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Scavenging the hidden impacts of non-coding RNAs in multiple sclerosis

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ABSTRACT

Multiple sclerosis (MS) is a chronic neuroinflammatory disease that causes severe neurological dysfunction leading to disabilities in patients. The prevalence of the disease has been increasing gradually worldwide, and the specific etiology behind the disease is not yet fully understood. Therapies aimed against treating MS patients have been growing lately, intending to delay the disease progression and increase the patients' quality of life. Various pathways play crucial roles in developing the disease, and several therapeutic approaches have been tackling those pathways. However, these strategies have shown several side effects and inconsistent efficacy. MicroRNAs (miRNAs), long noncoding RNAs (lncRNAs), and circular RNAs (circRNAs) have been shown to act as key players in various disease pathogenesis and development. Several proinflammatory and anti-inflammatory miRNAs have been reported to participate in the development of MS. Hence, the review assesses the role of miRNAs, lncRNAs, and circRNAs in regulating immune cell functions better to understand their impact on the molecular mechanics of MS.

1. Introduction into MS

Multiple sclerosis (MS) is one of the most common neurological disorders and a leading cause of non-traumatic disability in young adults in many countries [1]. The disease is more common in adults than children, with an incidence peak between the age of 20 and 40, and incidence rates usually decrease after the age of 50, with women twice at risk of the disease than men. As per the systemic analysis done during the Global burden of disease study in 2016, an estimated 2.2 million people worldwide had MS corresponding to a prevalence rate of 30.1 per 100,000 [2]. The etiology of MS is quite complex and, to a great extent, unpredictable as well. It is suspected to be a multi-component disease mediated by the infection-induced autoimmune process superimposed on genetic predisposition. A various number of aetiological factors have been identified to play a role in MS, including genetic susceptibility, smoking, exposure to the Epstein-Barr virus (EBV), low exposure to sunlight (presumed to be mediated through vitamin D insufficiency), obesity, high salt intake and sedentary lifestyle [3].

Concluding an accurate description of the clinical phenotype of a typical MS case is essential for treatment decisions and prognosis. Initially, in 1996, the US National Multiple Sclerosis Society (NMSS) Advisory Committee classified MS disease into four main subtypes; Relapsing-remitting (RR), secondary progressive (SP), primary progressive (PP), and progressive relapsing (PR) [4]. However, the committee decided to revisit this phenotyping as it lacked objective biological support. In 2014, the International Advisory Committee on Clinical Trials of MS updated the previous classification of MS subtypes based on recently identified clinical aspects, imaging, biological markers, activity, and progression. The new MS classification divides the clinical courses into four main subtypes: clinically isolated syndrome (CIS), relapsing-remitting MS (RRMS), primary progressive MS (PPMS), and secondary progressive MS (SPMS) [5]. Experimental autoimmune encephalomyelitis (EAE) is the commonly used experimental model for MS [6]. The model is usually induced by active immunization with myelin-derived proteins or by passive transfer of activated myelin-specific $CD4^+$ T lymphocytes [7]. Like MS in human patients, EAE is characterized by paralysis caused by CNS inflammation, demyelination of neurons, axonal damage, and neurodegeneration. Some EAE models exhibit remission and relapse (relapsing-remitting EAE) while other models represent chronic EAE state making them similar to human disease. This review focuses on the role of non-coding RNAs (ncRNAs) in regulating immune cells and immune pathways responsible for MS pathogenesis. This review tackles miRNAs, lncRNAs and circRNAs as common regulatory non-coding RNAs (ncRNAs) modulating the expression of other genes/proteins. The impact of miRNAs and lncRNAs in MS pathogenesis has been extensively reviewed previously.

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Nevertheless, this review reports data investigating different models (MS patients and EAE) involving different samples (blood, serum, cerebrospinal fluid (CSF), oligodendrocytes, brain tissue) and reporting information regarding the method of assessment or the experimental design used in the involved studies. Finally, the review worked on exploring and concluding the possible interplay or areas of overlap between miRNAs and lncRNAs regulations and addressed the possible reasons for results discrepancies among reported data from different studies.

The research was conducted at the States National Library of Medicine (PubMed) to achieve the proposed goal. For the search in databases, the descriptors used were: “non-coding RNAs” or “microRNAs” or “miRNAs” or “lncRNAs” or “long non-coding RNA,” “circRNA,” and “Multiple sclerosis.” Research papers, books, and published data were reviewed for relevance to the review’s aim and summarized. The selection was made by reading abstracts first and then reading full-text articles to relevant publications. Criteria for inclusion were: complete, relevant publication, available online, in English, without a limit of the publication date, with detailed information about participants, methods, and analyses. Criteria for exclusion: duplicate publication and out-of-scope publications. Data abstracted were in the form of descriptive information, covering the type of samples used, type of patients, techniques, and findings or effects reported. Bias was limited by evaluating the studies through their internal validity rather than the conclusion.

2. Molecular pathogenesis of MS

MS is an idiopathic chronic inflammatory demyelinating disease of the central nervous system (CNS) with distinct numerous demyelinating lesions known as plaques. The exact etiopathogenesis of the disease is complex but known to be a mix of genetic, environmental, and immune factors [8]. Regarding the immunopathogenesis of MS, it is proposed to be a myelin-specific T cell attack that initiates an inflammatory process resulting in CNS demyelination. In 1986, the available facts led to the hypothesis that MS develops under the influence of a combination of factors causing demyelination in the CNS. These factors are (1) a genetically susceptible individual, (2) an environmental event resulting in a symptomless systemic illness, probably immune-mediator initiator, (3) a subsequent alteration of the blood-brain barrier (BBB), (4) a myelinoclastic plaque-forming mechanism in the CNS [9]. The pathogenesis has been reviewed extensively since then, and Fig. 1 simplifies the immune pathogenesis of the disease from peripheral activation leading to the destruction of the myelin sheath.

3. What are non-coding RNAs

Non-coding RNAs (ncRNAs) are RNA species beyond messenger RNA that appear to include a layer of internal signals that regulate various gene expression levels. The regulation could be chromatin architecture/epigenetic memory, transcription, RNA splicing, editing, translation, and turnover. These regulations may dictate most human complex characteristics and play a role in disease and genetic variation within

