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REVIEWS

Epigenetic Mechanisms of the Pathogenesis of Multiple Sclerosis

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Abstract—Multiple sclerosis is a chronic autoimmune inflammatory and neurodegenerative disease leading to demyelination of nerve cells in the brain and the spinal cord. Despite extensive research, the pathogenesis of this disease is not fully understood. A review of most recent experimental studies shows that epigenetic mechanisms regulating gene expression, such as DNA methylation, histone acetylation, and microRNAs, play the crucial role in the pathogenesis of multiple sclerosis. Analysis of the published data suggests that multiple sclerosis develops as a result of abnormal regulation of gene expression in the nervous and immune systems.

Keywords: multiple sclerosis, epigenetics, DNA methylation, microRNA
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Multiple sclerosis (MS) is a chronic progressive autoimmune disease of inflammatory and neurodegenerative nature that affects the central nervous system. According to the recent data, the number of MS patients worldwide approaches two million, and the number of female patients is significantly higher than the number of affected men. The disease occurs more frequently in the families of MS patients: the risk level in patients' relatives is 20–50 times higher than the population mean [1–3].

On the pathomorphological level, MS develops in the form of inflammation and demyelination involving oligodendrocytes, axons, and neurons, with subsequent formation of sclerotic plaques in the white matter of the brain and the spinal cord, which decreases the rate neurotransmission, causes impulse dissipation, and produces a broad range of clinical signs. Myelin sheath of neurons is disrupted as a result of focal infiltration of lymphocytes, macrophages, and antibodies, which is accompanied by local connective tissue growth at the affected sites and development of inflammation and neurodegenerative processes [4]. In spite of the longstanding research concerning the clinical presentation of MS, as well as its genetic, immunological, and environmental aspects, the mechanisms of its pathogenesis still have not been clarified [4]. The current consensus opinion holds that this disease is induced by a combination of genetic and environmental factors (e.g., smoking, insufficient insolation and vitamin D deficit, or viral infections).

The hypothesis that there exists genetic predisposition to MS was proposed long ago and has been consistently confirmed in numerous epidemiologic, population-based, and twin-based studies. These aspects have been comprehensively discussed in a number of reviews [5–11]. In monozygotic twins, MS concordance constitutes approximately 30%, which is six times higher than in dizygotic twins (5%) [12].

Studies aimed at identifying genes of predisposition to MS have been employing different approaches; they were analyzed in detail by Favorova et al. [9, 10]. The most informative were genome-wide association studies (GWAS). Using this approach, a total of 13 studies have revealed 120 loci (according to some sources, 200 loci) significantly associated with MS. In nearly all of these studies, MS exhibited significant association with the *HLA* locus (OR = 2.05–3.3) and specifically with *HLA-DRB1* class II. The group with the highest risk of MS are carriers of *HLA-DRB1**15:01 haplotype. Other MS-associated genes that do not belong to the *HLA* locus have moderate *OR* values (1.03–1.3); among them, a considerable number is involved in the functioning of T cells and development of inflammatory processes. Extended lists of MS-associated polymorphic loci and their putative role in the pathogenesis of MS are provided and comprehensively discussed in other reviews [9–11].

It should be noted, however, that the lists of candidate genes of MS risk identified in different association studies are not quite consistent [13]. This fact has invited several hypotheses supposing, in particular, that this may be due to ethnic heterogeneity of the groups studied, differences in MS phenotypes, limited ethnic diversity of patients' samples, genotyping

errors, lack of information on environmental factors, diagnostic errors, and other possible factors.

Certainly, association studies provide important information concerning the genetic component of MS; however, in the absence of information about the functional state of each particular gene accounting for tissue specificity of their expression, it is rather difficult to evaluate their contribution to MS pathogenesis. From this point of view, it is critically important to investigate the mechanisms that regulate gene expression irrespective of their nucleotide sequence, i.e., epigenetic mechanisms. This notion is based on the above-mentioned fact that MS concordance in monozygotic twins is incomplete, which suggests that nongenetic factors also play a significant role in predisposition to MS. Moreover, it was supposed that epigenetic modifications may be involved in the initiation and development of MS, probably while the pattern of epigenetic modifications of DNA and histones changes in response to environmental factors [14].

