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Molecule of the month: miRNA and Multiple Sclerosis

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Great strides are being made in our understanding of the large sea of non-coding RNAs that are found within eukaryotic cells. Regulation of gene expression in cells is subject to microRNA (miRNA) in normal and neuropsychiatric diseases **[1, 2].** Here we discuss the involvement of miRNAs in the neurological disease, Multiple Sclerosis (MS).

Many physicians and scientists have worked on the problem of MS with a goal to find a cure since Jean-Martin Charcot discovered and characterized MS. We briefly mention a few researchers here who contributed to this field.

Today, many years after Charcot, although the cause of MS has not been identified, MS has been shown to involve major immune-related mechanistic components. These mechanisms of pathogenesis comprise processes that occur within the brain so that the brain tissue itself including myelin sheath-producing oligodendrocyte cells become targets. Specifically, MS, characterized by axonal damage, demyelination, and chronic inflammation, is considered a central nervous system (CNS) autoimmune disease. There is a long-standing paradigm that MS is a neurodegenerative disease associated with defects in the blood-brain barrier (BBB) as well as immunological mechanisms. Furthermore, molecular genetics and gene expression studies have widened the scope and understanding of the risk and mechanisms of MS pathogenesis. In addition to contributions of immunological studies, putative viruses have been associated with MS and viral and viral-immunological hypotheses have been addressed over time. Wallace W. Tourtellotte greatly contributed to the utilization of laboratory methods for the diagnosis of MS as well as possible viral factors and immunological mechanisms of pathogenesis **[3-10].**

Several aspects of MS pathogenesis involve miRNAs. In myeloid cells in MS, expression of miRNA, mir-155, is increased. Regulation by mir-155 of adaptive immune response and CNS resident and blood-derived myeloid cells occurs in MS **[11].** In MS, BBB dysfunction is pathognomic with MS pathogenesis. Consistent with this, miRNA miR-125a-5p is a component of regulation of immune cell efflux and tightness of endothelial cells in brain **[12].** In brain, miR-124 was increased in *hippocampi* from MS patients and demyelination was increased in these areas. Neuronal gene expression (mRNA) was decreased for 26 proteins including ionotrophic glutamate receptors AMPA2 and AMPA3. In a mouse model, similar results were found and these changes were reversed by remyelination **[13].**

In astrocytes from brain tissue of active MS plaque lesions, ten miRNAs were upregulated including miRNA-155, miRNA-34a, and miRNA-326. The mRNA for protein CD47 (that inhibits macrophage phagocytosis of myelin) was correspondingly decreased. This implies that macrophages are thereby released from inhibition and this process is associated with demyelination under these conditions in MS active plaque lesions **[14].**

In MS, miRNAs show tissue specificity. However, there are similar profiles among different tissues. In blood and in active MS lesions/plaques, miR-326 is upregulated. However, miR-323 is not upregulated in serum but is upregulated in T-reg cells, active brain lesions/plaques, and whole blood **[15].**

Conceivably, dysregulation of gene expression in hematopoietic cells could be caused by altered miRNA expression. Twenty-two miRNAs involved in immunity were studied in peripheral

blood mononuclear cells (PBMCs) of healthy controls vs. MS patients. Only three miRNAs showed increased expression and none showed decreased expression. Mir-155 was most upregulated. A three-SNP haplotype was identified that should be studied further; mir-155 is derived from a region involving B-cell Integration Cluster non-coding RNA (BIC) and is located at band q21.3 on chromosome 21 **[3, 16].**

In conclusion, an analytic technique for analysis of several miRNA databases developed methods to integrate their information related to MS. Results indicated differences among blood and brain tissue from MS patients. Sixteen miRNAs were associated with MS. MiRNA-mRNA prediction studies indicated 1,498 possible target genes in a network. Five hundred genes, each, were predicted as central hubs for hsa-miR-20b-5p and hsa-miR-20a-5p. Transcription factor activity, T cell activation, and signaling accounted for many of the target genes. Thus, miRNAs behave in a super-stratum of regulators of gene expression regulation in MS **[17].**

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