Placental Responses to Changes in the Maternal Environment Determine Fetal Growth

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Placental responses to maternal perturbations are complex and remain poorly understood. Altered maternal environment during pregnancy such as hypoxia, stress, obesity, diabetes, toxins, altered nutrition, inflammation, and reduced utero-placental blood flow may influence fetal development, which can predispose to diseases later in life. The placenta being a metabolically active tissue responds to these perturbations by regulating the fetal supply of nutrients and oxygen and secretion of hormones into the maternal and fetal circulation. We have proposed that placental nutrient sensing integrates maternal and fetal nutritional cues with information from intrinsic nutrient sensing signaling pathways to balance fetal demand with the ability of the mother to support pregnancy by regulating maternal physiology, placental growth, and placental nutrient transport. Emerging evidence suggests that the nutrient-sensing signaling pathway mechanistic target of rapamycin (mTOR) plays a central role in this process. Thus, placental nutrient sensing plays a critical role in modulating maternal–fetal resource allocation, thereby affecting fetal growth and the life-long health of the fetus.

Keywords: placental nutrient sensing, maternal–fetal exchange, mechanistic target of rapamycin, fetal programming, syncytiotrophoblast, pregnancy

INTRODUCTION

Adverse maternal influences in pregnancy are linked to alterations in the intrauterine milieu, which are associated with short-term complications including altered fetal growth and increased perinatal morbidity, as well as long-term adverse consequences for the health of the offspring. This concept of fetal programming or developmental origins of health and disease (Forsdahl, 1977; Barker and Osmond, 1986; Barker et al., 1989; Hales et al., 1991; Ravelli et al., 1998; Armitage et al., 2004; Gluckman and Hanson, 2004) suggests that successful prevention of adult metabolic disease relies on interventions during pregnancy.

The placenta senses and responds to changes in the maternal environment by altering its structure and function, which can lead to changes in blood flow, fetal nutrient supply, and secretion of hormones and other signaling molecules. Changes in transplacental nutrient transport may influence fetal nutrient availability, which determines fetal growth and body composition, and thus may link maternal perturbations to fetal programming.

The mechanisms by which altered maternal environment during pregnancy may lead to disease in the offspring are poorly understood. Here, we discuss maternal circulating factors that
regulate placental function and highlight the role of placental mechanistic target of rapamycin (mTOR) signaling as a placental nutrient sensing signaling pathway that modifies placental nutrient transport in response to a multitude of factors.

PLACENTAL NUTRIENT SENSING

The placental nutrient sensing model proposes that the syncytiotrophoblast integrates maternal and fetal signals to regulate placental function. The model emphasizes the importance of changes in the maternal compartment (Gaccioli et al., 2013; Jansson and Powell, 2013) to which the placenta responds by matching fetal growth with the ability of the maternal supply line to allocate resources to the fetus. Maternal signals that provide information to the placenta may include metabolic hormones, nutrients levels, and oxygen. In conditions of compromised ability of the maternal supply line to deliver nutrients and oxygen to the placenta, placental functions including transplacental nutrient transport and placental growth, may be inhibited, directly contributing to decreased fetal growth. In contrast, in conditions of over-nutrition, placental nutrient sensing may lead to enhanced placental function, directly contributing to fetal overgrowth (Figure 1).

THE PLACENTAL BARRIER

The syncytiotrophoblast, the transporting and hormone-producing epithelium of the placenta, constitutes the primary barrier for maternal–fetal exchange. The syncytiotrophoblast is a polarized epithelium with a maternal-facing microvillus plasma membrane (MVM) and a fetal-facing basal plasma membrane (BM). MVM and BM have distinct biological characteristics including different membrane composition and their expression of nutrient transporters. The expression and function of these nutrient transporters influence the placental capacity to transfer nutrients from the mother to the fetus, an important determinant of fetal growth.

Maternal factors including hormones, growth factors, and some cytokines have been shown to regulate transplacental nutrient transport. Insulin (Jansson et al., 2003; Roos et al., 2009), insulin-like growth factor 1 (IGF-I; Fang et al., 1997; Roos et al., 2009), leptin (Jansson et al., 2003), interleukin-6 (IL-6; Jones et al., 2009a), and tumor necrosis factor alpha (TNF-α; Jones et al., 2007) positively regulate system A, a transport system that mediates non-essential neutral amino acid (AA) uptake. Receptors for numerous hormones, including IGF-I, insulin, and leptin are also present in the MVM (Desoye et al., 1994; Fang et al., 1997; Ebenbichler et al., 2002) suggesting that maternal hormones regulate trophoblast function. Concentrations of maternal serum IGF-I (Holmes et al., 1997) and leptin (Yildiz et al., 2002) are decreased in intrauterine growth restriction (IUGR) while pregnancies associated with obesity and diabetes have higher maternal serum IGF-I, insulin, and leptin (Lauszus et al., 2001; Jansson et al., 2008). This suggests that maternal factors can regulate the activity and expression of transporter proteins in the syncytiotrophoblast, which may influence fetal growth and health.

