Review Article

The miR-223: An Inflammatory MicroRNA Involved in Pathogenesis of Multiple Sclerosis

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A B S T R A C T

Multiple sclerosis (MS) is the most common autoimmune inflammatory demyelinating disease that affects the brain and spinal cord. Dysregulation or mutation of miRNA genes have been linked to the pathogenesis of MS. The miRNAs are short, 20-22 nucleotide long, single-stranded regulatory and non-protein coding RNAs that modulate the expression of multiple target genes. Among miRNAs, miR-223 has been reported to play a critical role in MS. This review concentrates on the emerging role of miR-223 in inflammatory responses and specifically discusses how alterations in miR-223 expression are associated with the development of MS. This review also suggests that miR-223 can be used as a biomarker for diagnosis of MS and discovering novel therapeutics for MS treatment.

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Introduction

Multiple sclerosis (MS), a chronic disorder of the brain and spinal cord, is the most common autoimmune inflammatory demyelinating disease primarily affecting young adults, which leads to irreversible disability [1, 2]. Similar to all complex traits, the development and clinical phenotypes of MS are affected by an interplay between environmental risk factors including infection, smoking, sunlight exposure and vitamin D deficiency with genetic susceptibility of polygenic nature [3-5]. The clinical course of MS is heterogeneous and is characterized by relapsing-remitting MS (RRMS), portrayed as a primary episode of neurological dysfunction followed by a remission period and then repeating bouts of relapse and remission, affecting twice as many women as men. Secondary progressive MS (SPMS) and primary progressive MS (PPMS) are other common clinical courses of this disease [6-8]. RRMS can progress to SPMS in 75% of patients within two decades.

MicroRNAs

The microRNAs (miRNAs) are short, single-stranded 20-22 nucleotide-long regulatory and non-protein coding RNA modulating the expression of multiple target genes. The miRNA function has been detected in different biological processes, including differentiation, cell proliferation, development and apoptosis in several cell types such as myeloid cells in the immune system and neuronal cells in the central nervous system [9-14]. They play important roles by regulating the expression of genes in transcription and post-transcription levels [15].

The capped, poly adenylated and double-stranded RNA structure of primary transcripts, which contains one or a number of miRNAs, is transcribed by RNA polymerase II. It is then cleaved at the base of stem-loop, processed into precursor miRNA (pre-miRNA) with hairpin structure60–100 nucleotides in lengths by a microprocessor complex containing at least Drosha (RNAase III endonuclease) and DGCR8 [16, 17]. The complex is then exported to the cytoplasm through exportin-5 and Ran-GTP co-factor and further processed into a mature miR/miR* duplex form by DICER1, RNase III endonuclease with TAR-binding protein and Argonaut (Ago2 in human). The mature miR/miR* duplex is separated by helicases, and the mature strand is then recruited to the RNA-induced silencing complex [18-21].

miRNAs may be able to regulate the expression of more than one target of mRNA and each mRNA can be modulated by more than one miRNA. These noncoding RNAs bind to their target miRNAs via seed sequence, which is a recognition sequence near the 5'terminus, further contributing to the specificity and activity of binding targets according to experimental evidence [22, 23].

Seed sequence with 6 to 8 nucleotides in miRNA molecules are highly conserved and even a slight change in the sequence may alter the miR target. Binding miRNAs to 3'UTRs of target miRNA can trigger mRNA

destabilization, resulting in a repression of protein translation or mRNA degradation and thus leading to a reduction in protein level [24-27]. It is also shown that the location of the central loop in miRNA:mRNA duplexes might affect the efficiency of gene regulation mediated by miRNAs [28]. In the past few years, improper miRNA expression and function were reported to be related to MS [29-36]. Recent studies have shown the presence of fixed miRNAs in biological fluids and also in cerebrospinal fluid [37, 38].

The miRNAs are able to modulate the expression of approximately 60% of genes [39] including other miRNA genes, thus producing a complicated system similar to the cytokine network, which plays an essential role in immune response regulation. Even a little change in miRNA action may lead to a remarkable change in gene expression resulting in pathological changes in the immune system. Today, mutation or dysregulation of miRNAs has been linked to autoimmune diseases, including MS [40-43]. Alterations in gene expression of miRNAs have been indicated in blood components, cerebrospinal fluid and brain lesions of MS patients [44, 45].