DNA METHYLATION

The best-studied epigenetic mechanism is enzymatic methylation of DNA. In mammalian DNA, methylation mainly occurs at CpG dinucleotides and is mediated by DNA methyltransferases that transfer a methyl group from S-adenosylmethionine as a donor onto C_5 atom of the cytosine base. DNA methylation is a dynamical process, and its level in individual tissues is determined by the relative activities of DNA methyltransferases and DNA demethylases, depending on the physiological state of the cells.

DNA methylation is a negative regulator of gene expression, which is due to changes in the chromatin structure, namely to its compacting. There is a hypothesis that DNA methylation is not the cause of gene silencing but rather its consequence and serves to stabilize the silencing of particular genes [15]. Modified DNA regions subsequently bind methyl-binding proteins and ATP-dependent multiprotein chromatin-remodeling complexes. It should be noted that methylation of individual DNA loci is accompanied by simultaneous histone desacetylation.

The role of DNA methylation in the pathogenesis of MS has been discussed in a number of reviews [16–18]. A comparative genome-wide study of DNA methylation in peripheral blood mononuclear cells of MS patients and healthy subjects revealed significant differences in the DNA methylation patterns. DNA of MS patients exhibits differential methylation of CpG dinucleotides, in particular, hypermethylation in patients with primary progressive MS and hypomethylation in those with relapsing-remitting MS. These results definitely indicate that DNA methylation is involved in the pathogenesis of MS and associated with its different clinical forms [19].

Comparative analysis of DNA methylation profiles in $CD4^+$ and $CD8^+$ T cells from peripheral blood of MS patients and healthy subjects performed by Bos et al. showed that DNA of $CD8^+$ cells had a distinct methylation pattern irrespective of the disease status and was hypermethylated in MS patients [20]. In the same study, no significant differences were detected in the methylation of individual CpG dinucleotides in the genomes of these cells, as well as in the structure of more than 140 genes associated with MS. At the same time, the data obtained by Maltby et al. showed an association between the pattern of DNA methylation in $CD8^+$ T cells and relapsing–remitting form of MS [21]. A study by Graves et al. analyzed the genomic profiles of DNA methylation in $CD4^+$ T cells of patients with relapsing-remitting MS and healthy subjects and revealed a higher level of methylation in the *HLA-DRB1* region in MS patients [22]. However, this result was not confirmed by a different study [23], which reported *HLA-DRB1* hypomethylation in $CD4^+$ T cells of MS patients; presumably, this may increase the risk of disease because of overexpression of this gene. At the same time, Rhead et al. [24] did not observe *HLA-DRB1* overexpression in $CD4^+$ T cells of MS patients, probably because demethylation involved not the gene promoter but rather CpG dinucleotides in the structural part of the sequence. The authors explain these contradictions by heterogeneity of the MS patients' group by the form of disease, the treatment status, and the presence of genetic variations at the methylation sites, i.e., the presence of single-nucleotide substitutions in the loci of interest.

In contrast to the mechanisms of inflammation, the pathogenesis of neurodegeneration in MS is understood insufficiently. From this point of view, an interesting study was performed by Chomyk et al. [25], who investigated demyelination patterns of hippocampal neurons in patients with MS and identified the genes that changed their transcriptional activity as a result of methylation or demethylation after demyelination of hippocampal cells, which may contribute significantly to changes in the synaptic plasticity, memory, and neuron survival in MS patients. The authors identified six such genes, in particular, *AKNA*, which exhibited demethylation of the promoter region and, accordingly, an increase in the transcriptional activity in demyelinated cells. Demyelination of hippocampal neurons is also accompanied by hypomethylation of the promoter region of *SFRP1*, which encodes a protein inhibiting the WNT signaling system [26]. At the same time, neuron demyelination is associated with hypermethylation of *WDR81*, *NHLH2*, and *PLCH1* promoters, and accordingly, with a decrease in their mRNA levels. NHLH2 is a positive regulator of melanocortin receptors and modulates memory and learning, while a decrease in PLCH1 levels is accompanied by impairment of short-term memory [27, 28]. A study by Moscarella et al. detected hypomethylation of

