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Review

An integrative view on the physiology of human early placental villi

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ABSTRACT

The placenta is an indispensable organ for intrauterine protection, development and growth of the embryo and fetus. It provides tight contact between mother and conceptus, enabling the exchange of gas, nutrients and waste products. The human placenta is discoidal in shape, and bears a hemo-monochorial interface as well as villous materno-fetal interdigitations. Since Peter Medawar's astonishment to the paradoxical nature of the mother–fetus relationship in 1953, substantial knowledge in the domain of placental physiology has been gathered. In the present essay, an attempt has been made to build an integrated understanding of morphological dynamics, cell biology, and functional aspects of genomic and proteomic expression of human early placental villous trophoblast cells followed by a commentary on the future directions of research in this field.

Contents

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The professional scientist will attack wherever he can… The point of attack is always a matter of tactics.

Crick (1966)

1. Introduction

Proper placental development and function are critical for the survival of the fetus. Despite the fact that all eutherian placentas share conserved characteristics there are major differences in placental shape (for example, diffuse, cotylendonary, zonary, discoidal, bidiscoidal), type of placental interface (for example, epitheliochorial, endotheliochorial, hemochorial), and nature of materno-fetal interdigitations (for example, folded, lamellar, villous, trabecular, labyrinthine). The anatomical characteristics of the human placenta include a discoidal shape, a hemo-monochorial interface and villous materno-fetal interdigitations (Bernirschke et al., 2006). The objective of the present review is to build an integrated understanding of first trimester villous trophoblast physiology. To this end, we shall discuss morphological dynamics, cell biology, and functional aspects of genomic/proteomic expression in trophoblast cells of early placenta. Finally, we shall forward a commentary on disease correlates for future direction of research in first trimester placental biology.

2. Early placental morphological dynamism

The trophectoderm of the blastocyst is responsible for the development of the human placenta (Huppertz, 2008a,b). In the first weeks after implantation, the trophoblast lineage gives rise to two main types of trophoblast with a variety of subtypes: (i) villous trophoblast: this type includes the syncytiotrophoblast that forms the entire epithelial lining of the villous trees, and the villous cytotrophoblast cells that represent the main germinative population giving rise to the syncytiotrophoblast via syncytial fusion. (ii) Extravillous trophoblast: this type comprises cells derived from trophoblast cell columns of anchoring villi that are non-proliferating and invade into maternal tissues in the placental bed of the uterine wall (Moser et al., 2010).

During the first week after implantation it is the early syncytiotrophoblast that is the embryonic tissue in direct contact to maternal tissues. Within the syncytiotrophoblast fluid filled lacunae develop into a single large space that will become the space for maternal blood later in pregnancy (intervillous space). The surface of the syncytiotrophoblast facing this space enlarges and forms villous structures. The villi remaining in direct contact to maternal tissues develop into anchoring villi fixing the placenta and the embryo to the uterine tissues. Using the anchoring villi as source, only in week five of pregnancy (post-menstruation) extravillous trophoblast cells develop and come into first contact with maternal tissues.

Villous development starts with syncytial sprouts outgrowing from core structures. These structures are built from the syncytiotrophoblast as outer layer followed by a complete layer of villous cytotrophoblast cells. The core of these structures, separated from the villous trophoblast by a basement membrane, is filled with mesenchymal cells derived from the early embryo. While further outgrowing from the cores, the syncytial sprouts are now filled by cytotrophoblast cells first, then also by mesenchymal cells. This process leads to the development of a villous tree with a main villus emanating from the chorionic plate and several lines of villous side branches. Since the syncytiotrophoblast remains the single cover of all these trees, even at term the whole villous surface (12–15 m^2) is still covered by a single syncytiotrophoblast layer containing billions of nuclei in a continuous cytoplasm without any lateral membranes (Bernirschke et al., 2006).

During the first trimester of pregnancy, only two out of five (mesenchymal, immature intermediate, mature intermediate, stem and terminal) villous types of the human placenta develop: mesenchymal villi and immature intermediate villi. Mesenchymal villi start to develop around week five of pregnancy. They are the most primitive villi comprising a dense and cell-rich stroma with only very small vessels that just start to develop and grow. With further growing of the villous trees, this first villous type develops into immature intermediate villi starting at around week eight of pregnancy. This villous type shows a unique feature not present in any other villous type. The villous stroma of immature intermediate villi contains fluid filled channels, called stroma channels that are not covered by any endothelial or epithelial lining. These channels start and end within this villous type and hence there is no connection to any other fluid filled structure in the villous trees. The channels are full of embryonic macrophages (Hofbauer cells) while in all other villi macrophages can be found in the extracellular matrix of the villous stroma. Beside stroma channels, the villous core of immature intermediate villi contains small vessels that are not necessarily localized in close vicinity to the villous trophoblast (Bernirschke et al., 2006).

Looking at the morphology of villous types in early pregnancy, these villi are not built to enable optimal transfer of nutrients and gases from the mother to the embryo. Rather, long distances between the two circulatory units and only a plasma flow on the maternal side do not provide an optimal basis for exchange. Flow of maternal blood cells into the intervillous space of the placenta only starts at the end of the first trimester and only then the partial oxygen pressure rises from below 20 mm Hg in the first trimester to about 60 mm Hg in the second trimester (Jauniaux et al., 2000). Villous development enabling optimal nutrient and gas exchange only starts after midgestation with the first appearance of terminal villi at around week 25–27 of pregnancy.

3. Cell biological aspects of early placental villi

3.1. Villous trophoblast

Throughout pregnancy, the metabolic demand of the fetus increases with its rapid growth. The placenta and especially the placental barrier need to adapt accordingly to meet the demands of the fetus. One of the main morphological changes of the villous trophoblast is the decrease in the diffusion distance between maternal and fetal blood. In the first trimester this distance ranges between 50 and 100 μm, while it is reduced to 4 and 5 μm at term (Bernirschke et al., 2006) (Fig. 1).

3.2. Syncytiotrophoblast

The syncytiotrophoblast is the outermost cover of all placental villi. It is a multinucleated layer without lateral cell borders, and hence is built of a single cytoplasm with an apical and a basal plasma membrane covering all villi of a given placenta. During the first trimester of pregnancy, the microvilli on the apical membrane are in contact to the maternal plasma flowing through the intervillous space. Initial development, growth and maintenance of the syncytiotrophoblast are achieved by continuous fusion with underlying cytotrophoblast cells, due to the absence of any proliferative capacity of the syncytiotrophoblast. Also RNA synthesis (transcription) is reduced in the syncytiotrophoblast. Most of the