



Relationship between LncRNAs and Multiple Sclerosis (MS)

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Abstract:

Multiple sclerosis (MS), the most common inflammatory demyelinating illness of the central nervous system (CNS), presents a range of clinical symptoms. The body's immune system attacking myelin causes the transmission block in MS, which increases the electrical capacity of axons. Studies suggest that epigenetic factors play a part in the development of MS. Longer than 200 nucleotides in length and widely distributed, lncRNAs are linear RNA transcripts that cannot code for proteins. For instance, evidence suggests that lncRNAs are essential for a number of cellular functions, including immune response regulation, epithelial mesenchymal transition (EMT), cancer cell proliferation and metastasis, cellular homeostasis, and embryonic development. Epigenetic mechanisms have been proven to have a significant impact on the pathophysiology of MS, and their participation has revealed the function of lncRNAs as epigenetic regulatory molecules in molecular processes. The major subjects of this study have been the relationship between lncRNAs and MS, the role of lncRNA in the pathophysiology of the disease, and the diagnostic and prognostic potential of lncRNA in MS.

INTRODUCTION

Because the motor, sensory, visual, and autonomic systems are affected, multiple sclerosis (MS), a chronic inflammatory illness, manifests as inflammation of the central nervous system (CNS) (1). The main symptoms of MS are optic neuritis, which is an inflammation of the optic nerve; Uhthoff's phenomenon, which is a temporary worsening or fluctuation of MS symptoms accompanied by an increase in body temperature; and Lhermitte's phenomenon, which is an abnormal electric shock to the spine and back of the neck that results in radiation of the arm or leg. It was previously believed that MS is primarily a T-cell-mediated autoimmune illness and that the most well-known mechanisms, such as human leukocyte antigen (HLA) associations, are the result of hereditary variables known to increase the vulnerability of MS patients (2). Clinical classification has not been altered in more than 20 years, despite the expansion of various therapeutic treatments based on disease-modifying medications. On the other hand, there is currently no effective treatment for multiple sclerosis that is in its advanced stages (3). Lack of understanding of the underlying processes

causing advanced MS is probably one of the causes. Recent criteria have been developed to characterize the course of the illness because MS has a gradually progressing course and people with MS experience a wide variety of symptoms. Many immunological and non-immune-linked ailments, such as cancer, autoimmune diseases, and infectious diseases, are brought on by impaired immune responses; yet, the underlying process is still poorly understood (4). Long non-coding RNAs (lncRNAs) have recently been demonstrated to have a critical role in regulating the immune response, immune cell growth, and immune system development. But so far, only a small number of lncRNAs have been shown to play a role in controlling the immune system (5). lncRNAs' capacity to regulate gene expression and their part in the pathophysiology of illness have just recently come to light. Despite the fact that studies on lncRNAs and their relationship to MS are still in their infancy, it has been noted that lncRNA-associated disorders in humans result from their abnormal expression. Using their involvement in signaling networks and the control of gene expression as our main points of focus, we review the lncRNAs implicated in the

pathogenesis of MS in this study(6).

Structure LncRNAs

The eukaryotic genome does have an extremely intricate structure. The human genome does not encode proteins in over 98% of it. The Human Genome Project's (HGP) complete identification of the human genome has resulted in the discovery and mapping of new human genes (7). High-throughput sequencing methods like next-generation sequencing (NGS) have revealed a whole new regulatory environment made up of lncRNAs. Currently, more than 28,000 lncRNA genes have been identified (8). Intergenic lncRNAs (transcribed entirely from introns of protein-coding genes), processed lncRNAs, overlapping lncRNAs (which contain an encoding gene in the intronic region), antisense lncRNAs (which are the opposite strand of protein-coding genes and can be both multi-exonic and -intronic), and intronic lncRNAs have all been classified as lncRNAs (9). Similar to how mRNA is processed, the majority of lncRNAs are processed via 5' end capping, splicing, 3' end cleavage, and polyadenylation (10). LncRNAs have a variety of biological functions in the nucleus and cytoplasm and are polyadenylated and catalyzed by RNA polymerase II. LncRNAs only impose extremely light sequence restrictions and gain secondary and tertiary structures (11). As a result, it is assumed that the majority of lncRNAs have more than two exons. LncRNAs are very prevalent, varied linear RNA transcripts that are longer than 200 nucleotides and do not function in the production of proteins (12). Small open reading frames (sORFs), which are found in a number of lncRNAs but do not encode proteins, have recently been demonstrated to be converted into functional small proteins (13). LncRNAs localized in the nucleus interact with genomic DNA transcription factors, chromatin, spliceosomes, and other nuclear proteins that affect transcriptional and epigenetic regulation (14). They also play a critical role in chromatin organization, transcription, and post-transcriptional modifications. LncRNAs' functions, like those of proteins, are based on where in the cell they are found (15). Numerous lncRNAs display distinctive nuclear localization patterns and appear to be involved in altering nuclear performance. The immune system, tumorigenesis, epithelial-mesenchymal transition, cancer cell proliferation and metastasis, cellular homeostasis, and even embryonic development have all been shown to be impacted by lncRNAs in recent years (16). Numerous studies have demonstrated a strong association between cancer-related genetic polymorphisms and lncRNAs as functional genomic components. The aetiology of autoimmune illnesses may also be influenced by lncRNAs, according to new research, which also implies that they play a significant

