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Review Article

MicroRNAs in Cancer

Focusing MicroRNAs in Cancer Gene Therapy

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Abstract: Non-coding RNAs, also known as microRNAs (miRNAs), emphasize an assortment of molecules to influence the synthesis of genes. Initial research has demonstrated that various tumor tissues and cancer cell lines exhibit large variations in miRNA expression. Practically every biological procedure, namely cell division, movement, survival, and differentiation, is known to entail such diversity. A growing body of experimental evidence suggests that miRNA dysregulation is a biomarker for a series of clinical illnesses, including cancer, and that miRNA may have a causative role, acting as oncogenes or tumour regulator genes, at various stages of the tumorigenic process. Anticancer medicines based on miRNAs are currently being created to enhance the effectiveness of cancer treatment. The interference of miRNAs in carcinogenesis and growth is reviewed in this study review, and the latest clinical possibilities and treatment plans aimed at miRNAs in cancer are also covered. Our review focuses on breast cancer, lung cancer, gastric cancer, prostate cancer, and Hepatocellular Carcinoma.

Keywords: miRNA, miRNA dysregulation, cancer cell lines, Breast Cancer and carcinogenesis

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1. INTRODUCTION

MicroRNAs (miRNAs), a class of short spontaneous non-coding functional RNAs, are found widely in both plants and animals. They range in length from 18 to 22 nucleotides. miRNAs are entailed in many biological techniques: gene regulation, development, and stress response. They bind to target mRNAs, inhibiting translation or promoting mRNA degradation[1].miRNAs are short, single-stranded molecules that act as regulators of gene expression in various organisms. They bind to specific target mRNAs and either inhibit the translation of proteins from the mRNA or promote the degradation of the mRNA itself, thus regulating the expression of the gene. This process is important in maintaining homeostasis and involves many physiological processes, such as development, metabolism, and immunity. Furthermore, miRNAs have been implicated in various diseases, including cancer, and are becoming increasingly important in biomedical research. miRNAs were discovered that they contribute to a selection of illnesses, notably cancer. RNA polymerase II is responsible for miRNA transcription from early processing through ultimate maturation. miRNAs can regulate gene expression by binding to the 3' untranslated region of target mRNAs, thus inhibiting translation or promoting mRNA degradation. This mechanism allows miRNAs to regulate multiple genes in a single cell, making them major controllers of many biological processes[2]. Furthermore, their involvement in disease processes has made them attractive targets for therapeutic interventions. For instance, drug targeting these pathways has been used to treat cancer, cardiovascular diseases, and many more. Many drugs have been developed to target these pathways, and numerous more are in the pipeline. This has made them a promising target for new therapies. In addition, miRNAs have become increasingly important biomarkers for diagnosis, prognosis, and monitoring of disease progression. The target messenger RNA (mRNA) is subsequently silenced by incorporating them into the RNA-induced silencing complex (RISC) with Argonaute, often by incorrect complementary base pairing to the 30-untranslated region. Therefore, miRNAs represent an important class of molecules that mightbe exploited therapeutically to control gene declaration and as biomarkers for disease diagnosis, prognosis, and monitoring[3].Plausible approaches for therapy would include achieving "gain" or "loss" of miRNA functions in the cancer cells (Figure 1).