It was demonstrated that miRNAs are crucial for the maintenance of immune tolerance, as indicated by a deletion of Dicer-mediated miRNA in regulatory T-cells (T-reg cells) in mice. These mice develop a fatal autoimmune disease, similar to the autoimmune syndrome in animals which is caused by complete deficiency of T-reg cells [46, 47].

The origin of these circulating miRNAs is still unknown. However, the simplicity of their detection and the minimally invasive approach for obtaining them, make circulating miRNAs ideal prognostic biomarkers for monitoring the disease course and it's response to treatment. The miR-223 has an important function in the development and homeostasis of the immune system. Recently, the involvement of miR-223 has been shown for different types of cancers, inflammatory diseases, autoimmune diseases and other pathological processes [48]. The present article reviews our today's grasp of the physiopathology of miR-223 and concentrates on this miRNA's dysregulation and its role in MS.

miR-223 function

The sequence of miR-223 has been surprisingly conserved during evolution, suggesting that miR-223 has a pivotal role in physiological processes [49]. The location of the miR-223 encoding gene is at q12 locus in X chromosome [50]. The miR-223 was discovered in silico and bioinformatically identified [51]. It was thereafter reported to have an important role in the hematopoietic system [52, 53]. Its gene resembles a myeloid gene and several transcription factors are recruited to regulate the expression of miR-223, such as CCAAT-enhancer-binding proteins (C/EBP)-α and -ß, nuclear factor I-A (NFI-A) and transcription factor PU.1, which are all myeloid transcription factors [54].

NFIA and C/EBPα are two transcription factors that compete for binding to miR-223 promoter, NFI-A maintains miR-223 at low levels whereas C/EBPα upregulates miR-223

expression. A negative-feedback loop controls the competition by C/EBPα as well as granulocytic differentiation via suppression of NFI-A translation by miR-223 [55, 56]. The semi-miRNA derived from miR-223 (smiR-223) nonetheless regulates the ability ofmiR-223 to suppress translation or degradation of target transcripts and hence modulates gene expression indirectly [57]. The miR-223 is involved in hematopoiesis by modulating the differentiation of hemato-poietic lineages in hematopoietic bone marrow and has an effect on hematopoietic stem cells as well as on asmyeloid, erythroid and lymphoid cells in different levels of their development [53], regulating granulocytic differentiation, maturation, and function during granulopoiesis [58].

In myeloid cells of the bone marrow, the expression of miR-223 is found to be induced during lineage differentiation of myeloid progenitor cells. These myeloid cells differentiate into monocyte/ macrophage and granulocyte cells and once granulocyte-monocyte progenitors start to differentiate into monocytes, the expression of miR-223 is suppressed. In contrast, miR-223 is found to be overexpressed whereas the granulocyte-monocyte progenitors enter the granulocyte differentiation phase [53]. The miR-223 also has a key role in monocyte/macrophage differentiation by targeting and repressing the IκB kinase subunit alpha (IKK-α), a component of nuclear factor-kappa B (NF-κB) signaling way. Reduced miR-223 expression results in increasing expression of IKK-α, which induces the expression of p52 followed by suppression of NF-κB pathways during

macrophage differentiation [59, 60]. miR-223-rich micro vesicles induce the differentiation of recipient monocytes, promote the production of hematopoietic cells in the bone marrow and subsequently induce the release of more micro vesicles [61]. Some studies have indicated that miR-223 expression is downregulated during monocytic, erythroid, and mast cell differentiation as well as duringcell maturation [56, 58], which happens during erythrocyte proliferation and differentiation at progenitor and precursor levels [58].

The miR-223 also plays an essential role in osteoclast formation and regulation of bone remodeling [62]. More specifically, miR-223 expression represses osteoclast formation by suppressing the differentiation of osteoclast precursors [63].

miR-223 is an inflammatory miRNA

miR-223 has been explained as a regulator of granulopoiesis. There is increasing number of hypermature granulocyte precursors that areparticularly sensitive to activating stimuli in mice with miR-223 deficiency [53]. Therefore, it canbe shown that miR-223 negatively regulates granulopoiesis by targeting the transcription factor Mef-2c. It is demonstrated that miR-223 is crucial in macrophage differentiation [60].

The miR-223 modulates the NF-kB pathway by targeting transcripts of the kinase IKKa into macrophage differentiation during certain pro-inflammatory stimuli, so the downregulation of this miRNA might prevent macrophage hyperactivation [60, 64].

Targeting Pknox1 by miR-223 shows its important role in obesity associated adipose

tissue inflammation by regulating macrophage polarization [65].