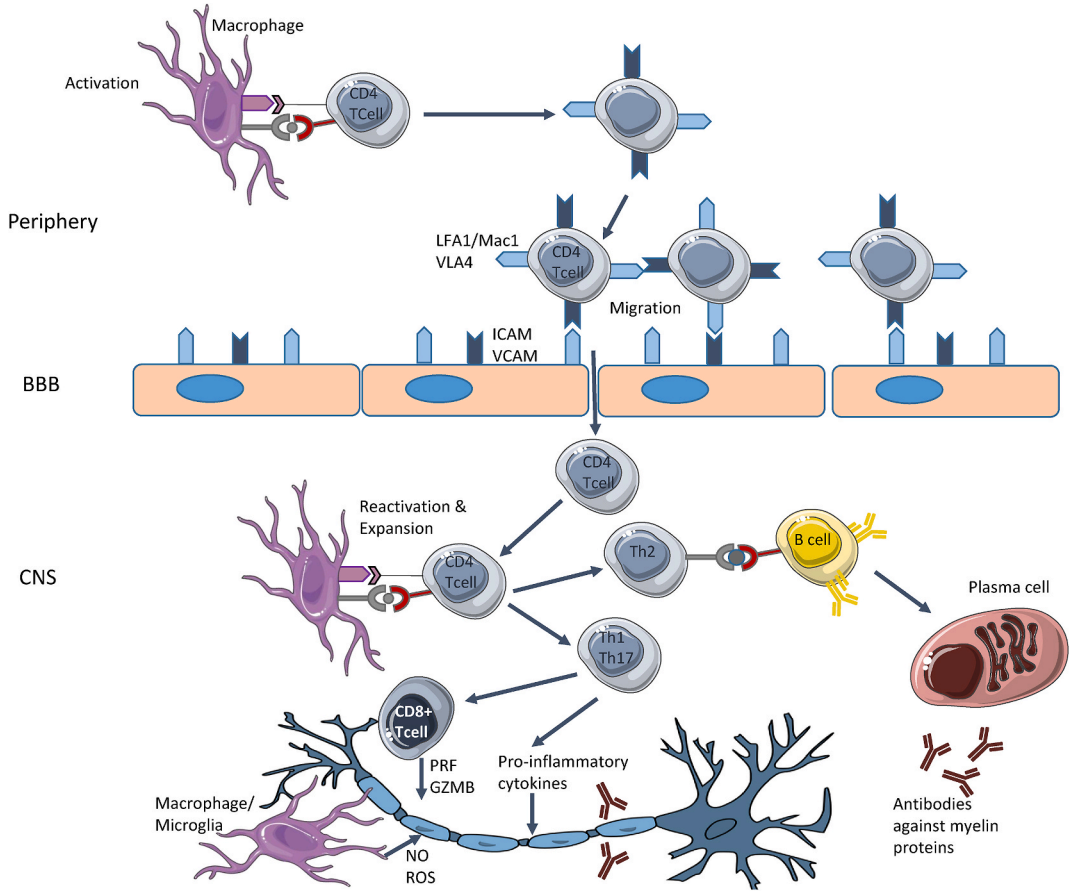

Fig. 1. Schematic diagram of possible pathogenesis of multiple sclerosis.
Lymphocytes activated in the periphery by a particular event will bypass the blood-brain barrier. Initially, they bind with the cell adhesion molecules present on the capillary endothelium and gain access into the brain. Once inside, the reactive cells activate the immune cell traffic (T-and B-cells) and mediate the devastating cascade. Cytotoxic T-cells release perforins and granzymes, and activated B-cells produce antibodies against the myelin sheath, thus mediating the demyelination process. Abbreviations: BBB, Blood-brain barrier, CNS, Central Nervous System, PRF, Perforin, GZMB, Granzyme B, NO, Nitric Oxide, ROS, Reactive Oxygen Species.

and between species [10]. According to function, ncRNAs are classified into two major categories: regulatory and structural ncRNAs [11]. Structural ncRNAs are rRNA and tRNA, while regulatory ncRNAs are further divided into three classes according to their sizes into small, medium, and lncRNAs, as illustrated in Fig. 2, showing the detailed classification of non-coding RNAs.

4. MicroRNAs

MiRNAs account for 1–5% of the human genome and regulate at least 30% of protein-coding genes [12,13]. It is known that miRNA plays a vital role in regulating gene expression hence modulating diverse cellular and metabolic pathways; however, the specific targets of miRNAs are not yet fully known [14]. They are small, evolutionary conserved, single-stranded, non-coding RNA molecules of less than 30 nucleotides in size. They usually bind to their target mRNA by base-pairing inhibiting protein production by either degradation or inhibition of translation of the mRNA [15]. Mature miRNA is generated through two-step cleavage of primary miRNA (pri-miRNA), which incorporates into the effector complex RISC. The degree of complementarity between the miRNA and mRNA dictates which silencing mechanism is employed [16].

4.1. Biogenesis

MiRNAs are derived from the double-stranded region of 60–70 nucleotides RNA hairpin precursor [17]. miRNAs are transcribed by RNA polymerase II or III generating pri-miRNA molecule, which is processed by the microprocessor complex comprised of DGCR8 and Drosha into precursor miRNA (pre-miRNA). This pre-miRNA is then exported to the cytoplasm in a nucleocytoplasmic transporter containing Exportin 5 and Ran-GTP. Following export, pre-miRNA is cleaved by Dicer to give miRNA duplex. This miRNA duplex releases the mature miRNA to assemble into the RISC loading complex consisting of Ago2, TRBP, PACT, and Dicer directing the silencing of the target mRNA through RNA interference (RNAi) [16]. Gene silencing could be at transcriptional

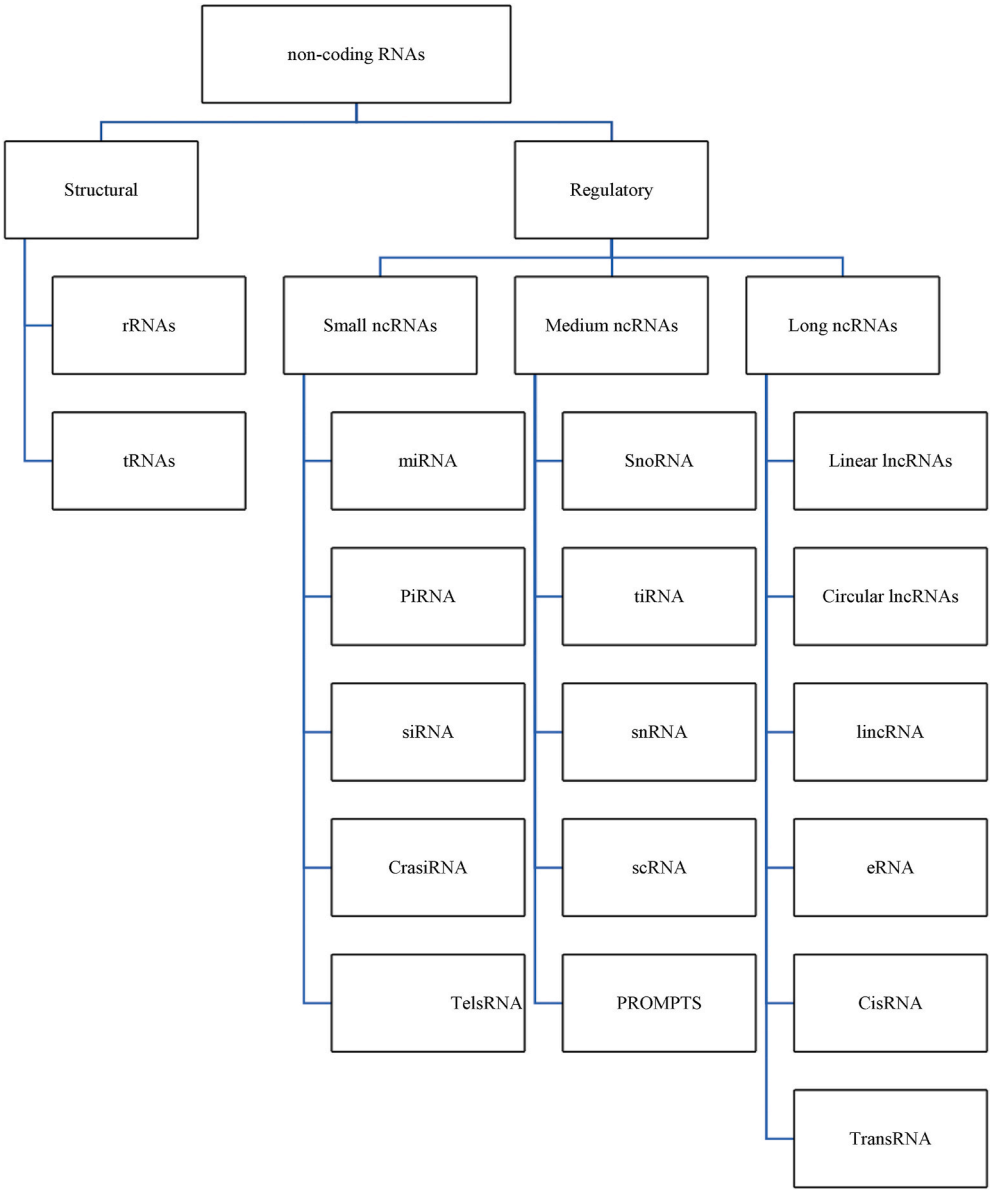

Fig. 2. Classification of non-coding RNAs.
Fig. 2 classifies non-coding RNAs into Regulatory and structural according to their functions. Further classification of regulatory ncRNAs occurs according to their size into small, medium, and long ncRNAs, while structural ncRNAs only have rRNAs and tRNAs.

gene silencing (TGS) or post-transcriptional gene silencing (PTGS) levels [18]. The TGS targets DNA by altering promoter or enhancer efficiencies, the methylation status of genes, and deleting gene sequences [19]. On the other hand, PTGS mechanisms rely on the breakdown of mRNA by using antisense RNA, ribozymes, DNases, miRNAs, and RNAi. RNAi is utilized to determine gene function and as part of therapeutic intervention to downregulate the expression of genes playing a role in disease pathogenesis [20]. Fig. 3 illustrates miRNA biogenesis and how it regulates mRNA expressions.

