Long Non-Coding RNAs, Novel Offenders or Guardians in Multiple Sclerosis: A Scoping Review

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Multiple sclerosis (MS), a chronic inflammatory demyelinating disease of the central nervous system, is one of the most common neurodegenerative diseases worldwide. MS results in serious neurological dysfunctions and disability. Disturbances in coding and non-coding genes are key components leading to neurodegeneration along with environmental factors. Long non-coding RNAs (lncRNAs) are long molecules in cells that take part in the regulation of gene expression. Several studies have confirmed the role of lncRNAs in neurodegenerative diseases such as MS. In the current study, we performed a systematic analysis of the role of lncRNAs in this disorder. In total, 53 studies were recognized as eligible for this systematic review. Of the listed lncRNAs, 52 lncRNAs were upregulated, 37 lncRNAs were downregulated, and 11 lncRNAs had no significant expression difference in MS patients compared with controls. We also summarized some of the mechanisms of lncRNA functions in MS. The emerging role of lncRNAs in neurodegenerative diseases suggests that their dysregulation could trigger neuronal death via still unexplored RNA-based regulatory mechanisms. Evaluation of their diagnostic significance and therapeutic potential could help in the design of novel treatments for MS.

Keywords: lncRNAs, multiple sclerosis, neurodegenerative disease, polymorphism, expression

INTRODUCTION

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system (CNS) and one of the most common neurodegenerative diseases worldwide (1). Pathogenic mechanisms underlying MS development have not been determined up to now. Clinically, different MS subtypes have been identified, including relapsing–remitting (RR), secondary progressive (SP), and primary progressive (PP) subtypes. These subtypes are heterogeneous among
affect individuals in terms of clinical course as well as genetic background (2). Complex interactions between genetic susceptibility and environmental factors lead to this neurodegenerative disease. Both innate and adaptive immune-mediated inflammatory mechanisms contribute to the demyelination and neurodegeneration in the context of MS. Previous studies have demonstrated that the inflammatory immune cells such as CD4 T-helper cells (Th1 and Th17) are the main contributors in disease pathogenesis (3, 4). The presence of these cells in the CNS is associated with neuronal demyelination, which can subsequently result in neuroinflammation and neurodegeneration (5, 6). Th17 cells that produce IL-17 are regarded as important inflammatory effectors in this disorder (7). However, the impact of Th17 cells in the pathogenesis of MS is not entirely dependent on the production of this cytokine, and it is supposed that an array of inflammatory factors is responsible in this regard (8). For example, expression of high amounts of the C-C chemokine receptor 6 (CCR6) on the cell surface of Th17 cells (9) facilitates the entry of these cells into the CNS via the choroid plexus (10). Th17 cells also participate in the pathoetiopathology of MS through production of other proinflammatory cytokines including TNF-α (11).

In recent years, genome-wide association studies (GWAS) and genetic mapping have nominated several candidate loci and variants in autoimmune conditions. However, MS pathogenesis cannot be explained by the genetic susceptibility factors alone. A large amount of evidence has revealed that long non-coding RNAs (lncRNAs) have critical roles in the regulation of cellular immunological pathways and autoimmunity. This new class of non-coding RNA (ncRNAs) contains a large part of the transcriptional output in the human genome but low protein-coding potential (12).

In the current review, we focus on recent reports performed on the roles of lncRNAs in MS pathogenesis. Then, we illustrate the role of some specific lncRNAs and their target genes. Therefore, our manuscript provides new insights into understanding the molecular etiology, diagnosis, and management of MS.

**Long Non-Coding RNA Classification and Function**

lncRNAs are a class of ncRNAs with sizes more than 200 nt and no protein-coding potential. They are commonly transcribed by RNA Pol II (13). lncRNAs have been detected in a variety of species such as animals, plants, and prokaryotes. The majority of them have a 5' cap structure, multiple exons, and 3' polyadenylated tails and are spliced in a way similar to mRNAs (14). Since lncRNAs do not encode proteins, they used to be called as “dark matter.” However, recent studies have demonstrated that they are regulatory molecules and play important roles in several biological processes (14, 15), including gene expression at the epigenetic, transcriptional, and posttranscriptional levels. The vital mechanisms of epigenetic regulation consist of DNA methylation, histone modification, and ncRNA-mediated regulation. Emerging evidence revealed that the normal execution of biological events is controlled by a combination of ncRNAs and transcription factor (TF)-mediated epigenetic modifications (16). Studies on the role of lncRNAs suggest that their dysregulation could trigger neuronal death via still unexplored RNA-based regulatory mechanisms (17). Gene signature in human CNS is precisely regulated by several mechanisms. LncRNAs have a substantial impact on normal neural development, so their abnormal expression affects development and progression of neurodegenerative diseases (18).

According to databases such as the NONCODE (version v5.0) (19), the number of lncRNAs in human has been estimated to be higher than the number of protein-coding genes. The classification of lncRNAs is based on subcellular localization, function, interaction with the protein-coding gene, their size, and their association with protein-encoding genes. Based on their association with protein-encoding genes, they can be categorized to different classes such as sense, intergenic, bidirectional, intronic, antisense, and divergent lncRNAs (20, 21). Long intergenic non-coding RNA (lincRNA) genes are an important group of ncRNAs that participate in many biological processes, such as regulation of gene expression. They also play an essential role in many autoimmune and inflammatory diseases (22). In the current study, we performed a systematic analysis of the role of lncRNAs in MS.

