REVIEW

Nutrient sensor signaling pathways and cellular stress in fetal growth restriction

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Abstract

Fetal growth restriction is one of the most common obstetrical complications resulting in significant perinatal morbidity and mortality. The most frequent etiology of human singleton fetal growth restriction is placental insufficiency, which occurs secondary to reduced utero-placental perfusion, abnormal placentation, impaired trophoblast invasion and spiral artery remodeling, resulting in altered nutrient and oxygen transport. Two nutrient-sensing proteins involved in placental development and glucose and amino acid transport are mechanistic target of rapamycin (mTOR) and O-linked N-acetylglucosamine transferase (OGT), which are both regulated by availability of oxygen. Impairment in either of these pathways is associated with fetal growth restriction and accompanied by cellular stress in the forms of hypoxia, oxidative and endoplasmic reticulum (ER) stress, metabolic dysfunction and nutrient starvation in the placenta. Recent evidence has emerged regarding the potential impact of nutrient sensors on fetal stress response, which occurs in a sexual dysmorphic manner, indicating a potential element of genetic gender susceptibility to fetal growth restriction. In this mini review, we focus on the known role of mTOR and OGT in placental development, nutrient regulation and response to cellular stress in human fetal growth restriction with supporting evidence from rodent models.

Key Words

- ▶ fetal growth restriction
- ▶ nutrient sensors
- ▶ mTOR
- ▶ O-GlcNAc transferase (OGT)
- ▶ placenta
- ▶ nutrient transport
- ▶ cellular stress
- ▶ sexual dymorphism

Introduction

The placenta is essential in maintaining fetal growth throughout pregnancy. Any alteration in placental structure or function can give rise to fetal growth restriction. Fetal growth restriction occurs when there is failure of the fetus to meet expected genetic growth potential (Resnik 2002, Baschat & Hecher 2004). The most common etiology of fetal growth restriction is placental insufficiency. Placental insufficiency is multifactorial in origin and arises from varying combinations of reduced utero-placental perfusion, abnormal placentation, impaired trophoblast invasion, spiral artery remodeling

and nutrient transport, resulting in overall fetal nutrient and oxygen deficits (Lager & Powell 2012, Yang *et al.* 2015). Transport of glucose and amino acids, the primary nutrients necessary for fetal growth and development, is a tightly controlled process involving multiple integrated nutrient-sensing pathways. The placenta has an array of nutrient sensing signaling pathways, which act in a coordinated way to regulate nutrient uptake and cellular signaling in response to maternal supply and fetal demand (Jansson & Powell 2006, Jansson *et al.* 2012, Diaz *et al.* 2014*b*). Mechanistic target of rapamycin (mTOR)

and O-linked N-acetylglucosamine transferase (OGT) are the primary nutrient-sensing proteins involved in glucose and amino acids utilization and signaling (Hart *et al.* 2007, Hanover *et al.* 2010, Jansson *et al.* 2012, Palin *et al.* 2014, Diaz *et al.* 2014*b*, Wu *et al.* 2017). mTOR and OGT signaling pathways are directly regulated by the availability of oxygen (Arsham *et al.* 2003, Inoki *et al.* 2003, Brugarolas *et al.* 2004, Jansson *et al.* 2012, Yang *et al.* 2015, Chang *et al.* 2018). Downstream targets of mTOR and OGT also have an important role in the regulation of placental development including trophoblast invasion and maternal spiral artery remodeling (Kim *et al.* 2013, Palin *et al.* 2014, Yang *et al.* 2015, Zhang *et al.* 2017). Impairment in either of these pathways is associated with placental insufficiency, oxygen and nutrient deficits and fetal growth restriction. These changes often occur in response to cellular stress, including hypoxia, oxidative and endoplasmic reticulum (ER) stress, metabolic dysfunction and nutrient starvation in response to impairments in mTOR and OGT signaling (Das *et al.* 1998, Wullschleger *et al.* 2006, Roos *et al.* 2007, 2009, Rosario *et al.* 2011, Howerton & Bale 2014, Yang *et al.* 2015, Zhang

et al. 2017). There is evidence that this occurs in a sexual dysmorphic manner, indicating a potential element of genetic gender susceptibility to fetal growth restriction (Pantaleon *et al.* 2010, Howerton *et al.* 2013, Buckberry *et al.* 2014, Hardiville & Hart 2014, Myatt *et al.* 2014). In this mini review, we focus on the role of mTOR and OGT in placental development, nutrient regulation and response to cellular stress in fetal growth restriction (Fig. 1).

