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Review

Dysregulated Network of miRNAs Involved in the Pathogenesis of Multiple Sclerosis

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ABSTRACT

Multiple sclerosis (MS) is a chronic and organ-specific autoimmune disease in which immune cells act against the myelin sheath, resulting in central nervous system (CNS) damage. It has been revealed that miRNAs can play significant role in the pathogenesis of MS. These regulatory molecules lead to the activation of different signaling pathways, regulation of several transcriptional factors, influencing the differentiation of Th17 cells, development of Tregs and alteration from Th2 to Th1 response in MS. New studies have discovered that dysregulation of miRNAs may trigger abnormal immune responses leading consequently in the emergence of autoimmunity. In this review, we have discussed the altered expression patterns of miRNAs discovered in MS patients. These types of dysregulated miRNAs have been associated with MS pathogenesis. Current outcomes propose that such dysregulated miRNAs are potential to serve as useful biomarkers to diagnose MS, and to recognize new healing targets for its treatment.

1. Introduction

Multiple Sclerosis (MS) is a chronic inflammatory autoimmune disease that damages the Central Nervous System (CNS) and affects almost 2.5 million people worldwide [1]. MS has been pathologically characterized by demyelinated regions in the white and grey matters of brain and spinal cord. These regions are recognized as plaques or lesions described by the loss of myelin sheaths and oligodendrocytes [2]. Despite the detectability of inflammation in all phases of the disease, it can be more obviously detected in acute types when compared to the chronic types. Macrophages are predominance cells in the infiltrate, that is followed by $CD8^+$ T cells. However, fewer $CD4^+$ T cells, B cells, and plasma cells may be found in the infiltrate [3]. Th1 and Th17 are known to be the major cells contributed in MS pathogenesis [4]. As the disease persists, diffuse inflammatory T cell and B cell infiltrates, microglia and astrocyte stimulation, and diffuse myelin reduction and axonal damage are also detected (Fig. 1). These events lead into the higher atrophy of grey and white matters in the CNS [5]. Even though, T cell composition of infiltrates does not change during disease progression, but the relative proportion of B cells and plasma cells are increased. Microglia and macrophages remain in the chronic stage of activation during the disease [3]. In general, there are four main types of MS described by the stage of disease progression: Relapsing-Remitting MS (RRMS) is characterized by relapses (attacks) followed by remission (recovery), Secondary Progressive MS (SPMS) occurs after an early RRMS period in which inability worsens continuously regardless of any new relapse episodes, Primary Progressive MS (PPMS) is defined by a stable deterioration of neurological functions from the beginning of the disease with no relapses. Progressive Relapsing MS (PRMS) is about those who have a steady neurological decline and in the similar time have as well noticeable MS attacks.

Epigenetic phenomena such as microRNAs plays vital roles in regulation of both normal cellular processes and abnormal events related to cancer and other human diseases [6].

MicroRNAs (miRNAs) are small non-coding RNA molecules compromised of about 22 nucleotides in length. The fundamental role of these molecules is to regulate the expression of genes either by translational repression or by cleavage of the target mRNA [7]. In MS, the

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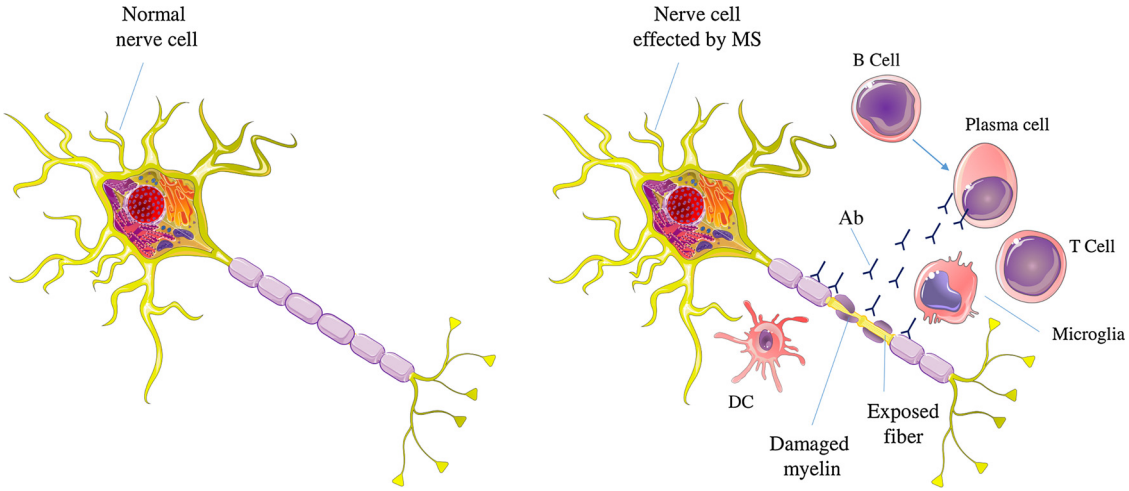

Fig. 1. MS Immunopathogenesis: MS is the brain most common autoimmune disease. In MS, demyelinating white matter lesions are along with infiltrates of mononuclear phagocytes, B lymphocytes, plasma cells, dendritic cells, and T cells, into the CNS. These events lead to creation of various distinct inflammatory demyelinated plaques situated predominantly in the white matter. Ab; Antibody. CNS; Central nervous system. DC; Dendritic cells. MS; Multiple sclerosis.

