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REVIEW ARTICLE

Epigenetic changes in neurology: DNA methylation in multiple sclerosis☆,☆☆

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Abstract
Introduction: Epigenetics is defined as the study of the mechanisms that regulate gene expression without altering the underlying DNA sequence. The best known is DNA methylation. Multiple sclerosis (MS) is a disease with no entirely known aetiology, in which it is stated that the involvement of environmental factors on people with a genetic predisposition, may be key to the development of the disease. It is at this intersection between genetic predisposition and environmental factors where DNA methylation may play a pathogenic role.
Development: A literature review of the effects of environmental risk factors for the development of MS can have on the different epigenetic mechanisms as well as the implication that such changes have on the development of the disease.
Conclusion: Knowledge of epigenetic modifications involved in the pathogenesis of MS, opens a new avenue of research for identification of potential biomarkers, as well as finding new therapeutic targets.

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Modificaciones epigenéticas en neurología: alteraciones en la metilación del ADN en la esclerosis múltiple

Resumen
Introducción: La epigenética se define como el estudio de los mecanismos que regulan la expresión génica sin modificar la secuencia de ADN, siendo entre ellos el más conocido la metilación del ADN. La esclerosis múltiple (EM) es una enfermedad de etiología no del todo conocida, en la que se plantea que la participación de factores ambientales sobre individuos con una determinada predisposición genética, pueden resultar claves para el desarrollo de la enfermedad. Es en esta intersección entre la predisposición genética y los factores ambientales donde la metilación del ADN puede desempeñar un papel patogénico.
Desarrollo: Realizamos una revisión bibliográfica de los efectos que los factores de riesgo ambiental para el desarrollo de EM pueden ejercer sobre los distintos mecanismos epigenéticos, así como la implicación que presentan dichas modificaciones en el desarrollo de la enfermedad.
Conclusión: El conocimiento de las modificaciones epigenéticas involucradas en la patogenia de la EM abre una nueva vía de investigación para la identificación de potenciales biomarcadores, así como para la búsqueda de nuevas dianas terapéuticas.

Introduction

Epigenetic regulatory mechanisms

The term ''epigenetics'' appeared in the literature for the first time in the mid-20th century (Conrad Waddington, 1905-1975),[1] but it was not until recently that it has become an emerging research field. It is now considered a promising source of knowledge, especially in the medical field.

Epigenetics is the study of mechanisms regulating gene expression without modifying the deoxyribonucleic acid (DNA) sequence. This discipline represents a link between genetic and environmental influences on phenotype development. Epigenetic changes modify the activation of some genes depending on external conditions, and they are essential in cellular and tissue differentiation, which takes place during foetal development. These changes also occur during adulthood. Human cells experience epigenetic changes during their lifetimes. In fact, identical twins (with the same genetic load) accumulate different epigenetic patterns depending on the environmental factors to which they are exposed, for example, tobacco, diet, or exercise.[2] This translates into observable differences in the phenotypes of both twins, which manifest as different susceptibilities to disease or disease outcomes.[3]

The main epigenetic mechanisms involve DNA methylation, histone modification, and the action of non-coding RNA. DNA methylation is the best-known mechanism and its association with the development of diseases has been the subject of many studies. This mechanism is the focus of our study.

DNA methylation

DNA methylation is a process by which methyl groups are added to cytosine residues in the RNA nucleotide chain. This binding occurs at cytosine-guanine dinucleotides (CpG), which accumulate in the genome to form CpG islands. These islands are especially abundant in gene promoter regions and other regulatory regions. Methylation is carried out by DNA methyltransferases (DNMT) that catalyse the transfer of a methyl group from S-adenosyl-L-methionine (SAM) to carbon 5 of cytosine.[4] This process may follow one of 2 models: establishing a de novo DNA methylation pattern catalysed by DNMT3a and DNMT3b,[5] or maintaining a genomic methylation pattern through successive DNA replication cycles mediated by DNMT1. Methylation occurs during DNA replication such that when a CpG sequence adopts a certain methylation pattern, this modification becomes stable, and therefore inherited during DNA replication and maintained in daughter strands.[6]

Hypermethylation at CpG islands in gene promoter regions is typically a gene repression mechanism since it inhibits transcription. This inhibition takes place through 2 processes: a direct one which prevents binding of transcription factors containing recognition sites for methylated CpG, and an indirect one, which blocks the access to regulatory elements, necessary for transcription factor binding, by adhering protein complexes known as methyl-binding domains (MBD), which bind to methylated CpG sites.[7]

As explained before, the SAM molecule is the methyl group donor; this molecule becomes S-Adenosyl-L-homocysteine (SAH) after losing the methyl group. SAM is hydrolised to homocysteine and subsequently remethylated to methionine by 5-methyltetrahydrofolate cofactor (5-MTHF). Methionine is finally transformed into a SAM molecule by methionine adenosyltransferase (MAT) (Fig. 1). The potential of DNA methylation will depend on the ratio between SAM level and SAH in blood. The higher the ratio, the greater the potential of DNA methylation.[8] We can therefore state that DNA methylation requires proper metabolism of homocysteine, methionine, other enzymes involved in this metabolic