Placental nutrient transport

Placental transport of essential nutrients and oxygen from the maternal circulation to the developing fetus is imperative to maintaining fetal growth. As the demand for these nutritional substrates increases throughout gestation, any alteration in this process has the potential to significantly impact fetal growth. Placental transport occurs primarily through the syncytiotrophoblast cellular layer, which is a multinucleated epithelial layer that lines the placenta villi. This is the most metabolically active portion of the placenta, accounting for 30% of the utero-placental oxygen consumption (Carter 2000, Schneider
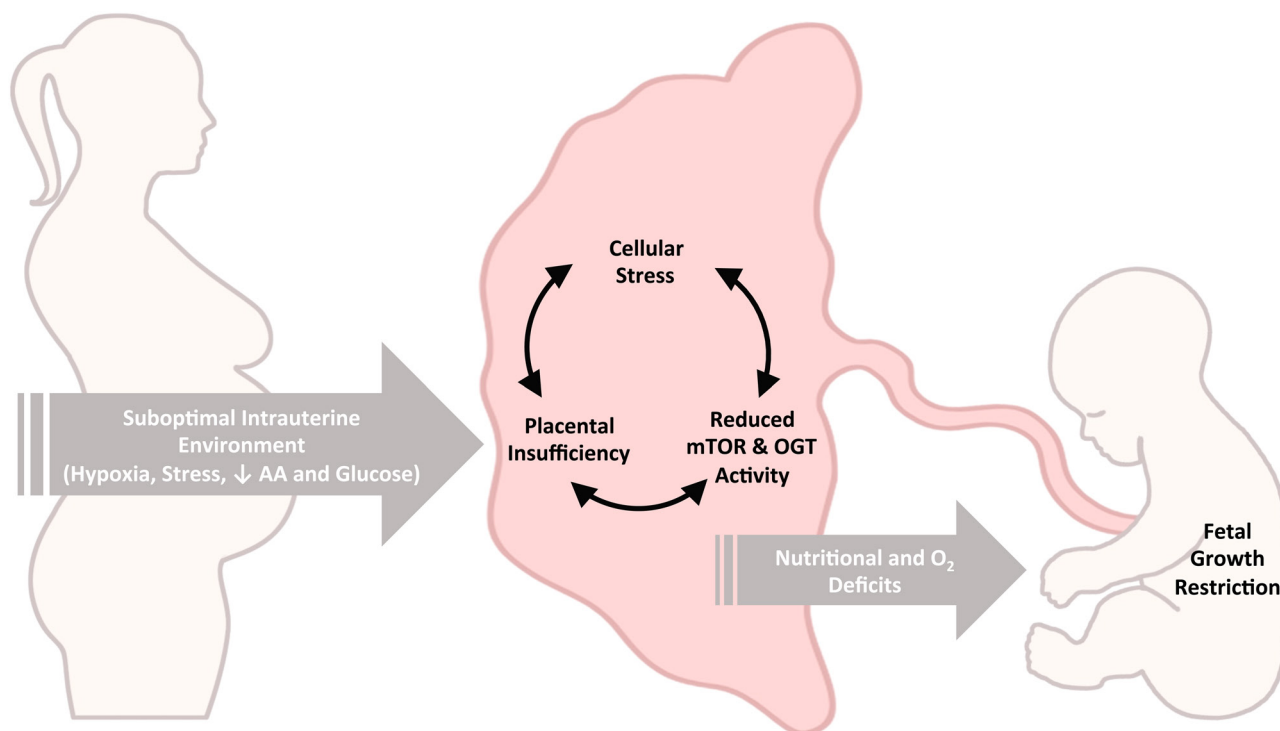
Figure 1
Factors in the development of fetal growth restriction. Fetal growth restriction is a result of changes in the maternal intrauterine environment, which influence placental function. This includes several integrated factors: (1) cellular stress, in the form of hypoxia, oxidative damage, metabolic dysfunction and nutrient deprivation; (2) reduced activity in mTOR and OGT nutrient signaling pathways, key regulators of placental development, nutrient uptake and cellular stress response and (3) placental insufficiency secondary to impairments in trophoblast invasion, uteroplacental blood flow and nutrient uptake, all contributing to fetal undernutrition and fetal growth restriction.

