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Review / Derleme

SYSTEMATIC REVIEW OF miRNAs IN THE FUTURE TREATMENT OF NEUROBLASTOMAS WITH SPINAL INVOLVEMENT: INSIGHTS FROM THE LITERATURE

OMURGA TUTULUMLU NÖROBLASTOMLARIN GELECEKTEKİ TEDAVİSİNDE miRNA'LARIN SİSTEMATİK İNCELEMESİ: LİTERATÜRDEN ELDE EDİLEN BULGULAR

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ABSTRACT

Introduction: In recent years, there has been growing interest in exploring the clinical potential of micro ribonucleic acid (miRNA) mimetics or anti-miRNAs to overcome drug resistance, enhance chemotherapy sensitivity, and improve treatment outcomes in neuroblastomas. This study aimed to address the question of whether miRNAs could play a role in the treatment of neuroblastoma with spinal involvement.

Methods: A systematic literature review was conducted in Dec 2024 following PRISMA guidelines. To achieve this, a systematic review of the literature was conducted through sequential searches of electronic databases. The obtained data were analyzed and presented in terms of counts and frequencies.

Results: Three relevant articles containing the specified keywords were identified.

Conclusion: Based on these findings, it is suggested that miRNAs hold promise for advancing the understanding of pharmacobiological mechanisms in neuroblastomas and for informing future therapeutic strategies, particularly for cases involving spinal involvement.

Key Words: MYCN amplification, miRNA, Neuroblastoma, Spinal involvement

ÖZET

Giriş: Son yıllarda, ilaç direncini aşmak, kemoterapi duyarlılığını artırmak ve nöroblastomların tedavi sonuçlarını iyileştirmek için mikro ribonükleik asit (miRNA) mimetiklerinin veya anti-miRNA'ların klinik potansiyelini araştırmaya yönelik ilgi artmaktadır. Bu çalışma, MiRNA'ların spinal tutulumlu nöroblastom tedavisinde rol oynayıp oynamayacağı sorusunu ele almayı amaçlamıştır.

Yöntemler: PRISMA kılavuzlarına göre Aralık 2024'te sistematik bir literatür taraması yapılmıştır. Bunu gerçekleştirmek için, elektronik veritabanlarında sıralı aramalar yoluyla literatürün sistematik bir incelemesi yapılmıştır. Elde edilen veriler sayı ve sıklık açısından analiz edilmiş ve sunulmuştur.

Bulgular: Belirlenen anahtar kelimeleri içeren üç ilgili makale tespit edilmiştir.

Sonuç: Bu bulgulara dayanarak, miRNA'ların nöroblastomlarda farmakobiyolojik mekanizmaların anlaşılmasını ilerletmek ve özellikle omurga tutulumu olan vakalar için gelecekteki tedavi stratejilerine bilgi sağlamak açısından umut vaat ettiği öne sürülmektedir.

Anahtar Kelimeler: MYCN amplifikasyonu, miRNA, Nöroblastom, Omurga tutulumu.

INTRODUCTION

Neuroblastoma, the most common extracranial solid tumor in childhood, is thought to originate from undifferentiated neural crest cells (1). Both genetic and epigenetic factors are considered critical in its pathogenesis (2). Among these, MYCN amplification, part of the MYC oncogene family, which is seen as a target in the treatment of cancers with natural products, remains the most well-characterized genetic risk marker for neuroblastoma (3). This amplification is associated with poor prognosis and is identified in approximately 25% of cases (4). Additionally, it has been reported that the amplification of the MYCN proto-oncogene, frequently observed in aggressive forms of neuroblastoma, accelerates tumor development by increasing cell proliferation and suppressing differentiation (5).

In addition to MYCN amplification, neuroblastomas exhibit other genetic and epigenetic alterations, such as mutations in the anaplastic lymphoma kinase (ALK) gene and modifications that regulate gene expression. ALK gene

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mutations are observed in approximately 10% of neuroblastomas, and these mutations support cell growth by continuously activating the ALK protein (6). Specifically, it has been reported that ALK-specific kinase inhibitors can improve clinical outcomes against the pathogenesis of advanced neuroblastoma (7).