4.2. Beginning of miRNA research in MS

Multiple studies investigate the role of miRNAs in MS as it is suggested they are involved in the pathogenesis of MS. They are studied in circulation, brain tissues, immune cells, and CSF. The first miRNAs that were shown to be dysregulated in MS are miR-18b, miR-493, and miR-599 in patients experiencing a relapse compared to controls [21]. In the second study, miR-17 and miR-20a were discovered to be downregulated in MS patients and are known to regulate genes accompanied by T cell activation [22]. miR-145 was discovered in the third study and was seen to be the best single disease-specific miRNA marker with a specificity of 89.5% and sensitivity of 90% [23] and was discovered to decrease during disease transition from RRMS to SPMS [24,25]. The subsequent study was able to distinguish between different subsets of cells and showed that miR-17-5p was upregulated in $CD4^+$ T cells which correlated with changes in the expression of probable target genes of miR-17-5p as phosphatase and tensin homology (PTEN) and phosphatidyl-inositol-3-kinase (PI3K) regulatory subunit 1 [26,27]. The following study studied the expression of miR-34a, miR-155, and miR-326 in MS lesions and were found upregulated in active lesions compared to inactive ones. These miRNAs are thought to target and reduce CD47 in brain resident cells, causing the release of macrophages from inhibitory controls [28]. The following study identified 23 miRNAs differentially expressed in $CD4^+$CD25 high T regulatory cells from MS patients compared to controls. miR-106b and miR-25 had higher T-reg/T-effector cell ratios in MS patients, and they worked at silencing the TGF-β signaling pathway involved in the differentiation and maturation of T-regulatory cells [29].

4.3. MiRNAs in EAE, human brain tissue, and blood-brain barrier

4.3.1. EAE

MiR-326 was correlated with disease severity in EAE mice and MS patients. Using the EAE model; silencing miR-326 led to fewer Th17 producing cells and milder EAE, while the overexpression caused the opposite effect by inhibiting Ets-1; a negative regulator of Th17 differentiation [30,31]. MiR-23b was significantly under-expressed in the acute phase of EAE, and ectopic overexpression led to a defect in leukocyte migration and resistance to EAE. Further investigations showed that it suppresses leukocyte migration through targeting CCL7; the adoptive transfer of miR-23b decreased EAE severity as it inhibited the migration of pathogenic T cells to the CNS [32]. In reactive astrocytes, miR-409-3p and miR-1896 simultaneously induce the production of inflammatory cytokines via SOCS3/STAT3 pathway, enhancing chemotaxis of $CD4^+$ T cells and worsening EAE [33]. miR-140-5p was found downregulated in $CD4^+$ T cells of EAE mice and inversely related with disease progression and its overexpression inhibited Th1 cell development through the mitochondrial respiratory pathway, STAT1 hypermethylation, and GATA3 demethylation [34]. A recent study on EAE mice showed that the knockout of miR-17-92 and miR-106b protected against neuroinflammation through the downregulation of inflammatory cytokines in the spinal cord of double knockout mice and a decrease in Th17 cells [35]. miR-134-3p is found protective in MS as its overexpression in MS rats enhanced mitochondrial activity of neurons and $CD34^+$ cells proliferation and decreased cytochrome *c* content, inflammatory response, and cell apoptosis, all through inhibiting serine protease 57 (PRSS57) [36]. An interesting study reported the critical role of miR-125a-5p in regulating vitamin D receptor activity in EAE as its inhibition blocked the decrease of VDRs in the spinal cord of EAE mice and hence a new probable therapeutic intervention [37].

MiRNAs have been reported to play an essential role in disease remyelination, a crucial repair process that highly affects disease course [38]. Hence, the research into the mechanisms of miRNAs in MS is of great importance as they are a new avenue for targeted therapeutic approaches. miR-125a-3p is prominently upregulated in the active lesion of MS patients and OPCs (oligodendrocyte precursor cells) isolated from EAE mice, and this negatively affects remyelination through its direct interaction with Slc8a3 sodium-calcium membrane transporter; necessary for oligodendrocyte maturation [39]. Moreover,

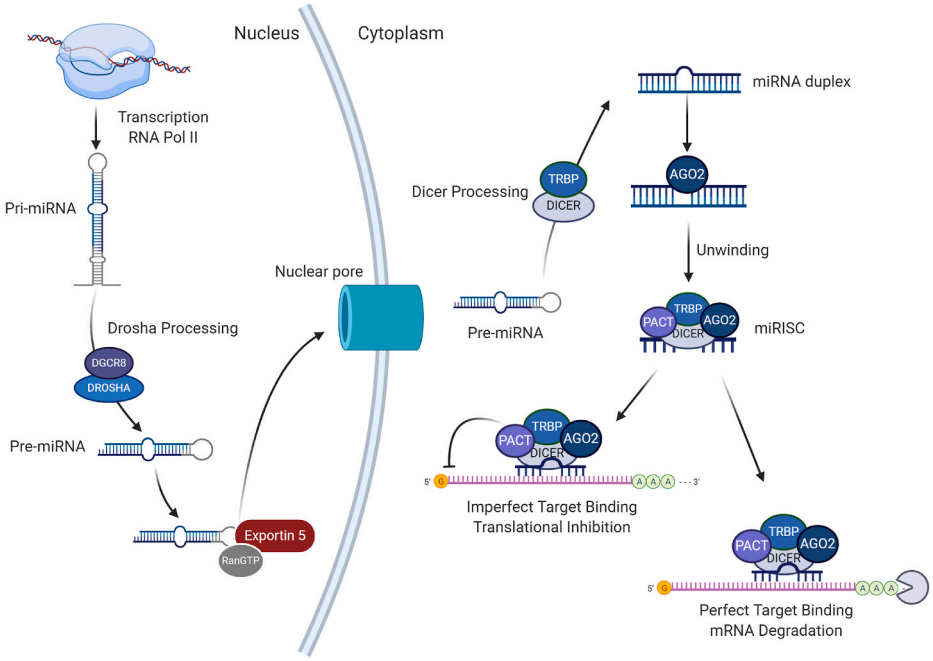

Fig. 3. MiRNA—biogenesis and function.
Fig. 3 Mammalian RNAi biogenesis and therapeutic opportunities. RNA polymerase II first transcribes a pri-miRNA transcript as primary miRNA, pri-miRNA. Pri-miRNAs are initially processed by the enzyme Drosha/DGCR8 into precursor miRNA (pre-miRNA), exported to the cytoplasm by Exportin-5, and cleaved by Dicer in a complex with Trbp. After strand separation, one strand of the miRNA, once loaded into the RNA-induced silencing complex (RISC), guides translation repression or degradation of the targeted mRNA. Created with BioRender.com.

miR-27a is a crucial regulator of oligodendrocyte development as increased levels of miR-27a leads to loss of myelination and remyelination, inhibition of OPCs proliferation through cell cycle arrest, and dysregulation of Wnt B-catenin signaling pathway [40].

4.3.2. Brain tissues/blood-brain barrier

Another set of studies looked at the brain tissues of MS patients where miRNA-125a-5p was found to play a role in BBB integrity. Its overexpression increases BBB tightness with thicker and more consistent tight junctions formed by vascular endothelial-cadherin (VE-cadherin) and zona-occludens-1 [41]. A mentioned earlier, miR-125a-3p was reported upregulated in active lesions of MS patients and negatively affects oligodendrocyte maturation [39]. A study on Iranian MS patients reported an increased expression of miR-142 isoforms in the white matter of MS patients and the spinal cord of EAE mice that could contribute to MS pathogenesis by interacting with SOCS1 and TGFβR1 [42].

4.4. Circulating exRNAs

4.4.1. CSF of MS patients

A study on CSF of MS patients showed consistent upregulation in miR-21 and miR-146a/b in Gd+ MS patients directly related to the number of Gd+ lesions; hence they represent a valuable biomarker for active MS lesions [43]. A large class III evidence study confirmed the upregulation of miR-181c and miR-663; they possess high diagnostic value in CSF of MS patients compared to patients with other neurologic disorders [44].