role in immune system regulation(17).

Various forms of sclerosis and their causes

There are many different clinical signs of MS, which is an inflammatory illness and demyelinating disease in the CNS, particularly in the spinal cord, optic nerves, and brain. Multiple localized regions of myelin degradation inside the CNS are the pathologic characteristic of MS, a chronic inflammatory condition that damages the CNS (18). Thus, the fundamental pathophysiological mechanism causing the conduction block is increasing neurodegeneration brought on by the breakdown of myelin, which is the primary outcome of autoimmune assaults in MS. This neurodegeneration increases the electrical potential of axons (19). Inflammation and blockage of nerve conduction appear to be the most significant variables involved in the pathogenesis of MS, despite the fact that it is a complicated illness with an unresolved underlying mechanism in its pathogenesis and etiology (20). However, MS is at least twice as common in women as it is in men, suggesting that epigenetic pathways play a role in the development of MS (21). Genetic factors do appear to be the most significant components involved in the etiology of MS. Smoke use, sun exposure, the Epstein-Barr virus (EBV), DNA methylation patterns, non-coding RNAs, and epigenetic determinants, including histone modifications, are examples of environmental influences (22,23). Smoking has also been linked to an increased risk of MS impairment progression. Epstein-Barr virus-related infections and MS have been linked, according to serologic and epidemiological research (24). A number of miRNAs, a family of short non-coding RNAs that interact with lncRNAs to control host gene expression, are also encoded by the EBV genome (25). These suggested an EBV and MS connection that could exist. Relapsing-remitting MS is linked to vitamin D deficiency. Low levels of vitamin D lead to immunodeficiency against viral agents because it regulates immune system activity (26). High dosages of vitamin D have been proven to lower interleukin-17 in clinical trials and observational research, but they have no effect on other inflammatory markers (27). The onset and development of MS may be impacted by epigenetic changes such as DNA methylation, histone modifications, and post-transcriptional gene silencing carried out by microRNAs (28). Regardless of the stage of the disease, there were significant changes in the DNA methylation profiles of T helper cells (CD4+ T cells), cytotoxic T cells (CD8+ T cells), and whole-blood acquired from MS patients (29). Evidence shows that, in contrast to the control group, hypermethylation only affects cytotoxic T cells and not helper T cells or genomic DNA taken from the whole blood of MS patients(30). The methylation of CpG sites across the individual's genome did not differ significantly. Genes associated with the immune system are expressed

excessively in MS patients, according to genome-wide association studies (GWAS) (31). Recent genome-wide association studies in MS have identified the genetic factors that contribute to this polygenic disease and more than 100 risk loci associated with the disease (32). However, every single locus, with the exception of the specific HLA-region genes, only marginally increases disease risk (33). Nucleotide polymorphisms work in a certain way to increase the risk of illness in a population, and this is how MS develops. A limited number of signals are linked to splicing alterations; however, the majority of these frequent polymorphisms do not impact the protein sequence of translated products (34). In fact, the majority are located in intronic regions flanking genes. So far, nothing is known about the basic mechanisms underlying MS pathogenesis, including its pathogenesis (35). As a result, the molecular mechanisms involved in the pathophysiology of MS and their etiology are still poorly understood. The chance of acquiring MS varies from person to person, with Caucasians having a higher risk than Asians and Spanish people (36). LncRNAs may have a role in the development of autoimmune illnesses as they regulate a number of biological activities and immune responses. There have been recent reports linking lncRNA-containing microvesicles to AIDS (37).

