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# Epigenetics and multiple sclerosis

Genetic studies have long been trying to describe the etiopathology of human diseases. Even though the cutting-edge approaches like whole human genome sequencing and genome wide association studies have largely improved our apprehension, there are numerous questions needing to be contemplated differently. Lessons from identical twins, in which there is no exact concordance pattern of autoimmune disease, emphasize on the role of non-genetic factors in the pathogenesis of such disorders.

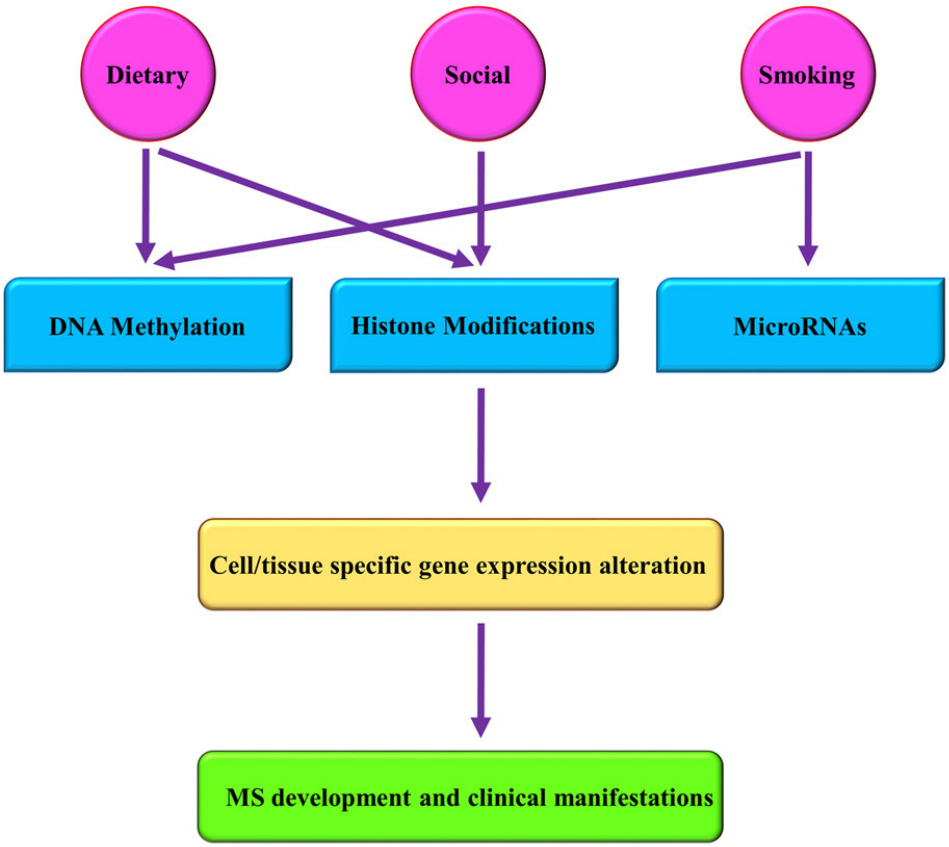


Fig. 1. Interactions between environmental factors and epigenetic changes to culminate in ins and outs in MS. Suggested environmental factors modulate the epigenetic landscape in MS that impress the gene expression patterns in cell/tissue specific manner, which in turn manifest as disease initiation or progression as well as the exacerbation of the clinical specifications.

Epigenetics is defined as stable and heritable changes in gene expression without changes in DNA nucleotides. Epigenetic phenomenon is of remarkable important for controlling the patterns of gene expression during normal physiological functions like cell cycle and development, as well in response to environmental factors. Epigenetic regulatory mechanisms are commonly evaluated in three levels. Modifications of the DNA strand through biochemical alterations mainly by methylation, post-translational

modification of histones proteins by acetylation, methylation and phosphorylation, and ultimately microRNAs. DNA methylation in the promoter region of genes suppresses gene transcription, whereas histone acetylation appropriates gene expression condition by resulting in a euchromatin structure, thereby promotes the availability of DNA regulatory regions to the transcriptional factors or to other DNA binding proteins.

Multiple sclerosis (MS) is a disorder of the central nervous system, characterized by both inflammatory and neurodegenerative features. A complex interaction between genetic and environmental factors has been assumed to be contributing in MS development. Genetic and epidemiological studies have demonstrated that only 60-70% of the total MS risk could be related to genetic risk factors. Moreover, concordance rate of 20-30% for MS between identical tweens suggests the probable role of epigenetics in the pathogenesis process. Sexual-based differences in epigenetic pattern such as X chromosome inactivation has also been responsible for higher frequency of MS in female than male. As a result, we need to deter our concentrations towards a much more sophisticated molecular explanation for the etiopathology and heredity pattern of MS.

Numerous studies have investigated the DNA methylation status in various cell types from MS patients. In addition to cells, there are unique disease- and state-specific changes of methylation pattern of cell-free plasma DNA in MS patients. These sort of findings potentially possess clinical importance for developing new biomarkers for MS. Moreover, histone acetylation patterns exhibit modifications in normal-appearing white matter (NAWM) in early MS lesions. Enhanced histone acetylation is associates with oligodendrocyte differentiation and demyelination process. In 2009, the very first study started to evaluate miRNA expression profiles in MS patients. It was not until recent years that a bulk of studies have assessed the whole blood, peripheral blood-derived lymphocytes or serum samples and reported different expression profiles of various miRNAs in MS patients. These modifications have been associated with various pathogenesis perspectives in MS.

Identification of the aberrant epigenetic regulations underlying the etiopathology of MS has attracted intensive attentions to identify tissue/cell specific epigenetic clinical markers for early diagnosis as well to develop novel therapeutic tools. This new therapeutic movement termed ‘epigenetic therapy’, which intends to discover drugs with the ability to reverse methylation patterns on DNA nucleotides or the modifications of histones tails. Histone deacetylase (HDAC) inhibitors such as Trichostatin A, vorinostat, and valproic acid have been investigated in MS patients, targeting the proteins responsible for controlling the chromatin modifications. Moreover, 5-aza-2′-deoxycytidine (Decitabine), as a DNA methyltransferase inhibitor, promotes an immunosuppressed status in MS patients.

It will be of significant importance for the forthcoming epigenetic surveys in MS to concentrate on the pertinent cell types as well the possibly underlying biological pathways. This would be beneficial to contribute the movement underway about devising novel therapeutic drugs in MS.

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## Publication

Epigenetic Modifications and Therapy in Multiple Sclerosis.
Aslani S, Jafari N, Javan MR, Karami J, Ahmadi M, Jafarnejad M
*Neuromolecular Med. 2017 Mar*