4.4.2. Serum/plasma of MS patients

Some studies researched the differential expression of miRNAs in plasma/serum of various classes of MS patients where miR-92a-1* was seen to be elevated in the plasma of RRMS patients compared to controls or SPMS patients. This miRNA's level could negatively correlate to disease duration and disability score, and according to ingenuity pathway analysis (IPA), it was predicted that miR-92 could target CD40 directly on immune cells and affect CD40 signaling [24]. The same study showed that let-7a was severely decreased in SPMS patients and could target Toll-Like Receptor 4 (TLR4) and TLR9 as well as Interleukin (IL-12RB2) and transforming growth factor-beta receptor 2 (TGF-βR2) as per IPA analysis [24]. Moreover, Let-7i was significantly increased in serum exosomes of MS patients. It was suggested to inhibit T regulatory cell induction via targeting insulin-like growth factor-beta receptor 1 (IGF1R) and transforming growth factor-beta receptor 1 (TGFBR1) as their expression is reduced in $CD4^+$ T cells of MS patients [45]. A study on Egyptian patients showed significant downregulation of miR-300 and miR-450b-5p expression in serum samples of RRMS and SPMS patients compared to healthy controls, strengthening their use as possible biomarkers for disease progression [46]. Serum miR-128-3p is reported inversely proportional to relapse rate as it was found to be upregulated in progressive compared to relapsing patients and higher in patients without relapses after sample collection than patients who experienced relapse [47]. Another study confirmed the upregulation of miR-155 and miR-146a in serum samples of MS patients compared to healthy controls and pointed that they are directly related to patients' EDSS and disease pathogenesis [48]. All these studies shine the light on new promising non-invasive biomarkers for disease activity that can be explored on larger cohorts.

4.4.3. Peripheral blood of MS patients

Most other studies looked for miRNA expression in peripheral blood immune cells. A study identified miRNA dysregulation in PBMCs of MS patients and concluded that miR-let-7d, miR-744, miR-93, miR-326, miR-21, miR-146a, miR-142-3p, miR-145, miR-146b, miR-200c and miR-125a were up-regulated while miR-328, miR-152, miR-199a, miR-1et-7g, miR-15a, miR-16-1 and miR-140-5p were down-regulated in MS patients compared to controls. By building a network of miRNAs and their susceptibility genes, they found that KRAS (an important MS susceptibility gene) is a possible target of miR-199a and that miR-142-3p could target IL7R and KRAS genes. These data suggest that miR-199a and miR-142-3p might act as MS therapeutic targets in the MAPK/JAK-STAT signaling pathway [49]. Using microarray analysis, a study by Yang et al. identified that miR-30a, miR-93, miR-20b, and miR-20a might be key players in MS pathogenesis. It also revealed that miR-328-3p was upregulated in MS patients targeting RAC2 that had downregulated tendency in MS while miR-20a-5p had upregulated tendency and its downstream target gene EIF4EBP2 also had the down-regulated tendency in MS patients [50]. A study by Martinelli-Boneschi et al. showed a significant decrease in miR-150 and miR-let-7g expression in MS and tried to identify their target genes, concluding that let-7g could target TLR4 and HIV-1 Tat interactive protein 2 (HTATIP2 or TIP30), which is usually overexpressed in MS chronic lesions. At the same time, miR-150 was found to target SOCS1, SPI1, and ephrinB2 (EPHB2) involved in the maturation of the immune system [51]. A study focusing on miRNA expression profile in PBMCs of SPMS patients confirmed the downregulation of miR-21-5p, miR-26b-5p, miR-29b-3p, miR-142-3p, and miR-155-5p and revealed that SOCS6 is targeted by most of the dysregulated miRNAs in SPMS patients, which are upregulated in their $CD4^+$ T cells and are involved in T cell activation regulation [52].

A study investigating the expression of prominent miRNAs in monocytes isolated from RRMS and PPMS patients reported upregulation of miR-146a, miR-223, miR-125a, miR-30c, and miR-23a in both patients' subtypes as compared to controls. miR-485 and miR-708 were reported significantly downregulated in RRMS patients compared to controls which correlated with upregulation of mRNA levels of survivin in $CD4^+$ T cells. This could explain the role of these miRNA in regulating apoptosis and, therefore, the persistent inflammatory milieu in MS patients [53]. While miR-181a was augmented in RRMS but not in PPMS patients compared to healthy controls, miR-124 was reduced in PPMS patients compared to controls and RRMS patients. Interestingly, miR-155 was found decreased in RRMS and PPMS patients compared to controls [54]. This increase in anti-inflammatory miRNAs and decrease in proinflammatory miRNAs in monocytes raises the idea that monocytes establish an anti-inflammatory/pro-regenerative response in MS or fluctuate through two distinct phenotypes during the disease course. Tables 1 and 2 summarize miRNAs in MS, showing their target proteins or pathways and their use as potential disease biomarkers.

Several miRNAs were found to enhance Th17 differentiation through different pathways. MiR-let-7e, miR-144, miR-155, miR-182, miR-183c, miR-200a, miR-233, miR-326, miR-384, miR-448, and miR-590 were found to increase Th17 differentiation through regulating various pathways such as IL-10 pathway, mTOR, Foxo1, IL-17, IFN-γ, HIF1α, PTPN2, tob1, CXCL3 and IL23R illustrated in Fig. 4. On the contrary, another group of miRNAs was found to modulate Th17 differentiation, including miR-let-7, miR-let-7f-5p, miR-15b, miR-20b, miR-26a, miR-132, miR-146, miR-301a, and miR-384 through regulating pathways and proteins such as STAT3, O-linked N-acetyl glucosamine transferase (OGT), RORγT, IL-6, IL7, IFN-γ, IL-21, IL1r1, Il23r, CCR2, CCR5 and PIAS3 as illustrated in Fig. 4 as well. Moreover, patients with MS have reduced expression of TGFβ signaling, reducing the ability of $CD4^+$ T cells to differentiate into T regulatory cells. The differential expression of miRNAs in those patients could be linked to the impaired TGFβ pathway. MiR-26a and miR-182 were reported to contribute to Treg differentiation through regulating Foxp3, as shown in Fig. 5. In addition, the TGFβ pathway was seen to be regulated by several miRNAs such as miR-let-7a, miR-let-7b, miR-let-7i, miR-21, miR-25, miR-27b, miR-106b, miR-128, miR-141, miR-142, miR-181c, miR-200a, and miR-500a leading to T regulatory cell differentiation as presented in Fig. 5 as well.

Table 1
MiRNAs in MS.
Table 1 lists the differentially expressed miRNAs in MS research stating their probable targeted pathway and the method of evaluation being either in vivo, in vitro, in-silico, or using bioinformatics software with the corresponding reference of the study.

miRNA	Expression	Pathway	Experiment	Reference
miR-125a-5p	Low	BBB integrity	In vitro	[41]
miR-92a-1*	High (plasma)	CD40 targeting	In vitro	[24]
miR-let-7a	Low	TLR4 and TLR9	In vitro	[24]
miR-145	Low	Disease Transition	In vivo	[23,24]
miR-17, miR-20a	Low	T cell activation	In vitro	[22]
miR-17-5p	High ($CD4^+$ T cells)	PTEN and PI3K regulatory subunit 1	In vitro and In vivo	[26,27]
miR-34a, miR-155, miR-326	High (active lesions)	CD47 on brain resident cells; macrophage activation	In vitro and In vivo	[28]
miR.106b, miR-25	High (CD127 low Tregs)	Silencing TGF-β pathway	In vitro	[29]
miR-326	High	Th17 differentiation through ets-1	In vivo	[30]
miR-199a	Low (PBMCs)	KRAS (MAPK/JAK-STAT)	Systemic analysis	[49]
miR-142-3p	High (PBMCs)	IL7R and KRAS (MAPK/JAK-STAT)	Systemic analysis	[49]
miR-328-3p	High	RAC2 (low in MS)	Systemic analysis	[50]
miR-20a-5p	High	EIF4EBP2 (low in MS)	Systemic analysis	[50]
miR-let-7g	Low	TLR4 and HTATIP2/TIP30 (high in chronic lesions)	Bioinformatics	[51]
miR-150	Low	SOCS1, SPI1 and EPHB2	Bioinformatics	[51]
miR-let-7i	High (serum exosomes)	Inhibit Treg induction via IGF1R and TGFBR1	In vitro	[45]
miR-27-b, miR-128, miR-141, miR-500a, miR-let7a, miR-let-7b	High (PBMCs)	TGFβR1 and TGFβ signaling in $CD4^+$ T cells hence Treg differentiation	In vitro	[92]
miR-142 isoforms	High (white matter of MS patients and spinal cord of EAE)	Targets SOCS1 and TGFβR1	In vitro and In vivo	[42]
miR-21-5p, miR-26b-5p, miR-29b-3p, miR-142-3p and miR-155-5p	Low ($CD4^+$ T cells of SPMS patients)	SOCS6/regulation of T cell activation	In vitro	[52]
miR-223	High (relapses)	Th17 differentiation	In vitro and In vivo	[110]
miR-301a	High (PBMCs)	NKRF and PIAS3 expressions	In vitro	[104]
	High ($CD4^+$ T cells)	Targets IL-6/IL-23-STAT3 pathway (PIAS3 is an inhibitor of STAT3)	In vitro and In vivo	[95]
		Induce inflammatory	In vitro and In vivo	[33]