Results of the MS and lncRNA association

Studies have shown that lncRNAs have a role in MS progression and control B cells and CD4⁺ T-helper cell differentiation. The growth-promoting gene known as BDNF (brain-derived neurotrophic factor) is recognized for its critical contribution to neuronal protection (38). The release of BDNF by neurons, T cells, macrophages, astrocytes, and microglia cells in an MS patient was demonstrated to have polytropic effects on immune cells that result in inflammatory reactions (39). It has been discovered that the lncRNA BDNF-AS, also known as BDNF-AS, suppresses the transcription of BDNF in various cells, acting as a negative BDNF regulator. BDNF-AS and BDNF were found to have a significant association in people with MS illnesses (40). The lncRNA known as GAS5 (specific for growth 5) was first discovered in a research study to be involved in the suppression of glucocorticoid receptors (GRs) in MS patients (41). Glucocorticoids might be thought of as a possible therapeutic agent in inflammatory and autoimmune illnesses since they have a significant impact on immune system regulation (42). By attaching to the DNA domains of glucocorticoid receptors, GAS5 can block glucocorticoid-dependent responses (GRs). Ghahesouran et al. demonstrated a relationship between GAS5 and NR3C1, the gene that codes for the glucocorticoid receptor (Nuclear Receptor Subfamily 3

Group C Member 1) (43). Additionally, Sun et al. demonstrated in different research that GAS5 interacts with PRC2 (the polycomb-2 suppressor complex) and inhibits the IRF4 transcription factor. As a result, it inhibits T-cell growth. Additionally, GAS5 enhances the polarization of the M1 microglia subgroup, which plays a role in MS pathogenesis, while inhibiting the M2 microglia polarization (44). Mammalian target of rapamycin complex 1 (mTORC1) is known to be inhibited by DNA damage-inducible transcript 4 (DDIT4), a cytoplasmic protein that promotes DNA damage in response to cellular stressors. A molecule called mTORC1 is involved in the development and expansion of T lymphocytes (45). According to Zhang et al., lncRNA DDIT4 (lncDDIT4) and DDIT4 were highly expressed in MS patients. The DDIT4/mTOR signaling axis is a target of lncDDIT4, which has a significant impact on Th17 differentiation (46). Mammals have an abundance of MALAT1, often referred to as NEAT2 (nuclear-enriched abundant transcript 2). The long noncoding RNA (lncRNA) MALAT1 (metastatic lung adenocarcinoma copy 1), which is housed in the cell nucleus, controls the transcription and maturation of RNA as well as the expression of many different genes. The neurological system, endocrine organs, the stomach, the bone marrow, and the lungs all express MALAT1 more than other tissues. Masoumi et al (47). discovered that primary activated macrophages and splenocytes express MALAT1 more highly. A shift in the differentiation of macrophages to a pro-inflammatory M1 phenotype, which releases a variety of inflammatory cytokines, has been shown in macrophages treated with specific MALAT1 siRNAs (48). Additionally, by inhibiting Treg differentiation and stimulating T cell differentiation to pathogenic Th1 and Th17 phenotypes, the reduction of MALAT1 expression in CD4⁺ T cells further increases the proliferative capacity of T cells (49). These results show that MALAT1 is involved in triggering anti-inflammatory responses. Additionally, they discovered that inhibiting MALAT1 increases CD4 T cells' capacity for proliferation, which is associated with a striking increase in the number of Th17 cells that produce IL-17 and IFN-producing Th1 cells while decreasing the number of Foxp3-positive (regulatory T lymphocyte) cells (50). MALAT1 has been shown to have an effect on the AS (alternative splicing) of pre-mRNAs in WI-38 and HeLa cells that control the activity of SR proteins. Its capacity to attach to other splicing elements, such as a number of hnRNPs that affect its own expression, has also been proven (51). The findings of a different investigation showed that MALAT1 regulates the expression of splicing factors as well as MS-related alternative splicing events, which strongly implies that it plays a role in MS pathogenesis (52). Dendritic cells (DC) express

