



Multiple Sclerosis and the Pathogenicity of Mir-155



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Mini Review

Multiple sclerosis (MS) is one of the complex diseases. Genetics, environmental and emotional factors have shown to play essential roles in evoking the disease pathology. More interestingly, epigenetic factors were established as major influencers of the disease severity [1]. Of those epigenetic factors; the microRNA (miRNA) plays a fundamental function in MS pathogenicity. MiRNAs are small noncoding RNA molecules with a size of approximately 22 nucleotides involved in post-transcriptional regulations of the genes [2-5]. In one of the first published papers on the relation between MS and miRNA, Otaegui and his group found differential miRNA profile between MS patient and healthy volunteers when analyzing 364 peripheral blood mononuclear cells (PBMC) samples. More so, they found that even between MS patients, miRNA profile can differentiate between remissions and relapses stages [6]. One of the most attractive miRNAs associated with MS was the miR-155. In 2009, Junker et al have for the first time identified miR-155 upregulation in active MS lesions [7]. Subsequently, many have established the role of this miRNA in relapsing stages of MS and experimental autoimmune encephalomyelitis (EAE) [4,8-15].

MiR-155 was of interest due to its important roles in immune system regulation. This miRNA has been proven to target the suppressor of cytokine signaling -1 (SOSC1); a negative regulator of cytokines signaling. It was also proven to induce T-cell differentiation along the T-helper 17 (Th17) and T-helper 1 (Th1) cells lines [16-19]. MiR-155 was, moreover, documented to target transcription factor Ets1; a negative modulator of Th17 differentiation [20]. Additionally, it targets CD47; a molecule involved in self-recognition and protect cells from phagocytosis [21]. It, more so, suppresses src homology 2 domain-containing inositol-5-phosphatase 1 (SHIP1); a known negative inhibitor of pro-inflammatory pathways to macrophages (M ϕ) and dendritic cells (DCs) [20]. Besides all that, miR-155 can suppress essential neuro-steroids in the white matter of MS cases [21,22]. And was noted to increase the tumor necrosis factor - α (TNF α) and monocyte chemoattractant protein-1 (MCP1) expression in a toll-like receptor -4 (TLR4)-dependent manner, resulting in neuro-inflammation in the cerebellum [23].

Captivatingly, several environmental factors associated with MS pathogenicity were proven to regulate this miRNA expression. Vitamin D deficiency, Epstein-Barr virus (EBV), obesity, alcohol consumption and cigarette smoking were all associated with MS pathogenicity previously and have been associated with miR-155 [19]. Vitamin D, one of the major environmental protective agents against MS, was found to attune M ϕ induced inflammation via targeting miR-155 [24]. While EBV, one of the major risk factors for MS, can upregulate this miRNA [25-33]. Obesity, another MS risk factor, is characterized by the over-accumulation of pro-inflammatory M ϕ (M1) [34-35]. M1 cells are marked by the increased miR-155-5p and it is thought that this miRNA control M1 polarization [36-37]. In an interesting article, miR-155 was found to be upregulated in the brain by alcohol diet, another MS stimulator [23,38]. Alcohol consumption was recorded to provoke neuro-inflammation in mice through miR-155 induction [23]. More so, cigarette smoke-induced inflammation could result from the upregulation of miR-155 [39]. Those points may indicate the importance of this miRNA and the need to be further analyzed regarding environment-induced MS.

This miRNA has been documented to manipulate MS patients' body by several means. When investigating MS, Moore et al have found significant increase of miR-155 in circulating CD14+ monocytes and active lesion (CD68+ cells) comparing to healthy controls cells. They have proven the role of miR-155 as a pro-inflammatory regulator of macrophages and microglia polarization. Also, in their report, they found that miR-155 transfected in myeloid cells can increase TNF α , M1-associated surface markers (CD80, CD86, and CCR7) and enhance the allogeneic T-cell responses [40]. Jevtić and his group, subsequently, have indicated the role of miR-155 in re-activation of encephalitogenic CD4+ T cells in EAE rats [41]. Interestingly, Lopez-Ramirez and his colleagues claimed miR-155 as a negative regulator of BBB function that targets cell-cell complex molecules (annexin-2 and claudin-1) and focal adhesion components (DOCK-1 and syntenin-1). In their report, miR-155 increased expression could mimic cytokine-induced alterations

in junctional organization and increase the permeability, while inhibition of miR-155 could prevent cytokine-induced increase in the permeability [42]. While, Cerutti et al indicated the role of brain endothelium miR-155 up-regulation in extravagating the adhesion to award monocyte and T cells. This was partially caused by the miR-155 modulation of leukocyte migration include intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) [42].

In Noorbakhsh et al paper, miR-155 was associated with the suppression of allopregnanolone, an important neurosteroid, in both MS patient and EAE models. Supplementation of this neurosteroid in EAE models was accompanied by decreased neuropathology, including neuroinflammation, myelin and axonal injury and reduced neurobehavioral deficits [43]. Notably, Singh et al identified miR-155 as a biomarker for MS that can increase in expression 6 days before the onset of the EAE disease in urine exosomes, plasma, and spinal cord; emphasizing it is role in early pathogenicity of EAE [44]. In 2011, Paraboschi and his group have identified the genetics factors that associate miR-155 with MS; a haplotype of 3 SNPs mapped in the mir-155 gene ($P = 0.035$; $OR = 1.36$, $95\% CI = 1.05-1.77$) [9]. Although, Quinn et al signify the role of the transcription factor Ets2 as a key regulator in miR-155 inflammatory response and that Ets2 deficient mice displayed defective immunological responses [45]. Ets2 was unfortunately not analyzed previously for its' relation to MS.

It is worth noting that while Waschbisch et al noted that glatiramer acetate (GA) treatment, the first approved treatment for MS, has no effect on this miRNA, Singh et al noted that miR-155 is one of the GA-responsive biomarkers [8,46-47]. Fortunately, natalizuma, fingolimod and Dimethyl fumarate (DMF) could regulate the miR-155 expression in MS patients [48,10]. Interestingly, high-dose ascorbic acid (AA) monotherapy can also modulate miR-155 [49]. One captivating article had discussed the effect of Autologous hematopoietic stem cell transplantation (AHSCT) on regulating miRNA profile; of which miR-155 [50]. In conclusion, miR-155 is one of MS biomarkers that can be detected in patient body fluids before the onset of the disease, contribute to disease pathogenicity and have been documented to increase in expression during relapses stages. This miRNA contributes to inflammation, BBB infiltration, and neuropathology processes. It is thought that MS patient genetics factors can affect the expression of this miRNA. Fortunately, current MS treatments have been documented to modulate the expression of miR-155. MS pathology and the true modulation effect of MS modulators are still questionable, here we explore one side of the story in aim to fully understand the whole picture.

Declarations

Author Contribution: Eiman M. A. Mohammed alone is responsible for the content and writing of this paper. The author has read and approved the final manuscript.

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