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. MiRNA 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 miRNA 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) [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 (SOCS1); 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 (Mφ) 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 (TNFα) 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 attenuate Mφ 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 Mφ (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 were 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 TNFα, 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 B cell 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 extragrafting 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 Noorabkhsh 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 [46,47]. Fortunately, natalizumab, fingolimod and Dimethyl fumarate (DMF) could regulate the miR-155 expression in MS patients [48,10]. Interestingly, Singh et al noted that miR-155 modulation of leukocyte migration include intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) [42].

Fingerlinum and Fingolimod are two drugs which are approved by FDA in the treatment of MS. They have been demonstrated to reduce inflammation and leukocyte infiltration into the spinal cord, which can be associated with an improvement in clinical disease activity [6]. They also reduce the expression of proinflammatory cytokines such as INF-γ and TNF-α and increase the expression of anti-inflammatory cytokines such as IL-10 and TGF-β [7]. Fingolimod also reduces the activation of both CD4+ and CD8+ T cells, and it has been demonstrated to reduce the expression of proinflammatory cytokines such as INF-γ and TNF-α and increase the expression of anti-inflammatory cytokines such as IL-10 and TGF-β [6].

Most importantly, fingolimod has been demonstrated to reduce the expression of proinflammatory cytokines such as INF-γ and TNF-α and increase the expression of anti-inflammatory cytokines such as IL-10 and TGF-β [6]. Fingolimod also reduces the activation of both CD4+ and CD8+ T cells, and it has been demonstrated to reduce the expression of proinflammatory cytokines such as INF-γ and TNF-α and increase the expression of anti-inflammatory cytokines such as IL-10 and TGF-β [6].

Fingolimod is approved by FDA for the treatment of relapsing-remitting MS and is used in combination with interferon-beta-1a in patients who have not responded to previous treatment [6]. Fingolimod is a highly selective inhibitor of the sphingosine-1-phosphate receptor-1 (S1P1) which is expressed on immune cells and is involved in the regulation of lymphocyte homing and migration [6]. Fingolimod has been demonstrated to reduce the expression of proinflammatory cytokines such as INF-γ and TNF-α and increase the expression of anti-inflammatory cytokines such as IL-10 and TGF-β [6]. Fingolimod also reduces the activation of both CD4+ and CD8+ T cells, and it has been demonstrated to reduce the expression of proinflammatory cytokines such as INF-γ and TNF-α and increase the expression of anti-inflammatory cytokines such as IL-10 and TGF-β [6].

In conclusion, fingolimod is a highly selective inhibitor of the sphingosine-1-phosphate receptor-1 (S1P1) which is expressed on immune cells and is involved in the regulation of lymphocyte homing and migration [6]. Fingolimod has been demonstrated to reduce the expression of proinflammatory cytokines such as INF-γ and TNF-α and increase the expression of anti-inflammatory cytokines such as IL-10 and TGF-β [6]. Fingolimod also reduces the activation of both CD4+ and CD8+ T cells, and it has been demonstrated to reduce the expression of proinflammatory cytokines such as INF-γ and TNF-α and increase the expression of anti-inflammatory cytokines such as IL-10 and TGF-β [6]. Fingolimod is approved by FDA for the treatment of relapsing-remitting MS and is used in combination with interferon-beta-1a in patients who have not responded to previous treatment [6].

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.

References


