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Review article

The omniscient placenta: Metabolic and epigenetic regulation of fetal programming

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ABSTRACT

Fetal development could be considered a sensitive period wherein exogenous insults and changes to the maternal milieu can have long-term impacts on developmental programming. The placenta provides the fetus with protection and necessary nutrients for growth, and responds to maternal cues and changes in nutrient signaling through multiple epigenetic mechanisms. The X-linked enzyme O-linked-N-acetylglucosamine transferase (OGT) acts as a nutrient sensor that modifies numerous proteins to alter various cellular signals, including major epigenetic processes. This review describes epigenetic alterations in the placenta in response to insults during pregnancy, the potential links of OGT as a nutrient sensor to placental epigenetics, and the implications of placental epigenetics in long-term neurodevelopmental programming. We describe the role of placental OGT in the sex-specific programming of hypothalamic–pituitary–adrenal (HPA) axis programming deficits by early prenatal stress as an example of how placental signaling can have long-term effects on neurodevelopment.

1. Introduction

Prenatal development is a particularly vulnerable period in life when tissues are rapidly developing and are susceptible to shifts in programming. Across gestation, fetal needs change to accommodate the trajectory of tissue development, making specific windows of pregnancy particularly important for tissue growth, and allowing environmental perturbations to have long-term effects on these developing systems. Throughout pregnancy, the placenta acts as the command post for incoming and outgoing messages to and from maternal and fetal compartments. Epigenetic responses to maternal and fetal signals are an obvious candidate for transforming early life inputs into long-term programmatic outcomes. We have gained a broader understanding of how specific insults during development impact the fetal brain, and are beginning to understand the importance of placental signaling in neurodevelopmental programming. This review summarizes evidence for the role of placental epigenetics in neurodevelopmental programming with a focus on the integration of nutrient signals into chromatin changes and the sex specificity of these findings.

2. The placenta is a diplomat for maternal–fetal relations

The placenta is a dynamic endocrine tissue displaying robust responses to alterations in the maternal milieu. As the fetal sustenance delivery system, placental health is critical for fetal growth and development, and acts at the interface to communicate maternal nutritional status and environmental disruptions. Studies in both humans and rodents have demonstrated that a wide array of maternal inputs, such as over and under-nutrition, smoking, drug and alcohol intake, infection and stress can induce marked transformations in placental physiology ranging from alterations in aspects of gross placental morphology such as obvious changes in placental weight, to the more subtle changes in placental gene expression that may predict altered transport of important signals to the fetus (not exhaustive: Amankwah and Kaufmann, 1984; Eguchi et al., 1989; Ganapathy, 2011; Gheorghe et al., 2010; Godfrey et al., 1996; Godfrey and Barker, 1995; Jauniaux and Burton, 2007; Kennedy, 1984; La Torre et al., 2006; Mairesse et al., 2007; Pastrakuljic et al., 1999; Zdravkovic et al., 2005). Many of these insults result in decreases in both placental and fetal growth, which can have long-term impacts on offspring health.

Across the timeline of *in utero* development, the primary placental function is to transfer nutrients and gases required for fetal development. The placenta serves as an arbitrator between the mother and fetus, guaranteeing fetal needs while concurrently negotiating with the maternal immune system. The dominant cell

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type within the placenta is the fetally-derived trophoblast cell. Although there are developmental and structural differences between the mouse and human placenta (as reviewed in Malassine et al., 2003), they share remarkably conserved profiles of mRNA and protein expression, and mouse models are widely accepted as proxies for many aspects of human placental function (Cox et al., 2009). Trophoblast cells are the first to differentiate post fertilization, comprising the outer layer of the blastocyst and eventually giving rise to all placental layers excluding the maternal decidua (see Rossant and Cross, 2001 for review of placental development). During early pregnancy, these cells initiate vascular remodeling during trophoblast invasion of the uterus, allowing the placenta to establish vascular inputs from the mother. This occurs during the first trimester in humans, but not until mid-gestation in rodents. Establishing robust connections with the maternal circulation is critical for gaining access to sufficient nutrients and has a direct impact on fetal and placental growth. In the mouse, this is achieved by a placental structure with two major zones: the labyrinth and junctional zones. Maternal–fetal exchange occurs within the branching labyrinth of cytotrophoblast cells encompassed by the multinucleated syncytiotrophoblast layer that compartmentalizes maternal and fetal blood. The labyrinth is separated from the maternal decidua by a junctional zone containing trophoblastic giant cells and spongiotrophoblastic cells. In humans, placental villi extend directly into maternal blood. These villi consist of a syncytiotrophoblast layer and villous cytotrophoblast cells that are anchored to the maternal decidua by extravillous cytotrophoblast cells (comparisons reviewed comprehensively in Carter, 2007; Georgiades et al., 2002; Malassine et al., 2003).

