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DERLEME **REVIEW**

Emerging Roles of miR-146a-5p in Multiple Sclerosis: Evidence from Recent Studies

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Abstract

Multiple sclerosis is a complex neuroimmune disorder characterized by chronic inflammation, demyelination, and neurodegeneration. Among the various molecular players, microRNA-146a-5p has emerged as a critical, albeit complex, regulator of the neuroimmune landscape in MS. This review brings together current evidence highlighting the dual role of miR-146a-5p, which, while primarily functioning as an anti-inflammatory regulator, is also thought to respond as part of compensatory mechanisms depending on cell type and context. Its expression is dynamically regulated in the central nervous system, cerebrospinal fluid, and blood, correlating with disease activity, treatment response, and clinical metrics such as the Expanded Disability Status Scale (EDSS). We explore its compartmentalized dysregulation, notably in active gadolinium-enhancing lesions, and its potential as a sensitive diagnostic and prognostic biomarker. The involvement of miR-146a-5p in key cellular processes -including microglial activation, oligodendrocyte maturation, and astrocyte pathology- underscores its therapeutic relevance. Furthermore, we discuss its interaction with environmental factors like Vitamin D and its role in exosome-mediated intercellular communication. Preclinical studies demonstrating that manipulating miR-146a-5p levels can ameliorate neuroinflammation and promote remyelination its potential as a novel therapeutic target. Future research should focus on clarifying the context-specific regulatory roles of miR-146a-5p and on developing safe, targeted delivery strategies to support its therapeutic potential.

Keywords: *Multiple Sclerosis, miR-146a-5p, Biomarker, MicroRNA, Neuroinflammation*

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Multiple Sklerozda miR-146a-5p'nin Ortaya Çıkan Rolleri: Güncel Çalışmalardan Kanıtlar

Özet

Multipl skleroz, kronik inflamasyon, demiyelinizasyon ve nörodejenerasyon ile karakterize karmaşık bir nöroimmün hastalıktır. Çeşitli moleküler düzenleyiciler arasında, mikroRNA-146a-5p, MS'te nöroimmün ortamın kritik ancak kompleks bir düzenleyicisi olarak öne çıkmıştır. Bu derleme, esas olarak anti-inflamatuvar bir düzenleyici olarak işlev görmesine rağmen, hücre tipine ve bağlama bağlı olarak kompansatuar mekanizmaların bir parçası olarak da yanıt verebileceği düşünülen miR-146a-5p'nin çift yönlü rolünü vurgulayan güncel çalışmaları bir araya getirmektedir. miR-146a-5p'nin ekspresyonu merkezi sinir sistemi, beyin omurilik sıvısı ve kanda dinamik olarak düzenlenmekte; hastalık aktivitesi, tedavi yanıtı ve Genişletilmiş Engellilik Durum Ölçeği (EDSS) gibi klinik göstergelerle ilişki göstermektedir. Aktif gadolinyumla zenginleşmiş lezyonlarda belirgin olan bölgesel düzensizliği ve duyarlı bir tanısal ve prognostik biyobelirteç olarak potansiyeli ele alınmıştır. miR-146a-5p'nin mikroglia aktivasyonu, oligodendrosit olgunlaşması ve astrosit patolojisi gibi temel hücresel süreçlerdeki rolü, terapötik önemini vurgulamaktadır. Ayrıca, D vitamini gibi çevresel faktörlerle etkileşimi ve eksozom aracılı hücreler arası iletişimdeki rolü de tartışılmıştır. miR-146a-5p düzeylerinin düzenlenmesinin nöroinflamasyonu hafiflettiğini ve remiyelinizasyonu desteklediğini gösteren preklinik çalışmalar, bu molekülün yeni bir terapötik hedef olarak potansiyelini vurgulamaktadır. Gelecekteki araştırmaların, miR-146a-5p'nin bağlama özgü düzenleyici rollerini netleştirmeye ve bu molekülün terapötik potansiyelini destekleyecek güvenli ve hedefe yönelik taşıma stratejileri geliştirmeye odaklanması önemlidir.