long non-coding RNA (Lnc-DC), which can mediate DC maturation via phosphorylation transducers and transcription activator 3 (STAT3). Through the transcription of downstream genes, Lnc-DC has been demonstrated to have a role in the differentiation of monocytes into DC and the activation of T cells. As a result, LNC-DC can distinguish between young and mature DCs (53). A thin line of evidence suggests that MALAT1 and Lnc-DC serum levels may be potentially promising indicators in MS preliminary screening, suggesting that these lncRNAs may be essential in the development of MS illness (54). MALAT1 and Lnc-DC have been suggested to be used as treatment strategies in MS, which is encouraging. In a study, it was discovered that three long noncoding RNAs (lncRNAs) called taurine-up-regulated gene 1 (TUG1), nuclear paraspeckle assembly transcript 1 (NEAT1), and P21-associated ncRNA DNA damage activated (PANDA) regulate immune responses and DNA damage responses (DDR) in MS patients (55). NEAT1 expression was found to be inversely related to the age at which the disease began and the length of the illness in female patients (56). TUG1 expression was also inversely correlated with the typical illness duration in female patients. In response to DNA damage, the interaction of TUG1 with p53 and PANDA controls the expression of genes that govern the cell cycle and stabilizes the p53 protein. Additionally, NEAT1 controls the production of cytokine genes, including interleukin (IL)-8, that are implicated in antiviral responses (57). In research by Imamura et al., a NEAT1-dependent SFPQ (Splicing Factor Proline and Glutamine Rich) translocation was shown to suppress IL-8 transcription, activate NEAT1 expression, move SFPQ from the IL8 promoter to the paraspeckles, and finally result in the transcriptional activation of IL8 (58). NEAT1 is important for innate immune responses because it controls the transcription of antiviral genes through SFPQ and NEAT1's stimulus responsiveness (59). LncRNAs are drawing increasing attention to the function of antisense noncoding RNA in the INK4 locus (ANRIL), which controls cell proliferation and senescence. ANRIL's regulatory function in inflammatory responses has led to increased interest in its potential significance in inflammatory diseases (60). According to research findings, ANRIL has a role in the etiology of MS. LincMAF-4, by regulating Th1/Th2 differentiation, has been considered one of the main drivers in MS pathogenesis, despite the fact that MS is an autoimmune disease that is related to immune dysregulation and an imbalance in Th1, Th2, and Th17 cells (61). However, more research is required to confirm this. In a newly released study, it was shown that linc-MAF-4 was markedly up-regulated in MS patients, indicating that it might control the development of Th1/2 cells (62). Linc-MAF-4 has been presented as

a newly discovered member of the lncRNA family that plays a role in the pathogenesis of MS. It has also been demonstrated that the antisense lncRNA FAS antisense transcript 1 (FAS-AS1) regulates the activity of the soluble Fas receptor (sFas) (63). This lncRNA modifies the Fas:sFas ratio and prevents exon skipping during the transcription of the Fas mRNA, leading to the development of Fas ligand (FasL)-mediated apoptosis. It does this by binding to the RNA-5 binding protein (RBM5) (64). It has been documented that this pathway affects lymphocyte growth and immunological responses by modulating apoptosis. It has been emphasized how important TNF and heterogeneous nuclear ribonucleoprotein L (THRIL) are as lncRNAs that are linked to innate immunity (65). After the innate activation of THP1 macrophages, it was chosen among a vast number of differentially expressed lncRNAs. Additionally, Eftekharian et al. demonstrated dysregulation of three lncRNAs, including FAS-AS1, THRIL, and plasmacytoma variant translocation 1 (PVT1), in MS patients. OIP5-AS1 was identified for the first time as a critical factor in early CNS development in zebrafish. It has been demonstrated that OIP5-AS1 decreases the cyclin G-associated kinase (GAK) mRNA stability required for mitotic development (66). These findings imply that OIP5-AS1 inhibits cell growth via lowering GAK levels in combination with RNA-binding proteins like HuR1. HuR1 accessibility seems to be restricted to the cyclin D1, cyclin A, and SIRT1 (silent information regulator 1) target mRNAs. Additionally, the results demonstrated that aberrant mitosis followed the down-regulation of OIP5-AS1 and was caused by a rapid up-regulation of GAK regulation, suggesting that OIP5-AS1 was at least repressed by lowering GAK expression. HUR1, a protein that interacts with OIP5-AS1 conserved sequence motifs, appears to have an effect downstream of OIP. AS1 has been found to be expressed in inflammatory diseases such as MS and encephalomyelitis, astrocytes, and the HUR1 gene (67).

CONCLUSION

The relevance of lncRNAs in the pathogenesis of MS has been shown through altering epigenetic mechanisms and their function in molecular processes. Epigenetic mechanisms have been found to play a significant part in the development of MS. Additionally, it has been shown that the abnormal expression of several lncRNAs is closely associated with the development of various tumors, leading to the consideration of many lncRNAs as possible therapeutic targets, stand-alone prognostic predictors, and important biological markers in malignancies. Several studies have indicated that lncRNAs are important direct targets for therapeutic treatments in hepatic illnesses. Due to their functional

role in controlling the expression of numerous genes at the transcriptional level or after transcription, along with proteins and signaling pathways, these studies identify lncRNAs as a key factor in the pathogenesis of MS. This information may one day be used to develop a therapeutic strategy for MS patients. But research in this area is still in its early stages, and more work needs to be done to figure out what lncRNAs do in MS.

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