2000). Glucose and amino acid transport proteins are located on both the microvillous or maternal side and basal plasma membrane or fetal side of the syncytiotrophoblast; nutrients must pass through both membranes to reach the fetal circulation (Sibley 2009). Nutrient transport through the placenta is directly dependent on the thickness of this exchange barrier, utero-placental perfusion and transporter concentration and capacity (Lager & Powell 2012). Glucose, amino acids and oxygen are the major nutritional substrates utilized for fetal growth.

Glucose

Glucose is the primary nutrient required for fetal growth and development and is transported across the placenta by sodium-independent facilitated diffusion by the GLUT family of transporters. GLUT 1 is the principal glucose transporter in the human placenta and is located on the basal side of the membrane (Tadokoro *et al.* 1996, Baumann *et al.* 2002, Baumann *et al.* 2014). GLUT1 receptor expression steadily increases throughout gestation, reaching its highest concentration in the third trimester in response to increasing fetal demand. Glucose transport is regulated by insulin growth factors (IGF-1 and IGF-2). IGF-1 and IGF-2 are single chain polypeptides that act as potent stimulators of cellular growth, affecting overall placental size and fetal growth (Sferruzzi-Perri *et al.* 2011*a*, Zhang *et al.* 2015). IGF-1 has a dominant role in regulating fetal growth based upon nutrient availability, while IGF-2 has a broader role in the overall regulation of placental and fetal growth (Fowden 2003, 2008, Sferruzzi-Perri *et al.* 2011*a*). IGF-1 acts to increase GLUT1 receptor expression and localization to the cell membrane, while IGF-2 indirectly alters expression of GLUT1 by interacting with IGF-1 receptor activating PI3K/AKT and MAPK signaling pathways (Baumann *et al.* 2002, 2014, Sferruzzi-Perri *et al.* 2011*b*, 2017). GLUT1 is insensitive to insulin, and therefore, insulin does not serve as a primary regulator of placental glucose uptake (Diaz *et al.* 2014*a*).

Amino acids

Amino acids are necessary for protein synthesis and fetal growth. Amino acids are actively transported across the placental membrane (Cetin *et al.* 1992). To date, more than 25 different acid transporters have been identified in the placenta (Jansson 2001, Kudo & Boyd 2002, Cleal & Lewis 2008). Two well-defined amino acid transport pathways are system A and system L (Jansson 2001, Roos *et al.* 2009). System A transports small neutral non-essential amino acids, including glycine, alanine and serine, in a sodium-dependent manner and is concentrated on the microvilli side of the syncytiotrophoblast. System A placental transport is composed of three isoforms: SNAT1, SNAT2 and SNAT 4 (Brett *et al.* 2014). System A activity is regulated by amino acid concentration, insulin, leptin and IGF-1 (Jansson *et al.* 2003, von Versen-Hoynck *et al.* 2009, Jones *et al.* 2010, Brett *et al.* 2014). Alternatively, system L actively transports large neutral amino acids in a sodium-independent fashion and is responsible for the exchange of essential amino acids such as leucine and is located throughout the syncytiotrophoblast layer. The major placental L system transporters are LAT1, LAT2, LAT3 and LAT4, which are regulated by maternal insulin and glucose levels (Brett *et al.* 2014).

Oxygen

Oxygen is a fundamental requirement for fetal growth, supplying the means for mitochondrial and oxidative metabolism (Murray 2012). Oxygen is transported by the placenta by means of simple diffusion (Mirbod 2018). Oxygen diffusion is dependent on multiple factors including oxygen tension, oxygen gradient, factors related to maternal and fetal hemoglobin exchange, thickness of the placental exchange barrier and utero-placental perfusion (Lager & Powell 2012, Mirbod 2018).

