What is the placenta?

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Abstract

Discarded at birth, the placenta is a highly complex and fascinating organ. During the course of a pregnancy, it acts as the lungs, gut, kidneys and liver of the fetus. The placenta also has major endocrine actions that modulate maternal physiology and metabolism, and provides a safe and protective milieu in which the fetus can develop. The human placenta undergoes dramatic transformations in form and function between the first trimester, when organogenesis occurs, and the remainder of pregnancy that reflect evolutionary responses to changing oxygen concentrations in the earth's atmosphere. Recent research indicates a more interactive dialogue between the placenta and the maternal tissues than previously recognized. The endometrial glands provide histotrophic support during the first weeks of pregnancy, and the placenta appears able to stimulate its own development by upregulating gland activity in response to endocrine signals. Extravillous trophoblast cells migrate from the placenta into the uterine wall, where they interact with cells of the maternal innate immune system. These interactions have a physiological, rather than a classical immunological, outcome, and most probably mediate remodeling of the uterine spiral arteries that supply the placenta. Furthermore, deportation of aggregates of transcriptionally active trophoblast nuclei, and the release of exosomes carrying micro-RNAs challenge our perceptions of fetal-maternal signaling and where the placental interface actually lies. Here, we reconsider definitions of the placenta in the light of these recent advances.

Aberrations of placental function are widely recognized as having immediate consequences on the outcome of a pregnancy, and more recently for influencing the life-long health of the offspring. There is thus an urgent need for research into the organ, but what exactly is the placenta that we should be studying? Although on a superficial level the human placenta is readily recognizable as the discoid structure that interfaces with the mother, it is in fact remarkably difficult to define biologically. For one thing, no organ can match the placenta for the diversity of its functions, since it performs the actions of all the major organ systems while these differentiate and mature in the fetus. For another, there is an astonishing range of morphological variations in placental types seen across mammals and even lower orders (Wooding & Burton, 2008). In his seminal monograph on comparative placentation, Harland Mossman attempted to simplify matters by stating 'the normal mammalian placenta is an apposition or fusion of the fetal membranes to the uterine mucosa for physiological exchange' (Mossman, 1937). It is clear from this widely quoted statement that the placenta has two components, a fetal and a maternal one that must interact successfully for a healthy pregnancy. While this is easy to appreciate in a species that has a non-invasive, epitheliochorial placenta, such as the sheep, it is less easy in the haemochorial situation where the maternal epithelium has been eroded. What is the maternal component of the human placenta and where is the maternal-placental interface? Recent advances are challenging some of our preconceptions of what the placenta is, and this Viewpoint touches upon new ideas and areas of uncertainty of significance for contemporary obstetrics and placental research.

According to Mossman, the maternal component of the human placenta must be the endometrium, which undergoes transition to form the decidua in early pregnancy. Although only a few layers of decidual cells are incorporated into the basal plate of the placenta, and are often considered as maternal contaminants following delivery, placental development and function is normally inextricably linked with the endometrium. Whilst it is true that the placenta can attach and sustain for several months a fetus at various ectopic sites, trophoblast invasion is often unregulated and the maternal-placental interface severely disorganized outside the intrauterine environment. Implantation in the human is typically described as a highly invasive

process, during which the conceptus becomes completely embedded within the superficial endometrium. Tongues of syncytiotrophoblast do infiltrate between the uterine epithelial cells, but there is increasing evidence that the endometrial stromal cells play an equally active role, sweeping around to encapsulate the conceptus. Hence, the embedded conceptus continues to protrude into the uterine lumen following implantation.

Development of the placenta is precocious, for the organ must be ready and able to support the fetus. Villous precursors cover the entire surface of the chorionic sac towards the end of the third week post-conception. It is now established that fetal organ development and growth during the first trimester of pregnancy occur in a physiologically low oxygen microenvironment, stimulated by secretions from the endometrial glands that are rich in nutrients and growth factors (Burton *et al.*, 2010). Data from other species demonstrate that the placenta is able to stimulate its own development by signalling to the glands to upregulate the secretion of what are generically referred to as uterine milk proteins (Spencer, 2014). Although there is no firm evidence yet that this occurs in the human, the hypersecretory morphological change seen in the glandular epithelium during early pregnancy, the Arias-Stella reaction, provides indirect support for this fascinating concept. We do know that maternal glycoproteins in the secretions are taken up by the syncytiotrophoblast, where they enter the lysosomal digestive pathway and presumably fulfill the nutrient requirements of the conceptus. In the absence of an effective chorionic circulation at this stage of pregnancy it is unclear how the nutrients reach the embryo. Amino acids accumulate within the fluid in the extraembryonic coelom, and the recent identification of specific transporter proteins on the outer surface of secondary the yolk sac raises the possibility that this structure, largely considered vestigial, plays an important role in transport in the early stages of human development (Jauniaux *et al.*, 2004). Hence, the early, primitive human placenta may function physiologically as a chorio-vitelline placenta, in common with those of many mammalian species (Wooding & Burton, 2008), although morphologically it never develops as such. Given this newly identified reliance on the gland secretions, there is a need to assess whether failure of one or more steps in the placental-endometrial dialogue may underpin some complications of pregnancy. It is notable, for example, that the placenta grows more slowly during the first trimester in

pregnancies that subsequently miscarry or go on to display growth restriction than in normal cases (Reus *et al.*, 2013).

