades maternal uterine tissues thus directly contacting maternal stromal and immune cells. A subset of extravillous trophoblast, endovascular trophoblast initially occludes the lumen of spiral arteries and comes into direct contact with maternal blood.

In recent years apoptosis has been described in both types of trophoblast and the importance of this cascade for the normal function of the trophoblast has become obvious. One feature of serious conditions such as preeclampsia or intrauterine growth restriction is changes in apoptosis regulation in villous and/or extravillous trophoblast resulting in altered trophoblast invasion and/or shedding into the maternal circulation. This review summarizes recent findings on trophoblast apoptosis in normal and pathologic pregnancies.

The trophoblast lineage is the first to differentiate during human development, at the transition between morula and blastocyst. Initially, at day 6 to 7 postconception, a single layer of mononucleated trophoblasts surrounds the blastocoel and the inner cell mass. At the site of attachment and direct contact to maternal tissues, trophoblast cells fuse to form a second layer of postmitotic multinucleated syncytiotrophoblast.[1] Once formed, the syncytiotrophoblast grows by means of steady incorporation of new mononucleated trophoblasts from a proximal subset of stem cells.[2] Only at around day 14 mononucleated cytotrophoblasts break through the syncytiotrophoblast and begin to invade the uterine stroma at sites called trophoblastic cell columns. Such cells are termed *extravillous trophoblasts*.

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Both types of trophoblast keep a subset of cells in direct contact to the villous basement membrane—these cells retain their generative potential (Figure 1) and are able to proliferate in response to growth factors such as FGF4.[3] In the extravillous compartment, cell proliferation advances rows of extravillous trophoblasts into the uterine stroma where they stop proliferating and undergo invasion as a result of differentiation. Similarly, differentiating cells resulting from mitosis in the villous compartment are postmitotic and undergo syncytial fusion directed by the transcription factor glial cell missing (GCM1).[4] Somehow the physical interaction of proximal cytotrophoblasts with the basement membranes allows them to retain a proliferative phenotype. Villous cytotrophoblasts can be made to form extravillous columns, indicating that they have stem cell-like properties.[3]

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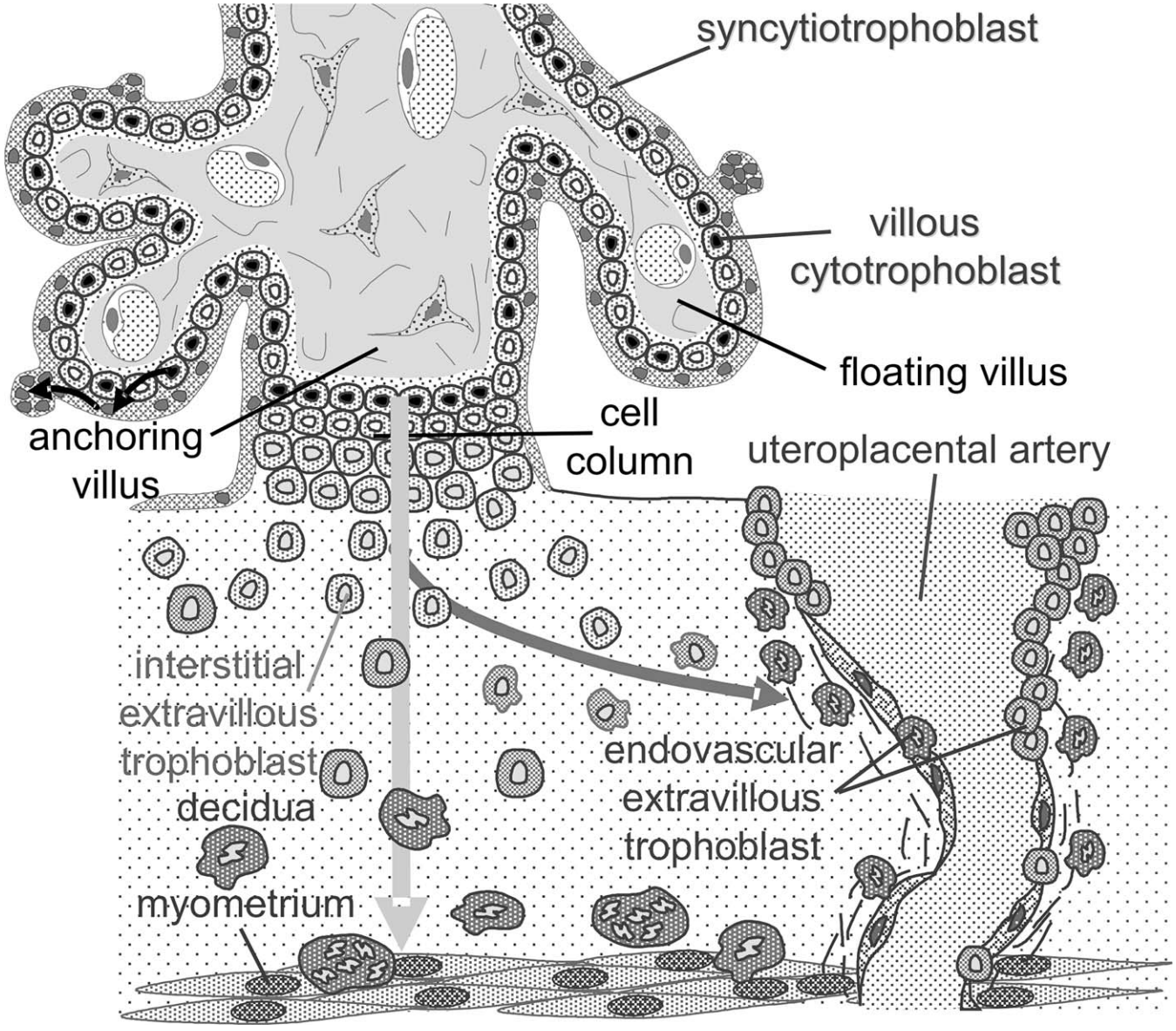

Figure 1 Schematic representation of the 2 types of trophoblast: villous and extravillous trophoblast. The villous trophoblast stem cells (with *dark nuclei*) differentiate, fuse, and maintain the multinucleated syncytiotrophoblast. Within the syncytiotrophoblast, a second differentiation pathway takes place resulting in the accumulation of aged nuclei in syncytial knots (*black arrows* in villus on the lower left). The extravillous trophoblast stem cells (with *dark nuclei*) are localized at the basement membrane of anchoring villi in the most proximal part of the cell columns. Their postproliferative daughter cells invade maternal tissues as interstitial trophoblast penetrating endometrium and the first third of the myometrium (*light grey arrow*). A subset of the interstitial trophoblast reaches the walls of spiral arteries and becomes endovascular trophoblast (*dark grey arrow* to the right).

Villous trophoblast and the role of apoptosis

In the last decade we and others have characterised the role of the apoptosis cascade in villous trophoblast turnover and syncytium formation. Observations indicate that the process of syncytial fusion is linked to the "initiator stages" of the apoptosis cascade within the cytotrophoblast cells, whereas the extrusion of syncytial knots from the syncytiotrophoblast is the result of the final "execution stages" of the apoptosis cascade within the syncytiotrophoblast.[5-9]

Cytotrophoblast and initiator stages of apoptosis

At present, the mechanisms through which the apoptosis cascade is initiated in cytotrophoblasts, then subsequently