Nutrient-sensing pathways

As fetal nutritional and oxygen requirements increase throughout gestation, an appropriate placental response is required to sustain appropriate fetal growth. This is coordinated by nutrient-sensing signaling pathways, a concept first introduced by Diaz *et al.* (Diaz *et al.* 2014*b*, Jansson & Powell 2006). These pathways are highly integrated and attempt to match fetal nutrient requirements to maternal nutrient supply (Jansson & Powell 2006). mTOR and OGT are the primary nutrient-sensing pathways involved in placental regulation of amino acids and glucose transport and are regulated by oxygen availability (Arsham *et al.* 2003, Inoki *et al.* 2003, Brugarolas *et al.* 2004, Palin *et al.* 2014, Yang *et al.* 2015, Chang *et al.* 2018).

mTOR

mTOR signaling pathways regulate cellular proliferation, metabolism and protein synthesis. Placental mTOR thus has a significant role in placental regulation of fetal

nutrition and growth (Peng *et al.* 2002, Wullschleger *et al.* 2006). mTOR is an atypical serine/threonine kinase, acting to couple signaling between nutrients and growth factors such as insulin. mTOR forms two complexes in the placenta: mTORC1 and mTORC2 (Wullschleger *et al.* 2006). mTORC1 is the major complex studied in mammalian placentas, and in humans is localized in both the cytoplasm and nuclei of human trophoblastic cells, with particularly high expression in the placental syncytiotrophoblast layer (Roos *et al.* 2007, Zhang *et al.* 2017). mTOR activity is mediated by the PI3K/Akt signaling pathway, through phosphorylation of tuberin (TSC2) and activation of Rheb, stimulating cellular growth. mTOR activity is regulated by amino acid, glucose, insulin and insulin-like growth factor concentrations (IGF-1 and IGF-2). mTOR also plays a central role in cellular stress coping mechanisms discussed below (Heberle *et al.* 2015).

OGT

The OGT signaling pathway similarly regulates cellular metabolism, growth and mitochondrial function. This regulation occurs through O-linked N-acetylglycosamine modification of serine/threonine residues of target proteins in the nucleus and cytoplasm, distinct of that of the ER. OGT is responsible for regulation of glucose through the terminal step in the hexosamine signaling pathway (Wells *et al.* 2003, Hart *et al.* 2007, Hanover *et al.* 2010, Palin *et al.* 2014, Wu *et al.* 2017). 3–5% of placental glucose is shunted through this pathway to form uridine diphosphate-N-acetylglucosamine (UDP-GlcNAc), the main substrate involved in O-GlcNAcylation used by OGT (Palin *et al.* 2014). Due to the myriad of OGT targets, O-GlcNAcylation has been implicated in multiple biological processes including glucose metabolism, cellular growth, mitochondrial and endoplasmic reticulum function, cellular growth and stress responses (Groves *et al.* 2013).

Placental development

Nutrient-sensing pathways are intricately involved in placental development. This is particularly important as placentation abnormalities are predecessors to placental insufficiency and fetal growth restriction. Impaired trophoblast invasion, spiral artery remodeling and utero-placental perfusion are key components in this process resulting in reduced placental perfusion, oxygen diffusion, nutrient transport and development of fetal growth restriction (Baschat & Hecher 2004, Lager &

Powell 2012, O'Tierney-Ginn & Lash 2014, Mirbod 2018). Placentas from growth-restricted pregnancies demonstrate reduced trophoblast proliferation and decreased number of capillaries per villous cross-section (Chen *et al.* 2002). Placental insufficiency is more likely to occur in pregnancies complicated by maternal medical conditions including hypertension, autoimmune disease, pre-eclampsia and diabetes and conditions associated with cellular stress, hypoxia and impaired placental invasion (Green *et al.* 2010).