Table 1 (*continued*)

miRNA	Expression	Pathway	Experiment	Reference
miR-409-3p and miR-1896	High (reactive astrocytes)	cytokines through SOCS3/STAT3		
miR-23b	Low	Leukocyte migration through targeting CCL7	In vitro and In vivo	[32]
miR-182	High	Modulates Foxp3 and Treg cell differentiation	In vitro and In vivo	[111]
Th17 and Th1 cells				
miR-590	High	Th17 differentiation via targeting tob1 of the tob/btg1 family; CXCl3, CDF2, and IL-23R	In vitro	[112]
miR-448	High	PTPN2 protein; triggering Th17 response	In vitro	[113]
Let-7e	High ($CD4^+$ T cells)	Enhance Th1/Th17 response through targeting IL-10	In vivo	[114]
miR-27a	High	Targets negative regulators of Th17 cell differentiation	In silico	[115]
miR-15b	Low ($CD4^+$ T cells)	Inhibit Th17 differentiation through targeting OGT	In vitro and In vivo	[116]
miR-132	Low ($CD4^+$ T cells)	The anti-inflammatory effect through inhibiting proinflammatory cytokine production	In vivo	[117]
miR-214	Low	Inhibits Th17 differentiation	In silico	[115]
miR-146a	Low	Inhibits IL-6 and IL-21; hence Th17 differentiation	In vitro and in vivo	[118]
miR-26a	Low	Targets IL-6, Foxp3 hence enhancing Treg and reducing Th17 differentiation	In vitro and in vivo	[102]
miR-181c	High	Smad7 and TGFβ signaling regulation	In vivo and in vitro	[89]
miR-141 and miR-200a	High	TGF-β, mTOR and JAK/STAT pathways modulation/Low Tregs and High Th17	In silico	[91]
miR-let-7f-5p	Low ($CD4^+$ T cells)	Targets STAT3	In vitro	[93]
miR-126/*		Regulate VCAM-1, E-selectin and CCL2	In vitro	[119]
miR-30a	Low ($CD4^+$ T cells)	Targets IL-21 receptor and Th17 differentiation	In vitro and in vivo	[120]
miR-384	High	RORγt (Th17 differentiation)	In vivo	[121]
miR-20b	Low (PBMCs)	RORγt and STAT3	In vitro and in vivo	[94]
miR-140-5p	Low	Inhibits Th1 differentiation through downregulation and hypermethylation of STAT1	In vitro	[34]
miR-21	High (Th17 cells)	Targets Smad7, Smad2/3 and Il-2 secretion	In vivo	[90]
miR-183c	High	Inhibits Foxo1	In vitro	[122]
miR-17-92 and miR-106b	High (spinal cord of EAE)	Increases Th17	In vivo	[35]

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Table 1 (*continued*)

miRNA	Expression	Pathway	Experiment	Reference
miR-134-3p	Low ($CD34^+$)	Inhibits PRSS57, enhances mitochondrial activity, decreases cytochrome *c* content, inflammatory response, and cell apoptosis	In vivo (rats)	[36]
miR-485 and miR-708	Low ($CD4^+$ T cells)	High survivin, persistent inflammatory milieu	In vivo	[53]
miR-125a-3p	High (active lesions of MS patients and OPCs from EAE)	Targets and inhibits remyelination	In vivo	[39]
miR-27a	High (OPCs and MS lesions)	Inhibits remyelination, OPCs proliferation, and dysregulates Wnt-B catenin pathway	In vivo and In vitro	[40]
Let-7	Low	Targets Il1r1, Il23r, Ccr2 and Ccr5	In vivo	[123]
miR-384	High	Targets IL17 secretion and Rorγt	In vivo	[124]
miR-140-5p	Low ($CD4^+$ T cells)	Targets mitochondrial respiratory pathways and DNA methylation	In vivo	[34]
miR-125a-5p	High	Modulates VDR expression	In vivo	[37]
miR-182	High	Increased IFN-γ production, repressed HIF1α, and increased TH1 and TH17	In vivo	[125]

5. Long non-coding RNAs

LncRNAs are non-coding RNAs ranging in length from 200 nts to 100 kilobases (kb) lacking specific open reading frames. RNA polymerase II transcribes them, and their expression levels are usually tissue-specific and lower than protein-coding genes. Surprisingly, recent studies showed that some lncRNAs have open reading frames, which could direct towards a translational ability to encode proteins [55,56]. lncRNAs have been associated with epigenetics, alternative splicing, nuclear import, serve as structural components, as precursors to small RNAs, and even regulators of mRNA decay [57].

5.1. EAE

LncRNA labeled 1700040D17Rik was found to be downregulated in EAE models, and studies revealed its function to be associated with Th17 cells differentiation through the regulation of RORϒT, a key transcription factor [58]. MALAT1 was investigated in EAE mice, and its expression was reduced in the spinal cords, activated splenocytes, and macrophages of diseased mice compared to controls. siRNA down-regulation of MALAT1 resulted in a shift in T cell differentiation pattern towards a Th1/Th17 profile, a decrease in T regulatory profile, and an increase in the M1 phenotype polymerization of macrophages. Hence, MALAT1 could have an anti-inflammatory effect in the context of autoimmune disease [59]. Another study investigated the role of TUG1 in MS by silencing and its downregulation enhanced mice behavior, reduced granulocyte-macrophage colony-stimulating factor (GM-CSF) level, reduced proinflammatory cytokines, and increased IL-10 in mice.

Table 2
MiRNAs as biomarkers in MS.
A list of the differentially expressed miRNAs in MS patients states the area of significance and the study's reference to being useful as disease biomarkers.

miRNA	Expression	Reference
miR-155 and miR 301a	Low (serum)	[106]
miR-326	High (serum)	[106]
miR-150	High (CSF)	[103]
miR-22-3p, miR-660-5p	High (serum exosomes of interferon treated patients)	[126]
miR-486-5p, miR-451a, miR-let-7b-5p, miR-320b and miR-122-5p	Low (serum exosomes of interferon treated patients)	[126]
miR-122-5p, miR-196-5p, miR-301a-3p and miR-531-5p	Low (serum exosomes)	[105]
miR-320a, miR-125a-5p, miR-652-3p, miR-185-5p, miR-942-5p and miR-25-3p	High (PBMCs)	[100]
miR-181c	High (CSF and serum)	[127]
miR-572	High (during relapses and SPMS patients)	[128]
miR-191-5p and miR-24-3p	High (serum)	[129]
miR-219	Low (CSF)	[130]
miR-20a-5p	Low	[99]
miR-26a	High (PBMCs)	[101]
miR-96	Higher is PBMCs of patients in remission (disease quiescence)	[131]
miR-18b	High	[132]
miR-497, miR-30a-3p and miR-149	Low ($CD8^+$ T cells)	[26]
miR-300, miR-450b-5p	Low (serum)	[46]
miR-128-3p	High in progressive and non-relapse patients (serum)	[47]
miR-155 and miR-146a	High (serum)	[48]
miR-146a, miR-223, miR-125a, miR-30c, miR-23a and miR-181a	High (monocytes)	[54]
miR-124 and miR-155	Low (monocytes)	
miR-21 and miR-146a/b	High (CSF)	[43]
miR-181 and miR-663	High (CSF)	[44]
miR-106a	Low (Peripheral blood)	[133]

TUG1 expression negatively correlates with miR-9-5p, positively with NF-κB1/p50, and it was verified that TUG1 negatively regulates miR-9-5p; hence NF-κB1/p50 is affected as a direct target of miR-9-5p [60]. Gm15575 is a proinflammatory lncRNA regulating Th17 function through acting as competing endogenous RNA for miR-686 and positively regulating CCL7 in TH17 differentiation in EAE [61].

