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Review: Where is the maternofetal interface?

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ABSTRACT

Ask where the maternofetal interface is and placental biologists will tell you, the syncytiotrophoblast and extravillous cytotrophoblasts. While correct, this is not full extent of the maternofetal interface. Trophoblast debris that is extruded into the maternal blood in all pregnancies expands the maternofetal interface to sites remote from the uterus. Trophoblast debris ranges from multinucleated syncytial nuclear aggregates to subcellular micro- and nano-vesicles. The origins of trophoblast debris are not clear. Some propose trophoblast debris is the end of the life-cycle of the trophoblast and that it results from an apoptosis-like cell death, but this is not universally accepted. Knowing whether trophoblast debris results from an apoptosis-like cell death is important because the nature of cell death that produced trophoblast debris will influence the maternal responses to it. Trophoblast debris is challenging to isolate from maternal blood making it difficult to study. However, by culturing placental explants in Netwells™ we can readily harvest trophoblast debris from beneath the Netwells™ which is very similar to debris that has been isolated from pregnant women. We have found that trophoblast debris from normal placentae shows markers of apoptosis and is phagocytosed by macrophages or endothelial cells, producing a tolerant phenotype in the phagocyte. Whereas, when we culture normal placental explants with factors such as antiphospholipid antibodies (a strong maternal risk factor for preeclampsia), or IL-6 (which is found at increased levels in the sera of preeclamptic women), the death process in the syncytiotrophoblast changes, such that the trophoblast debris becomes more necrotic. Phagocytosis of this necrotic debris leads to activation of endothelial cells. Trophoblast debris greatly expands the maternofetal interface and the nature of that debris is likely to strongly influence the responses of the maternal vascular and immune systems to the debris.

1. Introduction: where is the maternofetal interface?

Traditionally the maternofetal interface in humans was considered to be located in the uterus with the major interactions between the fetal trophoblast and maternal cells at two sites, the placental bed and the syncytiotrophoblast. At the leading edge of the implantation site, in the placental bed, invading cytotrophoblasts migrate deeply into the interstitium of the decidua where they encounter cells of the decidual stroma, including cells of the maternal immune system such as macrophages, T cells and uterine natural killer cells. In the placental bed, invasive cytotrophoblasts also breach the walls of the spiral arteries and invade antidromically, against the flow of maternal blood, where they may replace the endothelial cells that line these vessels and erode the musculoelastic walls of the spiral arteries transforming them into large-bore low- resistance vessels [1]. The placental bed is a relatively confined area of interaction between maternal and fetal cells, but has in the past received a great deal of attention due to the prolonged intimate contact between fetal trophoblasts and maternal cells.

Probably a much larger surface for interaction between maternal and fetal cells is the syncytiotrophoblast, the multinucleated single cell that lines the entire surface of the human placenta, which is bathed in maternal blood. The syncytiotrophoblast is estimated to have a surface area of some 11.3 m^2 at the end of gestation [2]. On a daily basis, billions of maternal cells, including leucocytes of the maternal immune system, pass by the syncytiotrophoblast, seemingly without noticing this vast area of fetal tissue.

While these have been the two most commonly recognised regions of the maternofetal interface, for the past 120 years it has been known that the maternofetal interface extends far beyond

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the uterus. In 1893, Schmorl first reported the presence of what appeared to him to be multinucleated fragments of the syncytiotrophoblast lodged in the small pulmonary vessels of women who had died during eclampsia (Fig. 1). Schmorl referred to these fragments as Placentarzellen (placenta cells) but the preferred term today is syncytial nuclear aggregates (SNAs) [3]. While Schmorl's original report described SNAs in women with eclampsia, within 10 years Schmorl himself and others had confirmed that SNAs were present in the lungs of pregnant women regardless of whether they had eclampsia or not (reviewed in Askelund et al. [3]). The process of the transport of SNAs from the placental site to the lungs is called trophoblast deportation. This term was coined by Veit although his original use of the term was in relation to an ectopic implantation [4]. In the largest study of its type, Attwood and Park [5] clearly demonstrated that SNAs are deported in all pregnancies but that there is an increase in the quantity of deported SNAs in preeclampsia/eclampsia. It was possible for Schmorl and other early pathologists to recognise SNAs due to their large size and distinctive multinucleated morphology, but it has become apparent over recent years that, in addition to SNAs, a wide range of trophoblast-derived material is shed or extruded from the placenta into the maternal blood (Fig. 2). Collectively this range of trophoblast material may be referred to as trophoblast debris [3].