Early pregnancy development, including initial blastocyst formation, implantation and trophoblast metabolic differentiation is dependent on a functioning hexosamine biosynthetic pathway and any disruptions in this system results in decreased cellular proliferation and apoptosis (Caniggia *et al.* 2000, Pantaleon *et al.* 2008). This illustrates the importance of nutrient signaling pathway early in embryo formation, implantation and placental development. Prior to 10 weeks of gestation, the placenta develops in a relative state of hypoxia as maternal spiral arteries are blocked by invading plugs of cytotrophoblast cells (Aplin 2000, Caniggia *et al.* 2000). This acts as a protective mechanism as the placenta undergoes implantation and spiral artery remodeling (Aplin 2000). During this time, the developing embryo is reliant on the hexosamine pathway for nutritional uptake (Pantaleon *et al.* 2008). After 10–12 weeks of gestation, the cytotrophoblast plugs resolve resulting in a sudden change in oxygen tension, a vulnerable time for hypoxic injury as trophoblast cells have not fully developed mechanisms to combat oxidative damage (Aplin 2000, Caniggia *et al.* 2000).

Hypoxia early in gestation is accompanied by decreased trophoblast proliferation (Aplin 2000, Caniggia *et al.* 2000). Trophoblast proliferation is directly mediated by mTOR's signaling response to angiopoietin-2 growth factor, glucose, leucine, arginine and glutamine levels (Kim *et al.* 2013, Zhang *et al.* 2017). Placenta growth, trophoblast proliferation and vascularization is additionally regulated by OGT and one possible mechanism occurs through post-translationally modified SHP-2 (Palin *et al.* 2014). OGT further impacts placental development through modulation of HIF-1a-induced angiogenesis (Yang *et al.* 2015). This pathway is impaired by hypoxia, with OGT-deficient placentas showing impaired response to hypoxia due to decreased vascularization in growth restriction (Yang *et al.* 2015). Early dysfunction in these nutrient-sensing pathways is likely the first early hit that occurs in the development of placental insufficiency and fetal growth restriction. We propose a subsequent hit occurs as

pregnancy progresses and increasing oxygen and nutrient requirements for fetal metabolism and growth are not met due to reduced oxygen availability and nutrient transport due to decreased placental vascularization, resulting in hypoxia and further placental dysfunction (Burton & Jauniaux 2018, Schoots *et al.* 2018).

Nutritional deficiency

The development of fetal growth restriction is associated with overall placental dysfunction. This occurs secondary to placental insufficiency from the processes described above. While the exact timing of these events in pregnancy are unknown and can likely be variable, there is some recent evidence that fetal growth restriction occurs when placental adaptation mechanisms become overwhelmed (Higgins *et al.* 2016). This is mediated by both the timing and severity of insulting events and explains the variability in observed severity and onset of fetal growth restriction in human gestation (Kimura *et al.* 2013).

Maternal nutrient supply

The most comprehensive evaluation of maternal nutritional status on fetal growth occurred during the Dutch famine from 1944–1945, where significant caloric restriction resulted in low neonatal birth and placental mass (Stein & Susser 1975*a*,*b*). Rodent studies have shown similar effects with low-protein diets leading to reduced placental and fetal weights, decreased system A activity and dysfunctional amino acid uptake (Malandro *et al.* 1996, Jansson *et al.* 2006). In baboons, overall maternal nutrient-restricted diets are accompanied by alterations in insulin, leptin, IGF-I levels and downregulation of placental nutrient transporters GLUT-1, SNAT-2, LAT-1 and LAT-2 (Kavitha *et al.* 2014). A similar reduction in insulin and IGF-I, SNA-1 and SNAT-2 is observed in rats fed low-protein diets (Rosario *et al.* 2011). While maternal nutritional supply is helpful in determining important placental changes that affect fetal growth, most cases of fetal growth restriction occur secondary to alterations in placenta function, leading to dysfunctional transport of nutrients, particularly glucose and amino acids, which have been associated with mTOR- and OGT-sensing pathways (Wullschleger *et al.* 2006, Roos *et al.* 2009, Brett *et al.* 2014). Studies showing direct causal role of mTOR in placental transport of amino acids are yet to be done in animal studies.

