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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.

Keywords

Placenta; epigenetics; OGT; neurodevelopment; fetal development; nutrition; stress

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 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 synctiotrophoblast layer and villous cytotrophblast cells that are anchored to the maternal decidua by extravillous cytotrophblast

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., 2005a; Murphy et al., 2006; Petraglia et al., 1996; Simpson and MacDonald, 1981). Placental hormones come in all varieties including steroids, peptides, eicosanoids and gylcoproteins (Fowden et al., 2005b). 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 (Figure 1; reviewed in Georgieff, 2007). Of course, the developmental timeline for specific brain regions differs, such that certain rapidly developing regions may be more sensitive to nutrient availability at particular gestational stages than others that are slower to develop or that have already been established. The hypothalamus, the brain's command center for neuroendocrine function, begins to develop around mid-gestation in humans and continues to mature until adolescence (Gunnar et al., 2009; Markakis, 2002), forming its most critical connections during late pregnancy. It is important to note that the rate and timing of development, and therefore sensitivity, differs between the hypothalamic sub-regions (Bouret, 2010).

3.1 Placental energy balance as a mediator of developmental programming

Barker's Developmental Origins of Health and Disease hypothesis has been widely accepted and supported by research across various systems within the field of developmental biology

(Barker, 2007, 2004; Godfrey et al., 2007; Wadhwa et al., 2009). This hypothesis states that developmental programming prepares offspring for conditions outside of the womb by taking external factors into account during development. The most famous examples of this hypothesis are seen in cases of maternal under- or over-nutrition, which program metabolic dysregulation in offspring preparing them for predicted conditions of feast or famine through alterations in placental signaling (Wadhwa et al., 2009). Studies in both humans and animal models demonstrate that while caloric-restriction is associated with *decreases* in nutritional signals, such as IGF-1, insulin, and leptin, obesity *increases* levels of these factors in maternal circulation. Receptors for insulin, IGF-1, and leptin are present at the maternal-fetal interface, and their signaling stimulates amino acid transporter activity in trophoblast cells (Lager and Powell, 2012), directly coupling maternal nutritional status to placenta function and undoubtedly altering the availability of nutrients crossing into the fetal circulation. Changes in the availability of these factors for the fetus and/or placenta promote cellular signaling events important for long-term metabolic programming. Numerous studies in animal models and humans have reported strong associations between maternal nutrition and alterations in postnatal adiposity, appetite, metabolism, and brain function (Bayol et al., 2007; Breton, 2013; Jones et al., 2009; Muhlhausler et al., 2006; Sullivan et al., 2010; Taylor and Poston, 2007). Leptin drives the formation of neural projections during hypothalamic development that are critical for feeding behaviors and metabolic regulation throughout life (Bouret et al., 2004), providing a potential molecular mechanism by which maternal over or under nutrition and adiposity can program offspring long-term food intake and weight gain. Another recent study found an association between gestational diabetes and an increased risk for offspring autism spectrum disorder (ASD; Xiang et al., 2015), once again highlighting the importance of maternal energy balance in brain development

4. Epigenetics: energy availability and long-term programming

Epigenetics are a means by which environmental stimuli drive short- and long-term gene expression patterns. As a mediator of maternal and environmental signals to the developing fetus, epigenetic processes within the placenta are particularly powerful such that alterations of placental gene expression, downstream function, and signaling during fetal development have the potential for dramatic changes in developmental programming. As the brain is an energetically-expensive organ, consuming massive amounts of maternal resources during its development, it is also a particularly vulnerable site dependent on and susceptible to changes in placental function. For example, increased methylation of the leptin receptor gene in the human placenta is associated with increased lethargy and hypotonicity in male, but not female newborns (Lesseur et al., 2014), supporting not only a connection between epigenetic regulation of the leptin receptor and the relay of important information to the fetal brain, but also a sex-specificity in these outcomes.