Anahtar Kelimeler: *Multipl Skleroz, miR-146a-5p, Biyobelirteç, MikroRNA, Nöroinflamasyon*

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INTRODUCTION

1. Multiple Sclerosis and miR-146a-5p

1.1. Multiple Sclerosis and miRNAs

Multiple sclerosis (MS) is an immune-mediated neurodegenerative disease of the central nervous system (CNS), with numerous genetic risk factors contributing to its pathogenesis (1). The disease is marked by demyelination and relapsing attacks, where reduced neuronal repair mechanisms and progressive neurodegeneration amplify neuroinflammation, further dysregulating the inflammatory milieu of surrounding CNS cells (2, 3). The majority (85%) of cases initially present as relapsing-remitting MS (RRMS), characterized by acute inflammatory attacks causing neurological dysfunction followed by partial or complete remission. Over time, typically within 20 years, most RRMS patients transition to secondary progressive MS (SPMS), marked by continuous neurological deterioration independent of relapses (4, 5).

MicroRNAs (miRNAs) are small non-coding RNAs that serve as critical regulators of diverse biological processes (6, 7). miRNAs regulate gene expression post-transcriptionally by mostly binding to complementary sequences in the 3'-UTRs of target mRNAs, leading to mRNA degradation or translational repression (8, 9). Figure 1 details the miRNA biogenesis pathway (10, 11). This process requires miRNA incorporation into the RNA-induced silencing complex (RISC), where the mature miRNA guides Argonaute proteins -the core catalytic component of RISC- to its target mRNA to execute silencing. Although miRNAs predominantly target 3′UTRs to promote mRNA degradation or translational repression, they can also bind to coding sequences (CDS) or 5′-UTRs or other non-canonical regions to inhibit protein expression. Similar to their interactions with 3′-UTRs, binding to these non-canonical sites contribute to miRNAmediated gene silencing (12).

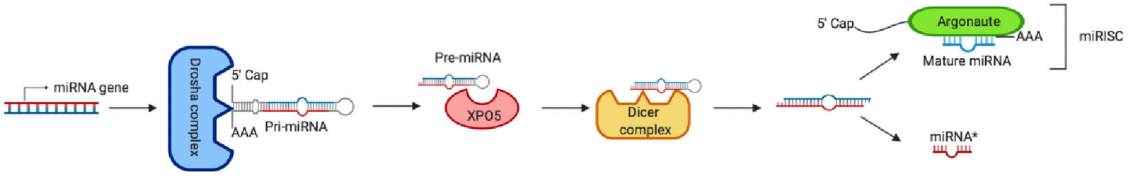

Figure 1: miRNA Biogenesis (10, 11)

1.2. miR-146a-5p

The dysregulation of neuroimmune responses is a hallmark of neuroinflammatory disorders, and miR-146a-5p has emerged as a critical post-transcriptional regulator of this process. By fine-tuning key pathogenic signaling pathways, miR-146a-5p represents a novel and promising therapeutic target and biomarker for these diseases (13). Endogenous miR-146a-5p is a promising, yet complex, inflammatory biomarker with expression that shifts with disease chronicity. Evidence indicates lower or stable levels during acute neuroinflammation, contrasting with a progressive increase in chronic settings. This later upregulation may represent a compensatory anti-inflammatory response aimed at resolving inflammation and restoring neuronal homeostasis (14).

In the following sections, we systematically evaluate recent evidence regarding miR-146a-5p in MS, focusing on its biomarker potential, compartment-specific regulation, therapeutic implications, and cell-type specific mechanisms.

2. Clinical and Mechanistic Dimensions of miR-146a-5p in Multiple Sclerosis

2.1. Vitamin D and Its Influence on miR-146a-5p in Multiple Sclerosis

Vitamin D is vital for maintaining bone integrity and also contributes to immune regulation as well as regulating cell growth and division (15). It has been shown to attenuate inflammation by reducing pro-inflammatory markers and increasing anti-inflammatory cytokines (16). Moreover, its status seems to be associated with both MS incidence and disease activity, with deficiency correlating to higher risk of development and worse clinical outcomes (17). Another study shows that Vitamin D may mitigate EAE, an animal model of MS, by suppressing pro-inflammatory Th17 cell differentiation and IL-17 production. This effect involves upregulation of specific microRNAs that regulate the Th17 transcription factor RORγ-t (18).