DIVERSE MATERNAL SIGNALS IMPINGE ON THE PLACENTA

A wide range of maternal factors impinges on the placenta, providing critical information about the ability of the maternal supply line to support pregnancy (Jansson et al., 2012; Gaccioli et al., 2013; Jansson and Powell, 2013; Díaz et al., 2014).

Utero-Placental Blood Flow

The development of certain pregnancy complications, particularly IUGR and preeclampsia, is associated with impaired utero-placental blood flow. Impaired utero-placental blood flow could cause “placental insufficiency”, i.e., impaired nutrient and oxygen supply to the fetus. Placental insufficiency is often assumed to be due only to a reduced placental blood flow (Krishna and Bhalerao, 2011). However, the placental blood flow reduction per se does not adequately explain the impaired placental transfer in IUGR. For example, the primary limiting factor for the transplacental transport of nutrients such as glucose and AAs is their transport across the syncytiotrophoblast. We have proposed that the placenta senses the decreased blood flow or possibly hypoxia, and responds by down-regulating key placental nutrient transporters, directly contributing to IUGR. Moreover, the IUGR placenta has reduced intervillous space volume, poorly developed peripheral villi and thicker trophoblastic epithelium that decrease the nutrient exchange area and compromise the exchange functions of the placenta (Burton, 2010).

Animal models of impaired utero-placental blood flow show decreased placent al nutrient transport capacity. Transplacental transport of glucose and AAs was decreased in IUGR following uterine artery ligation in the rat (Nitzan et al., 1979), however MVM system A activity in vitro (Glazier et al., 1996) and placental expression of glucose transporters GLUT 1 and GLUT 3 (Reid et al., 1999) were unaffected. In the guinea pig, IUGR induced by unilateral artery ligation was associated with decreased transplacental AA transport (Jansson and Persson, 1990). In a sheep model of IUGR induced by maternal hyperthermia and decreased utero-placental blood flow, transplacental transport of leucine (Ross et al., 1996), threonine (Anderson et al., 1997), glucose (Thureen et al., 1992), and ACP (branched-chain AA analog) (de Vrijer et al., 2004) was reduced.

In human IUGR associated with reduced utero-placental blood flow, the activity of several placental AA transporters is reduced whereas placent al GLUT1 expression and activity are unaffected (Jansson et al., 1993, 2002b). System A activity is consistently lower in MVM isolated from IUGR placentas (Mahendran et al., 1993; Glazier et al., 1997), especially in preterm IUGR (Jansson et al., 2002b) and is related to the degree of fetal compromise (Glazier et al., 1997). Similarly, the activity of transporters of essential AAs, including system β (taurine) and system L (lysine and leucine), is reduced in MVM and/or BM of IUGR placentas (Jansson et al., 1998; Norberg et al., 1998), consistent with the reduced placental transfer of the essential acids leucine and phenylalanine observed in vivo in IUGR pregnancies at term (Paolini et al., 2001). Decreased transplacental AA transport to the fetus may account for the
low plasma levels of certain AAs in growth-restricted fetuses (Economides et al., 1989; Cetin et al., 1990). The activity of lipoprotein lipase (LPL), an enzyme responsible for hydrolysis of lipoproteins, is reduced in MVM of IUGR placentas (Magnusson et al., 2004). IUGR is also associated with a reduced placental expression of lipoprotein receptors, low-density lipoprotein (LDL), and scavenger receptor class B type-I, key receptors for cholesterol uptake from maternal LDL and/or HDL (Wadsack et al., 2007). Thus, placental lipid transport may be impaired in IUGR, possibly contributing to the decreased lipid stores in the IUGR fetus (Padoan et al., 2004). Collectively, these data suggest that the effect of reduced uterus-placental blood flow on fetal growth is mediated, in part, by decreased placental nutrient transfer capacity.

