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REVIEW: The Possible Involvement of miR-34 in Cancer Treatment

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ABSTRACT

Cancer is one of the major causes of morbidity and mortality worldwide, resulting from complex interactions between genetic, epigenetic and environmental factors. In the present study, the multifaceted nature of cancer, epidemiology, pathogenesis, and the complex role of genes and microRNAs in the development and progression of tumors have been investigated. We delved into the importance of oncogenes and tumor suppressor genes, especially the pivotal role of the p53 gene in cell cycle regulation and DNA repair mechanisms. In addition, in the current study, the therapeutic potential of microRNAs, especially miR-34, in overcoming chemotherapy resistance and Increasing the effectiveness of treatment has been discussed. By understanding these underlying mechanisms, we aim to provide insight into innovative cancer prevention and treatment strategies.

Introduction

Cancer is a complex and multifaceted disease that poses significant challenges to public health globally. Defined as the uncontrolled proliferation of abnormal cells, cancer arises from a series of genetic mutations and epigenetic modifications that disrupt normal cellular processes (1). The pathogenesis of cancer involves the accumulation of mutations in critical genes that regulate cell growth, division, and apoptosis. Oncogenes, which drive cell proliferation, and tumor suppressor genes and inhibit uncontrolled growth, are central to this process. Among these genes, the p53 tumor suppressor gene stands out due to its role in maintaining genomic stability and regulating the cell cycle. Mutations in p53 contribute to a wide range of cancers, highlighting the significance of genetic integrity in preventing tumorigenesis (2). In addition to genetic alterations, epigenetic mechanisms play a crucial role in cancer biology. Epigenetic changes, such as DNA methylation and histone modification, can lead to the silencing of tumor suppressor genes or the activation of oncogenes without altering the underlying DNA sequence (3). Recent researches have also illuminated the

role of microRNAs (miRNAs) in cancer disease. These small non-coding RNAs are key regulators of gene expression and can function as oncogenes or tumor suppressors, depending on their targets (4). Dysregulation of miRNAs contributes to the development and progression of various cancers, making them promising candidates for therapeutic intervention. miR-34 has emerged as a critical player in cancer treatment, with studies suggesting its potential to overcome chemotherapy resistance by targeting multiple signaling pathways involved in cancer stem cell maintenance and tumor growth (2). The current study explores the pathogenesis and etiology of cancer, focusing on the roles of oncogenes, tumor suppressor genes, and epigenetic changes. It also highlights the emerging importance of miR-34 in cancer biology and their potential as therapeutic targets

Cancer Disease

In mature human cells, environmental mutations lead to a hereditary illness known as cancer disease. Transforming a normal cell into a cancerous cell requires several mutations. Over several years, these mutations are constantly being generated (5).

The Pathogenesis and Etiology of Cancer

Although it is a genetic condition, cancer is not typically inherited as a Mendelian trait. Lack of control over the cell cycle leads to cancer disease. Genes associated with cancer include those that code for transcription factors, growth factors, and telomerase. It's possible that several mutations are combined to cause cancer. Typically, somatic cells undergo genetic alterations. Cancer is produced when a somatic mutation is paired with an inherited ability, or when an environmental trigger results in a somatic cell mutation. Compared to normal cells, cancer cells differ in certain ways (6).

