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Association of Micro RNA in Multiple Sclerosis Patients

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Abstract:
Multiple sclerosis (MS) is a chronic condition characterised by immune system involvement and is the primary contributor to disability in the young adult population. Post-transcriptional regulation of gene expression is largely dependent on microRNAs (miRNAs). In the context of multiple sclerosis, miR-155 is one of these variables that plays a critical role in the regulation of inflammatory processes and the modulation of the autoimmune response.
In inflammatory conditions, MiR-155 plays a role in the breakdown of the blood-brain barrier (BBB) by down-regulating key junctional proteins. Demyelination is facilitated by a number of processes, including the activation of microglia, the polarization of astrocytes, the down-regulation of CD47 protein, and the manipulation of key transcription factors. Since miR-155 indirectly affects the development of regulatory T (Treg) cells, which are essential in reducing pain hypersensitivity, it plays an important role in the etiology of neuropathic pain.
In addition, this analysis looked at how MS-related symptoms develop in response to disease-related stresses, brain atrophy, and pro-inflammatory factors. Recent studies have shed light on miR-155's role in controlling stress, anxiety, hippocampal inflammation, and treatment-resistant depression. Reducing miR-155 expression has been shown to be an effective strategy for halting the pathophysiological processes that lead to multiple sclerosis (MS). The purpose of this review was to better understand the wide-ranging effects of miR-155 dysregulation on the pathophysiology of MS and to highlight possible future research avenues.

Keyword : Micro RNA , Multiple sclerosis (M.S) , CNS.

Introduction

Multiple sclerosis (MS) Progressive degeneration of the central nervous system is a hallmark of multiple sclerosis, a neurological condition . The central nervous system (CNS) is most affected by this disease, with the myelin sheath around neuronal axons being a key neurological target. Given that the disease is classified as an autoimmune syndrome, it is widely believed

that brain activity demyelination and disturbance mainly arise due to the pathophysiology of inflammatory reactions (1).

At different points in the progression of multiple sclerosis (MS), the body's inflammatory response might become weakened. T cells target myelin in the brain, which then activates cytokines due to immune system malfunction and blood-brain barrier breakdown. The blood-brain barrier is weakened by the action of these cytokines. This phenomenon enhances the likelihood of a central nervous system (CNS) attack facilitated by other immune cells, namely B cells. These B cells are responsible for releasing antibodies that target myelin and oligodendrocytes, marking them for subsequent consumption by macrophages. To some extent, myelin degradation leads to the development of lesions, which serve as critical diagnostic indicators for multiple sclerosis (1).

Multiple sclerosis is a multifaceted condition characterised by the involvement of numerous genes that contribute to a moderate increase in disease susceptibility (1). Furthermore, several established environmental factors have been identified, including vitamin D or ultraviolet B light (UVB) exposure, Epstein-Barr virus (EBV) infection, obesity, and smoking (2). This provides more evidence that a diet high in salt may play a role in the increasing incidence of MS (3). Relapsing-remitting multiple sclerosis (RRMS) is the most common form of the disease, and relapses are triggered by inflammation.

The manifestation of disease progression in patients leads to significant neurological impairments, which can be attributed to demyelination and loss of axons. About 15% of patients, as reported in the literature, exhibit a primary progressive course of disease, which is characterized by the gradual accumulation of neurological deficits over time(3). Significant favourable long-term outcomes have been observed in patients who undergo high-intensity immunosuppressive protocols. However, this treatment's advantageous effects diminish when it begins later, perhaps when the underlying pathological process transitions from an inflammatory nature to a degenerative one. The prevailing view posits that the successful therapy of early multiple sclerosis can halt the progression of disease. However, it must be noted that this notion lacks clinical evidence to substantiate its claims (3). People with dormant John Cunningham virus (JCV) infections have been found to develop progressive multifocal leukoencephalopathy (PML). (4). Maaixantrone, also known as Novantrone, is a cytotoxic drug with immunosuppressive effects and is employed in treating several cancers. The compound is thought to exert its effects via multiple mechanisms, such as the suppression of T-cell, B-cell, and macrophage proliferation, the impairment of antigen presentation, the prevention of macrophage-mediated demyelination, and the attenuation of pro-inflammatory cytokines. (5).