**Hypoxia**

Despite compensatory mechanisms such as fetal polycythemia, transplacental transfer of oxygen decreases in maternal hypoxia, which typically is associated with IUGR (Giussani et al., 2007). Women residing at high altitude with reduced oxygen tension have higher risk to deliver IUGR babies than women living at sea level (Zamudio and Moore, 2000; Mehta and Mehta, 2008). Nelson and co-workers reported that hypoxia caused a reduced system A transporter expression and activity in cultured primary human trophoblast cells (Nelson et al., 2003), suggesting that adequate oxygen supply is important for the function of nutrient transporters. Furthermore, high altitude hypoxia decreases the expression of GLUT1 in the syncytiotrophoblast plasma membrane (Zamudio et al., 2006).

**Maternal Hormones**

Maternal hormones can influence fetal health by altering placental function (Fowden et al., 2015). Maternal IGF-I promotes placental nutrient uptake and transport (Sferruzzi-Perri et al., 2011a). In animal models of IUGR, elevating maternal IGF concentrations improved fetal growth (de Boo et al., 2008). Acute maternal IGF-I treatment in the late pregnant ewe is associated with enhanced glucose delivery to the fetus (Liu et al., 1994). This was also observed in a mouse model of IUGR where placental glucose transporter expression was increased following intraplacental injection of adenovirus-mediated IGF-I (Jones et al., 2013) restoring fetal weights (Keswani et al., 2015). In human trophoblasts, IGF-I increases GLUT1 expression (Baumann et al., 2014) and stimulates glucose and system A-mediated AA uptake (Karl, 1995; Roos et al., 2007). Also, reduced maternal circulating IGF-I is associated with small-for-gestational age and growth-restricted babies (Hernandez-Valencia et al., 2001). IGF-I receptor protein levels were reduced in IUGR (Laviola et al., 2005) and elevated in pregnancies complicated by macrosomia (Jiang et al., 2009).

Insulin and leptin stimulate placental system A activity (Karl et al., 1992; Jansson et al., 2003; von Versen-Hoyneck et al., 2009) while adiponectin inhibits insulin-stimulated AA transport (Jones et al., 2010; Rosario et al., 2012; Aye et al., 2014a, 2015). Administration of maternal corticosteroids to pregnant mice during mid-gestation down regulates placental system A transport (Audette et al., 2011) leading to reduced fetal weight (Vaughan et al., 2012). Therefore, maternal hormones influence fetal growth by altering the activity of placental nutrient transporters and placental secretion of hormones (Sferruzzi-Perri et al., 2011a).

**Maternal Nutrition**

Fetal growth is greatly influenced by maternal nutrition, and is believed to be mediated, in part, by changes in maternal metabolism and hormone levels.

In a rat model of maternal protein restriction, maternal insulin, IGF-I, and leptin levels were decreased (Rosario et al., 2011) and similar changes were observed in a mouse model of calorie restriction (Sferruzzi-Perri et al., 2011b). Maternal corticosterone levels were also increased in this mouse model (Sferruzzi-Perri et al., 2011b). In contrast, pregnant mice on...
a high fat diet showed increased levels of maternal leptin and decreased adiponectin (Jones et al., 2009b). Consistent with these observations, levels of maternal insulin and leptin were elevated in obese pregnant mice on a high-fat/high-sugar diet (Rosario et al., 2015b).

Maternal endocrine and metabolic changes in response to altered nutrition are similar in experimental models and women. In human IUGR, maternal serum concentrations of IGF-I, insulin, and leptin are decreased (Jansson et al., 2006) while obese pregnant women and pregnancies complicated with gestational diabetes have higher serum levels of leptin, insulin, IGF-I, and decreased levels of adiponectin (Lauszus et al., 2001; Jansson et al., 2008; Aye et al., 2013a, 2015).

