Early life programming and metabolic syndrome

Xiu-Min Wang

Hangzhou, China

Abstract: **Metabolic syndrome (MS) has reached epidemic proportions worldwide among children. Early life "programming" is now thought to be important in the etiology of obesity, type 2 diabetes, cardiovascular disease and MS. Nutritional imbalance and exposures to endocrine disruptor chemicals during development can increase risk for MS later in life. Epigenetic marks may be reprogrammed in response to both stochastic and environmental stimuli, such as changes in diet and the in utero environment, therefore, determination of targets for early life effects on epigenetic gene regulation provides insight into the molecular mechanisms involved in the epigenetic transgenerational inheritance of a variety of adult onset disease phenotypes. The perinatal period is a crucial time of growth, development and physiological changes in mother and child, which provides a window of opportunity for early intervention that may induce beneficial physiological alternations.**

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Introduction

Abdominal obesity, insulin resistance and hyperinsulinemia are the common characteristics of youth with metabolic syndrome (MS). In order to describe the prevalence of MS in children allowing for differences in MS definitions, Friend et al[1] made a systematic review which included 85 studies. When all studies were considered, the median prevalence of MS in whole populations was 3.3%, in overweight children was 11.9%, and in obese populations was 29.2%.[1] MS has reached epidemic proportions worldwide with far-reaching health care and economic implications. The rapid increase in the prevalence of these disorders suggests that environmental and behavioral influences, rather than genetic causes, are fueling the epidemic.

The "developmental origins of health and disease" (DOHaD) hypothesis proposes that environmental conditions during fetal and early postnatal development influence lifelong health and capacity through permanent effects on growth, structure and metabolism. This has been called "programming". Early life programming is now thought to be important in the etiology of obesity, type 2 diabetes, cardiovascular disease and MS, which is supported by epidemiological evidence in humans and by experiments in animals showing that maternal under- and over-nutrition and other interventions during pregnancy lead to abnormal metabolism and body composition in the adult offspring.[2] Early development is particularly sensitive to developmental disruption by nutritional factors or environmental chemical exposures and other stressors, with potentially adverse consequences for health later in life. Plasticity is more prominent prenatally and during early postnatal life, i.e., during the time of cell differentiation and specific tissue formation. The elucidation of underlying mechanisms is an area of interest and intense investigation.

Nutritional imbalance and exposures to endocrine disruptor chemicals (EDCs) during development can increase risk for disease later in life

The early work of Barker and colleagues[3] highlighted fetal nutrition as the primary factor driving the developmental origins of adult disease. In particular, altered maternal nutrition, including undernutrition and overnutrition, can lead to metabolic disorders in offspring, which provides proof of principle of nutritional programming of chronic disease in later life. Both nutritional imbalance and environmental EDCs affect the phenotype, thereby impacting on organ functions and disease susceptibility later in life during sensitive windows of development.

Author Affiliations: Department of Endocrinology, Children's Hospital, Zhejiang University School of Medicine, Hangzhou, China (Wang XM)

Corresponding Author: Xiu-Min Wang, MD, PhD, Department of Endocrinology, Children's Hospital, Zhejiang University School of Medicine, 57 Zhugan Xiang, Hangzhou 310003, China (Email: wangxiumin1019@yahoo.com.cn)

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Fetal undernutrition

The underlying causes of fetal undernutrition include: poor or unbalanced maternal nutrition; suboptimal body composition; excessive physical workload before and during pregnancy; and poor function of the fetal supply line. In a recently established cohort, women exposed to the 1959–1961 famine in China during gestation or early childhood are reported to have a greater risk of MS.[4] It is important to make the point here that it would be a misconception to think that lower birth weight, in itself, causes later disease, but rather the early-life restructuring of the body's tissues, and re-setting of endocrine and metabolic axes. Studies have shown that programming can occur in the absence of changes in birth weight.[5] The associations with birth weight occur because the same insults that programmed function often also reduce growth and lower birth weight.

Fetal overnutrition

In many developed societies, maternal and postnatal caloric intake is either sufficient or excessive, there is now increasing epidemiological evidence that fetal overnutrition (as judged from indicators such as maternal obesity, excessive gestational weight gain, and gestational diabetes) can produce a similar offspring phenotype to that of undernutrition. There is mounting evidence linking maternal obesity during pregnancy to obesity and the MS in children. Offspring of over-nourished mothers display common metabolic derangements including obesity and insulin resistance. Activation of signal transducer and activator of transcriptions 3 (STAT-3) signifies leptin sensitivity; and recent study in female rats showed that at birth, despite IUGR offspring being hypoleptinemic, hypothalamic leptin signaling was activated by enhanced STAT-3.[6] Further, offsprings of high-fat fed dams exhibit an alteration in the hypothalamic leptin-dependent STAT-3 phosphorylation, independent of the level of post-weaning nutrition.