Targeting micro RNAs (miRNAs) in neuroblastoma treatment is emerging as a promising area for developing new therapeutic approaches against this disease. miRNAs are known to influence tumor growth and metastasis by regulating oncogenes and tumor suppressor genes in cancer cells. Therefore, regulating miRNA levels could be an effective strategy for neuroblastoma therapy. Treatment approaches may involve either activation or inhibition of specific miRNAs to modulate their functional effects.

Epigenetic modifications, including those mediated by miRNAs, play a significant role in neuroblastoma pathogenesis by modifying gene expression without altering the DNA sequence. miRNAs contribute directly to the regulation of cellular processes involved in neuroblastoma development (8).

Key processes such as cell proliferation, apoptosis, metastasis, and angiogenesis, which determine the biological behavior of neuroblastomas, are influenced by distinct miRNA profiles. Acting as oncogenes or tumor suppressors, these miRNAs significantly impact the tumor's aggressive behavior, resistance to therapy, and overall clinical outcomes (9).

In recent years, studies have highlighted the dual roles of various miRNAs in neuroblastoma development and progression. For example, the miR-17-92 cluster is highly expressed in neuroblastomas with MYCN amplification, promoting tumor growth by enhancing cell proliferation (9). Conversely, the tumor suppressor miRNA miR-34a inhibits neuroblastoma cell growth by downregulating MYCN expression, with low miR-34a levels being linked to poor prognosis (10). Similarly, miRNAs of the Let-7 family facilitate neuroblastoma cell differentiation by suppressing oncogenes such as RAS and MYCN. However, reduced expression of Let-7 contributes to neuroblastoma progression (11). In contrast, increased expression of miR-9 in neuroblastomas is associated with the upregulation of genes involved in cell invasion and metastasis (12).

Further evidence indicates that the miR-17-92 cluster not only promotes tumor growth but also accelerates the cell cycle (13). Additionally, miR-221 and miR-222 contribute to the aggressive behavior of certain neuroblastoma subtypes by accelerating cell proliferation (14). High miR-9 expression has also been implicated in increasing the metastatic potential of neuroblastoma cells (15).

Studies have identified additional miRNAs with significant roles in neuroblastoma pathogenesis and potential therapeutic applications. miR-181a-5p, which is highly expressed in neuroblastomas, has been shown to promote metastatic characteristics by increasing cell invasion (16). Similarly, miR-210 has been found to target anti-apoptotic Bcl-2 and mediate hypoxia-induced apoptosis in neuroblastoma cells (17). miR-145 has also emerged as a critical regulator in neuroblastoma. Its overexpression reduces cell viability and increases apoptosis in SH-SY-5Y cells, while low miR-145 expression has been associated with poor prognosis in neuroblastoma patients. Overexpression of miR-145 has been reported to inhibit the growth of neuroblastoma cells by downregulating Metadherin, suggesting its potential as a target for miRNA-based therapies (18).

The inhibition of specific miRNAs has been proposed as a therapeutic strategy. For instance, targeting the highly expressed miR-17-92 cluster in neuroblastomas associated with MYCN could limit tumor growth by slowing the cell cycle. The use of anti-miR-17-92 has been shown to reduce cell proliferation in neuroblastoma models (9). Similarly, inhibiting miR-21, which upregulates BCL-2 expression and suppresses apoptosis in neuroblastoma cells, could reverse oncogenic effects and increase apoptosis, offering a potential therapeutic avenue (19).

A study investigating the roles of plasma miR-21, miR-155, and circulating monocyte plasticity in neuroblastoma revealed correlations between the expression of these miRNAs, monocyte subgroups, and disease pathogenesis. This study also highlighted their relationship with clinical outcomes following induction therapy, providing insights into their diagnostic and prognostic value (20).