It was also shown that miR-223 affects the production of IL-1β via NF-κB signaling pathway [26, 15, 22]. Recently, a research demonstrated that the production of IL-1β is under the influence of miR-223 by targeting classic inflammasome NLRP3 during lipopolysaccharide stimuli [66]. These results support that miR-223 is an essential modulator in macrophage during variant inflammatory responses [64].

The miR-223 is also upregulated in CD4$^+$CD25$^+$T-reg cells in comparison to naive T-cells [67]. Up-regulation of miR-223 has been shown in the blood from MS patients compared to healthy controls [43] as well as in CD4$^+$CD25^{high} bona fide T-reg cells of MS patients [44] versus healthy donors, and also in active MS lesions in the brain compared to the healthy brain [36, 68].

Dysregulation of miR-223 in MS

Using a miRNA microarray and Geniom Real Time Analyzer platform, Andreas Keller et al, analyzed the expression profiles of 866 miRNAs in blood cells of 20 RRMS patients and 19 healthy controls. They reported that miR-223 was significantly up-regulated in patients with RRMS as compared to healthy controls [43].

Quantitative real-time polymerase chain reaction analysis revealed up-regulation of 20 miRNAs (including miR-223) in the active white matter lesions of brain from patients with MS compared with the normal white matter of brain [36].

Further studies assessed the miRNA genome-wide expression profile by microarray analysis on CD4$^+$CD25^{high} T-cells from 12 patients with relapsing-remitting MS and 14 healthy controls. De Santis discovered that 17 miRNAs (including miR-223) were significantly up-regulated in T-regs from peripheral blood of MS patients [44].

The results from alaboratory study examining 84 miRNAs in a serum from a cohort of MS samples versus healthy controls showed significantly reduced expression levels of miR-223 in the sera of PPMS samples compared with controls [29].

Another study explored the expression profile of 1145 miRNAs using miRNA from peripheral blood mononuclear cells (PBMCs) of 19 MS patients and 14 controls. The study indicated that theexpression level of 45 miRNAs, including miR-223, miR-524-3p and miR-550*, increased in PBMCs from MS patients compared to controls [34].

Fanglio et al. investigated the expression of three free-circulating miRNAs in serum from MS patients compared to controls. Statistically, the level of miR-223 was remarkably decreased in MS patients. Down-regulation of these miRNA can result in overexpression of target genes that play a role in pathogenesis of MS [41].

In another study by Fanglio et al. the expression level of three miRNAs including miR-223, miR-23a and miR-15b has been explored in PBMCs and sera from MS patients. In this study, they found altered expression levels of miR-223 and miR-23a in PBMCs of MS patients compared to controls,

suggesting a possible contribution of these two miRNAs in pathogenic mechanisms of MS. They reported significant up-regulation of miR-223 and miR-23a levels in RRMS [69]. miR-223 is one of the most up-regulated miRNAs in multiple sclerosis patients. Ifergan et al. demonstrated that miR-223 knockout mice have significantly reduced active experimental autoimmune encephalomyelitis, which is determined by reduced level of myeloid dendritic cells and Th17 cells in the central nervous system. Myeloid cells play a crucial role in the induction and maintained inflammation in neuro-inflammatory disorders such as multiple sclerosis [70].

In another study, miR-223 is reported as a novel miRNA that controls the experimental autoimmune encephalomyelitis (EAE). miR-223 expression was up-regulated in spinal cords and lymphoid organs of mice. It has been shown that miR-223-/- mice have delay in EAE onset, decline in spinal cord lesion and reduction in neurological symptoms. It has also been found that miR-223 deficiency decreases Th1 and Th17 infiltration into spinal cord [71].

Conclusion

According to current literature, it is now increasingly evidenced that miR-223 is involved in the pathogenesis of MS. As stated above, miR-223 is highly dysregulated in MS patients as well as EAE mouse models. It might have the potential to generate a further understanding of the mechanisms underlying MS. The miR-223 has been reported to be upregulated in T-reg cells, plasma, blood cells, PBMCs and brain white matter tissue from MS patients and EAE mice. Such reports provide evidence that miR-223 may be a suitable choice for further studies as a novel therapeutic goal. It can also be used as a biomarker for diagnosis and monitor disease status in MS and a prognostic marker of treatment responsiveness.

Conflict of Interest

The authors declare no conflict of interest.

Acknowledgments

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