

Targeting MicroRNAs with Small Molecule Drugs for Cancer Therapy

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Introduction

Cancer remains one of the leading causes of death worldwide, despite advances in early detection, surgical interventions and conventional therapies such as chemotherapy and radiation. The heterogeneity of cancer cells and the ability of tumors to rapidly adapt to treatment make cancer an incredibly complex disease to treat. These molecules are crucial in maintaining cellular homeostasis and their dysregulation is increasingly recognized as a significant factor in the development, progression and metastasis of cancer. Medicinal chemistry, coupled with advances in molecular biology and drug delivery, is playing a key role in designing small molecule drugs that can specifically modulate miRNA activity to inhibit tumor growth, sensitize cancer cells to conventional therapies and overcome resistance mechanisms. MiRNAs have been shown to function as both tumor suppressors and oncogenes, depending on their specific targets within the cell. In cancers, the expression of certain miRNAs is often altered, leading to the activation of oncogenic pathways or the inhibition of tumor-suppressive pathways. However, the challenge lies in developing small molecule drugs that can specifically interact with miRNAs and modulate their expression or activity in a precise and effective manner. Unlike traditional small molecule drugs that target proteins, miRNAs require a different approach for therapeutic intervention due to their non-coding nature and their ability to interact with numerous targets within the genome. This requires the design of highly selective molecules that can specifically modulate miRNA functions without causing widespread off-target effects [1].

Description

MicroRNA dysregulation in cancer occurs through a variety of mechanisms, including genetic mutations, deletions and epigenetic modifications. The expression of miRNAs can be altered by changes in the genes encoding them, leading to their loss or overexpression. Another critical aspect of miRNA dysregulation is the involvement of miRNA processing enzymes, such as Dicer and Drosha, which are responsible for converting precursor miRNAs into mature, functional miRNAs. Defects in these enzymes can lead to the accumulation of precursor miRNAs or the production of dysfunctional miRNAs that fail to properly regulate their target mRNAs. The complex roles of miRNAs in cancer are exemplified by their ability to regulate multiple signaling pathways simultaneously. OncomiRs, such as miR-21, are often overexpressed in cancer cells and contribute to the promotion of proliferation, invasion and resistance to cell death. Conversely, TSmiRs, such as let-7, are frequently downregulated in cancer, allowing for the unchecked activity of oncogenes. The dual roles of miRNAs in cancer make them attractive targets for therapeutic intervention, as modulating their activity could provide a means of halting cancer progression at multiple stages [2].

Given the potential of miRNAs as therapeutic targets, the field of medicinal chemistry has made significant strides in designing small molecules that can selectively interact with miRNAs and modulate their function. One approach is to develop small molecules that directly bind to the miRNA itself, preventing its interaction with its target mRNAs. These molecules, known as miRNA inhibitors or antagomiRs, can block the function of specific miRNAs by binding to them and preventing their association with the RNA-Induced Silencing Complex (RISC). By inhibiting the activity of oncogenic miRNAs, it is possible to suppress cancer cell growth, induce apoptosis and improve the efficacy of conventional treatments such as chemotherapy and radiation. Conversely, small molecules can also be designed to mimic the activity of tumor-suppressive miRNAs, thereby restoring their function and reactivating tumor-suppressive pathways. These miRNA mimics can be used to replace lost or downregulated miRNAs in cancer cells, thereby inhibiting the activity of oncogenes and suppressing tumor growth. However, the clinical development of MRX34 was halted due to issues with toxicity, highlighting the challenges of delivering miRNA-based therapies safely and effectively. Despite this setback, the development of miRNA mimics and inhibitors remains a highly active area of research, with ongoing efforts focused on improving the specificity, stability and delivery of these molecules to tumor sites [3].

Another approach being explored involves small molecules that modulate the biogenesis of miRNAs. Since miRNAs are processed from primary transcripts by enzymes like Dicer and Drosha, small molecules that modulate the activity of these enzymes could be used to enhance or inhibit the production of specific miRNAs. For example, small molecules that increase the expression of tumor-suppressive miRNAs or decrease the expression of oncogenic miRNAs could offer therapeutic benefits. Additionally, small molecules can be designed to inhibit the interaction between miRNAs and their target mRNAs, preventing the silencing of tumor-suppressive genes. This approach, known as miRNA sponges, can involve the use of synthetic oligonucleotides or small molecules that sequester miRNAs and prevent them from binding to their natural targets. Despite the promise of miRNA-targeted therapies, several challenges remain in their development and clinical translation. One of the key obstacles is the delivery of miRNA mimics and inhibitors to the tumor site. MiRNAs are often rapidly degraded in the bloodstream and their delivery to specific tissues is hindered by the lack of efficient and targeted delivery systems. Nanotechnology-based drug delivery platforms, such as nanoparticles and liposomes, are being explored as potential solutions to enhance the stability, bioavailability and tumor-targeting properties of miRNA-based therapies. These delivery systems can encapsulate miRNA mimics or inhibitors, protecting them from degradation and facilitating their targeted delivery to cancer cells [4].

Another area of significant interest in the development of miRNA-targeted cancer therapies is the potential for combination therapies. Cancer is inherently complex and the molecular mechanisms driving tumor growth and resistance to therapy often involve multiple pathways. Therefore, targeting a single miRNA or pathway may not be sufficient to achieve durable responses. By combining miRNA-targeting drugs with other forms of treatment, such as chemotherapy, immunotherapy, or targeted small molecule inhibitors, it may be possible to overcome the heterogeneity and adaptability of tumors. Furthermore, the role of miRNA signatures in predicting patient response to therapy and monitoring treatment outcomes is another important avenue of research. MiRNA

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Received: 01 April, 2025, Manuscript No. mccc-25-165739; Editor assigned: 03 April, 2025, PreQC No. P-165739; Reviewed: 15 April, 2025, QC No. Q-165739; Revised: 22 April, 2025, Manuscript No. R-165739; Published: 29 April, 2025, DOI: 10.37421/2161-0444.2025.15.776

expression profiles are known to be altered in various types of cancers and specific miRNA signatures may serve as biomarkers for cancer diagnosis, prognosis and therapeutic response. By analyzing these signatures, clinicians could potentially predict how patients will respond to miRNA-targeted therapies, enabling more personalized and tailored treatment plans. Additionally, monitoring changes in miRNA expression during treatment could provide real-time insights into therapeutic efficacy, helping to guide adjustments in the treatment regimen. This level of personalized care, powered by miRNA biomarkers, could revolutionize the way we approach cancer therapy, making treatments more effective and less toxic [5].

Conclusion

Targeting microRNAs with small molecule drugs presents a promising avenue for cancer therapy, offering the potential to manipulate complex gene regulatory networks involved in tumorigenesis. Medicinal chemistry approaches are at the forefront of designing and optimizing miRNA inhibitors, mimics and modulators that can precisely target specific miRNAs involved in cancer. While significant progress has been made in understanding the role of miRNAs in cancer and developing small molecules to modulate their activity, challenges remain in terms of delivery, specificity and safety. However, with continued advancements in drug delivery systems, high-throughput screening techniques and computational drug design, miRNA-targeted therapies hold great promise for improving cancer treatment outcomes. As research in this area progresses, it is likely that miRNA-based therapies will become an integral part of the cancer treatment landscape, providing more effective and personalized therapeutic options for patients.

Acknowledgment

None.

Conflict of Interest

None.

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How to cite this article: KKhanie, Anne. "Targeting MicroRNAs with Small Molecule Drugs for Cancer Therapy." *Med Chem* 15 (2025): 776.