A study examining the overexpression of miR-138 demonstrated its superior effectiveness compared to hTERT degradation in enhancing the pro-apoptotic effects of apigenin (APG) in both in vitro and in vivo neuroblastoma models. Specifically, the direct overexpression of miR-138 was found to significantly enhance APG's ability to control the growth of malignant neuroblastoma in cell cultures and animal models (21).

Despite these findings, a review of the literature reveals a scarcity of high-quality evidence regarding the roles of miRNAs in the treatment of neuroblastoma with spinal involvement. This study aims to address this gap by discussing the rationale, potential benefits, and challenges of miRNA-based therapies for neuroblastoma with spinal involvement. Furthermore, it seeks to systematically evaluate existing clinical studies related to miRNA applications in this context.

METHODOLOGY

Search Strategy, Study Selection, and Eligibility

To determine the roles and therapeutic potentials of miRNAs in the treatment of neuroblastomas with spinal involvement, the "population, intervention, comparison, outcome, study type" criteria were used. During the

Table 1. Searches performed before a detailed examination of the full texts of the articles.

Keywords	Case reports	Randomized controlled trial	Review	Systematic review	Meta-analysis	Amount of results (year range)
miRNA + NB	0	1	73	2	0	865 (2005-2025)
NB with SI	45	0	23	1	0	229 (1976-2024)
NB with SI + miRNA	0	0	1	0	0	3 (2015-2024)

comprehensive literature search, the PubMed, Embase, Scopus, and Cochrane Library databases were utilized.

Sequential searches were conducted using keywords such as “miRNA,” “neuroblastoma,” “spinal involvement,” “therapeutic targets,” “tumor suppression,” and “gene regulation” in various combinations with “and/or” operators.

To establish inclusion and exclusion criteria, studies focusing on human neuroblastoma with spinal metastasis were prioritized. Detailed evaluations were planned for research addressing the regulation of miRNAs in neuroblastoma progression, metastasis, and spinal involvement. Data on the roles of individual miRNAs in tumor growth, metastasis, apoptosis, and spinal invasion were collected, and the mechanisms by which miRNAs affect spinal involvement, such as their effects on cell adhesion, migration, or interaction with bone/spinal cord tissue, were summarized.

For this purpose, a systematic sequential literature search was conducted to create a list of studies examining the prevalence, etiological agents, pathogenesis, and potential therapeutic applications of miRNAs in neuroblastoma with spinal involvement. This review also included new treatment strategies, drugs, and techniques currently under clinical investigation. Relevant keywords were used to search electronic databases, including MEDLINE/PubMed, Google Scholar, and ClinicalTrials.gov.

The included studies were selected based on the following criteria:

1. Only published clinical research conducted on human subjects was included. Preclinical studies, such as in vivo studies on mammalian subjects or in vitro studies on cell cultures, were excluded.
2. General clinical studies were excluded, but double-blind, randomized clinical trials were included.
3. Reviews, letters to the editor, protocols, guidelines, reviews, systematic reviews, and meta-analyses were excluded.
4. Studies with high levels of evidence were prioritized. The criteria outlined by Lijmer et al. were used to assess evidence levels (22,23).