5.2. Circulating exRNAs

5.2.1. Serum/plasma of MS patients

Studies on serum samples of MS patients reported increased expression in MALAT1 and lnc-DC lncRNA in RRMS and SPMS patients compared to controls, with SPMS patients showing higher differences to controls [62]. Another study reported upregulation in NEAT1, TUG1, and RN7SK RNA in RRMS patients [63], in TUG1 in SPMS patients, in long intergenic non-protein coding RNA 293 (LINC00293) and RP11-29G8.3 in PPMS patients, and downregulation in non-protein coding RNA 188 (LRRC75A-AS1) in PPMS patients, all compared to controls [64]. Moreover, lncRNA Growth arrest-specific transcript (GAS5) is upregulated in serum samples of MS patients. It positively correlates with disease severity while acting as a competing endogenous RNA for miR-137 that is downregulated in serum samples of MS patients and is a negative predictor of MS risk [65].

5.2.2. Peripheral blood of MS patients

Looking into the role of lncRNAs in different immune cells, lncRNA DDIT4 was found to be upregulated in PBMCs of MS patients compared to healthy controls with a 4.32-fold increase. Further experiments on naïve $CD4^+$ T cells proved that lncRNA DDIT4 regulates Th17 cell differentiation through targeting DDIT4 and the mTOR pathway [66]. Growth arrest-specific transcript (GAS5) was an epigenetic regulator of

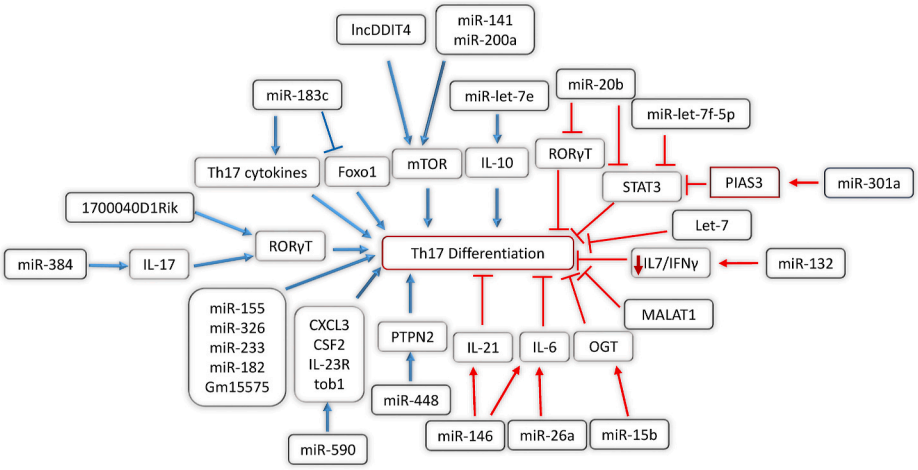

Fig. 4. ncRNAs enhancing Th17 cells differentiation.
Fig. 4 displays various miRNAs and lncRNAs that modulate Th17 differentiation by activating or inhibiting the pathway's proteins or surface receptors. Th17 differentiation is one of the critical players of MS pathogenesis.

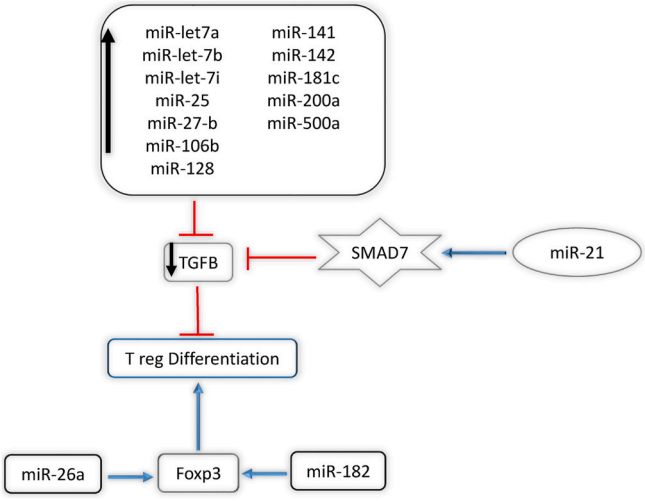

Fig. 5. miRNAs contributing to Treg differentiation.
Fig. 5 shows two miRNAs miR-182 and miR-26a, that contribute to T regulatory cells differentiation through the modulation of Foxp3, a transcription factor of T regulatory cells along with miRNAs that inhibit or halt the signaling of TGFB, which inhibits T regulatory cell differentiation contributing to MS pathogenesis.

microglial polarization by suppressing microglial M2 polarization. This may be done through GAS5 suppression of transcription of TRF4 by recruiting the polycomb repressive complex 2 (PRC2) and inhibiting M2 polarization [67]. Linc-MAF4 was found upregulated in PBMCs of MS patients and participates in the pathogenesis of MS with its main activities in regulating Th1/Th2 differentiation by inhibiting MAF, a Th2 cell transcription factor [68–70]. A recent study showed a consistent upregulation in MALAT1 in MS patients with its overexpression/knockdown experiments showing modulation in endogenous expression of splicing factors and alternative splicing of MS-associated genes possibly contributing to its pathogenesis [71].

Several studies reported expression levels of lncRNAs in peripheral blood for their use as promising biomarkers of the disease; NEAT1, TUG1, PANDA [72], THRIL [73], lnc-DC [74], APOA1-AS, IFNG-AS1 [75], PINK1-AS [76], GAS8 and GAS8-AS1 [77] were upregulated in RRMS patients. In contrast, lincR-Gng2-5-AS [78] was upregulated in both RRMS and SPMS patients correlating to disease severity (EDSS) and showing excellent diagnostic power. NEAT1 expression was inversely correlated with age at onset and disease duration in female patients, while TUG1 was inversely correlated with disease duration in females [72]. LincR-Epas1-3′AS was downregulated in peripheral blood of RRMS, and SPMS patients [78], PVT1, FAS-AS1 [73], lnc-MKI67IP, HNF1A-AS, LINC00305 [79], NR_003531.3 [80], SPRY-IT1, HOXA-AS2, LINC-ROR, and MEG3 [81] were significantly downregulated in peripheral blood of MS patients compared to controls with high diagnostic power. Tables 3 and 4 summarize lncRNAs in MS used as biomarkers and their target proteins or pathways.

6. Circular RNAs

Recently, another family of non-coding RNAs, circular RNAs, has emerged as a new player in the complex network of gene-expression

Table 3
LncRNAs in MS.
A listing of differentially expressed lncRNAs in MS research stating their probable targeted pathway and the method of evaluation being either in vivo, in vitro, ex vivo, in-silico, or using bioinformatics software with the corresponding reference of the study.

LncRNA	Expression	Pathway	Experiment	Reference
1700040D1Rik	Low	Th17 differentiation (RORϒT)	In vitro and In vivo	[58]
DDIT4	High (PBMCs)	mTOR	Ex vivo	[66]
GAS5	High (microglia)	Inhibit M2 polarization	In vitro and In vivo	[67]
Gm15575	High	Regulates CCL7 and Th17 differentiation	In vivo	[61]
Linc-MAF4	High (PBMCs)	Inhibit MAF	In vitro	[69]
MALAT1	Low (Spinal cord, activated splenocytes, and macrophages)	Increase in Th1/Th17 profile and decrease in Tregs and high M1 polarization	In vitro	[59,62]
PVT1	Low (EAE)	Sponge miR-21-5p, increase SOCS5, Treg cells, decrease JAKs/STAT3 pathway and Th17 cells	In vivo	[96]
TUG1	High	Regulates miR-9-5p and NF-κB1/p50	In vivo	[60,63,72]

Table 4
LncRNAs as biomarkers in MS.
A list of the differentially expressed lncRNAs in MS patients stating the area of significance (if stated) and the study's reference to being useful as biomarkers of the disease.

