Intrauterine Growth Restriction

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Intrauterine growth restriction (IUGR) is a pathological condition by which the fetus deviates from its expected growth trajectory, resulting in low birth weight and impaired organ function. The developmental origins of health and disease (DOHaD) postulates that IUGR has lifelong consequences on offspring well-being, as human studies have established an inverse relationship between birth weight and long-term metabolic health. While these trends are apparent in epidemiological data, animal studies have been essential in defining the molecular mechanisms that contribute to this relationship. One such mechanism is cellular stress, a prominent underlying cause of the metabolic syndrome.

intrauterine growth restriction (IUGR) metabolism cell stress cell death metabolic syndrome

1. Introduction

The metabolic syndrome refers to a group of physiological symptoms that increase an individual's risk for cardiovascular disease and type II diabetes. These symptoms, including dyslipidemia, obesity, hyperglycemia, and hypertension, are often assessed independent of each other; however, their simultaneous occurrence is synergistic toward onset of the metabolic syndrome. It is well known that these symptoms are influenced by factors such as genetics and lifestyle, but the role of developmental priming is often overlooked. The developmental origins of health and disease (DOHaD) posits that there is an inverse relationship between birth weight and long-term metabolic health, as adverse events in utero may permanently influence the function of metabolic organs. Infants affected by intrauterine growth restriction (IUGR) exhibit impaired organ growth with metabolic disease in adulthood, as early epidemiological studies by Sir David Barker and colleagues determined that low birth weight individuals have high rates of obesity, glucose intolerance, and coronary artery disease [1][2][3]. These studies have since led to widespread investigation of the underlying causes of IUGR, as well as the metabolic pathologies that arise in response to impaired organ development.

IUGR occurs as a consequence of utero-placental insufficiency, whereby the placenta does not meet metabolic requirements set by the fetal genome [4]. When placental tissue is unable to support proper nutrient and oxygen exchange, select fetal organs exhibit reduced growth and decreased cell size [5]. This 'organ-sparing' effect occurs such that vital organs (i.e., the heart and brain) receive greater shares of available resources at the expense of other organs, such as the liver [6]. Utero-placental insufficiency is often secondary to insults of maternal origin, including maternal malnutrition, drug use, and infection among others; therefore, maternal lifestyle has a significant

influence on offspring health [4][5]. Importantly, the postnatal environment has also been demonstrated to play an indirect role in provoking long-term metabolic dysfunction, as offspring born into an environment that is 'mismatched' from that in utero are subject to maladaptive changes in fetal programming [7]. Animal studies have revealed several mechanisms that govern this relationship, including epigenetic regulation of gene expression, the microbiome, and the hypothalamus-pituitary-adrenal axis. In addition, cellular stress is known to have a major role in causing adverse metabolic health across various models of IUGR.

Fetal growth and development consist of intricate cellular processes that are highly sensitive to intra- and extracellular stressors. Because of this, it is plausible that the presence of metabolic disease in adult IUGR offspring is attributed in part to cellular stress and programmed cell death. While events of cell stress and cell death are often protective, they can also be destructive and contribute to the development of metabolic disease. Studies have demonstrated that a suboptimal prenatal environment initiates cell stress and cell death in the placenta, giving rise to compromised fetal growth. This may further lead to cellular stress and dysfunction in metabolic organs, including oxidative stress and mitochondrial dysfunction, endoplasmic reticulum (ER) stress, inflammation, apoptosis, and autophagy. Alternatively, the occurrence of rapid postnatal weight gain (i.e., catch-up growth) in low birth weight offspring can lead to cellular stress and metabolic disease in an indirect manner.

2. Programmed Cell Death and Metabolism in IUGR Offspring

As mentioned previously, cell stress often occurs in a protective manner. That said, an organism's response to cell stress is dependent on the type and severity of the gestational insult. When an insult is severe and/or chronic enough that the resulting cell stress is overwhelming, cellular death may occur. Programmed cell death is a controlled cellular response that works to eliminate damaged or dysfunctional cells, either by means of apoptosis or autophagy.