One study reported a possible association between altered miR-146a-5p expression, low vitamin D levels, and increased disease burden in individuals with RRMS. miR-146a-5p expression was found significantly lower in RRMS patients compared to healthy individuals. miR-146a-5p, known for its anti-inflammatory function, initially showed increased expression with rising vitamin D levels, suggesting a potential protective response. However, the finding that miR-146a-5p's expression declined when vitamin D levels exceeded 40 ng/ml (19) may reflect a regulatory shift towards immune balance once sufficient Vitamin D status is achieved. Additionally, miR-146a-5p was downregulated in patients with higher EDSS scores, indicating a possible link between reduced anti-inflammatory regulation and increased disease severity (19). Given the central role of neuroinflammation in MS pathogenesis, these findings may have broader implications, supporting the potential of vitamin D-miR-146a-5p interactions as a therapeutic avenue in MS as well.

2.2. Compartmentalized Dysregulation: miR-146a-5p as a CSF Biomarker for Active MS Lesion

To assess and characterize active lesions in MS patients, gadolinium-enhanced magnetic resonance imaging (MRI) can be used. Its mechanism lies in enhancing areas at which the integrity of the BBB has been compromised due to an inflammation caused by immune-related responses (20). Recent evidence suggests that certain miRNAs may show localized expression in MS, with cerebrospinal fluid (CSF) often presenting a more disease-relevant profile than peripheral compartments.

A recent study reported that differentially expressed miR-146a-5p in the CSF was noticed in RRMS patients. miR-146a-5p was significantly upregulated in cerebrospinal fluid, a differential expression pattern that effectively distinguishes RRMS from controls (21). In RRMS patients, cerebrospinal fluid analysis revealed that miR-146a-5p expression was elevated in those who were untreated or receiving first-line therapy, and was higher compared to patients receiving second-line treatment. Moreover, its expression was upregulated in gadolinium-enhancing (Gd+) active white matter lesions in the brain, suggesting a link between miR-146a-5p dysregulation and MRI detectable inflammation (22) . Additionally, Muñoz-San Martín et al. found an overexpression of miR-146a-5p in the CSF of gadolinium-enhancing MS lesions, which shows a similar pattern to the previous study. There was also a correlation between this miRNA and the CSF neurofilament light chain, which is reported as one of the biomarkers for axonal damage in MS. However, while an increased regulation of miR-146a-5p was detected in the CSF, no difference between its regulation in plasma was noticed between Gd+ and Gd- patients again pointing to the compartmentalized nature of regulation (23).

2.3. miR-146a-5p as a Biomarker for Treatment Response and Disease Course

The clinical relevance of miR-146a-5p in MS appears to be linked to its association with treatment response and longitudinal disease activity rather than serving as a static marker of tissue damage. Evidence suggests that miR-146a-5p may function as a context-dependent indicator of ongoing inflammatory dynamics and compensatory regulatory mechanisms. In patients treated with Glatiramer Acetate (GA), serum levels of miR-146a-5p were elevated in those who experienced confirmed disability progression at two years, indicating an association with continued disease activity (24). This observation aligns with findings from Dominguez-Mozo et al., who reported a positive correlation between miR-146a-5p levels and EDSS scores. The authors proposed that this upregulation likely reflects a compensatory anti-inflammatory response rather than a direct pathogenic effect, where higher levels correspond to a greater underlying disease burden (25).