While the precise role of B cells in MS is still unclear, studies have shown that removing B cells with a monoclonal antibody targeting CD20 can significantly reduce disease activity and the rate of annual relapses. The immune system disorder multiple sclerosis (MS) is thought to be T-cell-mediated and affects a specific organ. However, the conventional concept of T-cell-mediated autoimmunity is challenged by the success of therapy aimed at B-cell (6). Multiple

sclerosis (MS) is conventionally perceived as a disease that occurs in two distinct stages. The initial stage involves inflammation, which gives rise to relapsing-remitting disease. The subsequent stage involves delayed neurodegeneration, leading to non-relapsing progression. This progression can manifest as either secondary progressive MS (SPMS) or primary progressive MS (PPMS)(7).

Genes, immune cells, antibodies, and cellular/metabolic pathways including enzymes and cell receptors are only some of the many potential target areas for pharmacological disease-modifying drugs. In most cases, these targets are connected to mechanisms that dampen inflammation. Cognitive rehabilitation has been used in addition to these therapeutic methods to help people with MS who are experiencing cognitive and functional difficulties. Multiple sclerosis patients have shown mixed results when undergoing cognitive rehabilitation, but early results are promising (8).

Micro RNA

Micro RNAs are small non-coding RNAs that can inhibit translation of mRNA or increase its degradation (9), so controlling gene expression after transcription. Small interfering RNAs (miRNAs) are a type of non-coding RNA that typically range in length from 20 to 24 nucleotides. They control how DNA is copied and how cells communicate with one another (10). In a broad sense, it is seen that a particular microRNA (miRNA) can govern several messenger RNA (mRNA) transcripts. These distinct transcripts can partake in diverse physiological processes, whereas a single mRNA transcript can be governed by many miRNAs (11).

MicroRNAs (miRNAs) play an important role in the development, proliferation, differentiation, plasticity, and other cellular processes of the central nervous system (12). MicroRNAs (miRNAs) exhibit significant expression levels in immune cells and play a crucial role in innate and adaptive immune responses (13). According to a publication, miRNA has been identified as a crucial regulatory component in maintaining immunological tolerance (14). The loss of Dicer and Drosha enzymes during miRNA synthesis is associated with T-cell malfunction and the development of autoimmune disorders (15). Differential miRNA production is observed among several subgroups of immune cells, suggesting that the regulatory mechanisms mediated by miRNAs play a crucial role in governing the functions of various T cell populations, including naïve, effector, memory, and regulatory T cells (15). Recent research has revealed a distinct pattern of miRNA expression in developing multiple sclerosis (MS). It indicates that miRNA expression dysregulation is a "priming factor" in the etiology of multiple sclerosis. Modulation of T-cell activation is a potential mediator of this pathogenic impact (16).

MicroRNAs (miRNAs) exhibit histological specificity and can be expressed in paracrine forms. They have been identified in several bodily fluids, including cerebrospinal fluid (CSF), serum, urine, and saliva (17). Therefore, it is reasonable to think about the potential value of peripheral

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circulating miRNAs as biomarkers in the context of multiple sclerosis, for objectives such as diagnosis, differentiation of MS subtypes, and prognosis prediction. In addition, the development of novel treatment approaches for MS therapy within the field of MicroRNA Biogenesis may result from doing in-depth research on the regulation of miRNAs (microRNAs) in T cells, which play a significant role in the progression of the disease.

The study of miRNA biogenesis is an important area of study since it covers the entire process, from genomic transcription through the production of mature, functional miRNA. Introns of protein-coding genes and ncRNA transcripts have been shown to contain miRNAs, either singly or in clusters. As shown in Figure 1A, 18 miRNAs have been found to be embedded in exons. "pri-miRNA," the initial RNA transcript produced by PolII, is typically longer than 1 kilobase and capped at the 5' terminus (19). The capacity of this single-stranded transcript to form stable stem-loop hairpin structures of about 70 nucleotides in length is noteworthy.