Gene and Epigenetic Alterations

Oncogenes, or genes that cause cancer, and cancer suppressor genes, are the two gene groupings that are implicated in the development of cancer disease. Through the production of stimulatory and inhibitory signals, both groups regulate the cell cycle. In their native form, oncogenes are proto-oncogenes that code for naturally occurring proteins involved in the regulation of cell division and growth. Proto-oncogenes such as myc, fos, and jun, for instance, encode proteins that act as transcription regulatory factors and are typically found in the nucleus (7). Additionally, proteins involved in message transmission in cells include oncogenes such as Abl, Src, and RAS. These kind of genes become active oncogenes due to mutations, and as a result, their expression rises and cell division results in the formation of a tumor. P53 is one of the genes that inhibit cancer (8, 9). In response to DNA damage, P53 protein concentration and activity increase significantly. Subsequently, this protein binds to the P21 protein-related regulatory region of the gene, promoting the transcription of this gene and elevating P21 production. The cyclin-dependent kinase inhibitor protein (CdK) complex is then inactivated by P21. Here, the cell is unable to transition from the G1 to the S phases. There is therefore a chance to fix the broken DNA. P21 protein, on the other hand, binds to Proliferating cell nuclear antigen (PCNA) and deactivates it when the cell is in S phase (10, 11). On the other hand, if the p53 gene is not expressed normally or this protein does not function properly, mutations and malignant cells are possible. P53 gene alterations are responsible for almost half of cancer cases. A protein known as Mdm2 inhibits the P53 protein's function (9). By binding to P53, this protein reduces the capacity of P53 to initiate transcription and catalyzes the addition of ubiquitin molecules, preparing the protein for proteasomal degradation. Apart from p21, two more proteins called p27 and p57 are also recognized as CDK inhibitors. These three proteins are together referred to as CIP inhibitory proteins (12). Since these three proteins inhibit the function of cyclin-Ckd2A, they must be degraded before DNA replication can begin. Serious consequences may arise from deleting genes or altering their

function that help control or prepare the body to repair genetic errors. We refer to these genes as caretaker genes (7). Cancer can arise or can be prevented in large part due to epigenetic mechanisms. Epigenome alterations have now been shown to affect several cancer markers, including cell self-renewal, differentiation inhibition, cell death evasion, and tissue invasion. One of the methods of treating cancer by manipulating epigenetic pathways is called epigenetic therapy. Epigenetic modifications are reversible, in contrast to gene mutations. Cancer cells can adjust to environmental changes thanks to epigenetic modifications (3). Certain anticancer agents bind to chromatin, histones, and DNA to induce structural changes. Thus, they affect DNA integrity and, ultimately, transcription and replication activities, which are critical for cancer initiation and spread. Conversely, the most widely used anticancer drugs that alter the epigenetic structure of tumor cells are histone deacetylase inhibitors and DNA methylation inhibitors. A set of regulated and reversible processes known as epigenetics lead to heritable changes in gene expression regardless of changes in the nucleotide sequence of DNA. Histone modifications, DNA methylation, and transitions from heterochromatin to euchromatin are all considered epigenetic processes that control the ability of the transcriptional machinery to reach target genes. (13).

The Role of microRNAs in the Cancer Disease

Two important facts became clear after the identification of miRNAs in mammals and subsequent research on the function of these molecules in cancer. First, the expression of miRNAs varies between different types of tumors. Second, changes in the expression of miRNAs in distinct tumor types lead to distinct symptoms (14-16). Oncogenes and tumor suppressors are two categories into which miRNAs are divided based on how they change their expression in cancer cells. Tumor cells express higher levels of oncogenic miRNAs, which can be oncogenic by suppressing inhibitory miRNAs with mRNAs that produce tumor suppressor proteins, such as miR-93, 17miR-17-92, miR-155, and miR125b. Decreased expression in malignant cells is observed in tumors (17-19). These miRNAs bind to mRNAs that encode carcinogenic proteins in the normal state, and when their expression is dysregulated, it leads to cancer in healthy cells, some examples of these miRNA are here: miR-34a, miR-143, and miR-145. Mutations, epigenetic modifications, genomic deletions, or modifications in miRNA processing may be the source of misregulation of miRNAs in tumor tissues. Research carried out on lab animals and cancer cells demonstrates that misexpression of miRNA might contribute to the development or spread of tumors. Since cancer genes can be expressed in various organs, many miRNAs have oncogenic or tumor suppressor properties that are not exclusive to any types of tumor (20). The findings of a recent study have changed the view of scientists towards cancer. Tumor cells are produced when several genes mutate. In fact, cancer has a complex genetic structure that makes it a valuable indicator for cancer diagnosis and treatment. The aim of miRNA-based therapy should be to restore the expression level of these molecules to normal. One of the advantages of using miRNAs as therapeutic targets in cancer treatment is that multiple mRNAs may be targeted by one miRNA and vice versa (21). Two strategies are available to control the expression of miRNAs in cancer disease. The first involves utilizing synthetic anti-miRNAs or miRNA antagonists, whose sequences are complementary to the mature oncogene miRNAs in the body, to suppress the expression of oncogene miRNAs (22, 23). The first involves the use of synthetic anti-miRNAs or miRNA antagonists whose sequences are complementary to mature oncogenic miRNAs in the body to suppress the expression of oncogenic miRNAs. When it comes to tumor suppressor miRNAs, whose expression is reduced in a variety of malignancies, a second approach is used. In this example, treatment involves re-

stimulating these miRNAs to express themselves normally, For this reason miRNA replacement therapy is used (24).