At present, the three major epigenetic players are post-translational histone modifications, DNA methylation, and small noncoding RNAs, such as microRNAs (miRNAs). All of these processes are closely intertwined. For example, changes in histone marks, such as acetylation or methylation, are necessary for DNA methylation and demethylation to occur (Cedar and Bergman, 2009). DNA methylation can regulate miRNA expression and vice versa (Han et al., 2007; Wu et al., 2010), and miRNA frequently target and regulate levels of

the histone-modifying enzymes deacetylases and methyltransferases (Guil and Esteller, 2009; Tuddenham et al., 2006; Varambally et al., 2008; Wong and Tellam, 2008). Modifications made to the N-terminal tails of histone proteins that change protein charge and attract or repel DNA, trigger the tightening or loosening of coiled DNA, ultimately impacting the accessibility of particular genomic regions for transcription (Berger, 2002). Histone tails are subject to several types of modification that typically occur on lysine, arginine or serine residues. At present, the most well-established histone modifications include phosphorylation, acetylation, methylation, ubquitation, sumoylation, biotinylation, and glycosylation, although additional modifications will likely be discovered as epigenetic research continues to expand (Peterson and Laniel, 2004). The exact location, titer and combination of these modifications form the so-called histone code, which ultimately determines small- and large-scale chromatin conformational changes (Jenuwein and Allis, 2001). DNA methylation is the direct addition of methyl groups to DNA nucleotides. The most well-known function for DNA methylation is transcriptional silencing by recruitment of histone modifying complexes to collapse chromatin structure or direct inhibition of transcription factor binding to promoter start sites (Bird, 1985). However, DNA methylation can also direct alternative promoter usage, or be a vestigial mark of previous transcriptional activity (Hon et al., 2013; Jones, 2012). microRNAs (miRNAs) are short, single-stranded non-coding RNAs that typically mediate post-transcription gene silencing (Filipowicz et al., 2008). Most miRNAs are transcribed into primary miRNAs (pri-miRNAs) by RNA polymerase II, although the largest human miRNA cluster, C19MC, which has received particular attention in the placenta, is transcribed by RNA polymerase III (Borchert et al., 2006). pri-miRNAs, precursors that can give rise to many mature miRNAs, are further processed into pre-miRNAs by the endonuclease activity of the enzyme Drosha, which cleaves hairpin pri-miRNAs leaving a two-nucleotide overhang on the 3′ end that is recognized by the nucleocytoplasmic shuttle, exportin-5 (Lee et al., 2003; Yi et al., 2003). Once in the cytoplasm, pre-miRNAs are further cleaved by the enzyme Dicer, resulting in mature miRNAs that are enabled for loading into the RNA-induced silencing complex (RISC) (Tijsterman and Plasterk, 2004). miRNAs target one or multiple mRNAs for degradation via complementary binding. miRNAs have more recently been shown to direct DNA methylation and histone modifications after being shuttled back into the nucleus via specific transporters (Benetti et al., 2008; Guan et al., 2011; Noh et al., 2013).

4.1 Histone modifications in the placenta

Histone modifications have a unique function in the placenta as the primary mediators of imprinting in some genomic regions. In fact, DNA methylation is not necessary to maintain imprinting in one location on chromosome 7, as it is chiefly maintained by H3K9me2 and H3K27me3 through the actions of the histone methyltransferase EZH2, a member of the Polycomb repressive complex (Lewis et al., 2004; Umlauf et al., 2004). Genomic compartments such as enhancers, promoters, and silenced regions are typically associated with the histone marks H3K4me1/H3K27ac, H3K4me3, and H3K27me3, respectively. Using ChIP-Seq against these marks, Julie Baker and colleagues discovered that enhancer regions in trophoblast cells are enriched for endogenous retroviruses, which are suggested to be important contributors to species-specific placental evolution (Chuong et al., 2013).

Despite their intriguing role in early placental development, changes in the histone code in response to changes in the maternal milieu have not been currently examined.

Sex differences in several epigenetic regulators have been identified across placental development. Expression of the X-linked H3K4me3 demethylase, Kdm5c, is higher in the female placenta, whereas expression of the Y-linked genes for the H3K27me3 and H3K4me3 demethylases, Uty and Kdm5d respectively, are higher in males (Figure 2A.; Howerton et al., 2013). These differences suggest that epigenetic control of gene expression within the placenta may lead to sex differences in placental function, and perhaps lead to known gender biases in sensitivity to insults associated with neurodevelopmental disorders.