Nutrient-sensing pathways

The relationship between fetal growth restriction and dysfunctional nutrient-sensing pathways has recently been identified. Given mTOR's role in regulating metabolism and growth, it is not surprising its levels and activity are decreased in trophoblast cells in pregnancies complicated by fetal growth restriction (Roos *et al.* 2007, Zhang *et al.* 2017). mTOR regulation is multifactorial, illustrating the complexity of regulatory inputs this pathway coordinates. In growth restriction models, glucose deprivation downregulates amino acid transportation by system L in an mTOR-dependent fashion (Roos *et al.* 2009). Fetal growth restriction is also associated with downregulation of placental mTOR and amino acid transporters (Roos *et al.* 2007). The hexosamine biosynthesis pathway and protein O-GlcNAcylation requires glucose, glutamine, glucosamine, acetyl-CoA to generate the end-product UDP-GlcNAc, a substrate for OGT (reviewed here (Hart *et al.* 2011)). Thus, nutrient flux from glucose, fatty acid and nucleotide metabolism in the placenta is expected to impact OGT's enzymatic activity the placenta. Less is known about the role of OGT regulation of nutrients in fetal growth restriction; however, OGT-deficient placentas and those from growth-restricted fetuses contain diminished levels of GLUT1 receptors (Yang *et al.* 2015). GLUT1 family of receptors is particularly sensitive to adverse conditions during pregnancy such as diabetes and malnutrition (Das *et al.* 1998, Illsley 2000). The role of oxygen, an important component of fetal growth restriction, has also recently been identified as a potent regulator of mTOR and OGT pathways. Hypoxia has been found to inactivate mTOR, decrease amino acid transport and decrease overall cellular metabolism (Arsham *et al.* 2003, Brugarolas *et al.* 2004, Jansson *et al.* 2012). While the exact mechanisms of inhibition are unknown, TSC1/TSC2 and AMPK components of the mTOR pathway are required (Inoki *et al.* 2003, Brugarolas *et al.* 2004). Oxygen tension additionally impacts fetal growth through the OGT pathway and regulation of placental vascular growth and development (Yang *et al.* 2015). Additionally, both mTOR and OGT nutrient-sensing pathways respond to multiple environmental mediators of metabolism, growth factors, hypoxia and stress (Wullschleger *et al.* 2006, Roos *et al.* 2009, Howerton & Bale 2014, Rosario *et al.* 2016).

Cellular stress

Prenatal exposure to stress in the intrauterine environment affects placental metabolism and fetal growth. This can

be multifactorial including oxidative stress, ER stress and autophagy and can directly impact mTOR and OGT pathways. Molecular mechanisms of O-GlcNAcylation regulation of cellular stress are reviewed by Groves *et al.* (2013).

Oxidative stress

The association between oxidative stress and fetal growth restriction has been well documented. The most classic example of this relationship occurs in mothers exposed to chronic hypoxia while living at high altitudes who are at higher risk of pregnancies complicated by fetal growth restriction. This effect is secondary to hypoxic damage, defects in spiral artery remodeling and subsequent reductions in nutrient transport (Yung *et al.* 2012*a*). Oxidative stress also directly impairs placental perfusion, a common factor in fetal growth restriction and maternal complications such as preeclampsia (Burton & Jauniaux 2004). The impact of oxidative stress in fetal programming and in the placenta is reviewed here (Thompson & Al-Hasan 2012, Wu *et al.* 2015, 2016).

Oxidative stress impairs activity of the electron transport chain resulting in overproduction of reactive oxygen species (ROS; Ejima *et al.* 1999). Mitochondria are the primary site of ROS generation and are particularly susceptible to oxidative damage (Holland *et al.* 2017). Overproduction of reactive oxygen species leads to mitochondrial cell damage, significantly reducing placental metabolism and protein translation (Yung *et al.* 2008, Simmons 2012). This decreased protein synthesis downregulated expression and function of system A amino acid transporters, a key pathway in growth restriction (Nelson *et al.* 2003, Colleoni *et al.* 2013).