**METHODS**

Review question: Which lncRNAs have been dysregulated in multiple sclerosis?

**Inclusion/Exclusion Criteria**

The inclusion criteria were as follows: 1) original studies, 2) studies focusing on the expression of lncRNAs in MS patients, 3) studies that confirmed results by RT-PCR, 4) studies with a sample of blood or tissue of human or animal model, and 5) studies that evaluated polymorphisms on lncRNAs. The following documents were excluded from this study: letters, reviews, *in vitro* studies, or papers with insufficient data.

**Search Strategy**

The current scoping review was performed according to the PRISMA statement (23). PubMed, Web of Science, ProQuest, and Scopus databases were searched to identify all published studies up to August 10, 2021.

**Study Selection**

Following the abovementioned search method, all obtained papers were loaded into EndNote version 20. Then, duplicate studies were removed. The title and abstracts of the remaining studies were evaluated, and their full texts were screened using the inclusion criteria. Then, lncRNAs with a role in the pathogenesis of MS were included.

**Data Extraction**

The required data were extracted using a self-constructed data extraction table. Author and year of publication, origin, sample...
type, studied patients, method for lncRNA analysis, identified lncRNAs and expression pattern, and polymorphisms were extracted from the studies. 

Figure 1 shows the flowchart of the study.

RESULTS

As shown in Figure 1, a total of 931 studies were identified through searching PubMed, Web of Science, ProQuest, and Scopus databases, and 26 studies were identified from other databases. After removing duplicated articles, 716 studies remained. In the next step, based on the evaluation of titles and abstracts, 656 studies were excluded and 60 studies remained. The full text of the articles was evaluated based on our inclusion criteria. After evaluation of the full text, seven studies were removed due to lack of inclusion criteria. At last, 53 studies conducted on both human samples and animal model (45). Also, 7 studies used animal models (45, 71)–76), 5 studies were in Egypt (37, 62)–76), while 9 other studies analyzed polymorphisms (version 5.2), and Ensemble genome browser 99, LincR-Gng2-5' is located on chromosome 14q22.1 on the plus strand and has a transcript size of 1,233 bp. LincR-Epas1-3'as is located on chromosome 2p.21 on the positive strand and has 758 bp length. They are located in an important place rich in genes with immune regulatory functions. Since they act as enhancers, they might participate in the regulation of neighboring genes, thus modulating immune responses (63). LincR-Gng2-5' is upregulated in MS patients, while LincR-Epas1-3'as is downregulated in these patients. Dysregulation of these lncRNAs has a role in the pathobiology of MS through affecting the balance between Th1 and Th2 cells (22, 81). LincR-Ccr2-5'AS is another lncRNA that is expressed in Th2 and has association with GATA-binding protein 3 (GATA3), the "master regulator" of Th2. Shaker et al. have reported the downregulation of lincR-Ccr2-5'AS in MS patients and the subsequent decrease in the production of Th2 cytokines (64).

GSTM1-AS1 and IFNG-AS1
Glutathione S-transferase, Theta1-Anti Sense1 (GSTM1-AS1), also known as lncRNA-CD244, is a novel 284-bp lncRNA, located on the minus strand 22q11.23 with partial overlap with 5' UTR of the GSTT1 gene (19, 82). This lncRNA was originally discovered as an lncRNA with a crucial role in the pathogenesis of tuberculosis (83). Ganji et al. show downregulation of GSTT1-AS1 in MS patients. Since this lncRNA suppresses the expression of TNF and INFγ through recruitment of the epigenetic complex PRC2 and via the EZH2 enzyme complex, it might be involved in the pathogenesis of MS (36).

IFNG-AS1 has been firstly identified as a transcript with a possible role in the regulation of immune system function (84). Also known as Tmevpg1, it is a 1,791-bp intergenic lncRNA located on the plus strand on 12q15 (19), adjacent to the INFγ gene (85). It has been shown to be dysregulated in several immune-related disorders (83, 86). This lncRNA acts as an important checkpoint for the expression of IFNG in Th1 cells (87).