PAD2 in MS patients; this gene encodes peptidyl-arginine-deiminase 2, an enzyme participating in citrullinization of myelin basic protein [29]. The modified form of myelin basic protein is less stable, and transformation of positively charged arginine residues into neutral citrulline can make the structure less compact, lead to protein disintegration, and provoke auto immune reaction to myelin basic protein.

POSTTRANSLATIONAL HISTONE MODIFICATIONS

Posttranslational histone modifications are a key mechanism of epigenetic regulation of gene expression, and their role in the development of autoimmune disease has been comprehensively discussed in a review by Wang et al. [30]. To date, eight modifications of histones H3 and H4 have been described; the best studied of them are acetylation/deacetylation and methylation/demethylation of lysine and arginine residues at certain amino acid positions of histone molecules. These modifications are of dynamical character, and their status in a cell depends on the activity of two opposing functional systems: histone acetyltransferases and histone deacetylases or methylases and demethylases, respectively. Neutralization of positively charged lysine residues in the N-terminal regions of histone molecules weakens the electrostatic interaction between histones and DNA and leads to decompacting of the chromatin structure, which in turn facilitates the access to DNA for transcription factors. Relaxed chromatin structure characterized by hyperacetylation of nucleosomal histones is a feature of areas containing actively expressed genes [31]. There exists convincing evidence that histone modification is involved in the regulation of different biological processes in immune system cells, in particular, in differentiation of Th1, Th2, Th9, Th17, and Treg cells. At the same time, very few studies have been investigating the role of this epigenetic mechanism in pathogenesis of MS. For instance, Shi et al. [32] showed that $CD4^+$ T cells of MS patients exhibited elevated expression of *ARRB1,* which encodes β-arrestine, a protein playing a central role in T cell survival. In a mouse model of experimental autoimmune encephalomyelitis, it was shown that ARRB1-dependent acetylation of histone H4 in the *BCL2* promoter region led to overexpression of this gene. These results suggest that epigenetic histone modifications might be contributing to the pathogenesis of MS.

MICRORNAs

Recent publications contain a substantial body of experimental data suggesting that the mechanisms of epigenetic regulation of gene expression include one more component that involves microRNAs (miRNAs). miRNAs are endogenous single-stranded nucleotide chains 19–22 bases long. Genes that encode miRNAs can be present in the genome as separate transcriptional units or be located within introns and exons of protein-coding genes, as well as at intron–exon boundaries [33]. They are transcribed by RNA polymerase II from their own promoters in the form of pre-miRNA precursors of ~100 bases. Similarly to protein-coding transcripts, a pre-miRNA undergoes capping at the 5' end and polyadenylation at the 3'-end. Next, this transcript is recognized and cleaved by protein complex Drosha-DGCR8 producing an intermediate sequence 70 bases long, which can form a hairpin structure. After that, the product binds to a GTP-dependent protein exportin 5, is transported to the cytoplasm, and processed by cytoplasmic RNA polymerase III Dicer to produce 22-bp-long double-stranded structures. One of the strands of this RNA is included in a large protein complex comprising miRISC, TRBP, and Ago2, subsequently giving rise to mature miRNA. Finally, miRISC is transferred onto an mRNA target, miRNA binds to the homologous sequence, and, depending on the force of this interaction, mRNA either is cleaved or forms a local double-stranded structure that prevents its translation. These events are discussed in detail in several reviews [33–37].

