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Review

Maternal care, the epigenome and phenotypic differences in behavior

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Abstract

The genome is programmed by the epigenome, which is comprised of chromatin and a covalent modification of DNA by methylation. Epigenetic patterns are sculpted during development to shape the diversity of gene expression programs in the different cell types of the organism. The epigenome of the developing fetus is especially sensitive to maternal nutrition, and exposure to environmental toxins as well as psychological stress. It is postulated here that not only chemicals but also exposure of the young pup to social behavior, such as maternal care, could affect the epigenome. Since epigenetic programming defines the state of expression of genes, epigenetic differences could have the same consequences as genetic polymorphisms. We will propose here a mechanism linking maternal behavior and epigenetic programming and we will discuss the prospect that similar epigenetic variations generated during early life play a role in generating inter-individual differences in human behavior. We speculate that exposures to different environmental toxins, which affect the epigenetic machinery might alter long-established epigenetic programs in the brain.

Keywords: DNA methylation; DNA demethylase; Epigenetics; Histone acetylation; Maternal care; Stress; Glucocorticoid receptor; CBP; MBD2 NGFIA

Contents

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1. Epigenetics and inter-individual differences

1.1. Genes, gene expression programs and phenotype

Different cell types execute distinctive plans of gene expression, which are highly responsive to developmental, physiological, pathological and environmental cues. The combinations of mechanisms, which confer long-term programming to genes and could bring about a change in gene function without changing gene sequence are termed here epigenetic. Epigenetic programming occurs during development to generate the complex patterns of gene expression characteristic of complex organisms such as humans, however epigenetic programs in difference from the genetic sequence itself are somewhat dynamic and responsive to different environmental exposures during fetal development as well as early in life. Epigenetic programs are potentially dynamic even later in life. Thus, many of the phenotypic variations seen in human populations might be caused by differences in long-term programming of gene function rather than the sequence *per se*. Any analysis of inter-individual phenotypic diversity should take into account epigenetic variations in addition to genetic sequence polymorphisms [1].

Some critical environmental exposure could alter the progression of epigenetic programming during development both in utero as well as postnatally. Thus, variation in environmental exposures during these critical periods could result in epigenetic and therefore phenotypic differences later in life. It stands to reason that exposure to nutritional deprivation and chemical toxins would affect the epigenetic machinery during development. Recent data suggests however that psychosocial exposures early in life could also impact on the epigenome resulting in differences in epigenetic program and as a consequence in behavioral differences later in life [2]. Thus, certain behavioral pathologies might be a consequence of early in life exposures which altered epigenetic programming.

It is important to understand the mechanisms driving variations in epigenetic programming in order to identify the behavioral pathologies that result from such mechanisms. In difference from genetic mechanisms, epigenetic mechanisms are dynamic and potentially reversible and are therefore amenable to therapeutic intervention [3]. Drugs, which target the epigenetic machinery, are currently tested in clinical trials in cancer [4,5] and psychiatry disorders [6]. Moreover, once we understand the rules through which different environmental exposure modify the epigenetic processes, we might be able to design behavioral strategies to prevent and reverse deleterious environmentally driven epigenetic alterations.

2. The epigenome

2.1. Chromatin

The epigenome consists of the chromatin and its modifications as well as a covalent modification by methylation of cytosine rings found at the dinucleotide sequence CG (Fig. 1) [7]. The epigenome determines the accessibility of the transcription machinery. Inaccessible genes are therefore silent whereas accessible genes are transcribed. We therefore distinguish between open and closed configurations of chromatin [8–12]. Recently another new level of epigenetic regulation by small non-coding RNAs termed microRNA has been discovered [13]. microRNAs regulate gene expression at different levels; silencing of chromatin, degradation of mRNA and blocking translation. microRNAs were found to play an important role in cancer [14] and could potentially play an important role in behavioral pathologies as well [15].

2.2. The histone code

The DNA is wrapped around a protein-based structure termed chromatin. The basic building block of chromatin is the nucleosome, which is formed of an octamer of histone proteins. There are five basic forms of histone proteins termed H1, H2A, H2B H3 and H4 [16] as well as other minor variants, which are involved in specific functions such as DNA repair or gene activation [17]. The octamer structure of the nucleosome is composed of a H3–H4 tetramer flanked on either side with a H2A–H2B dimer [16]. The N-terminal tails of these histones are extensively modified by methylation [18], phosphorylation, acetylation [19] and ubiquitination [20]. The state of modification of these tails plays an important role in defining the accessibility of the DNA wrapped around the nucleosome core. Different histone variants, which replace the standard isoforms also play a regulatory

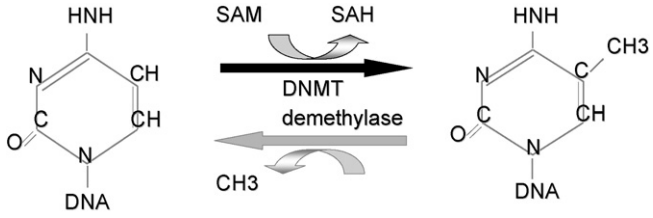

Fig. 1. The reversible DNA methylation reaction. DNA methyltransferases (DNMT) catalyze the transfer of methyl groups from the methyl donor *S*-adenosylmethionine to DNA releasing *S*-adenosylhomocysteine. Demethylases release the methyl group from methylated DNA as either methanol or formaldehyde.