expression profile of miRNAs are changed in both CNS lesions and the immune system, resulting in considerable effects on gene expression in numerous cell types that consequently contributes in the disease [8]. In mammals, miRNAs are transcribed as a long primary transcript known as primary miRNA (pri-miRNA). The pri-miRNAs are cut into pre-miRNAs in the nucleus. These pre-miRNA molecules are transported into the cytoplasm where they are cleaved to create a duplex of 20–22 nucleotides [9]. The duplex is overloaded onto the RNA-induced silencing complex (RISC) while the passenger strand is released. The passenger strand has been proved to be degraded after the release [10]. In this review, we have provided an overview of emerging data that are tried to describe the alterations in the expression profile of miRNAs in MS. Also, we have argued over the possible role of miRNAs as diagnostic and predictive biomarkers of different MS types and as new therapeutic targets in MS.

2. Dysregulation of miRNAs

The dysregulated expression of miRNAs is accompanied by the onset of diseases such as immune disorders, neurological pathologies, cardiovascular conditions, and cancers [11]. Regarding to MS complicated pathobiology and the contributions of both innate and adaptive immunity to the disease, understanding the changes that occur in miRNA expression profiles of specific immune cell subsets can provide new potential biomarkers for MS and shed light on the new mechanisms underlying its development and progression. Most studies published so far analyzing miRNA expression have used Peripheral Blood Mononuclear Cells (PBMCs), whole blood, plasma, Cerebrospinal Fluid (CSF), and MS lesions (Fig. 2). Also, the quantitative Polymerase Chain Reaction (qPCR) platform has been recommended to be a valid and potent method to evaluate low levels of circulating miRNAs [9].

2.1. Dysregulation of miRNAs in PBMCs

The expression analysis of 346 miRNAs in PBMCs of MS patients during relapse and remission has indicated considerable differences with that of healthy controls. The results of study carried out by Otaegui has demonstrated that altered miRNA expression profiles are observed between MS patients and healthy individuals, and as well is found between patients with active disease and without it [12].

2.1.1. Dysregulation of miRNAs in $CD4^+$ T and $CD8^+$ T cells

Numerous investigations have detected dysregulated miRNAs in the peripheral $CD4^+$ T cells of MS patients [13]. Accordingly, miR-18a, miR-20b, miR-29a and miR-103, expressed dominantly in $CD4^+$ T cells, are found to be decreased in RRMS patients when compared to the healthy controls, implying that these miRNAs could involve in the pathogenesis of MS [14]. The expression of miR-27b and miR-128 is discovered to be increased in naïve $CD4^+$T cells, and miR-340 expression is up-regulated in the MS patients' memory $CD4^+$T cells [15,16]

In another study, it has been revealed that miR-17-5p (belongs to the miR-17-92 cluster), miR-126, miR-193a, miR-376a, miR-485-3p and miR-497 are up-regulated, but miR-34a is decreased in MS patients' $CD4^+$ T cells, suggesting the substantial role of these dysregulated miRNAs in the development of encephalitogenic $CD4^+$T cells related to MS pathogenesis [17]. MiR-16, and miR-142-3p are indicated to be up-regulated in $CD4^+$ T cells [18]. Moreover, some other studies illustrated that the combination of miR-142-3p, miR-146a, and miR-155 yields into the greatest achievements in the prediction of disease with a sensitivity of 77.8% and a specificity of 88.0% [18]. In contrast, the expresssion of miR-15a and miR-16-1 is reduced.

It has been suggested that increased levels of potent anti-apoptotic gene BCL-2 in $CD4^+$ T cells of MS patients is caused by down-regulation of miR-15a and miR-16-1, targeting BCL-2 [19].

miR-15a targets multiple genes including BCL-2, Cyclin D1, Cyclin D2 and MCL1 (Induced myeloid leukemia cell differentiation protein). MiR-15a-mediated suppression of BCL-2 might induce apoptosis [19]. BCL-2 is recognized to be extensively expressed in MS patients because of the reduced levels of miR-15a. This may account for inhibiting apoptosis in $CD4^+$ and $CD8^+$T cells, thus stimulating the formation of excessive auto-reactive immune cells and, finally MS pathogenesis [19]. Accordingly, down-regulation of miR-15a in $CD4^+$and $CD8^+$ T cells has the potentiality of enhancing the proliferation, migration and invasion of immune cells by increasing the expression of TNF-α-induced protein 1 (TNFAIP1), NF-κB, Yes-Associated Protein 1 (YAP1), and Rictor, and Sox5 could subscribe to MS pathogenesis [20,21].

miR-16-1 targets and represses the expression of BCL-2. Reduced levels of miR-16-1 stimulate the enhanced expression of BCL-2 in MS patients, causing the prevention from apoptosis, extreme numbers of auto-reactive immune cells, and MS pathogenesis [19]. It is interesting to demonstrate that whether down-regulation of miR-16-1 can enhance the expression of CCND1 (Cyclin D1), Cyclin E1, Sox5, Wilms Tumor protein (WT1) and YAP1, leading to the elevated proliferation of T cells, and derived pathogenesis of MS [22,23].

It has been revealed that miR-629 is up-regulated, but miR-30a-3p, miR-149 and miR-497 are down-regulated in $CD8^+$ T cells from peripheral blood samples of RRMS patients[24]. Dysregulation of miRNAs