4.2 DNA methylation in the placenta

Changes in DNA methylation in the placenta have only recently been explored with regard to sex and developmental programming. In mice, female placental tissue has higher levels of global DNA methylation compared to male placentas (Figure 2B; Gallou-Kabani et al., 2010), which may provide females additional protection from dynamic changes in gene expression resulting from environmental insults. In addition, tighter regulation of gene expression in females provides a plausible mechanism by which males are preferentially affected by exogenous insults, such as maternal stress during gestation. This sex difference in DNA methylation likely accounts for aspects of the reported sex differences in gene expression in the placenta described in numerous studies (Gallou-Kabani et al., 2010; Howerton et al., 2013; Mao et al., 2010; Osei-Kumah et al., 2011; Sood et al., 2006). Although a recent paper reported finding no sex differences in mRNA levels of the enzymatically active DNMT isoforms (Gabory et al., 2012), DNMT enzyme activity might differ in the placenta by sex as it does in the neonatal brain (Nugent et al., 2015).

DNA methylation likely plays an important role in temporal control of gene expression across pregnancy in order to meet the changing needs of the developing fetus. Overall levels of DNA methylation increase toward the end of pregnancy (Chavan-Gautam et al., 2011; Novakovic et al., 2011). Genome-wide analysis of human placental tissue across gestation revealed widespread differences in methylation across trimesters, likely reflecting changes in cellular composition and differentiation across gestation (Novakovic et al., 2011). Most of the genes displaying differential methylation between the first and third trimesters were associated with immune related pathways and corresponded with gene expression patterns previously described across gestation (Mikheev et al., 2008; Winn et al., 2007).

Genomic imprinting is the epigenetic process whereby specific genes are epigenetically silenced based on parent of origin via DNA methylation and histone modifications. Although the best known examples of the developmental functions of imprinted genes stem from the well-know conflict theory of genomic imprinting, wherein paternally-derived genes are thought to promote pre- and postnatal growth, while maternally-expressed genes suppress growth (Hurst and McVean, 1997), regulation of cellular differentiation within the placenta is likely a more critical function of genomic imprinting (Miri and Varmuza, 2009). Elevated expression of the majority of known imprinted genes within the placenta, compared to embryonic and adult tissues, signifies the importance of imprinted genes in placental development and function (as thoroughly reviewed in Coan et al., 2005). Imprinted

genes are not found in non-mammalian species leading some to theorize the co-evolution of genomic imprinting and placentation.

4.3 miRNAs in the placenta

miRNAs are undoubtedly the most well-studied epigenetic regulators of placental function in relation to maternal and fetal health and disease (Mouillet et al., 2011), most likely due to the relative ease of quantifying their expression in placental tissue as well as in maternal circulation. miRNA expression differs significantly between the fetal and maternal sides of the placenta, and mRNA targets of these differentially expressed miRNAs suggest their importance in epigenetic regulation of maternal blood vessel development and fetal neuronal differentiation (Wessels et al., 2013). Analysis of miRNA expression from first and third-trimester human placentas has identified distinct miRNA-cluster expression profiles across pregnancy (Gu et al., 2013). This study found that miRNAs epigenetically regulate the expression of gene sets associated with both adaptive and innate immune responses throughout pregnancy, while miRNAs controlling oncogenic, angiogenic and anti-apoptotic genes appear dominant during the first trimester, and miRNAs promoting cell differentiation are highly expressed in late pregnancy (Gu et al., 2013).

In addition to their role in controlling gene expression necessary for normal placental development and function, several studies have examined the effects of maternal health and environmental insults on placental miRNA expression. Comparisons of miRNA expression in human placenta samples from patients with preeclampsia and fetal growth restriction have revealed several miRNAs associated with these conditions (Enquobahrie et al., 2011; Higashijima et al., 2013; Zhu et al., 2009). In preeclampsic tissue, miRNAs regulating genes involved in cardiovascular and reproductive system development, immunological function, and other cellular processes were significantly altered, suggesting, not surprisingly, that epigenetic processes are disrupted following abnormal placenta implantation (Enquobahrie et al., 2011; Zhu et al., 2009). Although the impact of prenatal nutrition on placental miRNA expression has yet to be thoroughly examined, specific miRNAs have been associated with birth weight, and suggest that decreased expression of miR-16 and miR-21 strongly increase the risk for being considered small for gestation age (Maccani et al., 2011). Interestingly, there are currently no reports of basal sex differences in miRNA expression in the placenta to our knowledge.