LncRNA	Expression	Reference
AC007182.6	Low (PBMCs)	[134]
AC007278.2	High ($CD4^+$ T cells)	[135]
AC009948.5	Low (PBMCs)	[134]
AK080435	Low	[136]
AL450992.2	Low (PBMCs)	[134]
AL928742.12	Low (PBMCs)	[137]
APOA1-AS and IFNG-AS1	High (Peripheral blood)	[75]
CPSF7	High (PBMCs)	[138]
CSTF2	Low (PBMCs)	[138]
FAS-AS1	Low (PBMCs)	[73]
GAS5	High (serum)	[65]
GAS8-AS1	High (Peripheral blood)	[77]
Gm14005	High (brain tissues and activated astrocytes)	[136]
Gm12478	High (brain tissues and activated astrocytes)	[136]
GSTT1-AS1	Low (PBMCs)	[139]
HULC	High	[140]
HUR1	High (PBMCs)	[138]
IFNG-AS1	Low (PBMCs)/high (high)	[135, 139]
LincR-Gng2-5	High (Peripheral blood)	[78]
LincR-Epas1-3′AS	Low (Peripheral blood)	
lincRNA0681	Low	[136]
lincRNA117	Low	[136]
Lnc-DC	High (Peripheral blood)	[62,74]
Lnc-MKI67IP, HNF1A-AS and LINC00305	Low (Peripheral blood)	[79]
NEAT1	High (Peripheral blood)	[63,72]
NR_003531.3	Low (Peripheral blood)	[80]
PANDA	High (Peripheral blood)	[72]
PINK1-AS	High (Peripheral blood)	[76]
PVT1	Low (PBMCs)	[73]
RN7SK	High	[63]
RP11-126K1.6	High (PBMCs)	[134]
RP11-530C5.1	High (PBMCs)	[137]
RP11-98D18.3	Low (PBMCs)	[134]
SPRY-IT1, HOXA-AS2, LINC-ROR and MEG3	Low (Peripheral Blood)	[81]
THRIL	High (PBMCs)	[73]
TUG1, LINV00293 and RP11-29G8.3	High (Serum)	[64]
LRRC75A-AS1	Low (Serum)	

regulation. They have the unique ability to inhibit miRNAs by blocking their activity and acting as sponges, and neutralizing them [82]. This regulating role and high stability in biofluids make them seemingly good candidates as biomarkers. They are classified according to their origin or relationship to adjacent coding RNAs and hence appear to be a complex group of transcripts of crucial biological roles [83].

6.1. Circulating exRNAs

Cardamone et al. identified over 400 differentially expressed circRNAs in PBMCs of RRMS patients compared to healthy controls, and in particular, circ_0106803 showed 2.8-fold upregulation in RRMS, which was generated by the alternative splicing abnormality of the Gasdermin B gene [84]. Expression profile of circRNAs comparing peripheral blood leukocytes of MS patients and controls revealed the downregulation of circ_0005402 and circ_0035560 inside ANXA2 gene in patients suggesting its use as biomarkers of the disease [83]. Moreover, Paraboschi et al. reported upregulated expression of circ_0043813, derived from STAT3, and plays a vital role in MS disease activity [85]. Candidate circRNA biomarkers for MS were reported by RNA sequencing of leukocytes from MS patients and healthy controls, concluding PADI4, ABCA13, AFF2, NEIL3, AGFG1, and ATP8B4 circRNAs as potential biomarkers for MS [86]. Another group analyzing circRNAs in PBMCs of MS patients and healthy controls showed the downregulation of circ_0000478 and circ_0116639 in patients compared to controls suggesting their use as biomarkers [87]. Another recent paper shed light on the mechanistic role of circINPP4B in promoting TH17 differentiation and progression of EAE through targeting miR-30a, suggesting a potential therapeutic target of Th17 mediated MS [88]. Table 5 summarizes circRNAs in MS and their differential expression for use as biomarkers.

7. Cross-over between regulation of lncRNAs and miRNAs in MS

A correlation between TUG1 and miR-9-5p was concluded as they were negatively correlated and resulted in a consequent effect on NF-κB1/p50 that is a direct target of miR-9-5p [60]. It is interesting to highlight a pathway regulated by various miRNAs in the setting of MS disease. MiR-let-7i inhibited TGFBR1, miR-181c decreased TGFB signaling, and miR-21 regulated it through SMAD7, a negative regulator of TGFB [45,89,90]. Moreover, an in-silico analysis showed that TGFB could be a target for miR-141 and miR-200a [91]. Another analysis of miRNAs in PBMCs from MS patients concluded that the up-regulation of miR-27b, miR-128, miR-141, miR-500a, miR-let7a, and b could be correlated to the disrupted signaling of TGFB [92]. Another protein noticed with multiple miRNAs interactions in MS is the STAT3 transcription factor. It is inhibited by miR-let-7f-5p, miR-20b, and regulated indirectly by miR-301a through its action of PIAS3, which inhibits STAT3 [93–95]. Some lncRNAs act as competing endogenous RNAs for miRNAs such as Gm15575 and GAS5 for miR-686 and miR-137, respectively [61,65]. Along with its effect on miR-686, Gm15575 positively regulates CCL7 enhancing Th17 differentiation in EAE while miR-23b was found to suppress CCL7 inhibiting the migration of pathogenic T cells in EAE development [32,61]. An interesting correlation is the role of PVT1 lncRNA in regulating Th17 cell response in EAE by sponging miR-21-5p, upregulating SOCS5, and inactivating the JAKs/-STAT3 pathway providing a potential therapeutic pathway [96]. These observations open the door to new investigations studying which ncRNA would have the upper hand in regulating those pathways influencing MS pathogenesis.

8. Possible factors affecting expressions of ncRNAs

8.1. MALAT1

From reviewing the lncRNAs in MS disease, some lncRNAs have the potential to be used as biomarkers such as linc-MAF4, lnc-DC, NEAT1, TUG1, PANDA, RN7SK, and MALAT1. However, studies on MALAT1 showed discrepancies as an investigation on EAE mice showed decreased expression of MALAT1 in spinal cords, activated splenocytes, and macrophages, while the study investigating human serum showed increased expression of MALAT1 [59,62,71]. The differences could be due to the differences between the mouse model and the actual disease in humans or due to distinct mechanisms in immune cell content and

Table 5
CircRNAs as biomarkers in MS.
A list of differentially circRNAs in MS patients stating the area of significance (if stated) and the study's reference to being useful as disease biomarkers.

CircRNA	Expression	Reference
Circ_0106803	High (PBMCs)	[84]
Circ_0005402, circ_0035560	Low (PBMCs)	[83]
Circ_0043813	High	[85]
PADI4, ABCA13, AFF2, NEIL3, AGFG1 and ATP8B4 circRNA	High (PBMCs)	[86]
Circ_0000478, circ_0116639	Low (PBMCs)	[87]
CircINPP4B	High	[88]

their secretory ability of ncRNAs. This is confirmed by other studies on SLE and RA patients showing increased expression of MALAT1 in circulation [97,98].