Various oxidative stress parameters are also altered in fetal growth restriction compared to normal pregnancies. Maternal serum total antioxidant capacity and total free sulfhydryl levels are reduced in fetal growth restriction, while total oxidative status, oxidative stress index, prolidase and malondialdehyde activity are increased (Toy *et al.* 2009 Maisonneuve *et al.* 2015, Biberoglu *et al.* 2016). Maternal serum total oxidant status and antioxidant status are additionally found in elevated levels in pregnancies complicated by fetal growth restriction (Mert *et al.* 2012). Higher levels of oxidative stress markers are also clinically correlated with worsening placental dysfunction as measured by abnormalities in umbilical artery Doppler indices prior to delivery (Kavitha *et al.* 2014, Maisonneuve *et al.* 2015, Biberoglu *et al.* 2016).

mTOR plays an important role in major functions of mammalian cells including stress responses like oxidative stress (reviewed here Proud 2004). mTOR signaling is highly regulated by nutritional conditions, such as reduced cellular energy or the availability of metabolic fuel ATP production (via glycolysis or mitochondrial oxidative metabolism). The effect of mTOR in placental mitochondrial metabolism is not clear. However, in non-placental cells, mTOR pathways regulate mitochondrial oxygen consumption and oxidative capacity (Schieke *et al.* 2006). In the placenta or non-placental cells, energy status is signaled to mTORC1 through AMP-activated protein kinase (AMPK), a sensor of intracellular energy status (AMP or reactive oxygen species (ROS)). Autophagy and apoptosis are two crucial interconnected stress processes (discussed below) that are often influenced by oxidative stress. As discussed below, mTOR plays a central role in autophagy (Jung *et al.* 2010).

OGT exists in multiple isoforms: two isoforms are localized in both cytosol and nucleus and one in mitochondria (Hanover *et al.* 2003). Zhao *et al* reviewed the regulatory roles of OGT in mitochondria (Zhao *et al.* 2016). Recent findings have demonstrated that O-GlcNAcylation is widely spread among mitochondrial proteins and that mitochondrial function and oxidative stress both can be regulated by O-GlcNAcylation (Tan *et al.* 2017). The role of OGT in placental mitochondria is under studied and warrants further investigation.

ER stress/autophagy/apoptosis

Enhanced oxidative stress leads to abnormal endoplasmic reticular (ER) function, resulting in trophoblast autophagy, autophagic vacuole formation and cellular apoptosis. These processes are associated with fetal growth restriction and are particularly more pronounced when trophoblasts are exposed to reduced oxygen tensions or nutrient-depleted environments (Curtis *et al.* 2013, Kimball *et al.* 2015, Zhang *et al.* 2017). Endoplasmic stress and protein synthesis blockage have also been demonstrated in women living at high altitudes, exposed to chronic hypoxia (Yung *et al.* 2012*a*). mTOR signaling pathways are directly involved in these processes, with lower protein levels and activity, increased ER stress and autophagy found in fetal growth-restricted placentas and cell cultures in response to glucose-oxygen deprivation (Hung *et al.* 2017, Zhang *et al.* 2017). Unresolved ER stress response eventually disrupts placental morphogenesis (Yung *et al.* 2012*b*). While less is known about placental OGT, a similar regulatory role of autophagy in response to nutrient deprivation and

hypoxia occurs in other tissues and disease processes (Guo *et al.* 2014, Ruan *et al.* 2017, Wani *et al.* 2017). Placental autophagy and cellular dysfunction can all contribute to reduced trophoblast invasion, placental cellular mass and nutrient transport found in fetal growth restriction.

Prenatal stress and sexual dimorphism

Emerging evidence surrounding fetal stress response has shown a sexually dimorphic pattern, indicating a potential element of genetic susceptibility to fetal growth restriction (Howerton *et al.* 2013). In humans, fetal growth restriction has shown an early sex-bias towards male children (Thayer *et al.* 2012). This dimorphic pattern may be directly linked to nutrient sensing pathways such as OGT, an X-linked gene, with further control through X inactivation (Hardiville & Hart 2014).