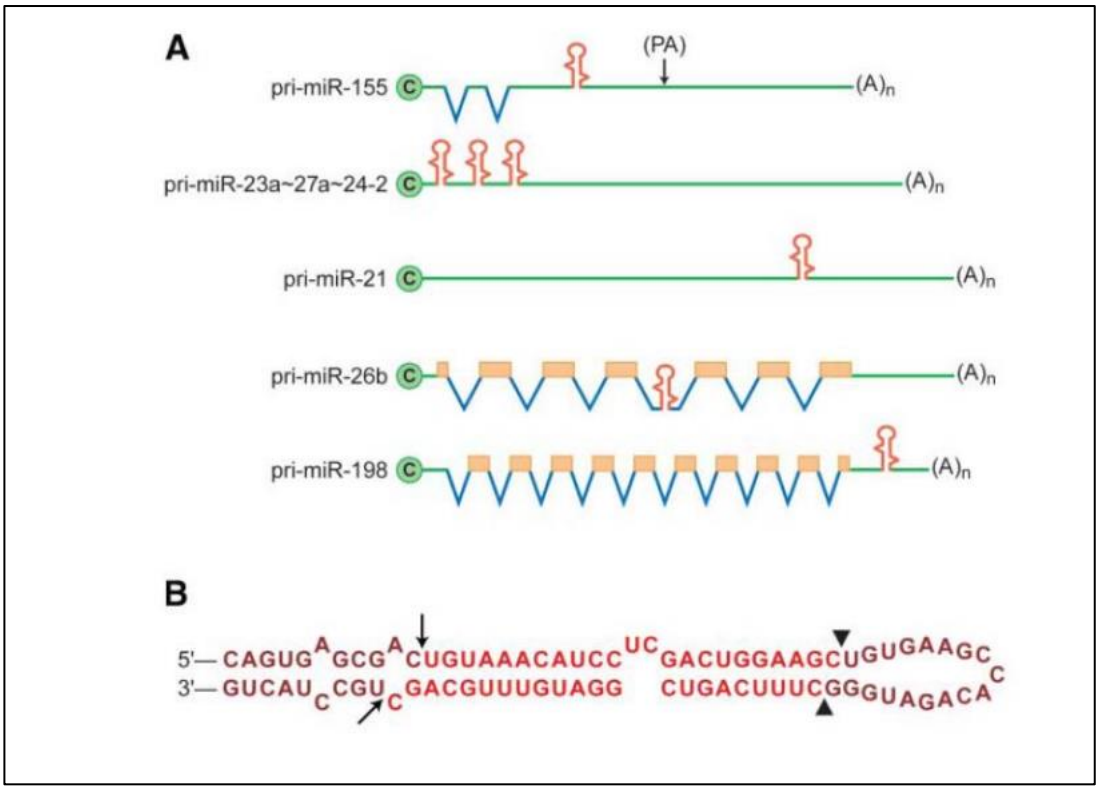

Figure 1 Biogenesis of MicroRNA Structures and the Molecular Mechanisms Behind It. Five fundamental microRNAs (pri-miRNAs) are represented here along with their schematic structures. MiRNA stems are depicted in red, non-coding sections in green, introns in blue, exons encoding proteins in beige, and alternative polyA sites indicated by (PA) in the figure. It is typical to see the stem-loop structure of miRNAs.

Drosha and DCGR8, two essential components of the Microprocessor complex, locate and bind to the base of each hairpin formation before carrying out a cleavage that removes about 11 nucleotides from the stem. The hairpin structure can be separated from the parent transcript

thanks to this cleavage. "pre-miRNA" refers to the resulting particle, which consists of a double-stranded stem attached to the beginning of a single-stranded loop with low complementarity (20). The structure also comprises a phosphate group attached to the 5' end and a unique overhang of 2 nucleotides at the 3' end. This overhang serves as a signal for Exportin-5, facilitating the nuclear export process (21). After the pre-miRNA has been delivered, Dicer cuts it in half along its loops to create a double-stranded RNA molecule with tiny bumps made of non-complementary nucleotides (22). The full miRNA complex, RNA-induced silencing complex (RISC) (23), is formed when the guide strand is identified and incorporated by Argonaut proteins, and the opposite strand is removed. The mature miRNA binds to the RNA-induced silencing complex (RISC) and then interacts with the 3' untranslated region (3'UTR) of target messenger RNAs. Inhibition of protein translation or mRNA degradation are two strategies by which this relationship reduces gene expression Figure 2; 24).