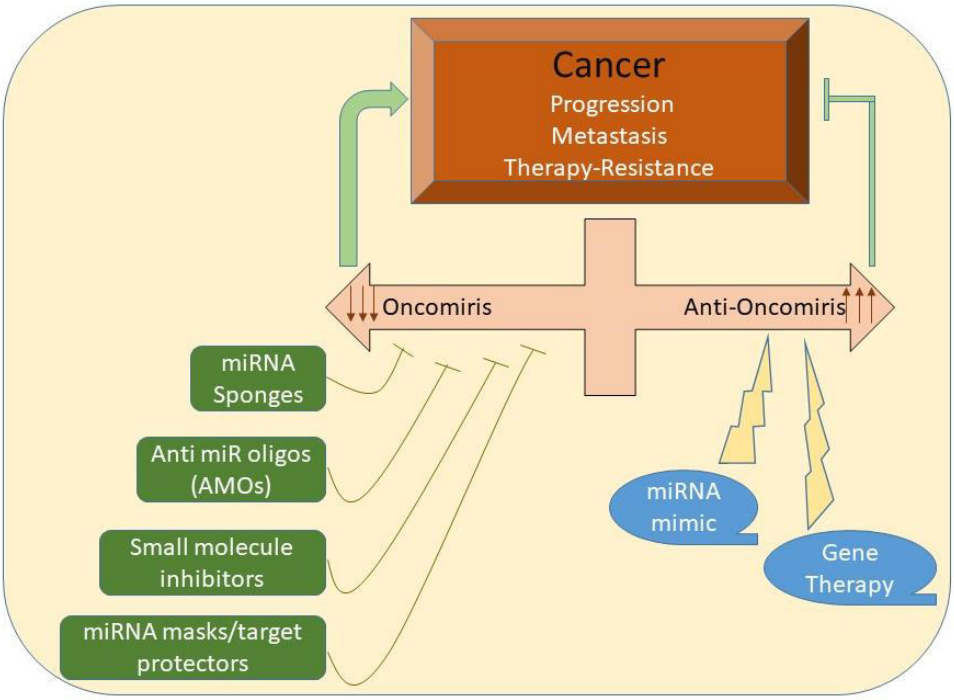

Fig 1: miRNA-based therapeutic strategies against cancer

2. BREAST CANCER

The substantial review studies of miRNAs in establishing breast cancer are becoming increasingly clear from investigations. Romero-Cordoba discovered that 113 miRNAs had a higher threshold in breast tumors than healthy surrounding tissue, whereas 17 miRNAs had decreased activity[4].According to extensive research, miR-892b production is unquestionably down-regulated in human breast cancer samples. Typically, miR-155 is regarded as an oncogenic miRNA in breast cancer[5]. This has been further evidenced by exploring greater articulation of miR-155 in breast cancer samples, possibly connected to decreased apoptosis, increased cell migration and invasion, and other hallmarks of cancer development. The increase in miR-155 expression has been linked to the upregulation of proteins involved in cell proliferation, migration, and metastasis, thus contributing to breast cancer's development, progression, and metastasis. Additionally, miR-155 has been found to suppress apoptosis, or programmed cell death, associated with more aggressive forms of cancer. This suggests that miR-155 may play an important role in cancer progression and metastasis, making it a potential target for cancer therapeutics[6]. According to reports, the utterance of miR-155 has been scientifically associated with a worse outcome in breast cancer patients.

3. HEPATOCELLULAR CARCINOMA

MiRNAs were recently linked to the proliferation of HCC. A recent review study found that miR-625 was consistently down-regulated in HCC samples. They discovered that

therapy with an LNA-derived miR-34a modulator significantly reduced malignancy rates[7].The capacity of luciferase was most significantly reduced by the miR-221 coenzyme-based miRNA, showing that HCC-targeting a miRNAs made from miR-221's precursor structure might be employed broadly to treat HCC[8].This indicates that miR-221-based amiRNAs could be used as an implications therapy for HCC. Further research is needed to confirm this hypothesis. However, results from in vitro assays confirmed that miR-34a modulators and miR-221-based miRNAs have the potential to inhibit cell proliferation and modulate cell cycle convergence in HCC cells[9]. Additionally, miR-221-based amiRNAs have been shown to decrease the affectation of tumor-promoting genes and increase the affectation of tumor-suppressing genes, thus further demonstrating their potential to inhibit HCC progression. Therefore, these results suggest that miR-221-based amiRNAs could be an effective therapeutic option for HCC.

4. LUNG CANCER

It turned out that the advancement of non-small cell lung cancer (NSCLC) was negatively linked with miR-340 activity[10]. miRNAs are frequently acknowledged as prospective cancer therapeutic objectives, but efficient administration requires further investigation. Both authors stated that the injection of manufactured suppressor miRNA mimics combined with a brand-new neutral lipid emulsion through the bloodstream was aimed specifically at lung tumors and demonstrated great tumor repression. The results from this study indicated that this method successfully delivered the miRNA mimics to the tumors and suppressed the cancerous cells. This study provides a promising new tool for the remedy of lung cancer. The miRNA mimics were proven beneficial in targeting and suppressing the cancerous cells, resulting in great tumor repression. Furthermore, the injection of the miRNA mimics along with the new lipid emulsion was proven to be a safe and efficient method of delivering the miRNA to the target tumors, making it a promising new tool for treating lung cancer[11]. This novel approach to lung cancer treatment has shown great potential, with the miRNA mimics demonstrating strong anti-tumor activity and the lipid emulsion providing efficient delivery. The miRNA mimics can target specific regions of the cancer cells. At the same time, the lipid emulsion provides an efficient way for the miRNA mimics to enter the cells and deliver their payload. As a result, the tumor cells are inhibited from growing and shrinking, thus providing a successful anti-tumor treatment. This leads to a reduction in the tumor size and, ultimately, a reduction in the symptoms associated with the cancer[12]. In addition, the treatment is non-invasive and has fewer side effects than traditional cancer treatments. As such, this could be a game-changing tool for those diagnosed with lung cancer.