A study in humans has recently linked miRNA signaling in the placenta to neurodevelopmental programming (Maccani et al., 2013). This study quantified the expression of six placental miRNAs previously shown to be responsive to environmental perturbations (Maccani et al., 2010), correlating their expression with infant neurobehavioral outcomes as measured by the NICU Network Neurobehavioral Scales (NNNS) (Lester et al., 2004). They found that expression of miR-16 in the placenta was negatively correlated with neonatal attention scores, while miR-146a and miR-182 were positively correlated with movement scores. These results suggest a potential link between placental miRNA signaling and neurodevelopment, although long-term follow-up and reassessment of neurodevelopmental outcomes is needed.

An aspect of placental miRNA signaling that makes these epigenetic regulators particularly intriguing in early life programming research is their ability to be detected in maternal blood (Chim et al., 2008), making them potential biomarkers for complications such as preeclampsia and ectopic pregnancy (Gunel et al., 2011; Miura et al., 2015; Zhao et al., 2013, 2012), as well as one day potentially for other maternal or fetal insults predictive of risk for neurodevelopmental disorders, such as autism spectrum disorders which have recently been associated with preeclampsic pregnancies (Walker et al., 2015). Although blood is rich in RNAses, miRNAs can travel through the maternal bloodstream complexed with Argonaute2 (Ago2), a key component of the RISC complex, or within extracellular vesicles termed exosomes providing protection from degradation (Arroyo et al., 2011; Fevrier and Raposo, 2004). Exosomes are small vesicles secreted by most cell types in the body that contain various signaling factors thought to be important in short- and long-term communication between cells and tissues. Although the function of circulating miRNAs is not well understood, they are presumed to direct gene expression in their recipient cells/tissues. Placentally-derived exosomes containing miRNAs have been identified in circulation during human pregnancy (Luo et al., 2009), although their maternal targets and their potential to reach the fetus is not currently understood. In a study using primary trophoblast cultures, exosome-mediated transfer of specific miRNAs from trophoblasts to non-placental cells conferred viral resistance to recipient cells (Delorme-Axford et al., 2013), suggesting an important role for placental exosome communication for immune system regulation during pregnancy.

5. OGT: a transceiver of nutrient signals

Various intra- and extra-cellular signals communicate the need to regulate chromatin repression/activation, determining which genes can be readily transcribed, and which mRNAs to target for destruction prior to protein translation. Signals related to nutrient availability are of particular importance for epigenetic programming in the placenta. The enzyme O-linked N-acetlyglucosamine (O-GlcNAc) transferase (OGT) is at the crossroads of nutritional signals and chromatin regulation. OGT catalyzes the addition of O-linked N-acetlyglucosamine (O-GlcNAc) to serine and threonine residues on thousands of intracellular proteins to extensively alter cellular signaling events in a nutrient-responsive manner. Discovered over 30 years ago in lymphocytes (Torres and Hart, 1984), the pervasiveness of this monosaccharide post-translation protein modification has only recently been widely appreciated, as we now know that O-GlcNAclyation impacts myriad signaling functions. O-GlcNAc competes with serine/threonine phosphorylation, affording OGT enormous potential to dynamically alter cellular signaling. In addition, O-GlcNAclyation can enhance proteosomal activity and protein stability and structure, as well as directly alter gene expression by guiding transcription factor localization and influencing RNA polymerase II activity (reviewed in Bond & Hanover, 2013). The *OGT* is located on the X-chromosome and escapes X-inactivation in the placenta resulting in higher OGT expression and O-GlcNAclyation in females, adding an additional level of importance to its role in sex-specific signaling.

Nutrient excess stimulates O-GlcNAc transfer to recipient proteins as the final step of the hexosamine biosynthetic pathway, a key mediator of glucose metabolism (Love and

Hanover, 2005; Marshall et al., 1991). As nutrient transfer in the placenta from maternal sources to the developing fetus is of paramount importance, placental OGT affectively serves as a molecular “canary in a coal mine”, sensing changes in maternal energy and altering placental signaling to ultimately impact fetal programing. Recently, OGT’s domain has been expanded to epigenetics with the discovery that O-GlcNAclyation regulates several critical epigenetic links, including DNA demethylases and histone marks (reviewed by Dehennaut, Leprince, & Lefebvre, 2014).