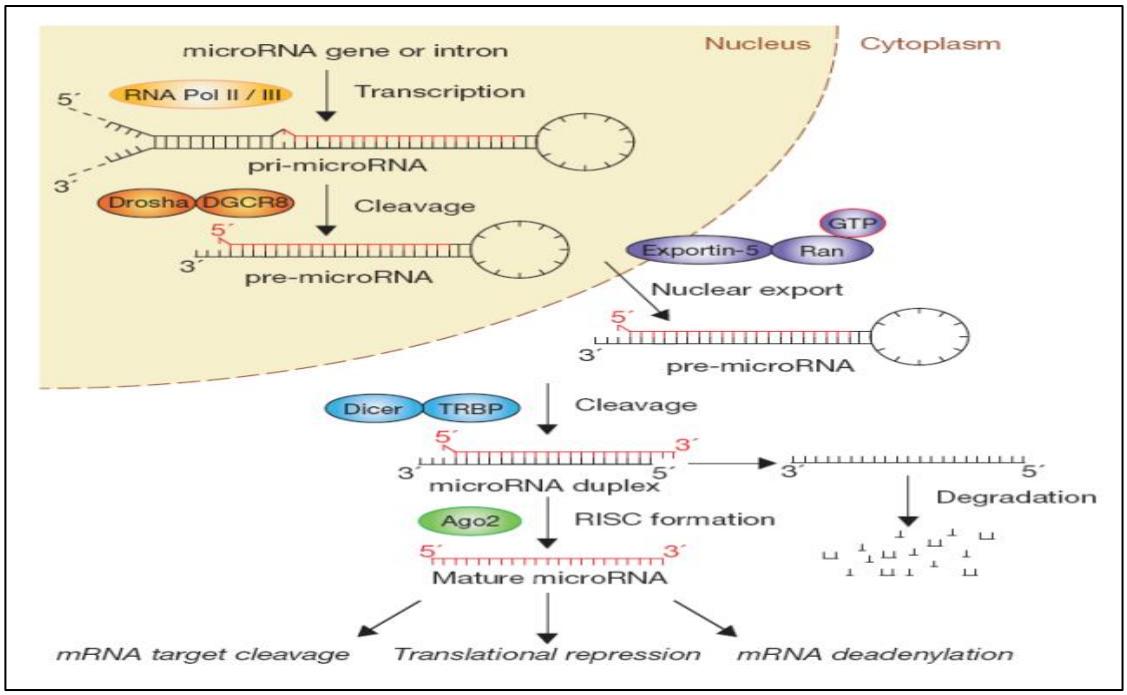

Figure 2. The standard biosynthetic route for microRNAs. Primordial transcript of microRNA (pri-miRNA) is synthesized by either RNA polymerase II or RNA polymerase III. Inside the nucleus, the Drosha-DGCR8 (Pasha) complex is responsible for cleaving the primary microRNA (pri-miRNA). The Exportin5-Ran-GTP pathway delivers the stem-loop of the pre-miRNA to the cytoplasm. After being processed by the Dicer enzyme, pre-microRNAs (pre-miRNAs) become double-stranded RNA molecules with bulges along their stems. Inside the RNA-induced silencing complex (RISC), the RNA double strand, often known as "diced," is processed by Argonaute proteins. Mature microRNA (miRNA) is produced by this pathway, and it inhibits protein translation at both the transcriptional and post-transcriptional levels.

MiRNAs and Inflammation

The regulation of inflammation is predominantly governed by microRNAs (miRNAs) due to their differential expression in specific immune cells (25). The regulation of miRNA biogenesis during the inflammatory response encompasses various steps, including synthesising, processing, and stabilising pre- or mature miRNAs (26). MicroRNAs (miRNAs) play a crucial role in regulating several phases of inflammation, including initiation, expansion, and resolution, through implementing both positive and negative feedback mechanisms (27).

The positive feedback mechanism not only hinders the infiltration of pathogens but also impedes the effective restoration of tissue integrity through a series of events. On the other hand, the negative feedback mechanism, triggered in acute inflammation cases, plays a crucial role in preserving tissue homeostasis. In the subsequent section, a concise examination is conducted of the diverse pro- and anti-inflammatory miRNAs (27).

MicroRNAs implicated in the pathogenesis of multiple sclerosis

Maintaining immunological homeostasis and efficient immune function is dependent on microRNAs' (miRNAs) regulatory role. The delicate balance of immunological tolerance may be tipped out of whack by the dysregulated production of miRNAs. Multiple sclerosis (MS) is an autoimmune disease that is triggered in part by the abnormal production of microRNAs (miRNAs) in the T cells of MS patients. Specifically, Th1, Th17, Treg, and CD8+ cells are activated during this phase (28). In multiple sclerosis (MS), Th1 cells are known to have a significant role in the pathophysiology of autoimmune demyelination.

