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Teaser Epigenetic mechanisms are important in the brain development, and have a key role in the programming of increased risk of neurological diseases resulting from early-life stress.

Gestational hypoxia and epigenetic programming of brain development disorders

Qingyi Ma, Fuxia Xiong and Lubo Zhang

Center for Perinatal Biology, Division of Pharmacology, Department of Basic Sciences, Loma Linda University School of Medicine, Loma Linda, CA 92350, USA

Adverse environmental conditions faced by an individual early during its life, such as gestational hypoxia, can have a profound influence on the risk of diseases, such as neurological disorders, in later life. Clinical and preclinical studies suggest that epigenetic programming of gene expression patterns in response to maternal stress have a crucial role in the fetal origins of neurological diseases. Herein, we summarize recent studies regarding the role of epigenetic mechanisms in the developmental programming of neurological diseases in offspring, primarily focusing on DNA methylation/demethylation and miRNAs. Such information could increase our understanding of the fetal origins of adult diseases and help develop effective prevention and intervention against neurological diseases.

Introduction

During the late 1980s, Barker and colleagues uncovered the correlation between the nutrition condition of early life (during the prenatal and postnatal periods) and the increased risk of adult ischemic heart disease [1], known as 'Barker hypothesis'. Thereafter, numerous retrospective and prospective clinical and preclinical studies have supported this 'fetal origins of adult disease' theory [2–4], showing a substantial correlation between an adverse maternal environment and the development of various diseases in later life, including cardiovascular disease, diabetes and neurological disease [5–9]. One general mechanism by which maternal stress can be linked to phenotypic changes later in life is the epigenetic programming of genes, which has a central role in determining the functional output of the information that is stored in the genome.

Epigenetics is defined as heritable changes in gene expression that are not associated with concomitant alterations in the DNA sequence. The genetic information for the transcriptional program of gene expression is controlled by epigenetic mechanisms, including methylation/demethylation of DNA, post-translational modifications of histone, and noncoding RNAs (ncRNAs) such as miRNAs [10]. Epigenetic events are processes responding to endogenous and environmental signals and have crucial roles in the regulation of appropriate sets of gene expression, especially in particular tissues at specific time windows [10–12]. Accumulating evidence from both human and animal studies indicates that epigenetic modifications serve as a memory of

Corresponding author: Zhang, L. (lzhang@llu.edu)

Lubo Zhang is professor of pharmacology and physiology and director of Center for Perinatal Biology at the Loma Linda University School of Medicine. He was president of the Western Pharmacology Society in 2008. He has been a member of various grant review study groups for the US National Institutes of Health and American Heart Association for more than 15 years. Lubo is also the (co)author of over 500 scientific articles, book chapters, and abstracts. His research interests focus on the molecular and epigenetic mechanisms in the regulation of uteroplacental circulation and developmental programming of health and disease.

Qingyi Ma received his PhD in physiology from Loma Linda University in 2011. He did his postdoctoral training in Zilkha Neurogenetic Institute, Keck School of Medicine, of the University of Southern California. Currently, he is a postdoctoral fellow in the Center for Perinatal Biology at the Loma Linda University School of Medicine. His primary research interest is in the molecular mechanisms of brain injury and protection following stroke and neurodegeneration disorders.