Fetal vulnerability to prenatal stress is amplified in the male fetus across a variety of mammalian species (Mauvais-Jarvis 2015, Cheong *et al.* 2016, Sundrani *et al.* 2017). A growing list of human studies recognizes sexually dimorphic effects in response to developmental insults ranging from prenatal alcohol and smoke exposure to maternal asthma, obesity and malnutrition. Animal studies show an analogous sex bias, again, with the majority of ill effect in the male offspring (Sundrani *et al.* 2017). Cortisone exposure in mice also leads to alterations in placental size and structure, IGF-2 and VEGF-α, a mediator of vasculogenesis, a response which was only appreciated in male offspring (Cuffe *et al.* 2015).

Genes encoding both mTOR and OGT have shown a sex bias in their placental expression. mTOR expression is regulated by the mammalian stress response in a sexually dimorphic manner (Buckberry *et al.* 2014). mTOR signaling is influenced by Deptor (DEP domain-containing mTOR-interacting protein), which binds mTORC1 and mTORC2 in response to maternal stress and elevated cortisol levels (Mparmpakas *et al.* 2012). This may explain the observed differences in male and female growth and development in stressful intrauterine environments.

Akin to mTOR expression, placental expression of OGT is notably diminished in male mice, with a further reduction in the presence of prenatal stressors. OGT mediates a deleterious response in placental size and structure to prenatal stress hormones in male offspring (Pantaleon *et al.* 2017). Due to the sex bias of reduced OGT expression, the male placental response to both increased cytokine production and apoptosis is amplified when compared to the female (Myatt *et al.* 2014). One theory is that the higher levels of OGT expression in female placentas may offer them additional protection against elevated levels of maternal stress when compared to males (Howerton *et al.* 2013, Howerton & Bale 2014). These factors may explain why human male infants born prematurely to preeclamptic mothers exhibit more severe growth restriction than similarly compromised female neonates (Reynolds *et al.* 2012, Myatt *et al.* 2014).

Despite advances in our understanding of the placental OGT signaling pathway and its correlation with fetal growth restriction in the mouse model, questions remain about the transportability of this model to the human maternal fetal placental unit. The gene encoding OGT, sits close to the gene locus involved with X-inactivation and patterns of X-inactivation, can significantly alter its expression. OGT can escape X-inactivation in mouse trophoblastic cells, however, in humans not only can X-inactivation escape occur up to five times more frequently, reactivation has also been demonstrated (Olivier-Van Stichelen & Hanover 2015). While OGT levels and expression are higher in female human placental samples compared to males, whether this differential expression correlates to similar sex-biased effects on human offspring remains to be seen. Continued study of sex-specific programming changes is necessary to define the underlying mechanisms involved in fetal growth disorders. In parallel, animal studies investigating the impact of OGT in placental function are also needed. Future studies directed toward understanding the roles of OGT in placental architecture and function, and placental targets would provide a clearer picture of the impact of OGT on the sex dimorphism impact in the development of fetal growth restriction.

Conclusions

Nutrient-sensing signaling pathways are vital to overall placental health and function. Disruption at any point in this process can lead to devastating placental dysfunction and development of fetal growth restriction, one of the leading causes of perinatal morbidity and mortality. mTOR and OGT nutrient-sensing pathways are complex and act in a multitude of fashions to maintain fetal growth throughout gestation. Future research should be directed toward mechanistic studies towards understanding the causal effects of these proteins and potential crosstalk for synergy between OGT and mTOR to impact growth and cellular response to stress (Carter 2000). This may lead to potential identification of target therapies to reduce the impact of ongoing cellular stress and reduce the incidence and evolution of fetal growth restriction.

Fetal growth restriction not only impacts perinatal outcomes, but also has long-term health consequences that extend through multiple generations (Nelson *et al.* 2003, Salvolini *et al.* 2012, Aljunaidy *et al.* 2017). Fetal growth restriction is linked to increased risks of developing cardiovascular disease, hypertension, diabetes, renal disease, obesity and dyslipidemia and neurological disorder later in life (Pettitt *et al.* 1991, Barker *et al.* 1993, Barker 1995, Eriksson *et al.* 2001, Hales & Barker 2001, Nelson *et al.* 2003, Luyckx *et al.* 2013, Vaag *et al.* 2014).

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