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Maternal obesity and prenatal programming

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ABSTRACT

Obesity is a significant and increasing public health concern in the United States and worldwide. Clinical and epidemiological evidence clearly shows that genetic and environmental factors contribute to the increased susceptibility of humans to obesity and its associated comorbidities; the interplay of these factors is explained by the concept of epigenetics. The impact of maternal obesity goes beyond the newborn period; fetal programming during the critical window of pregnancy, can have long term detrimental effects on the offspring as well as future generations. Emerging evidence is uncovering a link between the clinical and molecular findings in the offspring with epigenetic changes in the setting of maternal obesity. Research targeted towards reducing the transgenerational propagation and developmental programming of obesity is vital in reducing the increasing rates of disease.

Obesity is a significant and increasing public health concern in the United States and worldwide (Flegal et al., 2010; Ogden et al., 2006, 2012). In 2010 almost one third of adults and 17% of children and adolescents were obese (Ogden et al., 2012). Obesity in pregnancy is associated with complications that include gestational diabetes, intrauterine growth restriction, infants born large for gestational age, increased caesarian sections and other obstetric interventions, as well as miscarriages (Schmatz et al., 2010; Lu et al., 2001; Morin, 1998). Understanding obesity on an epidemiologic and molecular level has become a significant area of focus within the scientific community. Particularly important, is the understanding of how maternal obesity may affect the outcomes of offspring from the neonatal period to adulthood. The impact of maternal obesity goes beyond the newborn period; fetal programming during the critical window of pregnancy, can have long term detrimental effects on the offspring and future generations (Nicholas et al., 2016; Simmons, 2008). Environmental exposures in utero, including alterations of the nutritional milieu are particularly important during a time of such rapid growth (Simmons, 2008). The rising prevalence of obesity and its associated comorbidities, (Bouret et al., 2015), has led to a need for a better understanding of the impact of obesity on population health, including an understanding of the impact of maternal obesity on pregnancy and childhood outcomes. This review will aim to describe clinical data as well as data from animal models, with a focus on fetal programming in the setting of maternal obesity.

1. Birth weight and obesity

Maternal obesity has been linked to macrosomia (Gaudet et al., 2014), which is a risk factor for obesity and metabolic syndrome later in life. The variation in fetal growth in the setting of maternal obesity may be related to diet composition or vascular factors, and result from differing underlying molecular mechanisms. Epidemiologic studies have shown a trend of increasing maternal obesity with an associated increase in prevalence of infants who were born large for gestational age (LGA) (Lu et al., 2001). In a systematic review by Yu et al., pre-pregnancy obesity in women correlated with an increased risk of having LGA baby, and increased risk of obesity later in life (Yu et al., 2013). A Mendelian randomization study performed by Tyrell et al., established genetic alleles associated with maternal obesity and elevated blood glucose were linked to higher birth weight in the offspring (Tyrrell et al., 2016). There is a clearly established link between birth weight and obesity later in life. In the U.S. Growing Up Today Study, a cohort study of over 14,000 adolescents, a 1-kg increment in birth weight in full term infants was associated with an approximately 50% increase in the risk of overweight at ages 9–14 year (Gillman et al., 2003). When adjusted for maternal BMI, the increase in risk remained

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significantly elevated at 30%. A study of Danish military conscripts showed that even after controlling for birth length and maternal factors, BMI at ages 18–26 strongly correlated with birth weight (Sorensen et al., 1997). Both paternal and maternal adiposity are correlated with a higher birth weight of the offspring. However, the association is much stronger for the mother compared to the father (Parsons et al., 2001; Guillaume et al., 1995; Whitaker et al., 2010; Oken, 2009) suggesting that the intrauterine environment plays an important role in the later development of obesity. In addition to birth weight, several clinical studies have shown a direct relationship between maternal obesity and childhood obesity (Parsons et al., 2001; Boerschmann et al., 2010). In a retrospective cohort study of 8500 low income children in the US, Whitaker et al. demonstrated a two-fold increase in prevalence of early childhood obesity in children who were born to obese mothers (Whitaker, 2004). Smith et al. looked at metabolic features of children born before or after mothers underwent bariatric surgery. They found that children born after maternal bariatric surgery had had lower birth weight, lower prevalence of severe obesity adjusted for age and gender, greater insulin sensitivity, improved lipid profile, lower C-reactive protein, and leptin and increased ghrelin than offspring born before maternal bariatric surgery (Smith et al., 2009). Guenard et al. also looked at offspring before and after bariatric surgery, finding epigenetic changes in genes involved in glucoregulatory, including insulin sensitivity, inflammatory, and vascular disease genes conferring a more favorable cardiometabolic profile in the offspring born after maternal bariatric surgery (Guenard et al., 2013). Catalano et al. specifically discusses that pre-pregnancy obesity has a stronger association with metabolic alterations of the fetus, than gestational weight gain. In one study, they showed the maternal pre-pregnancy BMI greater than 30 kg/m^2 was associated with increased body fat percentage at age 8. Furthermore, they demonstrated that at age 8, children of obese mothers had higher systolic blood pressures, waist circumference, triglycerides, insulin resistance and leptin levels (Catalano et al., 2009).