Towards the end of the first trimester, the primitive placenta undergoes remodeling to form the definitive organ and the smooth membranes. This process is associated with onset of the maternal arterial circulation, and is mediated by locally induced oxidative stress due to the concomitant rise in oxygen concentration (Burton *et al.*, 2010). These morphological changes are a reflection of millions of years of adaptation to changes in oxygen concentration in the earth's atmospheric environment. The absence of a continuous maternal circulation inside most of the primitive placenta during the first trimester placental barrier is essential to control the oxygen levels inside the gestational sac during organogenesis. It also adds to the natural defence of the fetus against parasites and viruses when it is at its most vulnerable. Recent changes in human environmental habitats caused by pollution, habits such as smoking, and the increased use of medical and recreational drugs have challenged the concept of a natural protective role of the placental barrier. The thalidomide and diethylstilbestrol teratogenic catastrophes tragically illustrate its limitations. By contrast, recent data from metagenomic sequencing showing that the placenta is frequently colonized with maternal commensal bacteria during pregnancy, and indicate the selective role of the placental barrier and indirectly its additional metabolic and immune contributions to the developing fetus (Romano-Keeler *et al*., 2015). More knowledge in this area is essential in order to better understand our interaction with the terrestrial environment in which placental mammals have evolved over the last 225 millions years.

The onset and subsequent development of the utero-placental circulation is dependent on the conversion of the endometrial spiral arteries from highly contractile muscular arteries into flaccid, dilated conduits. Extravillous cytotrophoblast cells play a key role in this process, and migrate from the tips of the placental anchoring villi into the wall of the uterus as far as the inner third of the myometrium. This deep invasion appears to be a uniquely human phenomenon amongst higher primates, and challenges our perception of the physical extent of the placenta. It is clearly not the basal surface of the delivered placenta, which is a mix of fetal trophoblast and maternal decidual and endothelial cells embedded in a fibrinous matrix. The interactions of the extravillous trophoblast cells

with the maternal innate immune system are also challenging our understanding of the maternal-fetal immune dialogue underpinning pregnancy. It is now evident that a degree of activation of the uterine Natural Killer (uNK) cells is essential for a successful outcome, and that this depends on the combination of HLA-C ligands on the trophoblast cells and killer immunoglobulin-like receptors (KIR) expressed by the uNK cells (Moffett *et al.*, 2015). Far from killing trophoblast cells, the uNK cells appear to encourage migration of the extravillous trophoblast cells into the endometrium. Their release of cytokines and growth factors in response to activation is thought to mediate the arterial conversion. The conversion has a profound impact on the velocity and the constancy of maternal blood flow into the placenta (Burton *et al.*, 2009), and is a key, but hidden, aspect of placental development.

Further challenges to our understanding of the location of the maternal-placental interface arise through a new appreciation of deportation of cells and particles from the placenta. It has long been known that fragments of placenta, in particular aggregates of syncytial nuclei, break off from the villous tree and are swept into the maternal circulation. Most become lodged in the capillary bed of the lungs where they appear to stimulate no local reaction, leading to the perception that this is a passive process. However, it is now realized that these aggregates are transcriptionally active, and may play an important role in maternal-fetal signaling (Rajakumar *et al.*, 2012). They also carry retroviral proteins that potentially have immunomodulatory properties. The situation has become even more complex since the recognition that the placenta releases large quantities of exosomes into the maternal circulation from early pregnancy onwards (Sarker *et al.*, 2014). These nanovesicles are highly stable and contain a wide array of proteins and micro-RNAs that may mediate signaling to the maternal endothelium, organ systems and immune cells. Hence, we need to think beyond traditional endocrinology when considering the influence of the placenta on maternal physiology. Furthermore, the exosomes provide an opportunity to obtain a minimally invasive 'biopsy' of the placenta that could provide insight into its wellbeing.

We have thus come far from the immunological paradox posed by Medawar in 1953, comparing the placenta to an allograft (Colucci *et al.*, 2014). Indeed, it appears that interactions between placental cells and the maternal immune system have evolved to

perform more physiological than classical immunological functions. Nonetheless, the placenta does represent an immunological shield for the fetus, since the absence of Class I and II HLA antigens renders the surface of the villous trees immunologically inert.

The definition of Mossman emphasises transport as the main purpose of the placenta. Whilst exchange is undeniably highly important, the definition fails to recognize the organ's other facets. For example, transport is selective and in general the placenta either excludes or renders inactive maternal hormones and xenobiotics to allow the fetus to develop in a safe and independent milieu. The placenta is also a major endocrine organ, secreting over one hundred peptide and steroid hormones that modulate maternal physiology. Early in pregnancy these promote the accretion of maternal nutrient reserves that are mobilized later for fetal use and lactation. Placental lactogens and growth hormone exert anti-insulin effects and promote lipolysis, boosting maternal glucose and free fatty acid concentrations for exchange to the fetus. Indeed, placental production of growth hormone is so powerful that secretion from the maternal pituitary is suppressed by mid-pregnancy. Hormones, such as erythropoietin and angiotensinogen, mediate maternal cardiovascular and other adaptations.

Given the more tenuous morphological ramifications of the human placenta that are emerging it is perhaps best not to try and define the organ in structural terms as Mossman did, but on a more physiological basis. Hence, we propose that the placenta is the extracorporeal organ that interacts with the endometrium to nourish and protect the fetus, and that orchestrates maternal adaptations to pregnancy. If we are to really understand this remarkable organ a truly multidisciplinary approach is required that takes into account all its diverse facets.

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