Endocrine disruptor chemicals (EDCs)

EDCs initially referred to substances interfering with reproductive hormones, the term extends to compounds that may affect any endogenous hormones that carry signals from one cell to another, and there are now about 900 chemicals characterized as EDCs.[7] Such compounds can alter the effects of the endogenous hormones by acting as receptor agonists or antagonists, thereby resulting in abnormal hormonal signaling and leading to altered hormone action. Several EDCs appear to affect specific genes due to alterations in epigenetic marks.[8] Exposure to EDCs may result in increased risk of obesity later or insulin resistance leading to type 2 diabetes in life (examples include phthalates, bisphenol A, tributyltins, and several pesticides). Other data indicate that developmental exposures to EDCs can also interact with unbalanced nutrition leading to aspects of MS later in life.[9]

Mechanisms of programming-epigenetic marks

Genetic causes as well as environmental and behavioral influences are fueling the epidemic of metabolic syndrome. The DOHaD hypothesis has highlighted the link between the periconceptual, fetal, and early infant phases of life and the subsequent development of metabolic disorders in later life. Early-life programming is a mechanism by which inter-generational (mother-offspring) transmission of disease risk occurs. The environmental sensitivity of the epigenome is viewed as an adaptive mechanism by which the developing organism adjusts its metabolic and homeostatic systems to suit the anticipated extrauterine environment. The developmental environment induces altered phenotypes through genetic, physiological (especially endocrine) and epigenetic mechanisms. The latter include DNA methylation, covalent modifications of histones and non-coding RNAs. Epigenetic phenomena may be one of the mechanisms underlying programming. Epigenetic marks may be reprogrammed in response to both stochastic and environmental stimuli, such as changes in diet and the in utero environment. Elucidation of epigenetic processes may permit perinatal identification of individuals most at risk of later MS and enable early intervention strategies to reduce such risk.[10] Within tissues and organs that control metabolic homeostasis, a range of phenotypes can be induced by sustained changes in maternal diet via modulation of genes that control DNA methylation and by histone acetylation, which suggests epigenetic programming. Such potential mechanisms underlying epigenetic modification of tissue function result in a predisposition to altered insulin signaling. Recent studies have shown that even subtle imbalances in maternal nutrition are associated with the epigenetic profile at birth, which in turn is linked to markers of metabolic risk.[11] Patterns of DNA methylation are largely established during embryogenesis, fetal development and early postnatal life, and are sensitive to the nutritional environment. Epigenetic changes have been shown in the offspring of women exposed to the Dutch famine, and epigenetic variation has been related to childhood adiposity. Maternal carbohydrate consumption during the first trimester of pregnancy is inversely correlated with methylation levels in umbilical cord tissue and, in turn, is associated with child's adiposity at 9 years of age.[12]

Epigenetic patterns can be inherited from one

generation to the next and could therefore explain inter-generational effects. Environmental compounds can promote epigenetic transgenerational inheritance of adult-onset disease in subsequent generations following ancestral exposure during fetal gonadal sex determination. All tissues derived from the epigenetically altered germ line develop transgenerational transcriptomes unique to the tissue, but common epigenetic control regions in the genome may coordinately regulate these tissue-specific transcriptomes.[13] A recent study[14] has shown the utility for perinatal epigenetic analysis in identifying individual vulnerability to later obesity and metabolic disease. In this study, epigenetic gene promoter methylation at birth was associated with adiposity in children. Therefore, the application of epigenomic approaches and the determination of targets for early life effect on epigenetic gene regulation provide insight into the molecular mechanisms involving in the epigenetic transgenerational inheritance of a variety of adult onset disease phenotypes.

Intervention or prevention and challenges

While the underlying molecular mechanisms linking impaired fetal development to these adult diseases are being elucidated, emerging human and animal studies are now investigating how we can intervene in early life to reduce or prevent these long-term programming events. Several studies have shown that some components of MS are potentially reversible by nutritional or targeted therapeutic interventions during windows of developmental plasticity.[15-17] The gestational period is a crucial time of growth, development and physiological change in mother and child. This provides a window of opportunity for intervention via maternal nutrition and/or physical activity that may induce beneficial physiological alternations in the fetus. Administration of pegylated leptin antagonist (increased half-life compared to standard leptin antagonist) to rat neonates can also modify their responsiveness to diet-induced obesity in adult life, but this is dependent upon prior maternal nutrition and post-weaning diet. Pancreatic duodenal homeobox 1 (PDX1) is a critical regulator of pancreas development and islet differentiation. Neonatal exendin-4 prevented the progressive reduction of insulin-producing ß-cell mass in the intrauterine growth retarded rats over time; exendin-4 may increase histone acetylase activity and reverse epigenetic modifications that silence PDX1 and then restore the expression of PDX1 to normal levels.[16] A few investigations of developmental programming have focused on indices such as physical activity and effects of exercise. Despite a predisposition to develop obesity under sedentary conditions, obesity development was prevented in IUGR offsprings when exercise was available. Postnatal resveratrol treatment has shown to prevent symptoms of MS in hypoxia-induced IUGR from developing in adulthood. To date, preliminary data also highlight the promising role of nuclear receptors as therapeutic agents in reversing early programming of long-term disease.[17]

Conclusion

Developmental programming research offers a novel approach to investigate the mechanistic basis of obesity and related metabolic disorders which in human populations predominantly arises from environmental factors and lifestyle choices. Epigenetics have now become a mechanism that is fundamental to research into DOHaD. Both nutritional imbalance and environmental chemicals act during specific windows of sensitivity and show time-, sex-, and tissue-specific effects. Of note, early methyl donor malnutrition (excess nutrition or undernutrition) could effectively lead to premature epigenetic aging and thereby confer an enhanced susceptibility to adult disease in later life. An increasing number of studies are now investigating avenues to reverse or ameliorate the detrimental metabolic effects associated with developmental programming. We therefore call for focus on primary prevention of disease based on the developmental origins of health and disease paradigm during a critical window of fetal development.

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