AC007278.2 (Expression in T Cells)
Another lncRNA is a 1,200-bp intronic lncRNA, AC007278.2, also known as Lnc-IL18R1-1. This lncRNA is located on the plus strand of the 2q12.1 chromosome and has two exons (19). AC007278.2 has a specific expression in Th1 cells. It is located within the introns of the protein-coding genes IL18RAP and IL18RI, with important roles in Th1 cell differentiation (43).
FIGURE 1 | Flowchart of the study (23).
| Author          | Year | Origin    | LncRNA measurement technique | Sample type | Number of studied patients | Identified lncRNA/expression pattern | Polymorphism                  | Ref               |
|-----------------|------|-----------|-------------------------------|-------------|---------------------------|------------------------------------|-----------------------------------|------------------|
| Bahrami et al.  | 2021 | Iran      | RT-PCR                       | PBMCs       | 50 RRMS                   | Lnc-DC †                           | TRPM2-AS1, rs933151, HNF1A-AS1, rs7953249 | (24)             |
| Bahrami et al.  | 2020 | Iran      | T-ARMS PCR                   | PBMCs       | 50 controls               |                                    |                                   |                  |
| Bina et al.     | 2017 | Iran      | RT-PCR                       | PBMCs       | 300 patients              | Inc-IL-7R [NS]                      |                                   |                  |
| Cardamone et al. | 2019 | Italy     | Microarray assay validation  | PBMCs       | 190 cases, 182 controls   | MALAT1 †                           |                                   |                  |
| Dastralchi et al.| 2018 | Iran      | RT-PCR                       | PBMCs       | 50 RRMS                   | NEAT1 †                            | TUG1 †, PANDA †, LCA1 †, CCAT2 †, TOB1-AS1 † |                  |
| Dastralchi et al.| 2018 | Iran      | TaqMan RT-PCR                | PBMCs       | 50 RRMS                   |                                    | MALAT1 †                           |                  |
| Dehghanzad et al.| 2020 | Iran      | RT-PCR                       | PBMCs       | 32 controls               |                                    |                                   |                  |
| Eftekharian et al.| 2019 | Iran      | T-ARMS-PCR Confirmed by the Sanger method | PBMCs | 428 MS                   | GAS5 †                             | MALAT1 rs619586, rs3200401, rs2607079, rs6790 | (32)             |
| Eftekharian et al.| 2019 | Iran      | T-ARMS PCR                   | PBMCs       | 505 controls              |                                    |                                   |                  |
| Eftekharian et al.| 2019 | Iran      | TaqMan RT-PCR                | PBMCs       | 410 controls              |                                    |                                   |                  |
| Eftekharian et al.| 2017 | Iran      | TaqMan RT-PCR                | PBMCs       | 50 RRMS                   | THRIL †                            | FAS-AS1 †, PVT1 †                  |                  |
| Fenoglio et al. | 2018 | Italy–Belgium | Real-time PCR validated with TaqMan and lastly confirmed by droplet digital PCR | PBMCs | 27 RRMS, 13 PPMs, 31 controls, 50 RRMS, 50 controls, 72 MS, 28 controls | MALAT1 †, MEG9 †, NRON †, ANRIL †, TUG1 †, XIST †, SOX2OT †, GOMAFU †, HULC †, BACE-1AS †, GSTT1-AS1 †, IFNG-AS1 †, RMRP †, APOA1-AS1 †, IFNG-AS1 † |                  |
| Ganji et al.    | 2019 | Iran      | RT-PCR                       | PBMCs       | 13 RRMS                   |                                    |                                   |                  |
| Ghaidi et al.   | 2020 | Egypt     | RT-PCR                       | PBMCs       | 72 MS                     |                                    |                                   |                  |
| Ghareasouran et al.| 2019 | Iran      | TaqMan RT-PCR                | PBMCs       | 50 RRMS                   | MALAT1 †                           |                                    |                  |
| Ghareasouran et al.| 2019 | Iran      | TaqMan RT-PCR                | PBMCs       | 50 RRMS                   | HOTARMI †                          |                                    |                  |
| Ghareasouran et al.| 2018 | Iran      | TaqMan RT-PCR                | PBMCs       | 50 RRMS                   | GAS5 †                             |                                    |                  |
| Ghareasouran et al.| 2018 | Iran      | RT-PCR                       | PBMCs       | 50 RRMS                   |                                    |                                   |                  |
| Ghareasouran et al.| 2018 | Iran      | RT-PCR                       | PBMCs       | 50 controls               |                                    |                                   |                  |
| Gharesouran et al.| 2019 | Iran      | RT-PCR                       | PBMCs       | 50 RRMS                   |                                    |                                   |                  |
| Gharezi et al.  | 2018 | Iran      | RT-PCR                       | PBMCs       | 50 RRMS                   |                                    |                                   |                  |
| Ghoveud et al.  | 2020 | Iran      | RT-PCR                       | PBMCs       | 25 controls               |                                    |                                   |                  |
| Hosseini et al. | 2019 | Iran      | RT-PCR                       | PBMCs       | 50 RRMS                   |                                    |                                   |                  |
| Kozin et al.    | 2020 | Russia    | PCR-RFLP performed by TaqMan RT-PCR | PBMCs | 444 RRMS, 96 SPMS, 406 controls, 5 RRMS |                                    |                                   |                  |
| Masourni et al. | 2019 | Iran      | RT-PCR                       | Human brain tissue | 5 RRMS                   | MALAT1 †                           |                                    |                  |
| Mazdeh et al.   | 2019 | Iran      | RT-PCR                       | PBMCs       | 50 RRMS                   |                                    | AFAP1-AS1 †                       |                  |
| Mazdeh et al.   | 2019 | Iran      | T-ARMS PCR                   | PBMCs       | 402 RRMS, 392 controls    |                                    | LncRNA H19 rs2839698, rs217727        |                  |
| Moradi et al.   | 2020 | Iran      | RT-PCR confirmed by RFLP    | PBMCs       | 300 RRMS, 300 controls   |                                    | GASS, rs55829688 and NR3C1, rs61896190, rs56149945, rs41423247 |                  |