2. What is trophoblast debris?

Syncytial nuclear aggregates are the largest known fragments of trophoblast debris but in addition to SNAs, mononuclear cytotrophoblasts, cytokeratin positive anucleate trophoblast ghosts,

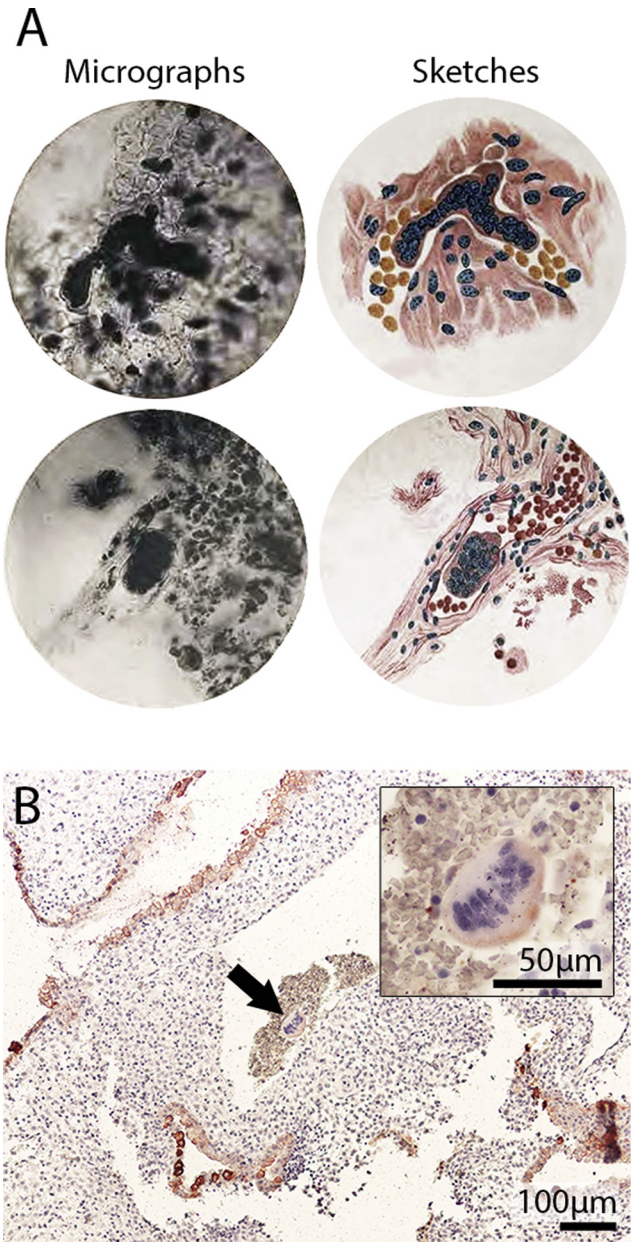

Fig. 1. A) Syncytial nuclear aggregates trapped in the smaller vessels of women who had died in eclampsia, micrographs and colour sketches. After Schmorl [45]. B) A syncytial nuclear aggregate (arrow) in a decidual vein from a normal pregnancy at eight weeks of gestation. The SNA and decidual glandular and surface epithelia were immunostained for cytokeratin, nuclei were counterstained with haematoxylin. Inset shows the syncytial nuclear aggregate at higher magnification.