The sensitivity of miR-146a-5p to different therapeutic mechanisms is further evidenced by studies on Dimethyl Fumarate and intensive immunomodulation. While plasma levels may be lower at baseline compared to healthy controls, longitudinal analysis under Dimethyl Fumarate treatment revealed that higher miR-146a-5p levels correlated with lower disability severity (ARMSS and EDSS scores) over time (26). This pattern may reflect stabilization of anti-inflammatory regulatory capacity under treatment. In contrast, downregulation of miR-146a-5p in whole blood and fecal samples has been reported in patients with RRMS compared to both healthy controls and CIS, suggesting a potential role in disease differentiation (27). Furthermore, the downregulation of miR-146a-5p in extracellular vesicles has been linked to cognitive decline and EDSS progression, providing a potential predictor for treatment non-responders (28).

This compartmentalized dysregulation is most clearly observed following high-efficacy interventions like autologous hematopoietic stem cell transplantation (aHSCT). In patients undergoing aHSCT, miR-146a-5p levels in the cerebrospinal fluid showed a significant decrease, approaching levels comparable to healthy controls (22). This reduction suggests that miR-146a-5p may respond to intensive immunomodulatory therapy and could potentially reflect changes in neuroinflammatory activity. Taken together (Table 1), these findings indicate that monitoring miR-146a-5p across different biological compartments may provide complementary information regarding a patient's response to specific Disease Modifying Therapies.

Table 1: Clinical and Compartment-Specific Expression Profiles of miR-146a-5p in MS

Clinical Context/ Therapy	Sample Source	Direction of Change	Interpretation	Ref.
Glatiramer Acetate (GA)	Serum	Increase	Associated with ongoing disease activity and possible compensatory anti-inflammatory response.	(24,25)
Dimethyl Fumarate	Plasma	Higher levels during treatment	Longitudinal elevation correlates with clinical stability and lower disability (EDSS).	(26)
aHSCT (Stem Cell Trans.)	CSF	Decrease (approaching HC levels)	Marked reduction suggesting resolution of active neuroinflammation	(22)
RRMS vs. CIS Diagnosis	Blood / Feces	Decrease	Associated with transition from CIS to established RRMS	(27)
Neurodegenerative Decline	Extracellular Vesicles	Decrease	Associated with cognitive decline and poor therapeutic response	(28)

2.4. miR-146a-5p in Oligodendrocytes: Modulating Remyelination and Repair

Oligodendrocytes play a crucial role in producing the myelin sheath that facilitates rapid signal conduction within the central nervous system (CNS). Disruptions in their development, survival, or functional maturation are linked to a range of neurological conditions -including both developmental defects and neurodegenerative disorders- and may also limit the CNS's capacity for regeneration after damage (30). One study has demonstrated that increasing miR-146a-5p levels enhances oligodendrocyte progenitor cell differentiation and remyelination in an EAE model, suggesting that miR-146a-5p may serve as a promising therapeutic target for demyelinating diseases such as multiple sclerosis (31). Interestingly, while the absence of miR-146a-5p was broadly protective against demyelination and inflammation, it also led to a slightly lower number of oligodendrocyte progenitor cells during remyelination, suggesting a complex, dual role for this microRNA in repair processes (32).

2.5. Microglial Modulation: miR-146a-5p in M1/M2 Polarization and Neuroprotection

As the resident macrophages of the central nervous system, microglia play a dual role in multiple sclerosis, mediating both neurotoxic and neuroprotective effects through their cytokine secretion, which makes them a promising therapeutic target (33). Microglia-mediated neuroinflammation plays a dual role in neurodegenerative diseases: while pro-inflammatory M1 microglia drive neurotoxicity, anti-inflammatory M2 microglia promote neuroprotection. Therefore, modulating M1/M2 polarization represents a promising therapeutic approach (34). One study demonstrates that microglia are the primary source of miR-146a-5p in the CNS, and its absence alters microglial function and protein expression, highlighting miR-146a-5p's key role in regulating gene expression in active multiple sclerosis lesions (35). Furthermore, miR-146a-5p can inhibit the apoptosis of hippocampal neurons induced by microglial activation, revealing a molecular basis for its neuroprotective effect (36).