RESULTS

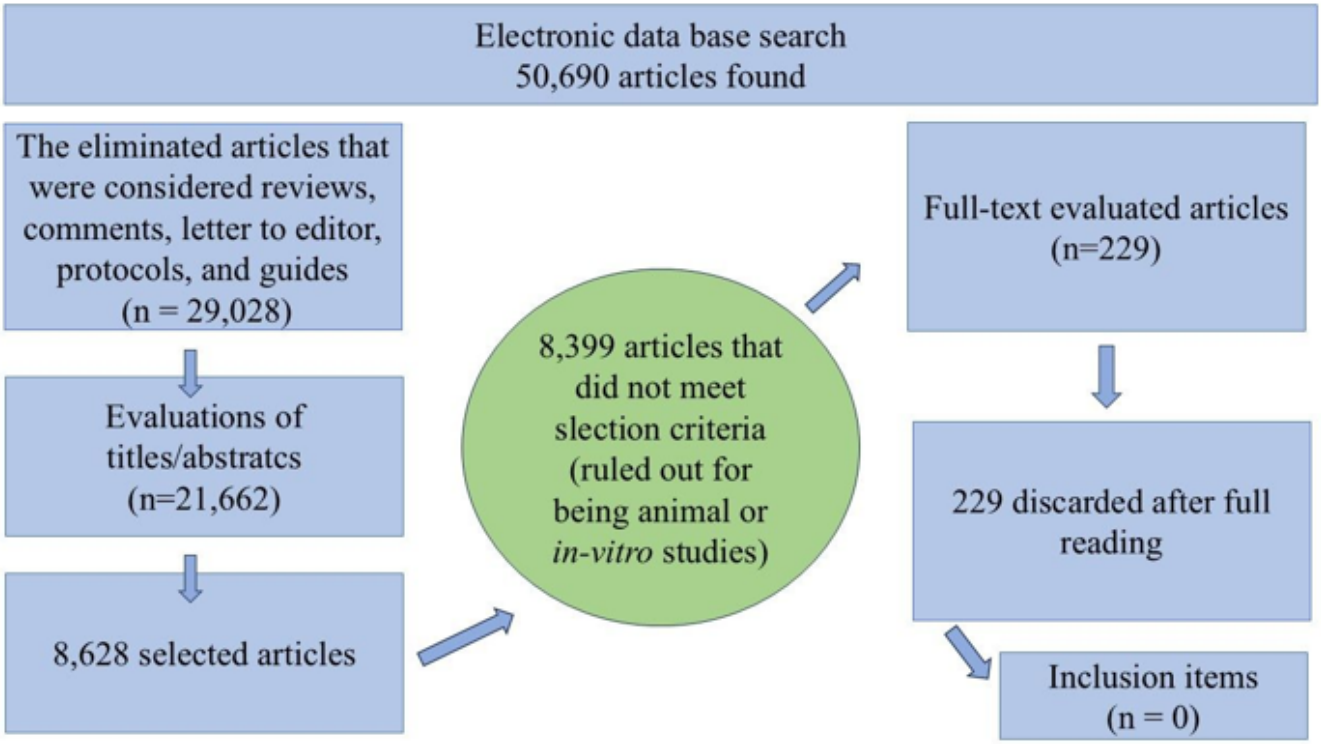
A keyword search for “neuroblastoma” alone yielded a total of 50,690 studies published between 1910 and 2025. These included 4,585 case reports, 102 randomized controlled trials, 3,792 reviews, 155 systematic reviews, and 96 meta-analyses. Similarly, a search for “miRNA” alone identified 178,387 studies published between 1970 and 2025, comprising 200 case reports, 387 randomized controlled trials, 28,828 reviews, 1,1212 systematic reviews, and 1,085 meta-analyses. The detailed results of the sequential keyword searches are presented in Table 1.

When searching using the keywords “neuroblastomas” and/or “miRNA,” one randomized controlled trial was found (24). Using the keywords “neuroblastomas with spinal involvement” and/or “miRNA,” three additional articles were identified (25-27). Upon closer examination, the first study was determined to be unrelated, focusing on Alzheimer’s disease rather than neuroblastoma. Of the three remaining articles, one study was a review aiming to analyze the potential effects of miRNAs in understanding chemoresistance and the biology of cancer stem cells in neuroblastoma, another study investigated the combined effects of miR-20a and miR-29b microRNAs in neuronal apoptosis caused by spinal cord injury, and a study by Mou et al. explored the dysregulation of miR-301a-3p in traumatic spinal cord injury and its relationship with inflammatory responses (24-27).