5.1. OGT’s influence on epigenetics

The core histone proteins (H2A, H2B, H3, & H4) are directly modified by OGT, establishing O-GlcNAclyation as an important regulator of the histone code (Fujiki et al., 2011; Sakabe et al., 2010; Zhang et al., 2011). In addition, OGT’s widespread impact on cellular signaling can promote changes in other histone modifications, such as histone methylation.

The Polycomb Group proteins are typically associated with histone modifications important from early embryogenesis throughout life, most notably histone H3 di- and tri-methylation at lysine 27 (H3K27me3). Mutations in polycomb repressive complex 1 (PRC1) proteins are associated with abnormalities in neurological, skeletal, and stem cell development, whereas polycomb repressive complex 2 (PCR2) mutations result in embryonic lethality (reviewed in Kerppola, 2009). Studies in *Drosophila* initially identified OGT’s importance for maintenance of Polycomb transcriptional repression (Gambetta et al., 2009), a finding that has since been expanded to mammals. OGT mediated O-GlcNAcylation of EZH2, a H3K27 histone methyltransferase integral to PRC2, is necessary for stabilization of EZH2’s structure. OGT knockout reduces H3K27me3 without altering other histone methylation sites on H3, presumably due to decreased EZH2 function (Chu et al., 2014).

In addition to mediating epigenetic silencing through its interactions with PRC complexes as discussed above, OGT can facilitate permissive epigenetic marks through its association with the ten eleven translocation (TET) family of proteins (Figure 2D). The TET proteins are best known for their role in DNA demethylation (reviewed in Pastor et al., 2013). OGT uses TET2 and TET3 as scaffolding proteins, allowing OGT to modify histone H2B at ser112 (Chen et al., 2013), a site-specific modification that is associated with transcriptional activation (Fujiki et al., 2011). Further, the transcriptional activation mark H3K4me3 is dependent on O-GlcNAcylation of host cell factor 1 (HCF1), a key component of the SET1/COMPASS histone methylatransferase complex, in a TET2/3 dependent manner (Deplus et al., 2013). Although the above studies described the control of OGT activity by TET proteins, a reciprocal interaction wherein OGT regulates TET protein activity was only recently identified (Bauer et al., 2015). As O-GlcNAcylation competes with phosphorylation at serine and threonine residues, OGT activity can prevent phosphorylation at specific loci, altering protein regulation and signaling. TET proteins are typically highly phosphorylated in their N-terminal regulatory regions and OGT’s interaction with TET proteins is associated with decreased phosphorylation and enhanced O-GlcNAcylation, which might be important for dynamic regulation of these enzymes and thus potentially important for DNA methylation.

6. Prenatal stress alters placental function and signaling: impact on neurodevelopment

Studies in both human populations and animal models suggest a strong relationship between maternal stress and altered offspring physiological and psychiatric outcomes (reviewed in Bale et al., 2010; Talge et al., 2007; Weinstock, 2005).

6.1 Fetal programming by prenatal stress

A hallmark of stress exposure is increased production and circulation of cortisol (CORT; corticosterone in rodents). During pregnancy, high levels of maternal CORT are converted to inactive cortisone in the placenta by the enzyme 11 β-hydroxysteroid dehydrogenase type 2 (11β-HSD2)(Benediktsson et al., 1997). Early prenatal stress reduces 11β-HSD2 in the female mouse placenta (Pankevich et al., 2009), and stress in mid-gestation decreases 11β-HSD2 mRNA in both sexes in rat placenta (Peña et al., 2012). Decreased placental 11β-HSD2 expression in response to stress is associated with increased 11β-HSD2 promoter methylation and DNMT3a expression in the placenta (Peña et al., 2012), providing an epigenetic link between prenatal stress exposure and long-term gene programming in the placenta. The opposite effect of stress on 11β-HSD2 methylation was reported in the human placenta in women exposed to the stress of socioeconomic hardship during pregnancy. Methylation of 11β-HSD2 was lowest in placental tissue from women classified as having experienced high levels of socioeconomic adversity during pregnancy, although this study did not assess circulating CORT or 11β-HSD2 mRNA expression, and methylation was quantified at only 4 CpG sites. Male placentas were particularly vulnerable to adversity-associated decreases in this methylation. The authors concluded that low levels of 11β-HSD2 methylation may be an adaptive mechanism to increase placental 11β-HSD2 expression and buffer the fetus from maternal CORT (Appleton et al., 2013).