2.6. Bridging the Evidence Gap: miR-146a-5p's Potential in Astrocyte Pathology

Astrocytes are increasingly recognized as active participants in the pathogenesis of multiple sclerosis, rather than passive or merely reactive components. A research group initially reported elevated miR-146a-5p expression in macrophages and later found its levels to be reduced in astrocytes from active MS lesions, suggesting cell type-specific regulation of this miRNA (37).

Laser microdissection of astrocytes from chronic active MS lesions has revealed decreased miR-146a expression compared to controls, while no similar reduction was ob-

served in microglia, suggesting a disrupted astrocyte-specific anti-inflammatory regulatory mechanism in chronic neuroinflammation (38). In a separate experimental study, fumarate treatment was shown to reduce miR-146a-5p expression in astrocytes in parallel with attenuated inflammatory signaling. Given that miR-146a-5p is typically upregulated in MS lesions as a compensatory response to neuroinflammation, this decrease may reflect treatment-associated normalization of the inflammatory milieu rather than a loss of regulatory capacity, suggesting a shift toward astrocytic homeostasis (39). While direct evidence for miR-146a-5p in astrocytes in MS is limited, findings from other neurodegenerative diseases underscore its critical role in glial pathology. For instance, in Amyotrophic Lateral Sclerosis (ALS), the restoration of miR-146a-5p in astrocytes reversed their pathological phenotype and mitigated the neurotoxic effects of their secretome on motor neurons and microglia (40). This compelling evidence from ALS, coupled with the related role of miR-146b-5p in modulating astrocyte-mediated inflammation in MS (41), strongly warrants further investigation into this miRNA family in the MS context.

2.7. Intercellular Communication: Exosomal miR-146a-5p and its Role in MS

Exosomes have recently gained attention as critical mediators of intercellular communication in the central nervous system. Because they can cross the blood-brain barrier and remain stable in peripheral fluids, exosomes are considered promising biomarkers and potential therapeutic vehicles in multiple sclerosis (42).
One study demonstrated that miR-146a-5p was significantly downregulated in the serum exosomes of IFN-β-treated RRMS patients compared to untreated individuals (43). In cerebrospinal fluid-derived exosomes from untreated relapsing-remitting MS patients, miR-146a-5p expression, which is known to be stimulated during Epstein-Barr virus (EBV) infection, was significantly upregulated compared to the healthy control (HC) group (21). Functional studies done with exosomes derived from bone marrow mesenchymal stem cells have highlighted the immunomodulatory role of miR-146a-5p, showing that it can influence microglial activation towards anti-inflammatory M2 polarization and may hold therapeutic potential in conditions involving neuroinflammation (44).

Conclusion and Future Perspectives

In conclusion, recent evidence solidifies miR-146a-5p as a central, yet complex, regulator in the neuroimmune landscape of multiple sclerosis. Its expression is dynamically regulated across different CNS compartments and cell types, reflecting a dual nature where it can exert both anti-inflammatory, protective functions, while context-dependent dysregulation may accompany ongoing pathogenic processes. Indeed, it is predominantly considered an anti-inflammatory molecule, and its observed increase in more severe disease states is often interpreted as a compensatory, yet ultimately insufficient, feedback response to counteract chronic inflammation. The consistent dysregulation of miR-146a5p in the CSF and blood of MS patients, its correlation with disease activity and treatment response, and its critical roles in modulating microglial activation, oligodendrocyte maturation, and astrocyte pathology collectively underscore its significant potential as a diagnostic and prognostic biomarker, with its utility also suggested in contexts like Vitamin D status and exosomal delivery. Furthermore, preclinical studies demonstrating that manipulating miR-146a-5p levels can ameliorate neuroinflammation and promote remyelination highlight its promise as a novel therapeutic target. Notably, the heterogeneous expression patterns reported across studies likely reflect differences in disease stage, cellular compartment, and therapeutic exposure, emphasizing the importance of contextual interpretation when considering miR-146a-5p as a biomarker. Future research should focus on resolving the cell-type and context-specific actions of miR-146a-5p and developing efficient delivery strategies to harness its therapeutic potential, ultimately paving the way for miR-146a-5p-based interventions in MS.

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