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Review

Development of the hemochorial maternal vascular spaces in the placenta through endothelial and vasculogenic mimicry

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ABSTRACT

The maternal vasculature within the placenta in primates and rodents is unique because it is lined by fetal cells of the trophoblast lineage and not by maternal endothelial cells. In addition to trophoblast cells that invade the uterine spiral arteries that bring blood into the placenta, other trophoblast subtypes sit at different levels of the vascular space. In mice, at least five distinct subtypes of trophoblast cells have been identified which engage maternal endothelial cells on the arterial and venous frontiers of the placenta, but which also form the channel-like spaces within it through a process analogous to formation of blood vessels (vasculogenic mimicry). These cells are all large, post-mitotic trophoblast giant cells. In addition to assuming endothelial cell-like characteristics (endothelial mimicry), they produce dozens of different hormones that are thought to regulate local and systemic maternal adaptations to pregnancy. Recent work has identified distinct molecular pathways in mice that regulate the morphogenesis of trophoblast cells on the arterial and venous sides of the vascular circuit that may be analogous to specification of arterial and venous endothelial cells.

Introduction

The placenta is a unique vascularized organ that acts as the exchange station for gases and nutrients between the maternal and fetal circulations. It also produces hormones that impact maternal and fetal physiology, and protects the fetus from the maternal immune system (Cross et al., 1994; Rawn and Cross, 2008; Watson and Cross, 2005). Proper placental function is therefore a crucial step in mammalian development and defects in the placenta can result in fetal abnormalities, death or pregnancy related complications in the mother. Most of the defects resulting in pregnancy complications in both humans and knockout mice are associated with the vasculature of placenta (Cross, 1996; Kaufmann et al., 2003; Rossant and Cross, 2001; Watson and Cross, 2005). The placenta has two vascular systems – fetal and maternal – coming in close proximity to facilitate nutrient and gas exchange. In primates and rodents, the maternal vascular space is unique in that, unlike other organs, placenta-derived trophoblast cells and not endothelial cells line the maternal side of the vasculature (Wooding and Flint, 1994). In mice, various subtypes of large, post-mitotic but polyploid trophoblast cells, called trophoblast giant cells (TGCs), lie at different positions within the maternal vascular space (Simmons et al., 2007). In humans, extravillous cytotrophoblast cells engage the arteries and veins. While the cells that invade the arteries have been well characterized in the human placenta (Zhou et al., 2003b), the characteristics of the trophoblast cells that lie at the venous outflow and bordering the intervillous space have not.

Within the placenta literature, the term vasculogenic mimicry has been used to describe the process of trophoblast cells invading into endothelial cell-lined spiral arteries and beginning to express several molecules that are characteristic of endothelial cells (Kaufmann et al., 2003; Khankin et al., 2010). Vasculogenic mimicry is a term adapted from tumor biology that means formation of fluid conducting channels without the participation of endothelial cells (Maniotis et al., 1999). Though this process of spiral artery invasion and displacement of endothelial cells puts trophoblast cells in the place of endothelial cells, for clarity in this review we define this process as vascular invasion and 'endothelial mimicry' and use the term 'vasculogenic mimicry' specifically for the process by which trophoblast cells within the placenta itself form vascular spaces de novo. We discuss the development of the maternal vasculature within the placenta of mice and humans, mechanisms of endothelial and vasculogenic mimicry suggested by recent studies in mice, and comparisons between trophoblast, endothelial and tumor cells.

Three anatomical layers of human and murine placentas

The mammalian placenta is a composite organ composed of both maternal and fetal tissue. Primate and rodent placentas are

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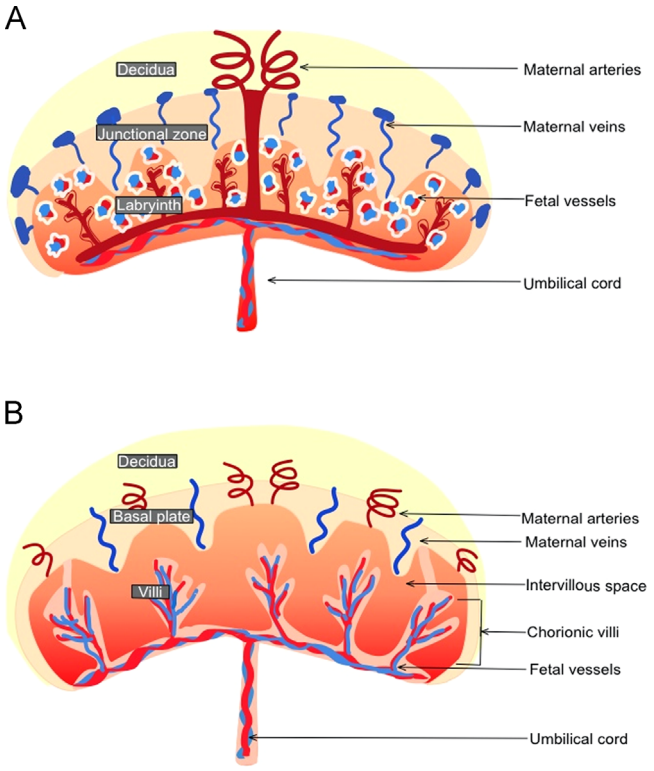

Fig. 1. Comparative anatomy of fetal and maternal circulation in the mouse (A) and human (B) placenta.