Other studies have examined methylation of key genes controlling CORT signaling in the placenta in association with infant neurobehavioral measures, an indication of future mental health and neurological function (Liu et al., 2010; Tronick and Lester, 2013). Impairments in infant neurobehavior (assessed by measuring reflex symmetry, excitability, and habituation to stimuli) were associated with increased methylation of *Nr3c1*, which codes for the glucocorticoid receptor (GR), in placentas from mothers who reported depression, and increased methylation of 11β-HSD2 in placentas from mothers who reported anxiety during pregnancy (Conradt et al., 2013). In a separate cohort of healthy patients, methylation at specific CpG sites on the *Nr3c1* promoter in the placenta was positively correlated with infant quality of movement and attention scores (Bromer et al., 2013). High levels of methylation in the promoter region of placental 11β-HSD2 were associated with low infant birth weight and reduced quality movement scores (Marsit et al., 2012). Further, infants with high placental *Nr3c1* methylation combined with low 11β-HSD2 methylation had greater reflex asymmetry, and infants with low placental *Nr3c1* methylation and high 11β-HSD2 methylation showed lower excitability. Infants with high methylation in both genes had impairments in stimulus habituation, suggesting that specific patterns of methylation of these critical regulators of CORT in the placenta give rise to divergent endophenotypes (Appleton et al., 2015). High methylation of FKBP5, a CORT binding protein that

negatively regulates CORT function, is associated with decreased expression of FKBP5 mRNA in the placenta and increased risk for infant arousal deficits (Paquette et al., 2014). Combined, these studies suggest that the placenta actively responds to exogenous hormonal cues, including those of maternal stress, via altered DNA methylation patterns that are associated with infant neurobehavioral outcome.

6.2 OGT regulates sex-specific programming of prenatal stress

Recently, our lab examined gene expression profiles in the male and female placenta in response to early prenatal stress across gestation (Howerton et al., 2013). Our model of early prenatal stress (EPS), in which pregnant mice are subject to chronic variable stress for the first 7 days of gestation, produces male offspring with endophenotypes characterized by hypothalamic mitochondrial dysfunction, HPA axis hypersensitivity, and enhanced stress responsiveness (Howerton and Bale, 2014; Howerton et al., 2013; Mueller and Bale, 2008). While the expression levels of thousands of placental genes dramatically changed across gestation, only 8 genes displayed significant sex differences across development. The X-linked OGT was significantly lower in the male placenta compared to the female placenta, and was further decreased following EPS, distinguishing it a potential mediator of the sex-specific effects of EPS on offspring programming. As detailed above, OGT is a perfect candidate to be the mediator of environmental signals from the maternal milieu to control placental homeostasis, ultimately directing the relay of information to the developing fetal brain. Importantly, the sex difference in OGT was accompanied by widespread sex differences in O-GlcNAcylation in the placental proteome, and EPS decreased O-GlcNAcylation levels extensively. These findings are exciting because they suggest widespread differences in OGT-mediated cellular signaling and potential differences in epigenetic regulation between the sexes and in response to stress, and indicate that OGT action in the placenta may be a key molecular mechanism for male-biased vulnerabilities to neurodevelopmental insults.

This hypothesis was supported by placental-specific knockout of OGT (pl-OGT), which completely recapitulated the EPS phenotype in male offspring (Howerton and Bale, 2014). As adults, pl-OGT males had decreased body weights and a hypersensitive HPA axis, as previously described in EPS males (Howerton et al., 2013; Mueller and Bale, 2008; Pankevich et al., 2009). In addition, both EPS and pl-OGT males showed similar placental gene expression patterns, with alterations in gene sets associated with endocrine and immune signals, suggesting that OGT regulates these genes in response to EPS and that these outcomes may be involved in signaling in the developing brain. Finally, when looking at hypothalamic function, both pl-OGT and EPS males had deficits in mitochondrial function, demonstrating that changes in placental signaling associated with stress can program long-term changes in the brain impacting neuroendocrine functioning. As OGT has numerous effectors in the proteome, the exact mechanism by which OGT programs gene expression in response to EPS is unknown. However, OGT's well-described interactions with critical epigenetic mediators suggests that sex and stress-related differences in OGT levels likely lead to lasting differences in placental gene expression via epigenetic mechanisms (Bauer et al., 2015; Chu et al., 2014; Dehennaut et al., 2014; Deplus et al., 2013; Gambetta et al., 2009; Olivier-Van Stichelen et al., 2014; Sakabe et al., 2010).