8.2. miR-17-92 cluster

Moreover, while reviewing the role of miRNAs in MS, a contradiction was found regarding the role of miR-17 in MS as the study by Cox et al. showed decreased expression of miR-17 in the peripheral blood of MS patients while the study by Lindberg et al. reported increased expression in $CD4^+$ T cells of MS patients. This could be the result of differences in methodology as Cox et al. used PAXgene RNA tubes that stabilize RNA on collection and include a high portion of neutrophil RNA due to the whole blood collection, while Lindberg study used RNeasy mini kit on isolated $CD4^+$ T cells and the resultant RNA could be very labile during the time needed to purify miRNA. Also, the pool of patients used differs as Lindberg et al. had 23 RRMS patients against 20 controls while Cox et al. performed the study on 59 MS patients of all subtypes and 37 controls [22,26]. miR-20a was also discussed in the study by Cox et al. and reported to be downregulated in MS patients, while the study by Yang et al. reported upregulated tendency of miR-20a-5p in MS patients compared to control. However, this was concluded from a qPCR experiment on whole blood samples from 3 patients vs. 3 controls and contradicted their results from microarray analysis that pointed to the downregulation of miR-20a in MS patients; hence the probability of low miR-20a expression is more robust [22,50]. Moreover, Keller et al. confirmed the downregulation of miR-20a-5p in whole blood samples of RRMS/CIS patients compared to healthy controls [99]. Since miR-20a is part of the miR-17-92 cluster, it suggests that the expression of miR-17 follows the same pattern as miR-20a and is under-expressed in MS patients.

8.3. miR-125a

miR-125a-5p showed a compelling contradictory expression in brain capillaries of MS as opposed to PBMCs or active lesions from MS patients. A study by Reijerkerk et al. showed decreased expression of miR-125a-5p in brain capillaries from post-mortem MS patients' samples vs. controls. Upon in vitro studies using brain endothelial cell lines, knockdown of miR-125a-5p reduced the barrier-enhancing effect of astrocytes and altered expression of VE-cadherin. Previous findings support this result as miR-125a-5p inhibits the proinflammatory protein, endothelin-1 expression in vascular endothelial cells. Important to mention, this study was performed using a total of 4 specimens, 2 PPMS and 2 SPMS patients vs. controls [41]. However, numerous studies confirm the upregulation of miR-125a, both -3p or -5p, in PBMCs [49], monocytes [54], active lesions of MS patients [39] and EAE [37,39]. Moreover, another study by Nuzziello et al. showed upregulated expression of miR-125a-5p in PBMCs of MS patients not specifying subtypes but untreated compared to controls. The study employed 40 patients and 40 controls, making the results robust [100]. Hence, the upregulation of miR-125a seems to be a more robust conclusion.

8.4. miR-26a

A study on 40 MS Egyptian patients and 20 controls reported increased expression of miR-26a in whole blood samples of patients compared to control [101]. However, a previous study examined the expression of miR-26a in PBMCs of RRMS patients and concluded an under-expression in all MS patients [102]. The difference in results could be due to a limited number of clinical subjects, differences in disease stages of subjects, the heterogeneity in the miR26 family members, or the genetic polymorphism between the different subjects' nationalities.

8.5. miR-150

miR-150 has shown differences in expression between CSF, serum, and PBMCs of MS patients. A study investigating the potential of miR-150 to act as a biomarker in CSF fluids showed increased expression of miR-150 in cell-free CSF samples of MS patients compared to controls correlating with immunologic parameters and inflammatory properties. However, treatment of those patients with Natalizumab caused reduced miR-150 expression in CSF but a surprising increase in plasma expression. This could be explained by the suggestion that miR-150 is released by immune cells, and these differences are owed to drug-induced changes in immune cell numbers in both compartments, CSF and plasma [103]. Moreover, a previous study by Martinelli-Boneschi concluded reduced expression of miR-150 in PBMCs of MS patients, suggesting that miR-150 is actively stored in immune cells and its export has a significant role in disease pathogenesis [51]. However, further studies with larger cohorts need to be done to conclude the potential diagnostic and prognostic use of miR-150 in biological fluids.

8.6. miR-142 and miR-21

miR-142-3p was reported downregulated in isolated $CD4^+$ T cells from SPMS patients while found upregulated in another study investigating miR-142-3p in PBMCs of RRMS and its relation with the function of T regulatory cells [49,52]. This difference could be owed to the nature of the secondary progressive disease compared to the RRMS and the higher average disease duration between the two cohorts. A similar difference was seen in the expression of miR-21 in $CD4^+$ T cells of SPMS patients, where it was reported downregulated while overexpression of miR-21 was reported in Th17 differentiating cells of RRMS patients [52,90]. However, a small amount of miR-21 was found in other subsets of T cells in RRMS patients, suggesting that samples are PBMCs or total $CD4^+$ T cells could yield results different from those concluded from single subsets of T cells.

8.7. miR-301a

We came across two studies discussing the upregulation of miR-301a in $CD4^+$ T cells from MS patients or EAE models and how it contributes to Th17 differentiation [95,104]. However, another study by Selmaj et al. reported the decreased expression of exosomal miR-301a in RRMS patients, especially patients encountering relapses [105]. This could be owed to miR-301a export and secretion in exosomes is decreased in patients with RRMS, and miR-301a stays in the immune cells to perform its functions. Moreover, another study evaluated the serum expression of miR-301 in RRMS patients and reported under expression, which increases relatively during the post-acute phase than during the stable phase of remission [106]. The expression differs depending on the inflammatory stage could be the reason for the discrepancies in the in vitro or in vivo experiments, mainly evaluating biomarkers around or just after induction of disease or inflammation.

8.8. miR-155

An interesting case is seen with miR-155 as it is reported under-expressed in serum of RRMS patients with lower expression in stable patients than post-acute patients [106] and monocytes of RRMS and PPMS patients compared to controls [54]. On the contrary, another study reported miR-155 overexpressed in serum samples of MS patients [48] and inactive lesions of RRMS patients compared to the inactive lesion and normal controls. This could suggest that miR-155 plays a role in the inflammatory process of the disease; hence is increased during an active inflammatory phase or relapse phase and decrease during the stable phase [28]. Moreover, the decreased serum levels could be explained by the process of miR-155 secretion by immune cells is an active process that is dysregulated in RRMS patients. Additionally, a

difference in the time of sample withdrawal from the last relapse or last therapeutic dose could yield such a difference in conclusions. On a side note, miR-155 was reported under-expressed in $CD4^+$ T cells of SPMS patients, and as mentioned previously, this could be due to the difference in nature of the two disease subtypes where the RRMS is more prone to the inflammatory profile than the SPMS and the apparent difference of duration of disease [52].

9. Limitations of miRNA/lncRNA as biomarkers/therapeutics for MS

The main issue in dealing with MS is that the disease is heterogeneous and for the diagnosis to be confirmed, a patient might have been experiencing the disease for several years. Also, the treatments do not necessarily work well with all patients, and there is no specific disease biomarker to reflect the prognosis following a particular treatment; hence a period of at least 6 months to a year needs to be given to consider a treatment ineffective. This is a lot of lost time for the patient with a demyelinating disease; however, with the current advances in understanding the pathogenesis of the disease and looking into the molecular and genetic contributions, a more focused approach in developing new therapies can be implemented with a brighter outlook for future therapies.

Some of the research limitations that appear in the MS field are that the EAE mouse model and other murine models will always show differences compared to the human disease; hence, the conclusions brought about from EAE studies will need to be verified somehow to show effectiveness in humans. A new direction of studies is emerging where scientists focus on biomarkers of therapeutic response to shorten the period of therapy trial where patients usually have to wait for at least 6 months to decide if the therapy is effective. In light of this, several studies are investigating serum, plasma, and blood expression of miRNAs in responders and non-responders of therapeutic agents [107–109]. Moving forward with this, the field requires several studies to have enough evidence for using specific ncRNAs as prognostic biomarkers of therapeutic efficacy. A patient is tested for that biomarker and can assume with particular specificity whether he will respond to a specific treatment or not.

This review worked on summarizing, evaluating, and concluding the roles of regulatory miRNAs and lncRNAs in MS pathogenesis. This shed light on a promising axis of molecular pathways that needs further investigation into how they contribute to MS pathogenesis and target them therapeutically. Moreover, the review pointed out certain overlaps between miRNA and lncRNA regulations for interesting studies reviewing which one has the upper hand in regulating such a pathway, which will be better as a therapeutic target. Nevertheless, due to disease heterogeneity, contradictions in the field have been spotted, and probably reasons were suggested for future references and discussions. Altogether, miRNAs and lncRNAs possess a crucial role in regulating disease pathogenesis, and understanding their interactions would aid in better targeting them therapeutically.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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