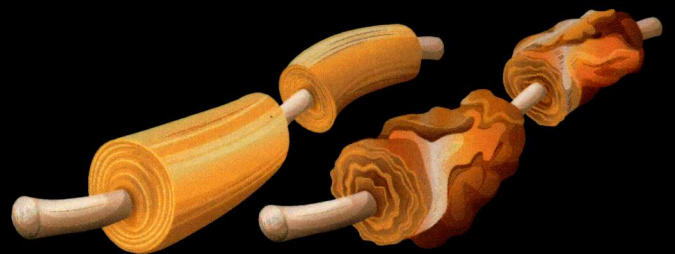




NUTRITION AND LIFESTYLE IN **NEUROLOGICAL AUTOIMMUNE DISEASES:** **MULTIPLE SCLEROSIS**



EDITED BY
RONALD ROSS WATSON
WILLIAM D. S. KILLGORE



NUTRITION AND LIFESTYLE IN NEUROLOGICAL AUTOIMMUNE DISEASES: MULTIPLE SCLEROSIS

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S E C T I O N I

MECHANISMS OF MS DISEASE
CAUSATION AND INTERVENTION

Epigenetic Changes in DNA Methylation and Environment in Multiple Sclerosis

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INTRODUCTION

Epigenetic Regulatory Mechanisms

The first time the term epigenetics appeared in literature dates back to mid-20th century (Conrad Waddington, 1905–1975).¹ However, it has been only in the last decade that epigenetics has become one of the emerging research fields, as a promising source of knowledge, especially in medicine.

Epigenetics has been defined as the study of the mechanisms regulating gene expression without changing the sequence of deoxyribonucleic acid (DNA). This discipline has built a bridge between genetic and environmental influences on the development of a phenotype; that is, it provides the means by which genetic material can respond to the diverse environmental conditions not requiring structural changes. Epigenetic changes allow some genes to be expressed or not, depending on the external conditions,

and those changes are essential in cell and tissue differentiation that occurs during embryonic development as well as in adult organisms. Thus, mammalian cells undergo epigenetic changes throughout life. In fact, identical twins with the same genetic background build different epigenetic patterns depending on the environmental factors to which they are subjected, such as smoking, diet, or exercise.² In addition, these epigenetics patterns cause observable differences in the phenotype of both twins, either a different behavior or different risk of disease.³

The main epigenetic mechanisms include DNA methylation, histone modifications, and action of noncoding RNAs. So far, DNA methylation is the best known of these mechanisms. Most studies have been focused on DNA methylation and how it is associated with the development of a disease. Therefore, our review has been focused on DNA methylation and its role in developing multiple sclerosis (MS).

DNA Methylation

DNA methylation is a biochemical process by which a methyl group is added to a cytosine residue in the DNA nucleotide chain. This binding occurs in cytosine–guanine dinucleotides (CpG), which are clustered in the genome, building the CpG islands. These are especially abundant in the promoter and other regulatory regions of genes. Methylation is performed by DNA methyltransferases (DNMTs) that catalyze the transfer of a methyl group from S-adenosyl-L-methionine (SAM) to carbon 5 of cytosine.⁴ This process may be carried out following two different models: the occurrence of a “de novo” methylation pattern catalyzed by the DNMT3a and DNMT3b⁵ enzymes, or by maintaining a methylation pattern in the following cycles of cell replication performed by DNMT1. The latter occurs during DNA replication. Therefore, when a CpG sequence acquires a certain methylation pattern, this modification becomes stable and is inherited as a clonal methylation pattern through subsequent cell divisions.⁶

Hypermethylation of CpG islands in the promoter region of the gene is typically a mechanism of gene repression as it inhibits transcription. This inhibition is basically performed through two processes: (1) by preventing the binding of transcription factors containing recognition sites for CpGs and (2) by means of adhering protein complexes known as methyl-binding domain (MBD) that are bound to the methylated CpG regions and block access to regulatory proteins or transcription factors.⁷

As mentioned earlier, the methyl group donor is the SAM molecule which, once it loses the methyl group, becomes S-adenosyl homocysteine (SAH). This molecule is hydrolyzed to homocysteine and then it is remethylated to methionine by 5-methyltetrahydrofolate cofactor (5mTHF). Finally, methionine is transformed back into a SAM molecule by the action of methionine adenosyltransferase (MAT). DNA methylation potential depends on the ratio between SAM level and SAH in blood. The higher the ratio, the more the methylation potential.⁸ Therefore, it can be inferred that for the process of DNA methylation, proper metabolism of homocysteine and methionine is critical, as well as the metabolism of the various enzymes involved in this metabolic route and of other substances, such as folic acid and vitamin B12⁹ (Fig. 1.1).

Relevance of DNA Methylation in Clinical Practice

Disruption of epigenetic mechanisms involved in human disease has been, for the last few years, an area of emerging research, yielding positive results in various diseases, especially in oncology. The first tumor related to mechanisms of epigenetic regulation was colorectal cancer (CRC). Initially, a loss of overall methylation

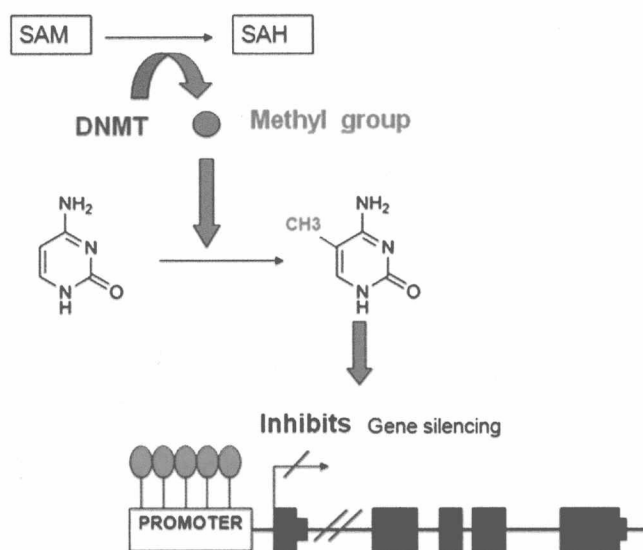


FIGURE 1.1 The process of how DNA methylation within gene promoters regulates transcription. SAM, S-adenosyl-L-methionine. SAH, S-adenosyl homocysteine. DNMT, DNA methyltransferases.

was observed in cancer cells of CRC patients compared to healthy controls.¹⁰ Also, the promoters of tumor suppressor genes were shown to be hypermethylated, which caused lower expression of those genes.¹¹ These findings supported that hypermethylation of tumor suppressor genes was associated with the occurrence of the disease.

However, in other areas of medicine, such as neurological disorders, how disruption of DNA methylation is involved in the disease is not well known yet. In the case of MS, epigenetic changes that might be involved in the pathogenesis of the disease have been identified, which has led to an exciting and new route of research.

MS is considered the leading cause of severe neurological disease affecting young and middle-aged adults. It is a chronic disease causing inflammatory, demyelinating, and neurodegenerative damage in the central nervous system (CNS). Its etiology is still unknown, although an autoimmune and multifactorial origin has been presumed and several genetic and environmental factors of susceptibility have been described for MS. Given the complexity of the disease and the participation of diverse, both genetic and environmental, etiological mechanisms, it is conceivable that there may be an alteration in the epigenetic regulation involved in its progression.^{12,13}

RISK FACTORS IN MS AND EPIGENETIC CHANGES

Epidemiological and family aggregation studies suggest that there is a genetic predisposition for MS. However, to date, the only *locus* consistently associated with MS is the major histocompatibility complex (MHC). This predisposition has been associated with DR2