7. Conclusions

Regulation of nutrient and metabolic sensing within the placenta is a critical aspect in homeostatic maintenance and guidance of appropriate signaling to the developing fetus. As with any biological system, the precise coordination required to produce a healthy brain is remarkable. Placental transmission of nutrients is merely a small part of this highly complex process, although the importance of its contribution is illuminated in instances of poor nutrition, stress or other environmental insults, which have long-lasting effects on offspring development. Metabolic programming is particularly vulnerable to these perturbations. Placental OGT is one known contributor to fetal programming, since it transduces environmental signals into epigenetic changes that can ultimately alter placental gene expression and function. While the literature reviewed above gives us a fundamental picture of the placenta's role in neurodevelopmental programming, it is by no means exhaustive and the intricacies of how placental function influences brain development will undoubtedly become increasingly clear with additional mechanistic studies aided by modern technologies, particularly powerful transgenic mouse models and Next-Generation Sequencing.

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Highlights

- The placenta is a critical mediator of maternal and fetal signals
- Nutrient cues and maternal insults alter placental function
- Alterations in placental epigenetics can have lasting impacts on fetal programming
- Fetal sex also influence placental function
- O-linked-N-acetylglucosamine transferase (OGT) is a key mediator of sex differences and stress responsivity in the placenta

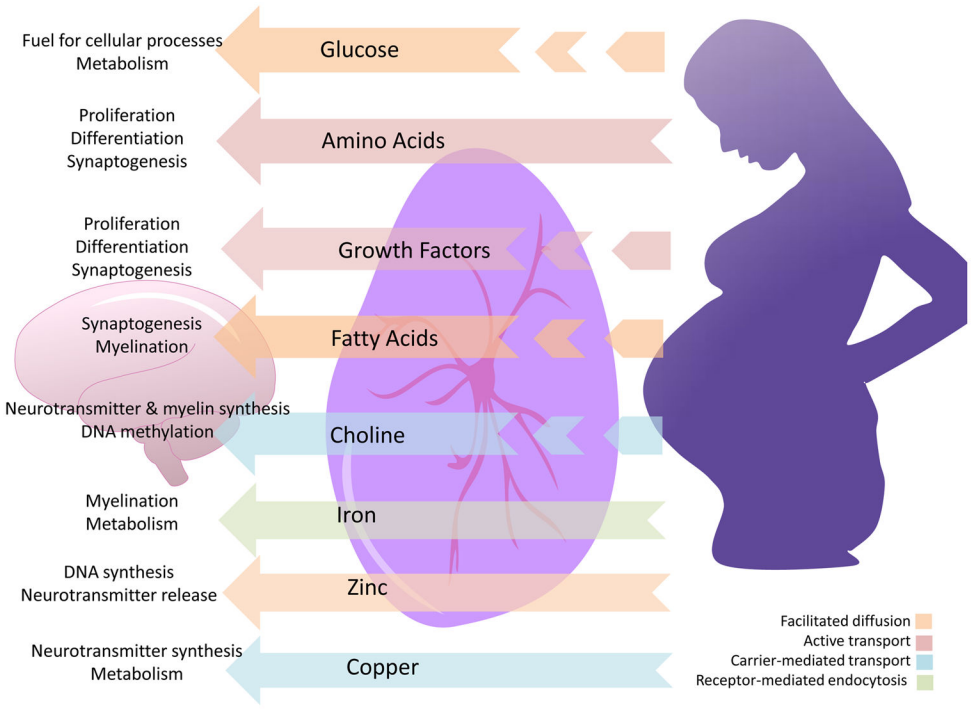

Figure 1.