Because hormonal regulation of placental nutrient transport is well established, one key mechanism by which maternal nutrition alters placental function and fetal growth could be through modulating placental nutrient transport. Consistent with this hypothesis, various animal experimental models of maternal undernutrition show decreased placental nutrient transport. For example, maternal calorie restriction in the baboon caused IUGR and showed decreased expression and in vivo activity of key AA transporters, decreased in vitro transplacental AA transport as well as lower fetal levels of essential AAs (Kavitha et al., 2014; Pantham et al., 2015b). Calorie restriction in mice resulted in reduced transplacental glucose and leucine transport (Ganguly et al., 2012). In rats, calorie, or protein restriction in late pregnancy decreased neutral AAs and glucose transplacental transport (Rosso, 1977a,b; Malandro et al., 1996; Jansson et al., 2006; Rosario et al., 2012). Therefore, the proposed cause-and-effect link between maternal undernutrition and decreased fetal growth involves the well-established physiological hormonal response to starvation. Specifically, the increase in the levels of catabolic hormones such as cortisol and the decrease in anabolic hormones including insulin and IGF-I are predicted to inhibit placental nutrient transport, resulting in decreased fetal nutrient availability and IUGR. Opposite placental responses have been reported in maternal over-nutrition in association with fetal overgrowth. In a mouse model of maternal obesity, in vitro glucose and AA transporter expression, and activity and in vivo transplacental glucose and AA transport are increased (Aye et al., 2015; Rosario et al., 2015b). Importantly, these findings are consistent with up-regulation of placental AA transport in obese women giving birth to large babies (Jansson et al., 2013) and increased placental capacity to transport AAs and glucose in women with diabetes and fetal overgrowth (Jansson et al., 1999, 2002a).

**Inflammatory Mediators**

Altered inflammatory profile in the mother, placenta, or fetus can affect placental function. Specifically, maternal systemic inflammation has been proposed to play a role in the developmental programming of metabolic disorders especially in pregnancies complicated with obesity and gestational diabetes (Ingvorsen et al., 2015; Pantham et al., 2015a). Male offspring of dams injected with lipopolysaccharide during mid-gestation had enhanced food intake, increased body weight and enlarged abdominal adipose tissue with reduced insulin uptake, consistent with development of obesity and insulin resistance (Nilsson et al., 2001). Offspring of dams exposed to high systemic levels of TNF-α or IL-6 showed increased body weight and adiposity, and exposure to IL-6 alone resulted in insulin resistance in female offspring (Dahlgren et al., 2001).

Maternal obesity in women is associated with a low-grade systemic maternal inflammation and signs of placental inflammation (Challier et al., 2008) However, levels of circulating MCP-1, IL-6, and C-reactive protein that were elevated in early pregnancy in obese women were comparable to those of normal-weight mothers at the end of pregnancy (Ingvorsen et al., 2014) suggesting attenuation of maternal inflammatory state in obese women with advancing gestation. Similarly, women with high BMI had increased circulating levels of MCP-1 and TNF-α and activation of placental inflammatory pathways p38-MAPK and STAT3 (Aye et al., 2014b) without signs of fetal inflammation, suggesting that inflammation associated with maternal overweight/obesity affects the fetus indirectly by modulating placental function.

Maternal circulating cytokines could affect placental function by altering the expression and activity of placental nutrient transporters. IL-6 and TNF-α have been shown to stimulate system A activity in cultured primary human trophoblasts (Jones et al., 2009a). In contrast, IL-1B decreases system A activity in BeWo cells (Thongson et al., 2005) and inhibits insulin-stimulated system A activity in cultured primary trophoblasts (Aye et al., 2013b). Collectively, these data suggest that a low-grade maternal systemic inflammation in maternal obesity influences fetal growth and programs the fetus for future disease by altering placental functions such as nutrient transport. Whether direct fetal exposure to inflammatory mediators also contributes remains to be established.

**Placental Malaria and IUGR**

Every year, ~85 million pregnant women are at risk of malaria, resulting in ~600,000 low birth weight deliveries (Steketee et al., 2001; Desai et al., 2007) mainly attributed to IUGR (Guyatt and Snow, 2004). Recent studies suggest that down-regulation of placental nutrient transport may contribute to IUGR associated with malaria (Boeuf et al., 2013; Chandrasiri et al., 2014).

Placental malaria is the sequestration of *Plasmodium falciparum*-infected erythrocytes in the intervillous space of the placenta (Boeuf et al., 2013). This sequestration can stimulate the recruitment of maternal inflammatory cells such as monocytes and macrophages, a condition termed intervillitis (Ordi et al., 1998) that is associated with an increased risk of low birth weight deliveries (Desai et al., 2007; Rogerson et al., 2007).