5. GASTRIC CANCER

miRNAs likely have a part in the productivity of stomach cancer tumors. miR-130a and miR-495, each of which may regulate Runt-related transcription factor 3 (RUNX3) and lessen apoptosis, were discovered by recent research to be oncogenic miRNA contenders[13].This suggests they can act as key regulators for cancer progression, potentially reducing apoptosis in cancer cells and increasing their survival. Furthermore, they may be able to modulate the expression of RUNX3, which can lead to changes in the cell cycle that can promote the proliferation and migration of tumor cells. This could ultimately lead to metastasis and an increased risk of recurrence. Therefore, targeting these proteins could be an effective strategy for cancer treatment. Cell productivity and emigration are reduced as a consequence of miR-1 mimic implantation. Furthermore, miR-1 and miR-130a in gastric cancer cells are being indicated to be overemphasized, and inhibitors decrease the survival rate of this cancer cells[14].Additionally, miR-130a allegedly encouraged tumor spread and invasion. The miR-1 mimic implantation is believed to interfere with the normal cell growth process, causing cells to be unable to divide and migrate, thus reducing the series of cancer cells present[15]. By interfering with the normal cell growth process, miR-1 mimic implantation affects the cell's ability to duplicate its DNA and reproduce, thus stopping the progression of cancer cells. This can help reduce the number of cancer cells present and potentially lead to cancer remission. MiR-1 mimic implantation is a promising approach to cancer therapy, as it targets cancer cells and does not damage healthy cells. This makes it a much safer and more effective treatment method than traditional chemotherapy and radiation. Additionally, the up-regulation of miR-1 and miR-130a increases cancer cell survival rate and promotes tumor invasion and metastasis[16].miR-1 and miR-130a have been officially acknowledged as potential oncogenic molecules that affect advancing tumors.

6. LEUKEMIA

In leukemia, miRNAs can act as tumor suppressor genes or oncogenes, creating novel therapeutic possibilities. miR-126 has an inhibitory effect on the growth of AML cells by downregulating the expression of several proteins involved in the proliferation and survival of the cells. This suggests it could be a potential therapeutic target for treating AML (Acute myelogenous leukemia**)**. miR-126 is downregulated in AML compared to healthy individuals, suggesting a role in disease progression. Therefore, further research is needed to understand the role miR-126 in AML and explore the potential of miR-126-based therapies. In this context, miR-126 could be used as a biomarker to detect AML at an early stage, as well as a therapeutic target to develop novel treatments. The development of early diagnostics based on miR-126 could help to detect AML in its early stages, which could lead to better outcomes and improved patient care.[29] miR-126 could be used to monitor the efficacy of treatments and provide personalized treatment regimens. Furthermore, miR-126 could be used to identify new targets for drug development and to help design more effective therapies. Further studies are also needed to identify the regulatory mechanisms that control miR-126 expression in AML and its potential as a therapeutic. The potential therapeutic target miR-126 for acute myeloid leukemia (AML) was first established[17].This was based on data from experiments of early studies which showed that miR-126 inhibited the proliferation of AML cells and induced apoptosis, thereby reducing tumor growth. The data from these experiments were then used to develop miR-126-based therapies for AML. These therapies are effective in clinical trials, leading to decreased AML cell proliferation and increased patient survival rates. In comparison to this, a non-viral method of miR-29b mimic transfection using transferrin (Tf)-conjugated anionic lipo polyplex nanoparticles had several benefits, including a relatively high miRNA transfection efficiency and low cytotoxicity in AML cells[18].Furthermore, Tf-conjugated