The fetal origin of the trophoblastic cell lineage prompts the maternal immune system to recognize these cells as foreign entities. Fortunately, evolution has designed mechanisms to suppress this maternal host response and defend the semi-allogenic fetus (reviewed in Munoz-Suano et al., 2011). The critical placental role in suppression of the maternal immune system has led some to consider it an immune organ, while others categorize it as an endocrine tissue due to its production and release of numerous hormones and factors into maternal and fetal circulation (Fowden et al., 2005; Murphy et al., 2006; Petraglia et al., 1996; Simpson and MacDonald, 1981). Placental hormones come in all varieties including steroids, peptides, eicosanoids and glycoproteins (Fowden et al., 2005). Interaction of the immune and endocrine systems occurs through placental production of the steroid hormone, progesterone, which is necessary for immunosuppression and anti-inflammatory processes involved in maintenance of pregnancy (Siiteri et al., 1977). In addition to mediating immunosuppression, placental-derived hormones are responsible for a range of necessary physiological changes during pregnancy, including uterine expansion, mammary tissue development, and eventually, the initiation of parturition (Linzer and Fisher, 1999). Importantly, during early pregnancy placental lactogen and progesterone signal the need for maternal resources to be dispatched for use by the fetus, altering maternal metabolism to increase fetal access to glucose (Fowden et al., 2006).

2.1. Sex differences in the placenta

As trophoblast cells originate from the embryo, they reflect fetal sex as either XX or XY, allowing for sex differences in placental biochemistry, function, and signaling. Although studies in rodent models identified preferential inactivation of the paternal X chromosome in the female placenta via imprinting (Takagi and Sasaki, 1975; Wang et al., 2001), analysis of the human female placenta revealed random patterns of X inactivation (de Mello et al., 2010; Looijenga et al., 1999). Further, silenced X chromosomes in the placenta are under less stringent epigenetic repression relative to those in somatic tissues, allowing for reactivation of the inactive X chromosome and non-random X inactivation within the placenta in response to intrauterine conditions (Migeon et al., 2005). This plasticity in X-inactivation in the placenta may be an important contributor to sex-differences in response to environmental perturbations during gestation, whereby females may be buffered from detrimental conditions to a greater degree than males due to increased expression of important X-linked genes.

In addition to sex differences determined by sex chromosomes, multiple studies have identified sex differences in autosomal gene expression in the placenta at both the mRNA and protein level (reviewed in Clifton, 2010), with striking female-biased expression of several key immune regulators in the human placenta (Sood et al., 2006), suggesting that sex dictates how the placenta negotiates with the maternal immune system. In addition to sex differences in immune system communication, fetal sex can also govern nutrient allocation from the mother. On average, male fetuses are larger than females (Forsen et al., 1999; Thomas et al., 2000), suggesting greater nutrient requirements in males during fetal growth. David Barker postulated that male fetuses are more dependent on maternal sources of nutrition allowing for this enhanced fetal growth. His group argued that male placentas are more efficient than female placentas at extracting nutrients, whereas female placentas may have a greater capacity to store energy (Eriksson et al., 2010). Studies in humans have shown that fetal sex may modulate nutritional input to the placenta/fetus, particularly during the second trimester of pregnancy wherein women carrying male fetuses have higher energy intake than those pregnant with female fetuses (Tamimi et al., 2003).

3. Nutritional requirements during fetal development

Macronutrients, gases and metabolites are transferred by the placenta into fetal circulation via passive (urea & carbon dioxide out, fatty acids & oxygen in) and facilitative diffusion (glucose, lactate, fatty acids), active transport (amino acids), and endo- and exocytosis (Watson and Cross, 2005). Glucose is the primary fuel for the fetus and placenta. During early pregnancy the fetus produces very small amounts of glucose, necessitating glucose transfer from maternal blood (Hay et al., 1984; Marconi et al., 1996). Not surprisingly, in human pregnancies low maternal blood glucose levels lead to small for gestation age (SGA) neonates, whereas hyperglycemia results in fetal macrosomia, which makes blood glucose during *in utero* development a potential predictive factor of later health and disease (Cianfarani et al., 2003; Combs et al., 1992). Fetal nutrient requirements change over the course of pregnancy, and studies in humans suggest that nutritional intake during early pregnancy is particularly critical for directing normal fetal growth and development (Moore et al., 2004).

The developing brain is a nutritionally-demanding tissue, and is particularly sensitive to insufficiencies or overabundance of specific nutrients and growth factors. Although the initial stages of nervous system development occur as early as 2–3 weeks post fertilization in humans, neuronal proliferation occurs later in the first trimester, extending into the second trimester. Neural migration and synaptogenesis occur predominantly in the late second and third trimesters (reviewed in Tau and Peterson, 2010). During early pregnancy the brain is extremely plastic but vulnerable to broad environmental fluctuations that can impact long-term programming. After 24 weeks of gestation, wherein myelination and synapse formation occur, nutrient requirements in the developing human brain become critical (Fig. 1; reviewed in Georgieff, 2007). Of course, the developmental timeline for specific brain regions differs, such that certain rapidly developing regions may be more