The Role of mir34 in Cancer

Resistance to chemotherapy is an ongoing and significant issue in cancer treatment, leading to recurrence and poor clinical outcomes. Various studies have proven that altered levels of circulating miR-34s or tumor-specific miR-34 expressions are correlated to poor chemotherapy responses (25-27). Cancer stem cells (CSC), which are self-renewing tumor cells with the ability to spread and develop into multiple tumor types, are one of the problems linked to chemotherapy resistance. Research has demonstrated that by blocking CSC activity, targeting CSCs with miR-34 mimics can overcome chemoresistance problem (28). Unlike other medications that target a single route, miR-34a can target numerous CSC signaling pathways at once. By concurrently targeting various pathways, co-delivering miR-34 mimics with other medicines such as natural substances, targeted therapeutics, and chemotherapeutic medications might improve the treatment of cancer (29). MRX34, a liposomal mimic of miR-34, has demonstrated potential in mimicking chemotherapy effects on cancer cells through the formation of liposomal complexes. miR-34 mimics are encapsulated in liposomes, which aid in internalization and regulated release, shield them from deterioration, and increase cellular absorption. Lipid nanoparticles, on the other hand, target ligands, improve cellular absorption, and provide stability for miR-34 (29). Though both liposomes and nanoparticles show promise in mouse models, vehicle-related issues in patients remain an issue. miR-34s are potential cancer therapeutic avenues as tumor suppressors, though future research should focus on signaling pathways regulated by miR-34s as well as identifying targets. Treatment results should be improved by miR-34 combination treatments that target several pathways and processes related to tumor development and resistance. The development of nano-delivery methods can improve the efficacy of miR-34-based therapeutics despite obstacles such as the stable and efficient delivery of miR-34 mimics. (**Table.1**)

Table 1. Summary of the role of miR-34 variant in several cancers.

Cancer Type	miR-34 Variant	Target Gene	Role	Mechanism	Reference
Liver Hepatocellular Carcinoma (HCC)	miR-34a	MET, CDK6, SIRT1	Tumor suppressor	Inhibits cell proliferation and promotes apoptosis	(29)
Lung Cancer	miR-34b	ZEB1, SNAIL	Tumor suppressor	Regulates EMT and metastasis	(30)
Breast Cancer	miR-34c	BCL2, CDK6, MYC	Tumor suppressor	Alters signaling pathways linked to cancer progression	(31)
Colorectal Cancer	miR-34a/b/c	WNT, KRAS, BCL2	Tumor suppressor	Inhibits oncogenic pathways and promotes apoptosis	(32)
Gastric Cancer	miR-34a	MET, CDK6	Tumor suppressor	Epigenetic silencing via DNA methylation	(33)
Prostate Cancer	miR-34b/c	MYC, AR	Tumor suppressor	Modulates androgen receptor signaling	(34)

Conclusion

In summary, cancer is a multifactorial disease characterized by genetic and epigenetic alterations that disrupt normal cellular functions. The interplay between oncogenes, tumor suppressor genes, and microRNAs plays a crucial role in cancer initiation and progression. Understanding these mechanisms not only enhances our comprehension of cancer biology but also opens avenues for innovative therapeutic strategies. The use of miRNAs, particularly miR-34, offers promising potential in overcoming challenges such as chemotherapy resistance. Future research should focus on refining these therapeutic approaches, improving delivery methods, and elucidating the complex signaling pathways involved. By advancing our knowledge of the molecular underpinnings of cancer, we can work toward more effective prevention and treatment strategies.

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Conflicts of interest

There is no conflict of interest to this study.

Authors' contributions

Oyinkansola Adebomojo contributed to the conception, design and drafting of the manuscript. Melika Izadpanah contributed to data collection, writing—review and editing. All authors read and approved the final manuscript.

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Abbreviations

miR: microRNA

CdK: cyclin-dependent kinase inhibitor protein
PCNA: Proliferating cell nuclear antigen
CSC: Cancer stem cells

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