Sequestered mononuclear cells and the syncytiotrophoblast can produce various cytokines and chemokines. In placental malaria, intervillous plasma levels of IFN-γ and TNF-α, IL-10, and MCP-1 are increased (Rogerson et al., 2003; Suguitan et al., 2003). Intervillous plasma MIP-1α, IL-8, and monocyte-attracting beta-chemokines such as CCL2 and CCL3 are also increased in placental malaria with intervillitis (Abrams et al., 2003; Bouyou-Akotet et al., 2004; Ioannidis et al., 2014). Inflammation could impair placental development and function, contributing to IUGR in placental malaria. Also, decreased...
Maternal circulating IGF-I levels were observed in women with placental malaria, especially with intervillositis (Umbers et al., 2011). Maternal leptin levels were reduced in mothers with placental malaria (Kabyemela et al., 2008). Importantly, placental malaria with intervillositis is associated with impaired placental AA uptake (Boeuf et al., 2013) and BM GLUT-1 expression (Chandrasiri et al., 2014). Therefore, inflammation, more so than infection, is associated with reduced placental nutrient transport function and deregulation of maternal hormones, which can impact fetal growth and development. The mechanisms underlying the decreased placental nutrient transport capacity and IUGR in placental malaria remain to be fully established.

**mTOR SIGNALING IN PLACENTAL NUTRIENT SENSING**

Mammalian cells have an array of nutrient-sensing signaling pathways, such as AMP-activated protein kinase (AMPK), AA response signal transduction pathway, glycogen synthase-3 (GSK-3), mTOR, and the hexosamine signaling pathway, which regulate cell metabolism in response to altered nutrient levels. Of these, mTOR is believed to play a central role in placental nutrient sensing (Jansson and Powell, 2006; Jansson et al., 2012). mTOR exists as two protein complexes: mTOR Complex 1 (mTORC1) that regulates cell growth, proliferation, and metabolism and mTORC2 that regulates cytoskeletal organization and cellular metabolism. Placental mTOR signaling likely constitutes a critical link between maternal oxygen and nutrient supply and fetal growth (Jansson et al., 2012).

Hypoxia inhibits mTORC1 signaling by increased expression of DNA damage response 1 (REDD1; Brugarolas et al., 2004) and by activation of AMPK (Inoki et al., 2003). Yung and coworkers also reported that placental mTORC1 signaling is inhibited in women residing at high altitude, consistent with the concept that hypoxia inhibits placental mTORC1 signaling (Yung et al., 2008). In addition, the activity of the placental mTOR signaling pathway is influenced by a multitude of upstream regulators such as amino acids, growth factors, and free fatty acids, which are likely to be affected by maternal nutrition. Protein restriction in rats (Jansson et al., 2006) and nutrient restriction in baboons (Kavitha et al., 2014) resulted in inhibition of placental mTORC1 activity, consistent with human IUGR (Roos et al., 2007; Yung et al., 2008; Chen et al., 2015). In contrast, placental mTOR is activated in animal models of maternal obesity (Jones et al., 2009b; Rosario et al., 2015b) and in obese women delivering large babies (Jansson et al., 2013).

mTOR also has a key role in regulating AA transporters in the human placenta. *In vitro*, mTORC1 positively regulates system A and system L, critical in transplacental AA transport (Rosario et al., 2013). mTORC1 regulates cellular uptake of AAs...
by affecting the plasma membrane trafficking of transporters by differential ubiquitination, possibly through the ubiquitin ligase, NEDD4-2 (Rosario et al., 2013, 2015a; Chen et al., 2015).

We propose that mTOR functions as a key placental nutrient sensing pathway responding to upstream maternal signals by modulating transplacental AA transport and influencing the trafficking of nutrient transporters (Figure 2).

**CONCLUSION AND PERSPECTIVES**

Changes in the maternal environment can impair fetal growth and development, which may result in increased susceptibility to diseases in postnatal life. We have proposed that *placental nutrient sensing* allows the placenta to integrate these perturbations with information from intrinsic nutrient sensing signaling pathways to regulate secretion of hormones and placental nutrient and oxygen transfer. Because fetal nutrient supply programs the fetus for future disease, placental function determines the growth and life-long health of the fetus.

Placental responses to perturbations in the maternal compartment are complex and remain poorly understood, highlighting an urgent need for further well-designed and mechanistic research in this area. Intervention strategies to alleviate pregnancy complications and prevent fetal programming of adult disease are likely to be most effective if placental function is targeted. mTOR constitutes an important nutrient sensing signaling pathway believed to play a key role in placental nutrient sensing. Maternal obesity with fetal overgrowth is associated with activation of placental mTOR signaling and up-regulation of placental nutrient transport both in animal models (Aye et al., 2015; Rosario et al., 2015a,b) and in women (Jansson et al., 2013). We recently reported that normalization of maternal circulating levels of adiponectin in obese mice completely prevented the activation of placental mTOR signaling, up-regulation of placental nutrient transport and fetal overgrowth (Aye et al., 2015) consistent with the idea that targeting placental mTOR may represent an effective intervention strategy in cases of abnormal fetal growth.

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