2.1. Apoptosis

Apoptosis is a highly regulated form of cell death consisting of morphological changes that are distinct from other forms of cell death. Apoptotic cells undergo cell shrinkage, membrane blebbing, and fragmentation of nuclei and chromatin, often without inducing inflammation. This is what distinguishes apoptosis from necrosis, a type of uncontrolled cell death that provokes an immune response. While apoptosis is an essential part of many developmental processes, it is also a large contributor to the impaired function of metabolic organs. For example, the apoptotic loss of pancreatic β-cells is believed to be a driving factor of type II diabetes, particularly after the pancreas experiences oxidative stress or ER stress [8]. Although apoptosis does not cause inflammation, it has been demonstrated to occur as a result of upregulated immune cell function and pro-inflammatory cytokines (as reviewed by Quan et al., 2013) [9]. Finally, the loss of cardiomyocytes via apoptosis may also contribute to chronic heart failure, as early studies have shown that apoptosis exists in myocardial tissue samples taken from patients following myocardial infarction, cardiomyopathy, and end-stage heart failure [10][11][12][13]. Taking all of this into account, the occurrence of apoptosis in IUGR offspring seems to be cause for concern when assessing for risk of the metabolic syndrome.

2.2. Autophagy

Autophagy, also known as “self-eating”, is a form of programmed cell death that aims to clear out damaged organelles, misfolded or aggregated proteins, and intracellular pathogens. Following the identification of unwanted intracellular cargo, an isolation membrane called the phagophore engulfs cell material to form the autophagosome structure. Through fusion with lysosomes, the autophagosome then becomes an autolysosome and permits enzymatic degradation of its contents. While highly complex and not as well understood as apoptosis, autophagy is important in the balance of energy sources during development or times of metabolic stress. Because of this, activation of the AMP-activated protein kinase (AMPK) pathway is recognized as being a promotor of autophagy, while the mammalian target of rapamycin (mTOR) pathway is inhibitory. Dysregulated autophagy in the pancreas and liver has been previously associated with obesity and diabetes, and it is for this reason that autophagy has become of interest in the field of DOHaD.

Much like apoptosis, most studies to date concerning the developmental consequences of autophagy tend to focus on its role in the placenta. That said, there has been some investigation of autophagy in the IUGR heart, pancreas, and liver. In the fetal baboon heart, autophagy occurs as a result of maternal caloric restriction [14]. Furthermore, male IUGR offspring display increased levels of autophagy-related 7 (ATG7) protein and LC3BII, along with fibrosis of the left ventricle [14].

3. Conclusions

Epidemiological studies have provided astonishing evidence for the role of developmental programming in affecting susceptibility to the metabolic syndrome. It is clear that the perinatal period is a critical window for fetal reprogramming, while the early postnatal environment also has influence on offspring metabolic health. Animal studies have established that the inverse relationship between birth weight and long-term metabolism is mediated by mechanisms of cell stress, including oxidative stress, mitochondrial dysfunction, ER stress, and inflammation. When cell stress goes unresolved, this can lead to programmed cell death and the failure of metabolic organs. That said, there are many other factors involved in this relationship that remain poorly understood. For example, androgen levels have been demonstrated to promote both oxidative stress and ER stress [15][16]; therefore, sex-specific differences of postnatal cell stress may exist due to altered estrogen and testosterone signaling. Furthermore, recent studies have begun to elucidate a paternal contribution to IUGR and postnatal cellular stress; paternal obesity has been demonstrated to alter placental vascular structure and postnatal liver development, likely due to the induction of ER stress in both of these organs [17]. Overall, future studies are warranted to further investigate all of these factors, and novel technologies will be required to validate the molecular findings of animal studies in human IUGR cohorts.

By better understanding the origins of cell stress and programmed cell death in IUGR offspring, postnatal therapeutic measures could be developed to reduce risk for the metabolic syndrome during adult life. Neonatal administration of exendin-4, an agonist of the glucagon-like peptide 1 receptor, has been previously shown to prevent hepatic oxidative stress in male offspring at 7–9 weeks of age, and in doing so mitigated hepatic insulin

resistance [18]. The therapeutic benefits of exendin-4 have been explored in several clinical trials, and it is currently used as a treatment for type II diabetes; however, its safety and efficacy as a treatment in infants remains unknown. Similarly, the ER stress inhibitor tauroursodeoxycholic acid (TUDCA) ameliorates the incidence of type II diabetes in obese rats, so it is possible that TUDCA could be effective in treating IUGR-induced diabetes when administered in early life like exendin-4 [19]. Finally, this evolving field of research has great potential to guide clinical policy and protocols that exist during prenatal care. The cooperation of health care professionals with pregnant women is essential in preventing IUGR, and this could contribute to reduced rates of the metabolic syndrome across the adult demographic.

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