(Continued)
| Author                  | Year | Origin                        | LncRNA measurement technique | Sample type | Number of studied patients | Identified lncRNA/expression pattern | Polymorphism | Ref |
|-------------------------|------|-------------------------------|-----------------------------|-------------|---------------------------|--------------------------------------|--------------|-----|
| Moradi et al.           | 2019 | Iran                          | RT-PCR                      | PBMCs       | 20 RRMS, 10 controls      | NF003531.3(MEG3a) ↓                  | AC000612.2_201 [NS] AC007182-6 [NS] | (48)         |
| Pahlevan-Kakhki et al.  | 2019 | Iran, North Khorasan, Sistani | RT-PCR                      | PBMCs       | North Khorasan 30 MS, 30 controls Sistani 21 MS, 21 controls | Sistani ↓ lnc-DC [NS] both groups | THRIL, North Khorasan † | (51)         |
| Pahlevan-Kakhki et al.  | 2018 | Iran                          | RT-PCR                      | PBMCs       | 42 RRMS, 32 controls      | HOTAIR ↑                            | ANRIL [NS] PINK1-AS ↑                      | (50)         |
| Patoughi et al.         | 2020 | Iran                          | RT-PCR                      | PBMCs       | 50 RRMS, 50 controls      | GAS8-AS1 ↑                           |                          | (53)         |
| Rahmani et al.          | 2020 | Iran                          | RT-PCR                      | PBMCs       | 83 RRMS, 83 controls      | ROHC ↑                              | DDX5 ↑ RMRP ↑                         | (54)         |
| Rezazadeh et al.        | 2018 | Iran                          | T-ARMS-PCR                  | PBMCs       | 410 RRMS, 419 controls    |                                      | ANRIL, rs1333045, rs4977574, rs1333048, rs10757278 | (55)         |
| Rodriguez-Lorenzo       | 2020 | Netherlands                   | Ref-seq validated by RT-PCR | Brain tissue | 6 MS patients, 6 controls | HIF1A-AS3 ↑                          |                                      | (56)         |
| Safa et al.             | 2020 | Iran                          | RT-PCR                      | PBMCs       | 50 RRMS, 50 controls      | LINC0200305 ↓ Lnc-MK067P-3 ↓ HNF1A-AS1 ↓ MIR31HG [NS] NKILA [NS] ADINR [NS] CHAST [NS] Dicer1-AS1 [NS] SPRY4-IT1 ↓ HOXA-AS2 ↓ LINC-POQ ↓ MEG3 ↓ TUG1 ↑ |                          | (57)         |
| Safa et al.             | 2020 | Iran                          | RT-PCR                      | Venous blood | 40 RRMS, 40 controls     |                                      |                                      | (58)         |
| Santoro et al.          | 2020 | Italy                         | RT-PCR                      | Serum       | 16 SPMS, 12 PPMS, 8 controls | LINC020293 ↓ RP11-29G8.3 ↓ NEAT1 ↑ TUG1 ↑ RN7SKRNA ↑ HULC ↑ |                          | (59)         |
| Santoro et al.          | 2016 | Italy                         | RT-PCR                      | Serum       | 12 RRMS, 12 controls      | LINC020305 ↓                         |                          | (60)         |
| Sayad et al.            | 2019 | Iran                          | TaqMan RT-PCR               | PBMCs       | 50 RRMS, 50 controls      | LINC020180 ↑                         |                          | (61)         |
| Senousy et al.          | 2020 | Egypt                         | TaqMan RT-PCR               | Serum       | 108 RRMS, 104 controls   | GAS5 ↑                              | rs2067079 rs1625579             | (62)         |
| Shaker et al.           | 2021 | Egypt                         | RT-PCR                      | PBMCs       | 74 RRMS, SPMS, 60 controls | Linc-R-Ccr2-5’-AS ↓                   |                          | (63)         |
| Shaker et al.           | 2019 | Egypt                         | RT-PCR                      | PBMCs       | 42 RRMS, 18 SPMS, 60 controls | THRIL ↑                             | Linc-R-Gng2-5’ ↑ Linc-Repas1-3’as ↓ |                          | (64)         |
| Shaker et al.           | 2019 | Egypt                         | RT-PCR                      | Serum       | 45 RRMS, 45 controls      | MALAT1 T ↑                           |                          | (65)         |
| Taheri et al.           | 2020 | Iran                          | T-ARMS-PCR                  | PBMCs       | 403 MS patients, 420 controls |                              | HOTAIR, rs12826786, rs1899663, rs4759314 |                          | (66)         |
| Teimuri et al.          | 2019 | Iran                          | RT-PCR                      | PBMCs       | 25 RRMS, 25 SPMS          | AL450992.2 ↓                         | AC009954.5 ↓                          | (67)         |

(Continued)
Several studies revealed significant correlations between IL18RAP and IL18R1 and their association with the lncRNA AC007278.2. On the other hand, elevated expression of IL18RAP and IL18R1 is involved in the differentiation of Th1 cells and the pathogenesis MS. During Th1 differentiation, STAT4 and IL-12 recruit chromatin remodeling complexes. Induction of histone acetylases and DNA methylases promotes the expression of IL18RAP and IL18R1 and the release of IL-18 and IL-12 which trigger the differentiation of Th1 and the release of pro-inflammatory cytokines and eventually the progression of MS (43, 88, 89).