Serum miR-155 levels are increased in people with MS, and this is especially true during MS relapses. Increased levels of miR-155 stimulate the production of the cytokines IL-17A and IFN-, hence encouraging the differentiation of Th17 and Th1 cells. Therefore, the experimental autoimmune encephalomyelitis (EAE) model's clinical symptoms are made worse by this ongoing inflammatory response. (29) Pathologically, multiple sclerosis (MS) is characterized by the invasion of Th17 cells into the CNS (30). Pathogenesis of autoimmune diseases, such as experimental autoimmune encephalomyelitis (EAE) and multiple sclerosis (MS), may include an unbalanced Th17/Treg ratio (31). Autoreactive CD4+ T cells that invade the brain show a dramatic upregulation of miR-155 expression. The development of Th1 cells is not impacted by the overexpression of miR-155, however it has been demonstrated to accelerate the creation of Th17 cells. Two genes, Dnaja2 and Dnaja1, which encode heat shock proteins, are targeted to produce this effect. Thus, miR-155 contributes to the development of experimental autoimmune encephalomyelitis (EAE) (32).

MicroRNAs (miRNAs) are now widely believed to play multiple roles in T lymphocyte maturation, activation, and function via pathways discovered in recent scientific studies. Figure 3 shows the mRNAs that play a significant role in regulating T lymphocyte development and transformation. In particular, they keep the ratio of Th1 to Th2 and Th17 to Tregs in check. The existence of phenotypic abnormalities in T cells is the major pathogenic mechanism underlying a variety of autoimmune illnesses, including multiple sclerosis (MS). Given the T-cell-specific

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miRNA expression patterns, evaluating differential miRNA expression has the potential to identify these miRNAs as diagnostic biomarkers for MS, complementing current diagnostic methods (33).

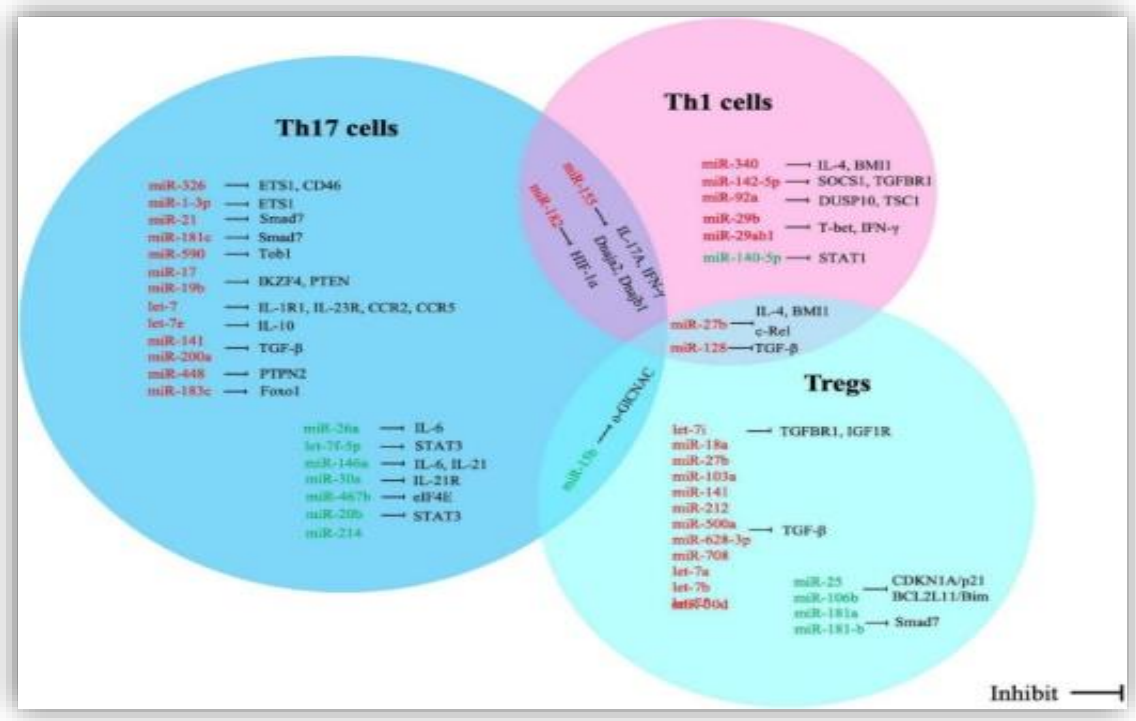

Figure. 3 This research looks into how alterations in miRNA levels affect the expression of direct targets in distinct subsets of T cells in people with multiple sclerosis. The up-regulated miRNAs are indicated by red text, whereas the down-regulated miRNAs are indicated by green text.