miRNAs can regulate gene expression both on the transcriptional and post-transcriptional levels. In the first case, miRNA binds to individual DNA loci and recruits proteins that participate in chromatin remodeling, in particular, heterochromatin formation, which hinders DNA accessibility for transcriptional factors and downregulates transcription. In the second case, mammalian miRNAs interact with complementary fragments of 3'- or 5'-untranslated regions of mRNA, inducing degradation of the mRNA target (only a short stretch of 2–7 bases needs to be exactly complementary) [38, 39]. Along with activating cleavage of the target transcript, mammalian miRNAs sometimes block mRNA translation or induce their deadenylation, decreasing their half-life period [40].

To date, more than 2500 miRNA species have been detected in the human genome; all of them have been sequenced and their sequences are deposited in the miRBase database [41]. It is known that the same miRNA type can participate in interactions with several mRNA targets, probably, to coordinate their expression levels under specific physiological conditions. On the other hand, one and the same mRNA can interact simultaneously with several miRNA species, which probably reflects the coordination among several signaling pathways involved in posttranscriptional regulation of the gene activity.

miRNAs are extensively transcribed in the cells of the immune and nervous systems, which indicates the importance of studying them to elucidate the pathogenetic mechanisms of inflammatory and neurodegenerative diseases, including autoimmune ones. For this reason, the number of studies aimed at comparative

analysis of miRNA expression in MS patients and healthy subjects has recently been growing like an avalanche.

A comparative study of miRNA expression in peripheral blood mononuclear cells of MS patients detected 21 differentially expressed miRNAs, and 12 of them were overexpressed [42]. In another study, 18 miRNAs were differentially expressed in peripheral blood cells of MS patients in comparison to controls; potentially, they might modulate the expression of 128 genes [43]. Below, we will consider individual miRNA species and their putative role in the pathogenesis of MS in more detail.

Involvement of miRNAs in autoimmune processes was first demonstrated in mouse T cells in 2007 [44]. Two miRNAs, miR-146a and miR-155, were shown to be the principal regulators of autoimmune reactions. It was found that the targets of miR-146a are TNF-receptor associated protein TRAF6 and IL-1 receptor-associated kinase 1 (IRAK-1). Elevated expression of this miRNA suppressed the activity of the NF-κB signaling cascade and inhibited the expression of TNFα, IL-1b, IL-6, and IL-8 [45].

It is interesting to note that miR-155 was the first miRNA investigated in the context of inflammation, because its expression in different subpopulations of immune cells exhibits pronounced modulation in response to activation of Toll-like receptors, proinflammatory cytokines, and exposure to specific antigens. MiR-155 regulates the activity of more than 300 genes involved in immune response [46, 47]. Among these genes, many encode proteins of critical importance: CEBPB, a transcription factor; SMAD2, which mediates TGF-β signaling and regulates cell proliferation, apoptosis, and differentiation; VCAM1, a cell adhesion molecule; CASP3, for which mRNA interaction with miR-155 inhibits apoptosis of activated macrophages [48]; MTS kinase activated by proapoptotic agents and participating in the regulation of cell proliferation; S1PR1 (sphingosine-1-phosphate receptor), the induction of which enhances intercellular interactions, and SOCS1 protein acting as a cytokine pathway suppressor. Thus, miR-155 is involved in the regulation of such fundamental biological processes as cell division, growth, and differentiation, intracellular signal transduction, adhesion, and apoptosis, which may be significant for the pathogenesis of MS.