TOB1-AS1

TOB1 antisense RNA 1 (TOB1-AS1) is transcribed from the opposite orientation of the TOB1 gene on chromosome 17q21.33, a region with an important role in maintaining immune tolerance (19). Dehghanzad et al. demonstrated the abnormal expression levels of TOB1-AS1 and its targets genes TOB1, TSG, and SKP2 in the blood of MS. Downregulation of TOB1-AS1 might cause dysregulation of the target genes and participate in the progression of MS (30). TOB1-AS1 enhances the expression of the TOBI gene via suppressing the production of IL-2 (90). An in vitro study revealed the positive feedback between TOB1 and S-phase kinase-associated protein 2 (SKP2). Elevation of TOB1-AS1 levels causes increased TOB1 and thus increased the TSG levels (30).

RMRP

Rahmani et al. demonstrated that RORC, DDX5, and RMRP have been significantly upregulated in patients with MS (54). RORC and DDX5 can affect MS pathogenesis through regulation of Th17 differentiation and the production of inflammatory cytokines such as IL-17A, IL-17F, and IL-22.

LncRNAs With Roles in Innate Immune Response

Lnc-DC and THRIL

TNF and HNRNPL-related immunoregulatory long non-coding RNA (THRIL) is a lincRNA located on the minus strand of the 12q24.31 chromosome. This lncRNA plays an important role in the regulation of the innate immune system (19). This lncRNA has been among the dysregulated lncRNAs in MS (31). THRIL

### TABLE 1 | Details of the included animal studies.

| Author       | Year | Origin | LncRNA measurement technique | Sample type | Type of EAE model                    | Identified lncRNA/expression pattern | Polymorphism | Ref  |
|--------------|------|--------|------------------------------|-------------|--------------------------------------|--------------------------------------|--------------|------|
| Bian et al.  | 2020 | China  | Microarray assay validation  | Spleen tissue | Not mentioned                        | GM15575                              | ↑             | (71) |
| Duan et al.  | 2018 | China  | RT-PCR                       | Microglia    | Cuprizone-induced demyelination       | HOTAIR                               | ↑             | (72) |
| Guo et al.   | 2017 | China  | Microarray confirmed by RT-PCR| Spleen tissue | Myelin oligodendrocyte glycoprotein (MOG) peptide-induced EAE | 1700040D17Rik                        | ↓             | (73) |
| Liu et al.   | 2021 | China  | RT-PCR                       | Spinal cords or astrocyte tissue | MOG peptide-induced EAE              | GM13568                              | ↑             | (74) |
| Masoumi et al.| 2019 | Iran   | RT-PCR                       | Lumbar spinal cord tissue | MOG peptide-induced EAE              | MALAT1                               | ↓             | (45) |
| Sun et al.   | 2017 | China  | Microarray assay validation  | Microglia    | MOG peptide-induced EAE              | GASP5                                | ↑             | (75) |
| Yue et al.   | 2019 | China  | RT-PCR Western blot          | Microglia BV2 cells | MOG peptide-induced EAE              | TUG1                                 | ↑             | (76) |

RT-PCR, real-time PCR; EAE, autoimmune encephalomyelitis; upregulation, ↑; downregulation, ↓.
regulates TNF-α expression via its interaction with heterogeneous nuclear ribonucleoprotein L (hnRNPL) and persuades a transcriptional-activating complex, finally connecting to the TNF-α promoter (91). THRIL can suppress STAT3 (51).

Lnc-DC (also known as Wfdc21) is a non-coding RNA gene on the minus strand of chromosome 17q23.1, which was firstly identified by Wang et al. to have an important role in the differentiation of dendritic cells and the regulation of the immune response (92, 93). Lnc-DC positively regulates STAT3 resulting in the differentiation of monocyte cell to dendritic cells (92). This lncRNA is involved in the pathogenesis of sepsis (93), coronary artery disease (94), pre-eclampsia (95), MS (51), and systemic lupus erythematosus (SLE) (96). Xie et al. showed the role of Lnc-DC on the regulation of TLR4 (93). Lnc-DC through the TLR9/STAT3 axis can regulate apoptosis and immune responses, thus can participate in the pathogenesis of MS (97, 98). Bahrami et al. demonstrated the upregulation of Lnc-DC level in HLADR1*15:01-negative MS patients compared with healthy controls (24).

LncRNAs Having a Role in Response to DNA Damage

LncRNA-p21 (Expression in T Cell)
P21-associated ncRNA DNA damage-activated (PANDA) is a lincRNA located on the minus strand 6p21.2. It has a role in response to DNA damage in a p53-dependent pathway (15). Dasmalchi et al. revealed the upregulation of this lncRNA in the peripheral blood of MS patients (28). PANDA controls the cell cycle through suppression of proapoptotic-related genes (15, 99). Dysregulation of the expression of this lncRNA in oligodendrocytes and neurons is associated with the release of free radicals and activation of the apoptosis process (100).

LncRNAs Involved in the Regulation of the Cell Cycle

TUG1, UCA1, and CCAT2
UCA1, CCAT2, and TUG1 are a subgroup of lncRNAs that have a role in the regulation of the cell cycle. UCA1 is located in the plus strand of chromosome 19p13.12 (19). It participates in the
pathogenesis of several cancers such as colorectal, breast, and bladder cancer through increasing cell proliferation, apoptosis-resistant cells, invasion, and drug resistance induction (101). UCA1 via modulation of the PI3K–AKT, ERK1/2, and MAPK pathways can regulate the proliferation of cells in various cancers (102). Dastmalchi et al. revealed the upregulation of UCA1 in the blood of MS patients. This lncRNA via inhibiting cell cycle inhibitors such as p27 may cause increased proliferation of T cells (29).