miR-155 and Immune Response

One of the miRNAs found to have important consequences in autoimmune illnesses is microRNA-155 (34). Both miR-155-3p and miR-155-5p are encoded by the same gene, known as the miR-155 host gene (mir155hg). In B-cell-activated lymphomas (35), this entity, formerly known as the B-cell integration cluster (BIC), was highly upregulated. Additional evidence confirming the existence of miR-155 in other human organs, such as the spleen, thymus, liver, lung, and kidney, has been uncovered via subsequent research. It has also been shown that miR-155 is highly selective for hematopoietic cells (36,37).

Based on these findings, miR-155 is critically important for preserving equilibrium and controlling the immune response. Specifically, B-cells regulate dendritic cells, stimulate cytokines, chemokines, and transcription factors, and modulate T-cells (including CD8+ cells), CD4+ cells (which can differentiate into Th1, Th2, Th17, and regulatory T (Treg) cells), and B-cells (which can regulate T-cells) (38). It has also been noted that miR-155 promotes pro-

inflammatory polarization towards an M1-like phenotype, which leads to neurotoxicity (39), and that it increases astrocyte activation.

MicroRNA-155 is very adaptable, and its transcripts are strongly correlated with those of immune response genes including tumor necrosis factor alpha and nuclear factor kappa-light-chain enhancer of activated B cells (NF-kB). The foregoing process is crucial in promoting the development of neuroinflammation, which is characterized by the activation of glial cells and the production of pro-inflammatory cytokines by the resident cells of the central nervous system. Several neurodegenerative diseases (40, 41, 42) have this pathology. Additionally, the pro-inflammatory action of miR-155 in microglia can be induced by the transcription factor p53. In this case, it has been determined that miR-155 targets the transcription factor c-Maf, which is responsible for initiating anti-inflammatory actions within immune cells. Inflammation is triggered as a result of this activity (43).

The phenomenon of miR-155 overexpression has been documented in several samples, such as brain cells in the central nervous system. These brain lesions undergo pathological changes, and blood cells are obtained from individuals diagnosed with multiple sclerosis (44). The study by Junker et al. provided evidence of the up-regulation of miR-155 in active white matter lesions compared to a group of healthy controls [63]. Paraboschi et al. conducted a study to examine the expression levels of 22 microRNAs (miRNAs) related to immune response, specifically in the peripheral blood mononuclear cells (PBMCs) of individuals with relapsing-remitting multiple sclerosis (RRMS) during the remission phase, in comparison to a group of healthy individuals serving as controls. Consequently, it was observed that miR-155 exhibited the highest level of up-regulation, suggesting its potential role in regulating multiple sclerosis pathogenesis (45).

Increased CD4+ T-cell expression was found in the spleen, lymph nodes, and central nervous system (CNS) in studies of experimental autoimmune encephalomyelitis (EAE), an animal model for multiple sclerosis (MS). Therefore, the results of this investigation support the hypothesis that miR-155 has a role in EAE vulnerability (46). Subsequent research within the context of MS and experimental autoimmune encephalomyelitis (EAE) has confirmed the association between miR-155 and these clinical diseases. In people with multiple sclerosis (MS), an increase in miR-155 expression level has been associated with a worsening clinical course and prognosis (47).

Multiple biological processes have been found to be affected by miR-155's pro-inflammatory effects. Among these are the upregulation of blood-brain-barrier (BBB) permeability and the infiltration of peripheral immune cells; the activation of microglia; the phagocytosis of myelin by macrophages; the differentiation of T-cells towards Th1 or Th2 phenotypes; and the contribution to greater permeability of the BBB. Recent studies have looked into the possible connections between miR-155 expression and mental health issues such depression, cognitive performance, and neuropathic pain (50). Given its known link to inflammation, miR-155's involvement in a wide range of pathophysiological processes and the emergence of MS-related

symptoms lends credence to the idea that it plays a significant role in the disease's manifestation.