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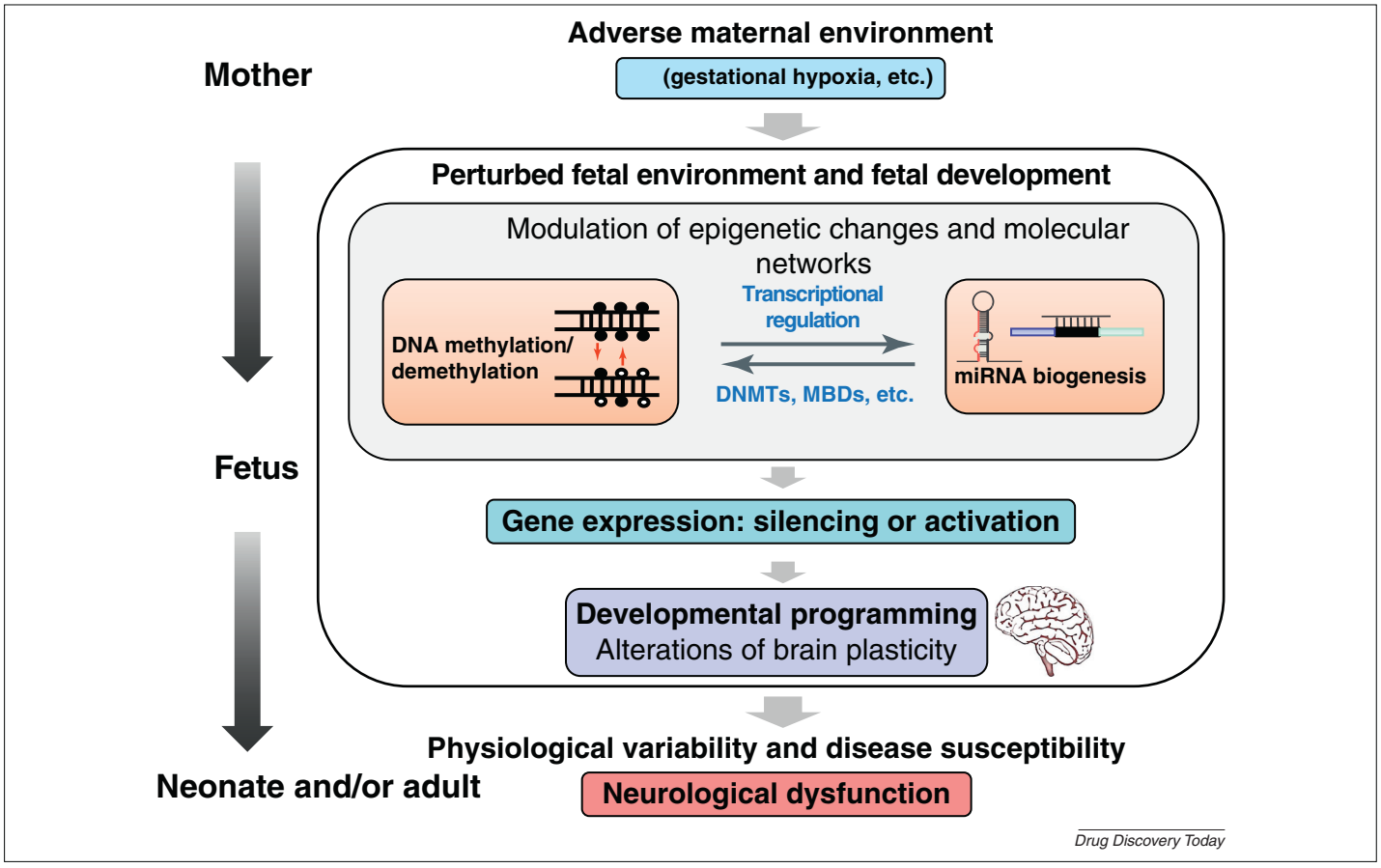

FIGURE 1

Schematic diagram showing the correlation between adverse maternal environment (e.g., gestational hypoxia) and epigenetic mechanisms in developmental programming of neurological diseases in the offspring. A tightly controlled gene expression profile has a crucial role during brain development and plasticity. Exposure of the mother to adverse factors during pregnancy, such as maternal hypoxia, results in a perturbed maternal–fetal environment and can lead to modulated epigenetic changes that alter the gene expression profile as an adaption of the developing fetus to the adverse environment. Different epigenetic mechanisms cooperatively orchestrate this process and also regulate each other. For example, DNA methylation/demethylation transcriptionally regulates miRNA biogenesis, and is conversely regulated by miRNAs modulating the expression of DNA methylation-related enzymes and proteins. Changes in physiology and neuroplasticity of the developing brain can permanently affect the structure and/or functionality, and result in increased disease susceptibility in the offspring. *Abbreviations*: DNMT, DNA methyltransferases; MBD, methyl-CpG binding protein.

early life events and can induce long-term changes in gene expression profiles, which potentially result in disease in later life [8,13,14] (Fig. 1). For example, in a recent study, epigenetic programming of the glucocorticoid receptor (*GR*) gene after maternal hypoxia was found to be related to the enhanced susceptibility of neonate hypoxic-ischemic encephalopathy (HIE) brain injury [15].

Hypoxia is a common form of intrauterine stress, and the fetus might experience a period of hypoxic stress under a variety of conditions, including pregnancy at high altitude, pregnancy with anemia, placental insufficiency, cord compression, pre-eclampsia, heart, lung and kidney disease, or with hemoglobinopathy. Intrauterine hypoxia contributes significantly to developmental malformations in the fetal tissues and/or organs, particularly the brain. The brain represents only 2% of the body weight, but consumes 20% of the oxygen requirements of the body. The immature fetal brain is particularly sensitive to changes in oxygen level. Low levels of oxygen result in neurovascular development malformations, such as cerebral palsy and periventricular leukomalacia, in the developing brain and increases risk of brain injury in the newborn [16,17]. Maternal hypoxia also delays neuronal migration and alters neurotransmitters expression during embryogenesis [18], subsequently compromising neuronal circuits and affecting neural organization in the brain tissue [19]. As a result, maternal hypoxia leads to increased susceptibility to seizures, epilepsy [20], and cerebral insults in affected offspring [15,19]. However, the molecular mechanisms of gestational hypoxia in the programming of brain disorders in postnatal life remain largely elusive. Thus, here we summarize recent findings of the role of epigenetic mechanisms, specifically DNA methylation/demethylation and miRNAs, in the neural development and pathogenesis of neurological disorders, with a view to addressing whether fetal hypoxia might contribute to these neurological disorders in affected offspring.

Epigenetic mechanisms and the machineries

DNA methylation and the machineries

DNA methylation refers to the biological process whereby a methyl group is added to a DNA nucleotide, and occurs almost exclusively on cytosines occurring directly before guanine molecules