CCAT2 is an intergenic lncRNA on the plus strand of the 8q24.21 chromosome (19). This lncRNA acts as an oncogene and participates in the metastasis, chromosomal instability, and tumor growth in colon cancer (103). Both UCA1 and CCAT2 can regulate the expression of genes participating in WNT pathway (104).

Fenoglio et al. showed the downregulation of TUG1 in MS patients compared with controls (35). TUG1 exerts a repressor function via recruitment of the PRC2 complex. Its promoter has many conserved binding sites for p53, thus after DNA damage, p53 regulates cell cycle and apoptosis via upregulation of TUG1 (35, 105, 106). TUG1 has been found to be upregulated in the serum and PBMCs of RMS patients (28, 59, 60). TUG1 targets and suppresses different miRNAs such as miR-20a-5p, which has a role in the regulation of p38 MAPK signaling pathway. p38 MAPK promotes the production of proinflammatory cytokines. Downregulation of miR-20a-5p by TUG1 activates p38 MAPK signaling and MS progression (60).

The growth arrest-specific 5 (GAS5) has been recognized as a lncRNA with a possible role in normal growth arrest in T cells. This lncRNA plays a central role in the suppression of cell proliferation (75).

GOMAFU
MIAT or GOMAFU is a lincRNA on the plus strand of 22q12.2 (19), which is highly expressed in the CNS and is suggested to have an important role in regulating the neural stem cell differentiation into oligodendrocytes (107). Fenoglio et al. showed the downregulation of this lncRNA in the blood of MS patients (35). GOMAFU using its repetitive sequence binds to the splicing factor 1 (SF1) protein and prevents the function of the spliceosome complex. Thus, deregulation of GOMAFU causes advent of alternative splicing patterns (108). GOMAFU has a possible role in inflammatory and neurodegenerative processes (35).

OIPS-AS1
OIP5-AS1 (Cyrano) was firstly detected in zebrafish models and it was suggested that it has a role in the development of the CNS (109). Kim et al. revealed that OIP5-AS1 causes a reduction in the stability a cyclin G-associated kinase (GAK) mRNA with important roles for mitotic progression (110). It seems that this lncRNA exerts its role in the suppression of cell proliferation through reducing GAK levels by associating with the RNA-binding proteins (RBPs) like HUR1 (ELAV-like protein 1). HUR1 is a protein that in humans is encoded by the ELAVL proteins. HUR1 contains three RNA-binding domains and binds to cis-acting AU-rich elements. Since the HUR1 gene is expressed in astrocytes, it might have a role in autoimmune diseases such as encephalomyelitis and MS (111).

BDNF-AS
Brain-derived neurotrophic factor-antisense RNA (BDNF-AS) is a 191-kb-long conserved lncRNA (112), located in the opposite orientation of BDNF on the 11p14.1. It negatively regulates the expression of BDNF at the mRNA and protein levels (113). BDNF is a neuroprotective factor that is synthesized in the brain and is expressed at a high level in the CNS. It has diverse functions such as the promotion of neuronal survival and elevation of growth, maturation, and synaptic plasticity. BDNF is produced and released by neurons and immune cells such as T and B cells under the circumstance of inflammation of the CNS in MS patients (114). BDNF-AS recruits PRC2 and inhibits BDNF expression (113).

Other LncRNAs
NEAT1
This lncRNA has been shown to be upregulated in MS patients compared with healthy individuals (59). NEAT1 plays an important role in the formation of paraspeckle, a nuclear body that comprises numerous protein factors. NEAT1 has been shown to be co-localized with splicing factor proline/glutamine-rich (SFPO) and NonPOU domain containing, octamer-binding (NONO) (115). Also, NEAT1 is activated by the Toll-like receptor 3 (TLR3)–p38 pathway in antiviral response or endogenous agonists that bind to TLR3 (116, 117). Imamura et al. revealed that upregulation of NEAT1 causes activation and excess IL-8 production via enhancing the relocation of SFPO proteins from the IL-8 promoter (118).

RN7SK RNA
The lncRNA 7SK small nuclear (RN7SK RNA) is transcribed from the plus strand of the 6p12.2 chromosome. It is involved in the formation of the 7SK snRNP complex with other specific proteins (HEXIM1/2, LARP7, and PIP7S) that can inhibit approximately half of the activity of the cellular kinase P-TEFb complex (119, 120). The P-TEFb complex and its protein component Cdk9/cyclin T1 heterodimer have a role in the activation of CD4+ T cells. So, upregulated RN7SK RNA may cause disturbance in the P-TEFb complex with resulting regulation effects on CD4+ T cells, thus participating in autoimmune diseases such as idiopathic inflammatory myopathy (IIM) and MS (59).

