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Epigenetic programming of hypoxic–ischemic encephalopathy in response to fetal hypoxia

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ABSTRACT

Hypoxia is a major stress to the fetal development and may result in irreversible injury in the developing brain, increased risk of central nervous system (CNS) malformations in the neonatal brain and long-term neurological complications in offspring. Current evidence indicates that epigenetic mechanisms may contribute to the development of hypoxic/ischemic-sensitive phenotype in the developing brain in response to fetal stress. However, the causative cellular and molecular mechanisms remain elusive. In the present review, we summarize the recent findings of epigenetic mechanisms in the development of the brain and their roles in fetal hypoxia-induced brain developmental malformations. Specifically, we focus on DNA methylation and active demethylation, histone modifications and microRNAs in the regulation of neuronal and vascular developmental plasticity, which may play a role in fetal stress-induced epigenetic programming of hypoxic/ischemic-sensitive phenotype in the developing brain.

Contents

Abbreviations: AID/APOBEC, activation-induced cytidine deaminase/apolipoprotein B mRNA-editing enzyme complex; BDNF, brain-derived neurotrophic factor; 5caC, 5-carboxylcytosine; CBP, CREB binding protein; CREB, cAMP response binding protein; DNMT, DNA methyltransferases; ECs, endothelial cells; FMRP, fragile X mental retardation protein; GFAP, glial fibrillary acidic protein; GR, glucocorticoid receptor; HATs, histone acetyltransferases; HDAC, histone deacetylase; HIE, hypoxic-ischemic encephalopathy; HIFs, hypoxia-inducible factors; 5hmC, 5-hydroxymethylcytosine; H3K4me3, histone H3 lysine 4 trimethylation; HMTs, histone methyltransferases; HRE, hypoxia response elements; JMJD, jumonji-domain; MBD, methyl-CpG-binding proteins; 5mC, 5-methylcytosine; MLL, mixed lineage leukemia; Ngn2, neurogenin2; NMDA, N-methyl-D-aspartate receptors; NPCs, neural progenitor cells; NSC, neural stem/progenitor cell; PHDs, prolyl hydroxylase domains; PRC2, polycomb repressor complex2; pre-miRNA, precursor miRNA; pri-miRNA, primary miRNA; PVL, periventricular leucomalacia; REST, repressor element 1-silencing transcription factor; SIRT1, sirtuin 1; SAHA, suberoylanilide hydroxamic acid; SVZ, subventricular zone; TDG, thymine DNA glycosylase; TET, ten-eleven translocation proteins; TSS, ranscriptional start site; UHRF1, ubiquitin-like, containing PHD and RING finger domains 1; 3′UTR, 3′ untranslated region; VEGF, vascular endothelia growth factor; VHL, von-Hippel–Lindau-tumor-suppressor.

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1. Introduction

Growing evidence from clinical and pre-clinical studies has clearly elucidated that intrauterine stress may have subtle or drastic impact on tissue/organ ontogeny, structure and function during the fetal development, leading to enhanced vulnerability or resiliency to challenges and diseases later in life (Dudley et al., 2011; Xiong and Zhang, 2013). The developing brain in the gestational stage is highly plastic and vulnerable to various adverse environmental conditions. Among these, hypoxia is of critical importance and may occur in various conditions, such as pregnancy at high altitude, placental insufficiency, pregnancy anemia, and other maternal diseases. Exposure of the fetus to persistent hypoxia can cause abnormal development of the brain *via* series of direct or indirect actions at cellular and molecular levels. As a major consequence, fetal hypoxia increases the risk of central nervous system (CNS) developmental malformations and may result in the development of neurological diseases in offspring (Gonzalez-Rodriguez et al., 2014; Li et al., 2012). However, the causative mechanisms of fetal hypoxia affecting the developing brain remain largely elusive.