2. Epigenetics

Clinical and epidemiological evidence clearly shows that genetic and environmental factors contribute to the increased susceptibility of humans to obesity and its associated comorbidities; the interplay of these factors is explained by the concept of epigenetics (Bouret et al., 2015). Epigenetics explains, as Barker describes, “developmental plasticity” in which environment impacts gene expression, particularly during vulnerable times of development (Barker, 2004). Epigenetics controls differentiation and development of different cell types by modulating chromatin architecture. It is a dynamic process that is influenced by environmental factors. The mechanisms include DNA methylation, histone modification and the presence of noncoding RNAs and microRNAs (Nicholas et al., 2016; Bouret et al., 2015; Pinney and Simmons, 2012). The epigenetic modifications can lead to stable propagation with transgenerational effects. Although human data is still limited, emerging evidence is uncovering a link between the clinical and molecular findings in the offspring with epigenetic changes in the setting of maternal obesity.

2.1. DNA methylation

DNA methylation is a class of epigenetic regulation, in which a cytosine base is modified by DNA methyltransferase at the C5 position of cytosine, a reaction that is carried out by various members of a single family of enzymes. Approximately 70% of CpG dinucleotides in human DNA are constitutively methylated, whereas most of the unmethylated CpGs are located in CpG islands. CpG islands are CG-rich sequences located near coding sequences and they serve as promoters for their associated genes. Approximately half of mammalian genes have CpG islands. The methylation status of CpG islands within promoter sequences works as an essential regulatory element by modifying the binding affinity of transcription factors to DNA binding sites. In normal cells, most CpG islands remain unmethylated; however, under circumstances such as oxidative stress, they can become methylated de novo. This aberrant methylation is accompanied by local changes in histone modification and chromatin structure, such that the CpG island and its embedded promoter take on a repressed conformation that is incompatible with gene transcription. It is not known why particular CpG islands are susceptible to aberrant methylation. DNA methylation is commonly associated with gene silencing and contributes to X-chromosomal inactivation, genomic imprinting, and transcriptional regulation of tissue-specific genes during cellular differentiation (Pinney and Simmons, 2012). In the case of maternal obesity and fetal programming, differential methylation of retinoid X receptor-α (RXRA) gene in umbilical cord tissue, was shown to be associated with childhood fat mass, when adjusted for sex (Godfrey et al., 2011).

2.2. Histone modifications

In eukaryotes, the nucleosome consists of DNA wrapped around an octameric complex of two molecules of each of the four histones: H2A, H2B, H3, and H4. The amino termini of histones can be modified by acetylation, methylation, sumoylation, phosphorylation, glycosylation, and ADP ribosylation. The most common histone modifications involve acetylation and methylation of lysine residues in the amino termini of H3 and H4. Increased acetylation induces transcription activation, whereas decreased acetylation usually induces transcription repression. Methylation of histones, on the other hand, is associated with both transcription repression and activation. Moreover, lysine residues can be mono-, di-, or trimethylated in vivo, providing an additional level of regulation (Pinney and Simmons, 2012). Histone methylation can influence DNA methylation patterns and vice versa (Cedar and Bergman, 2009). For example, methylation of lysine 9 on histone 3 (H3) promotes DNA methylation, while CpG methylation stimulates methylation of lysine 9 on H3 (Schubeler et al., 2000). Recent evidence indicates that this reciprocal relationship between histone methylation and DNA methylation might be accomplished by direct interactions between histone and DNA methyltransferases (Cedar and Bergman, 2009). Thus, chromatin modifications induced by adverse stimuli are self-reinforcing and can propagate.

2.3. Noncoding RNAs

Noncoding RNAs such as microRNAs (miRNA), small RNAs, and long or large RNAs, play a significant role in epigenetic gene regulation and chromosomal dynamics and transcription (Bernstein and Allis, 2005). With the discovery that most of the eukaryotic genomes are transcribed into RNAs that have no protein-coding potential, evidence has emerged of the different regulatory functions of noncoding RNAs. Studies have shown differential expression of miRNAs in the amnion, plasma, and other tissues of obese mothers (Nardelli et al., 2014; Yan et al., 2013; Carreras-Badosa et al., 2015). Yan et al. demonstrated that the offspring of obese pregnant ewes had decreased expression of miRNA let-7g in skeletal muscle, which correlated with increased adipose deposition in skeletal muscle (Yan et al., 2013). This demonstrates the role non-coding RNAs may play in regulation of adipogenesis through differential gene expression. Carreras-Badosa et al. conducted a study in which plasma circulating miRNAs were measured in normal pregnancies