DISCUSSION

This Genetic and epigenetic factors play a significant role in the development of neuroblastoma, with miRNAs taking on an important regulatory role in epigenetic modifications. A detailed understanding of these processes can enable the development of new treatment strategies for neuroblastomas. These miRNA profiles are crucial regulators that shape the biological characteristics of neuroblastomas, including those with spinal involvement. miRNAs that increase proliferation, suppress apoptosis, promote metastasis, or support angiogenesis play a decisive role in the aggressive behavior of this cancer type, particularly in cases with spinal involvement where tumor invasiveness can exacerbate clinical outcomes. Targeting

Figure 1. PRISMA flowchart resuming the articles' selection process.



specific miRNAs can contribute to the development of new treatment strategies for neuroblastomas, including those affecting the spinal region. Targeting miRNAs in the treatment of neuroblastoma offers a potentially effective therapeutic strategy. It is possible to reduce the aggressiveness of neuroblastomas by suppressing oncogenic miRNAs or inducing tumor suppressor miRNAs. However, for miRNA therapies to be successfully used in clinical applications, further research is needed on issues such as the development of delivery systems, their specificity, and their ability to target spinal lesions effectively.

This study aimed to highlight miRNAs with therapeutic potential that could act as tumor suppressors or regulators of gene expression in neuroblastoma with spinal involvement by conducting a systematic review.

During sequential searches using the keywords "miRNA" and/or "neuroblastoma," one article was found (24). However, after a full-text evaluation, it was understood that the article was related to investigating how simvastatin, a statin used to lower lipids, improves memory loss and inflammation in Alzheimer's disease and whether this effect occurs through miR-106b expression. It emphasizes the significant roles of miRNAs and cancer stem cells in resistant cancers, such as neuroblastoma, and suggests that miRNA targeting could be a critical strategy in future therapeutic approaches (25). The role of epigenetic changes, particularly MYCN amplification, in understanding the biology and treatment of neuroblastoma, a pediatric tumor of the sympathetic nervous system and one of the most common solid tumors in the neonatal and juvenile periods, has been highlighted (28). In the context of spinal involvement, MYCN amplification is particularly relevant as it is associated with aggressive tumor behavior and poor prognosis, potentially influencing spinal invasiveness. Additionally, the focus on regulatory networks linking miRNAs, transcription factors, and target genes in neuroblastoma has been emphasized (29).

Small non-coding RNAs, especially miRNAs, play a crucial role in regulating gene expression and can act as either oncogenes or tumor suppressor genes (30). In a study examining the functional significance of differential miRNA expression in tumor biology (30), it was found that oncogenic miRNAs, such as those from the miR17-92 cluster and the miR-181 family, were overexpressed in cases associated with unfavorable outcomes, including those with spinal involvement where tumor aggressiveness is pronounced.

A case-control study investigated the expression levels of miR-21 and miR-155, which are involved in cancer biology due to their immunomodulatory functions, and examined their relationship with circulating monocyte subgroups in neuroblastoma. The study also assessed whether these miRNAs correlated with disease pathogenesis and clinical outcomes, including in cases with spinal involvement. A total of 39 pediatric cases were evaluated (20). The study concluded that miR-21 could serve as a sensitive biomarker for the development of neuroblastoma in children, but both miR-21 and miR-155 had no significant impact on the clinical outcome of neuroblastoma, including cases with spinal involvement (20).

In a study reporting that p53 processes miR-34 and suppresses the transcriptional activity of β-catenin-T cell factor and lymphoid enhancer factor complexes by targeting a series of untranslated regions, it was emphasized that gene expression signatures reflecting the transcriptional activity status of β-catenin-T cell factor and lymphoid enhancer factor complexes in pediatric neuroblastoma patients correlate with the functional status of p53 and miR-34 (31). Additionally, the loss of p53 or miR-34 was reported to contribute to neoplastic progression by triggering Wnt-dependent, tissue-invasive activity in colorectal cancer cells, with potential implications for spinal involvement in neuroblastoma (31). It was reported that direct overexpression of miR-138 is stronger than hTERT downregulation in enhancing the pro-apoptotic effect of apigenin to control the growth of human malignant neuroblastoma in cell culture and animal models (32).

