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Review

Diet and the epigenetic (re)programming of phenotypic differences in behavior

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ABSTRACT

Phenotypic diversity is shaped by both genetic and epigenetic mechanisms that program tissue specific patterns of gene expression. Cells, including neurons, undergo massive epigenetic reprogramming during development through modifications to chromatin structure, and by covalent modifications of the DNA through methylation. There is evidence that these changes are sensitive to environmental influences such as maternal behavior and diet, leading to sustained differences in phenotype. For example, natural variations in maternal behavior in the rat that influence stress reactivity in offspring induce long-term changes in gene expression, including in the glucocorticoid receptor, that are associated with altered histone acetylation, DNA methylation, and NGFI-A transcription factor binding. These effects can be reversed by early postnatal cross-fostering, and by pharmacological manipulations in adulthood, including Trichostatin A (TSA) and L-methionine administration, that influence the epigenetic status of critical loci in the brain. Because levels of methionine are influenced by diet, these effects suggest that diet could contribute significantly to this behavioral plasticity. Recent data suggest that similar mechanisms could influence human behavior and mental health. Epidemiological data suggest indeed that dietary changes in methyl contents could affect DNA methylation and gene expression programming. Nutritional restriction during gestation could affect epigenetic programming in the brain. These findings provide evidence for a stable yet dynamic epigenome capable of regulating phenotypic plasticity through epigenetic programming.

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Abbreviations: HAT, Histone acetyltransferase; HDAC, histone deacetylase; HMT, histone methyltransferase; DNMT, DNA methyltransferase; SAM, S-adenosylmethionine; HDACi, HDAC inhibitor; CBP, CREB binding protein; TSA, Trichostatin A; MBD2, METHYLATED DOMAIN DNA BINDING PROTEIN 2; NGFI-A, NERVE GROWTH FACTOR-INDUCIBLE PROTEIN A; LG, Licking/Grooming

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Contents

1. Genes, gene expression programs, diet and mental health

Different cell types execute distinct patterns of gene expression that are highly responsive to developmental, physiological, pathological and environmental cues. The combination of mechanisms that confers long-term programming to genes leading to a change in gene function without a change in gene sequence is termed here epigenetic. The epigenetic programming of gene expression is somewhat dynamic in response to environmental exposures — especially though perhaps not exclusively during fetal development and early in life. Thus, much of the phenotypic variation seen in human populations might be caused by differences in long-term programming of gene function rather than the genetic sequence *per se*. Any analysis of inter-individual phenotypic diversity should take into account epigenetic variations in addition to genetic sequence polymorphisms (Meaney and Szyf, 2005b).

Some critical environmental exposures such as variations in maternal behavior and diet could alter the progression of epigenetic programming during development postnatally as well as in utero. 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 would affect the epigenetic machinery during development. Recent data suggest that psychosocial exposures early in life also impact the epigenome resulting in differences in epigenetic program and as a consequence in behavioral differences later in life (Meaney and Szyf, 2005a). Thus, certain behavioral pathologies might be a consequence of early in life exposures that alter 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. Unlike genetic mechanisms, epigenetic mechanisms are dynamic and thus potentially reversible and amenable to therapeutic intervention (Szyf, 2001). Because various drugs used in the treatment of psychiatric disorders such as schizophrenia and mood disorders have known epigenetic effects, interventions targeting the epigenetic machinery could have important consequences for normal cognitive function. Thus, components of diet that influence the epigenetic machinery should be considered interventions that could affect mental as well as physical health. Once the rules governing the effects of environmental exposures on epigenetic processes are understood, it might be possible to design behavioral and nutritional strategies to prevent and reverse deleterious environmentally driven epigenetic alterations.

2. The epigenome

The epigenome consists of chromatin, a protein-based structure around which wrapped the DNA, and its modifications as well as a covalent modification of cytosines residing at the dinucleotide sequence CG in DNA itself by methylation (Razin, 1998). These modifications determine the accessibility of the transcriptional machinery to the genome. Recently, an additional level of epigenetic regulation by small non-coding RNAs termed microRNA has been discovered (Bergmann and Lane, 2003). microRNA expression is itself regulated by epigenetic factors such as DNA methylation and chromatin structure (Saito and Jones, 2006). Therefore microRNAs should be considered under the headings of chromatin and DNA methylation, as they also act by changing chromatin structure (Chuang and Jones, 2007).