AFAP1-AS1
Actin Filament-Associated Protein 1 Antisense RNA 1 (AFAP1-AS1) is a conserved non-coding RNA transcribed from the plus strand of chromosome 4p16.1 on the opposite strand of the AFAP1 locus. This lncRNA regulates the expression of AFAP1 at the translation level (121). AFAP1-AS1 was found to modulate
AFAP1 and act as an adapter molecule that links other proteins such as SRC and PKC with a hypothetical function in blood-brain barrier (BBB) integrity. BBB dysfunction in MS patients allows the enormous influx of immune cells into the brain and, after a series of interactions, leads to demyelination (122). Based on the bioinformatics analyses, AFAP1-AS1 affected the expression of molecules with a vital role in the actin cytoskeleton signaling pathway such as multiple small GTPase family members. As small GTPases are involved in the regulation of immunity and inflammation response, its dysregulation leads to disease progression in many diseases such as autoimmune diseases (123). Upregulation of AFAP1-AS1 promotes metastasis via modulation actin filament integrity (124). Due to its antiapoptotic properties in peripheral immune cells, it might be involved in the pathogenesis of MS (40).

GAS8-AS1
A previous study showed that GAS8-AS1 is a tumor suppressor and regulates the expression of another lncRNA, namely, AFAP1-AS1 (125). GAS8-AS1 has been downregulated, while AFAP-AS1 has been upregulated in MS patients. Regarding the role of AFAP1-AS1 in the pathogenesis and progression of MS, it can be hypothesized that dysregulation of GAS8-AS1 might be involved in the pathogenesis of MS (40, 125). Zha et al. revealed that GAS8-AS1 negatively regulated the expression of UCA1. UCA1 has been shown to regulate various signaling pathways such as FGFR1/ERK and TGF-β (126). TGF-β has a role in the inflammatory condition and acts as an anti-inflammatory factor to inhibit Th1 and Th17 cells (127), so upregulation of GAS8-AS1 resulting in the downregulation of UCA1 and reduced TGF-β might cause progression and aggregate MS.

PINK1-AS
PTEN-induced kinase 1-AS (PINK1-AS) is an intronic non-coding RNA transcribed from the minus strand of chromosome 1p36.12 on the opposite strand of the PINK1 locus. This lncRNA regulates the expression of PINK1. Patoughi et al. (53) revealed the upregulation of the expression level of the PINK1-AS in male MS patients compared with male healthy controls. This might be due to the existence of a gender-based regulatory direction for PINK1-AS expression or variance in the pathogenic process of disease in female and male MS patients. PINK1 is a serine/threonine kinase that preserves the mitochondria and supports its normal function (128). Further studies by Fenoglio et al. have identified 10 lncRNAs with abnormal expression. These lncRNAs consist of MALAT1, MEG9, NRON, ANRIL, TUG1, XIST, SOX2OT, GOMAFU, HULC, and BACE-1AS (35).

The highly upregulated liver cancer (HULC) is another lncRNA found to be upregulated in MS patients in one study (61), whereas Fenoglio et al. have reported an opposite result (35). This lncRNA attaches to miR-200a-3p and also acts as an endogenous sponge for miR-122. Since miR-122 has an anti-inflammatory effect and is significantly downregulated in the blood of MS patients, HULC may be involved in the progression of MS. On the other hand, HULC activates miR-200a-3p/ZEB1 signaling. miR-200a plays an important role in the regulation of the TLR4 pathway and ZEB1 has a neuroprotective protein (129).

Dysregulated LncRNAs in the Animal Model of MS
One of the useful animal models of MS is EAE mice that share several characteristics with MS. However, there are few studies in this area. Yue et al. (76) demonstrated the abnormal activity of the TUG1/miR-9-5p/NF-kB1/p50 axis in the mouse model of MS. In fact, upregulation of TUG1 causes suppression of miR-9-5p and an increase in the expression of NF-kB1/p50. This transcription factor causes activation of Th17 cell and the production of IL-17 and IL-6. NF-kB also regulates matrix metalloproteinases (MMPs). Downregulation of TUG1 leads to increased levels of miR-9-5p and a decrease in NF-kB1/p50.

Another study by Guo and colleagues showed that lncRNA-1700040D17Rik is a specific mouse lncRNA that is located adjacent to the RORγ gene on chromosome 3 and is downregulated in EAE (73). Then, an in vitro approach revealed that IL23R-CHR is a soluble IL23R that counteracts IL-23 and blocks its signaling pathway, thus inhibiting differentiation of Th17 cell (130). These findings demonstrated that 1700040D17Rik regulates the expression of RORγt, which is an essential transcription factor for Th17 (73).

Liu et al. revealed that IL-9 inducing lncRNA Gm13568 in astrocytes has interaction with CBP/P300. It promotes Notch1 pathway activation and is involved in the construction of inflammatory cytokines in astrocytes in the progression of EAE development (74).

Variants Within LncRNAs and Association With MS
According to the important roles of lncRNAs in the regulation of immune responses, it is expected that functional variants within their coding region or adjacent to them can affect the risk of MS. However, there are few studies on this issue. Bahrami et al. have evaluated the association between rs933151 and rs7953249 polymorphisms in TRPM2-AS and HNF1-AS1, respectively, and MS risk in the Iranian population. They revealed that rs7953249 within HNF1-AS1 has an association with C-reactive protein (CRP) (25).

Taheri et al. assessed the association between three SNPs (rs12826786, rs1899663, and rs4759314) within HOTAIR and MS in 403 Iranian MS patients and 420 controls. Their results showed that the G allele of rs4759314 might be involved in the risk of MS (66).