Epigenetic modifications result in stable and heritable gene expression patterns without changes in the coding sequences and are the important mechanisms in developmental programming of health and disease (Chen and Zhang, 2011; Egger et al., 2004; Gluckman et al., 2008). Epigenetic mechanisms mainly include DNA methylation/demethylation, histone modifications and non-coding RNAs such as microRNAs, which regulate lineage-specific expression profiles of different cell types and the information for the transcriptional program of gene expression (Cantone and Fisher, 2013). Epigenetic modifications are very sensitive to various environmental stimuli, and are essential in controlling proper gene expression patterns in particular tissues at specific time points in response to endogenous or environmental signals (Cantone and Fisher, 2013; Gicquel et al., 2008; John and Lefebvre, 2011). The brain is the central organ responsible for stress responses, and undergoes parallel alterations in its structure and function in response to stress events (McEwen, 2008). There is increasing evidence suggesting that epigenetic machinery orchestrates the development, plasticity, homeostasis and evolutionary innovations of the brain (Feng et al., 2007; Mehler, 2008; Mehler and Mattick, 2007; Tsankova et al., 2007). Recent studies suggest that epigenetic programming in response to fetal hypoxia is responsible for the development of hypoxic–ischemia sensitive phenotype in the brain (Gonzalez-Rodriguez et al., 2014; Li et al., 2012), implicating a key role of epigenetic modifications in fetal stress-mediated developmental programming of neuronal and vascular dysfunctions in the brain.

During the fetal development, the neuronal organization is remodeled and developed into the adult phenotype and functional properties, which is affected by intrauterine environment (Fagiolini et al., 2009). In addition to neurons, vascular development is also a critical portion of the development and maturation of the CNS by providing metabolic nutrition, physical support and protection to the developing brain. The neurovascular cross-talk is initiated in the early stage of embryonic development and lasts throughout the life. For example, in the mouse the blood–brain barrier is functional at E15.5 (Ben-Zvi et al., 2014) and protects the fragile CNS tissue from metabolic and cellular changes (Bautch and James, 2009). Neurovascular coupling is developed to undertake important physiological functions, such as the regulation of cerebral blood flow (CBF) in response to local neural activities, and its abnormality implicates various brain diseases, such as cerebral cavernous malformations and vascular dementia (Attwell et al., 2010; Iadecola, 2004).

Recently, "active" DNA demethylation has been brought forward and is under extensive study in the developmental plasticity of the brain. Its role has been revealed in regulating a series of gene expression and cell fate determination in neural progenitor cell differentiation, which eventually determines the brain growth and function during the embryogenesis (Miller and Sweatt, 2007; Wheldon et al., 2014). Moreover, the epigenetic mechanisms, *i.e.* DNA methylation/demethylation, histone modifications and miRNAs interact and determine the development of the brain. Nonetheless, relatively little is known about the epigenetic mechanisms in fetal stress-mediated programming of the brain susceptibility to neurological dysfunction. Indeed, most current studies in stress-induced fetal programming of developmental abnormalities in the brain have focused on long-term functional outcomes. Few investigated molecular and cellular mechanisms underlying the effect of fetal hypoxia on the lineage specification of neural stem cells, neurogenesis, vasculogenesis, astrogliogenesis, and the interaction and communication of neuron, vascular and glial cells in the developing brain. In the present review, we summarize the current knowledge of epigenetic mechanisms in regulating the development of the brain, specifically neuronal and vascular development, and propose that the epigenetic programming of the developing brain at the cellular and molecular levels in response to fetal hypoxia may result in abnormal neuronal and vascular development, leading to the enhanced susceptibility of immature brain to postnatal hypoxic-ischemic encephalopathy (HIE). Of importance, findings in these studies may help provide insights in the design of effective diagnostic and therapeutic strategies in preventing and managing the adverse effects of fetal stress on the development of the brain.

2. Fetal hypoxia and hypoxic–ischemic encephalopathy

Hypoxia during gestation contributes to developmental malformations in the fetus. Exposure to severe hypoxia *in utero* results in acute neuronal and glial injury, an increase in apoptosis, and a reduction of brain growth and neural complexity, consequently contributing to chronic functional deficits in the brain. Fetal