A study by Junker et al. [49] showed that miR-155 expression was elevated in brain cells of MS patients at the stage of relapse, which was accompanied by enhanced phagocytosis of myelin caused by macrophage activation due to decreased CD47 expression in CNS cells. These data indicate the progression of neurodegenerative processes in MS patients. It should be noted that some authors disagree with this point of view. For instance, Fenoglio et al. [50] did not detect significant changes in miR-155 expression in MS patients, probably because its expression was evaluated at different clinical stages, e.g., relapse or remission. The role of miR-155 in the pathogenesis of MS is not limited to the examples described above; in particular, miR-155 is considered as a key factor modulating development, maturation, maintenance, and functioning of different immunocompetent cells; in more detail, this information is available in other reviews [51–53].

miR-30a inhibits IL-17-mediated activation of NF-κB and MAPK signaling pathways, which decreases the synthesis of proinflammatory cytokines and chemokines. The inhibiting effect of miR-30a is due to its binding to *TRAFIP2* mRNA. Therefore, downregulation of miR-30a expression in autoimmune diseases can aggravate inflammation induced by IL-17 [54]. A study by Qu et al. showed that the expression of miR-30a decreased during Th17 differentiation and in the course of demyelination both in MS patients and in the model of experimental autoimmune encephalomyelitis [55]. In vivo, high levels of miR-30a suppress differentiation of naive T cells to Th17; subsequently, it was shown that this process is mediated by miR-30a interaction with *IL21R* mRNA; i.e., this transcript is targeted by miR-30a, which probably inhibits the inflammatory process.

A study by Lorenzi et al. showed that the posttranscriptional level of *BCL-2* expression in $CD4^+$ T cells is regulated by miR-15a [56]. In MS patients, the level of miR-15a expression is relatively low, which is accompanied by elevated expression of *BCL2*. Therefore, miR-15a may be responsible for inhibition of apoptosis in $CD4^+$ and $CD8^+$ T cells and for an increase in the pool of autoreactive immune cells. Moreover, further miR-15a targets are *TNFAIP1*, *NFKB1*, *YAP1*, *SOX5*, and *RICTOR*, and their elevated expression in $CD4^+$ and $CD8^+$ T cells can facilitate their proliferation, migration, and invasion and thus promote progression of the pathological process [57, 58].

Similarly to miR-15a, miR-16-1 inhibits the apoptosis of $CD4^+$ and $CD8^+$ T cells [56]. It was supposed that decreased miR-16-1 expression in $CD4^+$ and $CD8^+$ T cells of MS patients can result in overexpression of the genes it controls: *CCND1*, *CCNE1*, *SOX5*, *WT1*, and *YAP1*, and stimulate proliferation of $CD4^+$ and $CD8^+$ T cells [51].

Decreased miR-20b expression in $CD4^+$ T cells of MS patients is accompanied by elevated expression of the genes encoding transcription factors RORγt and STAT3, which shifts differentiation of naive T cells into the Th17 direction and accordingly, promotes an increase in the levels of proinflammatory cytokine IL-17 [59, 60]. It has been supposed that miR-20b can play an important role in the pathogenesis of MS by modulating the expression of HIF-1 transcription factor and VEGF [51]. These factors regulate angiogene-

sis, cell proliferation (in particular, in vascular endothelial cells), apoptosis, and glucose metabolism.

$CD4^+$ T cells of MS patients exhibit elevated expression of miR-27b [25]. By interacting with the 3'-untranslated regions of *BMI1*, *GATA3*, and *PPARG* transcripts, miR-27b suppresses their expression, which shifts the balance from Th2 to Th1 cells, i.e., promotes the synthesis of proinflammatory cytokines. At the same time, miR-128 in T cells of MS patients inhibits only *BMI1* and *GATA3* expression, which also induces a shift from Th2 to Th1 and thus contributes to the pathogenesis of MS [61].

Miyazaki et al. detected a significant increase in miR-132 expression in B cells of MS patients [62]. The target of miR-132 is the transcript of sirtuin-1, and decreased expression of this protein induces the synthesis of proinflammatory cytokines LTα and TNFα, important elements of MS pathogenesis. In contrast, B cells of MS patients exhibited significantly decreased expression of miR-320a, which is targeted against *MMP9* [63]. Increased levels of MMP-9 metalloproteinase can damage the blood–brain barrier, increase its permeability, and, as a consequence, promote the development of MS.