Nutritional requirments for brain development. During late gestation, specific nutritional inputs (center) to the brain are necessary for specific neurodevelopmental processes (left). These nutrients come from either maternal circulation and the placenta combined (broken arrows) or maternal circulation alone (solid arrows). Their mechanism of transport across the placenta also differs (indicated by arrow color).

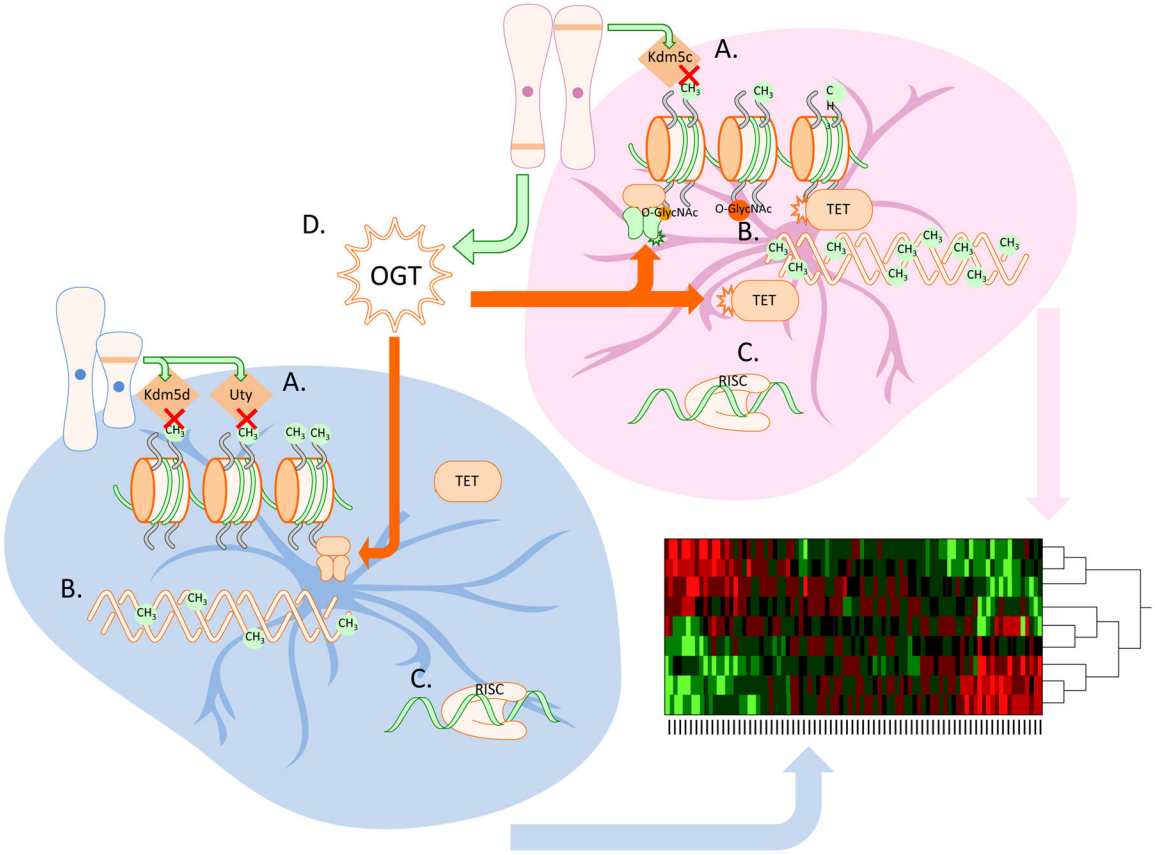

Figure 2.

Sex differences in epigenetic regulation of placental gene expression. A. Sex chromosome complement leads to male biased expression of the Y-linked histone demethylases Kdm5d and Uty, and female biased expression of the histone demethylase Kdm5c. B. DNA in the female placenta is more heavily methylated than in the male placenta. C. To date, there have not been reports of sex difference in miRNA expression in the placenta. D. Expression of the X-linked nutrient sensing enzyme O-linked N-acetylglucosamine (O-GlcNAc) transferase (OGT) is higher in the female placenta, leading to numerous sex differences in chromatin regulatory processes.