CONCLUSION
In conclusion, the pathogenesis of MS is highly complex including several molecular signaling pathways. Most of the abovementioned studies have assessed the expression of lncRNAs in serum or PBMCs. Although several of these lncRNAs have essential roles in the CNS processes, modulation of peripheral immune responses is the most appreciated route of participation of lncRNAs in the pathogenesis of MS. Few studies have assessed the expressions of lncRNAs in the brain tissues of EAE models. An important study in this field has identified dysregulation of Gm14005, Gm12478, mouselncRNA1117,
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AUTHOR CONTRIBUTIONS

AJ, MT, BH, and SG-F wrote the draft and revised it. MR, HS, JG, and MA collected the data and designed the figures. HD performed the bioinformatics analysis. All authors contributed to the article and approved the submitted version.
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**GLOSSARY**

| Term                  | Description                                                                 |
|-----------------------|-----------------------------------------------------------------------------|
| lncRNA                | long non-coding RNA                                                          |
| MS                    | multiple sclerosis                                                           |
| RT-PCR                | real-time polymerase chain reaction                                          |
| AFAP1-AS1             | actin filament-associated protein 1 antisense RNA 1                          |
| RRMS                  | relapsing–remitting multiple sclerosis                                       |
| SPMS                  | secondary progressive multiple sclerosis                                       |
| CNS                   | central nervous system                                                       |
| HOTAIR                | Hox transcript antisense intergenic RNA                                       |
| miRNAs                | microRNAs                                                                   |
| CD4+ T cells          | T helper cells                                                               |
| CD8+ T cells          | cytotoxic T cells                                                            |
| GWAS                  | genome-wide association studies                                              |
| BDNF                  | brain-derived neurotrophic factor                                            |
| BDNF-AS               | BDNF antisense RNA                                                           |
| NR3C1                 | nuclear receptor family 3 group C member 1                                   |
| PRC2                  | polycarbonate 2 suppressor complex                                            |
| DDIT4                 | DNA-damage-inducible transcript 4                                            |
| mTORC1                | mammalian target of rapamycin complex 1                                      |
| IncDDIT4              | IncRNA DDIT4                                                                 |
| Th17                  | T helper 17 cell                                                             |
| Tregs                 | regulatory T cells                                                           |
| IFN-γ                 | interferon gamma                                                             |
| hnRNP                 | heterogeneous nuclear ribonucleoproteins                                     |
| DC                    | dendritic cells                                                              |
| Inc-DC                | IncRNA expressed in DC                                                       |
| PANDA                 | P21-associated ncRNA DNA damage-activated                                    |
| FAS-AS1               | FAS antisense transcript 1                                                   |
| Inc-MAF-4             | A IncRNA                                                                    |
| THRIL                 | TNF-α and heterogeneous nuclear ribonucleoprotein L                          |

**Continued**

| Term                  | Description                                                                 |
|-----------------------|-----------------------------------------------------------------------------|
| PVT1                  | plasmacytoma variant translocation 1                                        |
| GAK                   | cyclin G-associated kinase                                                   |
| HuR1                  | Huantigen R                                                                 |
| SIRT1                 | silent information regulator 1                                               |
| OIP5-AS1              | OIP5 antisense RNA                                                           |
| TUG1                  | taurine-upregulated gene                                                     |
| IL-8                  | interleukin 8                                                                |
| SFPQ                  | splicing factor proline- and glutamine-rich                                  |
| IL-17                 | interleukin 17                                                               |
| STAT4                 | signal transducer and activator of transcription 4                          |
| EZH2                  | enhancer of zeste homolog 2                                                  |
| TNF-α                 | tumor necrosis factor                                                        |
| TLR4                  | Toll-like receptor 4                                                          |
| NF-κB                 | nuclear factor kappa-light-chain-enhancer of activated B cells               |
| MAPK                  | mitogen-activated protein kinase                                              |
| PI3K                  | phosphoinositide 3-kinases                                                   |
| ERK1/2                | extracellular signal-regulated kinases 1/2                                   |
| AKT                   | protein kinase B                                                             |
| WNT                   | Wnt signaling pathway                                                         |
| SF1                   | splicing factor 1                                                             |
| GAK                   | G-associated kinase                                                          |
| NonPOU                | non-POU domain-containing octamer-binding protein                            |
| P-TEFb                | positive transcription elongation factor                                      |
| BBB                   | blood–brain barrier                                                          |
| FGFR1                 | fibroblast growth factor receptor 1                                           |
| ERK                   | extracellular signal-regulated kinase                                        |
| TGF-β                 | transforming growth factor beta                                               |
| CRP                   | C-reactive protein                                                           |
| PINK1-AS              | PTEN-induced kinase 1-AS                                                     |
| HIF1-AS3              | hypoxia-inducible factor 1-AS                                                 |
| RMRP                  | RNA component of the mitochondrial RNA-processing endoribonuclease (RNase MRP) |
| GATA3                 | GATA-binding protein 3                                                        |
| GR                    | glucocorticoid receptor                                                       |
| HULC                  | highly upregulated liver cancer                                               |
| ZEB1                  | zinc finger and homeodomain transcription factor 1                            |