To understand the mechanisms of MS pathogenesis, it also seems interesting to consider miR-let-7, which is targeted against the mRNA of transcription factor PLZF. Inhibition of its expression stimulates differentiation of INFγ-producing NKT1 cells while suppressing NKT2 and NKT17 cells, which produce IL-4 and IL-17 [64].

Abnormally high levels of miR-125a-3p expression were detected in the cerebrospinal fluid of MS patients with active demyelinating lesions by Reijerkerk et al. [65]. This miRNA regulates the expression of myelin genes in CNS; therefore, its aberrant expression can block differentiation of oligodendroglial cell precursors because of remyalination difficulties.

A study by Wu et al. [66] found that miR-448 expression was significantly increased in mononuclears of peripheral blood and cerebrospinal fluid of MS patients, and these miRNAs were mainly produced by $CD4^+$ T cells, especially Th17. Expression of miR-448 is induced by IL-1β, and its principal target is *PTPN2* mRNA, which encodes protein tyrosine-phosphatase non-receptor type 2, a known antiinflammatory agent that can suppress Th17 differentiation. Downregulation of *PTPN2* expression may promote Th17 differentiation in MS patients and thus aggravate the disease, so a positive correlation between miR-448 expression levels and the disease severity seems a logical finding.

It is important to note that the provided list of miRNAs for which expressional dysregulation is related to pathogenetic mechanisms of MS is not an exhaustive one. Our review mainly describes the involvement of certain miRNA classes in the regulation of T-cell differentiation, inflammation, demyelination, neurodegeneration, and apoptosis in MS. In more detail, the role of miRNAs in the development of autoimmune diseases, including MS, was analyzed in recent reviews and experimental articles by Huang et al. [51], Kiselev et al. [67], Baulina et al. [68], Wang et al. [69], and Esmailzadeh et al. [70].

Thus, the data discussed above indicate that the pathogenesis of MS involves a large number of genes and epigenetic mechanisms regulating their expression. All these mechanisms work in coordination and serve to maintain homeostasis in the cells.

As suggested by the results of experimental studies, epigenetic modification in MS involves genes of individual transcription factors, genes regulating apoptosis and proliferation, as well as genes that control the functional state of the immune and nervous system cells. Furthermore, epigenetic processes in MS lead to changes in T cell polarization in favor of Th1 and Th17 and production of proinflammatory cytokines, as well as to decrease in the subpopulation of regulatory T-cells as a result of methylation of the gene encoding transcription factor FOXP3.

To date, it remains unclear whether it is primarily epigenetic modifications that affect the risk of MS or the disease itself alters the patient's epigenetic profile. The fact is that the key genes and particular environmental factors that interact to trigger the development of MS have not been identified so far. In this context, much effort has been invested into comparative analysis of differential gene expression in MS patients and healthy subjects, which indeed revealed significant differences in the expression levels of individual genes between these two phenotypic states. However, the results of these studies may be inconclusive, because the differences in the expression patterns of individual genes may be caused by single-nucleotide substitutions in either regulatory or the coding region, as well as by epigenetic processes. Therefore, as it was noted by Creanza et al., the results obtained exclusively by differential expression analysis of individual genes are insufficiently informative for identification of the key genetic factors of complex diseases [71].

A further difficulty in identifying the initial functional state of the key genes aberrant expression of which induces the pathological condition in MS is related to the fact that the patients are, as a rule, receiving permanent drug treatment. It is known that the pharmacological effect of medical agents is frequently mediated by modulation of gene expression, in particular, via epigenetic mechanisms. For instance, interferon beta-1b, an immunomodulating drug used for MS therapy activates the transcription of interferon-sensitive genes, e.g., *IFI27, MX1, IFI44L, XAF1*, *ISG15, SAMD9L,* and *LGAL9* [72]. Demethylfumarate, another compound used for MS treatment, causes DNA hypermethylation and histone deacetylation, inhibiting the expression of certain proinflammatory cytokines [73, 74].