'hemochorial' in that while fetal blood is contained within endothelial cell-lined vessels, maternal blood is in contact with specialized subtypes of trophoblast cells (Wooding and Flint, 1994). Despite gross dissimilarities between murine and human placentas, they share several structural, cellular and molecular features which have been described extensively elsewhere (Georgiades et al., 2002; Rossant and Cross, 2001; Watson and Cross, 2005). The murine placenta is composed of three distinct cellular layers: maternal decidua derived from uterine stromal cells across which maternal blood comes to the implantation site through spiral arteries; the junctional zone where maternal vessels lead into and out of TGC-lined vascular spaces; the labyrinth which is the highly branched, large surface area for nutrient and gas exchange (Fig. 1). The human placenta has three analogous layers: an outermost decidua layer with spiral arteries; the basal plate in humans is analogous to the junctional zone; the collection of placental villi in humans into cotyledons is analogous to the labyrinth, though the villi are much less densely packed and the intervillous space is more open compared with the labyrinthine arrangement in rodents (Fig. 1). These layers are well designed to bring blood into and away from the implantation site, and expedite maximum nutrient and gas exchange while maintaining a barrier between the fetal and maternal circulations.

Development of the mouse placenta — from blastocyst to placenta

The major developmental steps giving rise to the mouse placenta are now very well understood both at a cellular and molecular level (Rossant and Cross, 2001; Simmons and Cross, 2005; Watson and Cross, 2005). The epithelial part of the placenta is composed of cell types of the trophoblast lineage, which develops from the trophectoderm layer of blastocyst. Polar trophectoderm cells overlying the inner cell mass follow a different cell fate than mural trophectoderm, cells that are not in contact with the inner cell mass. After implantation, polar trophectoderm cells proliferate in response to FGF4 and Nodal signaling from the inner cell mass and give rise to stem cells that later produce the rest of the trophoblast lineage, whereas mural trophectoderm cells terminally differentiate into primary TGCs (Copp, 1979; Rossant and Cross, 2001; Tanaka et al., 1998). Decidua formation is stimulated by the attachment and invasion of these primary TGCs into the uterine wall, resulting in initial proliferation and subsequent differentiation and hypertrophy of the uterine stromal cells (Ramathal et al., 2010). The differentiation of decidual cells is regulated by factors produced by TGCs (Austin et al., 2003; Bany and Cross, 2006; Herington and Bany, 2007). By mid-gestation, trophoblast cells stimulate the release of growth and immunoregulatory factors from the decidua that are necessary for growth of the fetus, and promote formation of maternal blood vessels that deliver blood to the placenta (Blois et al., 2011; Cross et al., 2002).

Morphogenesis of the polar trophectoderm after implantation gives rise to the ectoplacental cone and extraembryonic ectoderm (later called the chorion). The cells in ectoplacental cone give rise to the junctional zone in the mature placenta which is composed of spongiotrophoblast cells, glycogen cells, and the different subtypes of TGCs that line maternal blood spaces (Simmons et al., 2007) and produce several pregnancy related hormones (Knox et al., 2011; Rawn and Cross, 2008; Tunster et al., 2010). Glycogen trophoblast cells accumulate vast amounts of glycogen and migrate into the maternal uterine wall after E12.5 (Adamson et al., 2002; Gasperowicz et al., 2013b; Mould et al., 2012). They are hypothesized to function as an energy reserve for fetal growth and/or the mother to fulfill her high-energy requirement during last phase of pregnancy (Coan et al., 2006; Cross and Mickelson, 2006; Tunster et al., 2010).

The labyrinth is a highly branched structure formed by trophoblast cells from the chorion and the allantois, and is specialized for nutrient and gas supply to the fetus (Simmons et al., 2008a; Watson and Cross, 2005). Around E8.5, the mesoderm-derived allantois attaches to the chorion and forms mesenchymal cells and fetal blood vessels of the labyrinth and umbilical cord (Cross et al., 2006). The chorion is a flat multilayered structure that undergoes branching morphogenesis after chorioallantoic attachment (Simmons et al., 2008a). Chorion trophoblast cells differentiate to form two types of syncytiotrophoblast cells (layers I and II) through cell–cell fusion. These cells surround the fetal blood capillaries forming the major barrier for the nutrient and gas exchange. Large, mononuclear TGCs line the maternal blood sinusoids in the labyrinth (Simmons et al., 2007; Watson and Cross, 2005).

Multiple TGC subtypes line the maternal vasculature in the mouse placenta

The defining feature of the hemochorial placenta is that trophoblast cells and not endothelial cells line the maternal vasculature within the placenta, starting at the level of spiral arteries for incoming blood and up to the point when nutrient- and oxygen-depleted blood leaves the placenta to enter into the uterine veins. In mice, all of the cells lining the maternal blood space are different subtypes of TGCs. These subtypes have been classified based on their location but also developmental origin and function (Fig. 2), including their differential expression of several hormones related to Prolactin (Gasperowicz et al., 2013b; Simmons et al., 2007). Proceeding from upstream to downstream within the maternal blood space, the five TGC subtypes are: (1) spiral artery TGCs (SpA-TGCs) that emerge from the ectoplacental cone and invade into the spiral arteries displacing the