MiR-155 in Multiple sclerosis

One of the best examples of a pro-inflammatory microRNA is microRNA155.One of the miRNAs that has been widely linked to autoimmune diseases is miR-155 (51), which has been studied extensively. Both miR-155-3p and miR-155-5p are encoded by the same gene, known as the miR-155 host gene (mir155hg). In B-cell-activated lymphomas (52), the B-cell integration cluster (BIC) was significantly overexpressed. The spleen, thymus, liver, lungs, brain, and kidney have all been found to contain miR-155 in subsequent studies. In addition, miR-155 has been found to be highly selective for hematopoietic cells (53).

According to the data we currently have, miR-155 plays a crucial role in preserving equilibrium and controlling immune responses. It has also been noted that miR-155 promotes pro-inflammatory polarization of microglia and macrophages towards an M1-like phenotype, leading to neurotoxicity (54). This is accomplished via increasing astrocyte activation. Activation of glial cells and production of pro-inflammatory cytokines by cells living in the central nervous system are hallmarks of neuroinflammation, which it drives forward. Several forms of neurodegeneration (55) exhibit this feature. Interleukin 13 receptor, alpha 1 (IL13R1) is one of the inflammatory inhibitors whose expression is regulated in macrophages/microglia after toll-like receptor (TLR) activation (56).

Activation of the transcription factor p53 may also trigger miR-155's pro-inflammatory impact in microglia. Here, miR-155 directs its attention to c-Maf, a transcription factor that normally triggers anti-inflammatory pathways within immune cells. Inflammation is triggered as a result of this activity (57). Multiple sclerosis (MS) miR-155 dysregulation was first noticed when white matter lesions were isolated from paraffin-embedded and frozen tissue samples by Meinl et al. In active white matter lesions, miR-155 expression was found to be 11.9-fold higher than in the white matter of healthy controls ($p=0.242$). White matter near active lesions in the brain of individuals with relapsing-remitting, primary progressive, and secondary progressive illness was found to have higher miR-155 levels in a separate investigation (59). Myeloid-derived macrophages, microglia, T/B lymphocytes, and astrocytes were all tested for miR-155 expression using laser capture microdissection. This observation demonstrates that miR-155 can be produced by both invasive immune cells and resident brain cells (58, 60). Notably, miR-155 expression was found to be enhanced in the neurovascular unit of active lesions isolated from the brains of MS patients (61).

The blood-brain barrier is typically thought of as being located in the neurovascular unit. Here, you'll find neurons, astrocytes, and endothelial cells. It has been noted that miR-155 expression occurs in a variety of cell types within this organism, not just hematopoietic ones. Several studies (62, 63) have confirmed that miR-155 levels are increased in peripheral blood mononuclear cells (PBMCs) isolated from the blood of MS patients. The expression levels of

IL-17, IFN, TNF, and IL-6 are positively correlated with their increases. This finding suggests that miR-155 overexpression is restricted to cells under an inflammatory situation. The expression of miR-155 was shown to be specifically elevated in CD14+ monocytes isolated from peripheral blood mononuclear cells (PBMCs) in a cohort of patients with relapsing-remitting multiple sclerosis (RRMS), as confirmed by a number of investigations. There is also evidence that miR-155 is present at increased levels in the serum on its own (64).

Conclusions

Genetic, exogenous, immunological, and environmental variables can all have a role in the development of multiple sclerosis (MS). To this day, it remains a formidable obstacle to develop simple, accurate, and highly responsive methods for diagnosing and monitoring the course of multiple sclerosis (MS). According to the results of these investigations, miRNAs show promise as a sensitive and specific indication of the exact stage of this disease. Among these compounds, miR-155 shows the most promise for use as a biomarker in future clinical studies. The fact that it has such a significant impact on inflammatory molecular pathways, is subject to observable changes in expression levels, and is amenable to targeted regulation by specialized anti-miRs are all major contributing factors. The results of this study show that miR-155 has an effect on the integrity of the BBB under inflammatory settings. MiR-155's regulatory function in inflammation has been studied extensively. Sequential research into its unique function, in particular regarding pathophysiological pathways in multiple sclerosis (MS), offers a promising avenue toward better understanding this complex disease and enhancing the precision, effectiveness, and monitoring of its diagnosis, treatment, and management.

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