CONCLUSIONS

To sum up, DNA methylation is a key epigenetic mechanism that controls gene activity on the transcriptional level. Immune system cells of MS patients exhibit differential DNA methylation patterns depending on the stage of the disease. The question of whether DNA methylation in MS is induced by exposure to environmental factors or represents a mechanism that consolidates aberrant gene expression in the course of disease development is currently a subject of vivid discussion. Indeed, the researchers generally assume that initiation and development of MS depends on environmental factors, so their contribution to this process must be significant. At the same time, taking into account the information that gene silencing and DNA methylation may be separated in time [15], it seems likely that DNA methylation in MS may serve to consolidate a molecular event that has already happened (in particular, for individual constitutively expressed loci). Accordingly, it cannot be ruled out that this mechanism is involved in the maintenance of permanent functional activity of aberrantly expressed genes that have acquired this status in the course of the autoimmune disease; i.e., in this case, DNA methylation is not the cause but a consequence of modifications in gene expression associated with disease progression. There is no real antagonism between these two points of view. In fact, DNA methylation is a reversible and dynamical process. As it was mentioned above, certain DNA loci exhibit hypomethylation in MS patients in remission, while the same loci can be hypermethylated at the stage of disease progression.

It is important to note that, in addition to CpG dinulceotides, mammalian DNA methylatransferases DNMT3a and DNMT3b can also methylate cytosines in dinucleotides CpA, CpT, and CpT, which is known as non-CpG methylation [75]. Although their role in the regulation of gene expression is unclear, these methylated dinucleotides, especially CpA, can interact with methyl-binding proteins, in particular, MeCP2, and alter chromatin structure. Unfortunately, there is hardly any data available on non-CpG methylation in the context of MS pathogenesis. Taking into account that the intensity of non-CpG methylation is the highest in neurons and glial cells, it seems reasonable to expect that this epigenetic mechanism can be involved in MS pathogenesis, which will probably become a subject of future research.

Among epigenetic mechanisms, the central position belongs to miRNAs, which regulate gene expression on the posttranscriptional level and are predominantly targeted against mRNAs of the genes transcribed in the cells of the nervous and immune systems. Under normal conditions, the principal role of miRNAs is to regulate the expression of genes that serve to maintain the homeostasis of innate and acquired immune response mechanisms in the cells. As a consequence, aberrant expression of individual miRNAs or their clusters can lead to different pathologies, including those of autoimmune character. Unfortunately, their role in this process has not been clarified yet. It is known that the major genetic risk factor for MS in nearly all populations studied is the haplotype *HLA-DRB*1*15:01. The initial aberrant expression of this gene observed in MS patients (the causes of which are unknown) can act as a factor of genomic destabilization, and actually give rise to a new functional state of the cell. If the cell does not subsequently undergo apoptosis, it will tend to consolidate the newly acquired state by synchronizing the expression of genes activated by a limited number of transcription factors, including those that control the expression of the principal risk-related gene. This process does not require dramatic changes in expression patterns, although they may occur in some cases. miRNAs can probably act to correct tissue-specific expression of the genes functionally related to the *HLA* locus in order to ensure homeostasis of the cell in its new state. This means that the pathogenetic mechanisms of MS are most probably related to molecular aberrations that affect the expression of numerous genes and transcription factors that control them. Finally, it should be underlined that investigation of the spectra of expressed miRNAs, including circulating ones, in different tissues is not only important for the understanding of MS pathogenesis, but could also be extremely useful for diagnostic purposes and for evaluation of the drug therapy efficiency in patients with MS.

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COMPLIANCE WITH ETHICAL STANDARDS

The authors declare that they have no conflict of interest. This article does not contain experiments performed using humans or animals as objects.

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