Although it is well known that miR-145 functions as a tumor suppressor in various cancer types, a study reporting that the effect of miR-145 on neuroblastoma remains unclear emphasized that miR-145 expression is significantly low in high-risk MYCN-amplified tumors and that low miR-145 expression is associated with poorer survival, particularly in aggressive cases with spinal involvement (33). Additionally, it was reported that miRNA-210 mediates hypoxia-induced apoptosis in neuroblastoma cells by targeting the expression of anti-apoptotic Bcl-2 (34). Recently, it has been noted that there is a direct connection between aromatase and sirtuin-1 in human neuroblastoma cells, and identifying key miRNAs targeting aromatase and sirtuin-1, such as hsa-miR-27a-3p, hsa-miR-30c-5p, and hsa-miR-181a-5p, will provide new insights into neurology-related diseases, including neuroblastoma with spinal involvement (35). In a study reporting that the RNA-binding protein LIN28B is identified as an oncogene in neuroblastoma and is associated with poor prognosis, it was highlighted that LIN28B exerts its effect by negatively regulating the biogenesis of tumor suppressor let-7 miRNAs. It was suggested that selective intervention in the LIN28B/let-7 miRNA interaction would increase let-7 miRNA levels and consequently lead to a reduction in neuroblastoma progression, potentially impacting spinal lesions (36).

In summary, targeting miRNAs in the treatment of neuroblastoma, particularly in cases with spinal involvement, is a potential strategy for overcoming chemotherapy resistance and enhancing treatment efficacy. The suppression of oncogenic miRNAs, such as miR-21 and miR-155, or the supplementation of tumor suppressor miRNAs, such as miR-34a and let-7, suggests that it could be effective in reversing resistance mechanisms in neuroblastomas. Translating preclinical findings into spinal-targeted therapies will require addressing challenges such as precise delivery to spinal lesions, which may involve the use of advanced nano-carrier systems to enhance tissue-specific targeting. Additionally, overcoming barriers to miRNA delivery, such as ensuring specificity to neuroblastoma cells in the spinal region and minimizing off-target effects, remains a critical area for future research. Clinical studies provide more data by exploring the ability of miRNAs to modulate both tumor suppressor and oncogenic effects. With further optimization of this treatment strategy, miRNA therapies could revolutionize neuroblastoma treatment, particularly for cases with spinal involvement.

In conclusion, while miRNA mimetics are used to increase the levels of tumor suppressor miRNAs with low expression, anti-miRs suppress oncogenic miRNAs with high expression. Clinical studies have shown that targeting miRNAs, especially miRNA-34a and miRNA-21, is promising in the treatment of neuroblastoma, including those with spinal involvement. However, more work is needed on challenges, such as developing targeted delivery systems, reducing side effects, and increasing specificity in miRNA-based therapies, particularly for spinal-targeted applications. Additionally, in the treatment of neuroblastoma, miRNAs could play a significant role in the treatment process by affecting the development of chemotherapeutic resistance or reversing resistance mechanisms, which are major causes of treatment failure and poor prognosis in cases with spinal involvement.

In preclinical studies, the inhibition of highly expressed oncogenic miRNAs has been effective in reducing proliferation and metastasis in neuroblastoma cells, including those with spinal involvement. Anti-miRNAs developed against miRNAs, such as miR-21 and miR-155, can slow down tumor growth in neuroblastomas. In particular, the delivery of these anti-miRNAs to target cells, including spinal lesions, via nano-carrier systems has the potential to increase clinical efficacy and become a more widespread treatment method in the future (37). Although miRNA-based therapies have not yet received broad clinical approval, many preclinical studies are promising. Challenges such as delivery specificity to spinal regions, side effects, and immune response remain obstacles to the widespread clinical use of miRNA therapies. To overcome these challenges, the development of new nano-carrier systems tailored for spinal-targeted delivery is necessary (38).

CONCLUSION

The available literature reveals a lack of sufficient studies, coupled with conflicting results, regarding the roles of miRNAs in spinal neuroblastoma. This highlights the need for the development of preclinical models to further investigate the therapeutic potential of miRNA-targeted treatments for spinal neuroblastoma. Establishing such models will be crucial for advancing future pharmacotherapies aimed at this condition.

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