anionic lipo polyplex nanoparticles could effectively silence AML cells, significantly decreasing the expression of genes associated with tumorigenesis. Additionally, this method was cost-effective, making it a viable option for clinical applicants. It is also less invasive and time-consuming than other methods, making it suitable for busy medical settings. Furthermore, it has been proven to produce reliable results with high accuracy. Cytokine signaling-1 (SOCS1), indicating that the antagonizing miRNA procedure could reactivate the processes of cytokine-stimulated tumor suppressor pathways in leukemia cells[19]. This could lead to the development of novel therapies for leukemia and other cancers. The research indicates that miRNA-based therapies have great potential to restore the activity of tumor suppressor pathways. This could be a breakthrough in the fight against cancer. In addition, studies have found that marine compounds such as fucoxanthin and astaxanthin could be effective in the treatment of oral cancer.[27] These compounds have been shown to inhibit the growth of cancer cells through their miRNA-mediated pathways. These findings suggest that miRNA-based therapies may be an effective treatment option for oral cancer, in addition to other forms of cancer. Further research is needed to explore the potential of miRNA-based therapies in the treatment of cancer. This could significantly reduce the side effects of existing cancer treatments and ultimately lead to longer-term remission rates and improved patient outcomes. The research is ongoing and holds great promise for the future of cancer treatment. Biosensors for Oral Cancer Detection and Treatment are being developed to detect cancer early, monitor treatment response, and provide a more precise way to deliver targeted therapy.[28] Biosensors can also provide real-time feedback on the effectiveness of treatment and detect recurrences earlier, allowing for timely intervention and improved patient outcomes. Additionally, the biosensors can be used to monitor side effects and adjust treatments as needed.

7. PROSTATE CANCER

Prostate cancer miRNAs are being demonstrated to be major post-transcriptional moderators. According to a study, miR-221/222 mimics transfected into prostate cancer cells can boost the growth of cells and reduce the pro-apoptotic impact by inhibiting caspase-10[20]. Understanding the functional role of miRNAs is crucial for developing effective miRNA delivery methods employing prostate cancer-targeted nanoparticles. Nanoparticles can deliver miRNAs to specific areas at high doses and with better bioavailability. Future perspectives on dental nanomaterials with nanoparticle-mediated miRNA delivery could potentially be used to treat oral diseases, such as caries and periodontal diseases, with improved efficacy and fewer side effects. This could be achieved by targeting specific cell populations in the oral cavity with tailored nanomaterials and the miRNA cargo. Such nanomaterials have the potential to revolutionize the treatment of oral diseases [30,32]. This could result in more effective treatments for prostate cancer, potentially reducing the risk of recurrence or metastasis. miRNAs are small non-coding RNAs that act as regulators of gene manifestation and can be used to control gene manifestation in prostate cancer cells. By delivering miRNA to these cells using targeted nanoparticles, it is possible to reduce the manifestation of genes associated with cancer progression[21]. This could contribute to a greater efficacy prostate cancer treatment, potentially reducing the risk of recurrence or metastasis. Such targeted delivery could thus provide a more focused yet powerful intervention to lessen adverse effects when treating prostate cancer.

8. miRNAs AND CANCER STEM CELLS

Cancer stem cell theory, which contends that a small minority of tumor cells have the remarkable capacity to start and maintain tumor development, has received substantial support from recent studies on cancer. These cells, also known as tumor-initiating or cancer stem cells, have traits in common with somatic and embryonic stem cells, such as self-renewal and multipotent differentiation. Furthermore, miRNAs appear to act in the upkeep and growth of healthy and malignant stem cells, according to mounting data[22].First, the capacity for self-renewal and differentiation is lost in embryonic stem cells with critical miRNA biogenesis pathway protein mutations. Second, compared to matured cells, somatic and embryonic stem cells have unique miRNA expression fingerprints[23].Third, it was recently discovered that specific miRNAs, like let-7, have essential functions in controlling self-renewal and/or differentiation in healthy and cancer stem cells. The pleiotropic effect of DCLK1 in cancer is partially explained by its regulation of let-7 miRNA expression. DCLK1 modulates the expression of let-7 miRNAs, which in turn control self-renewal and/or differentiation in stem cells. This connection between DCLK1 and let-7 miRNAs provides a potential target for therapeutic intervention in cancer. Furthermore, the regulation of let-7 miRNAs by DCLK1 also suggests its involvement in other diseases where stem cell control is essential [33]. This suggests that miRNA-based therapies may be developed to control stem cell proliferation, differentiation, and reprogramming. Thus, further understanding of miRNA-mediated regulation of stem cell biology is imperative for improving regenerative medicine. With further study, miRNA-based therapies can be developed to target specific genes, allowing for more precise control of gene expression and manipulation of stem cell behavior. This could open up new possibilities for regenerative medicine and provide new treatments for diseases[24]. Thus, such research could be the key to unlocking novel therapies in regenerative medicine and providing solutions for diseases that have traditionally been difficult to treat. miRNA biogenesis, an approach to enhance miRNA biogenesis processing, is discussed (Fig. 2).

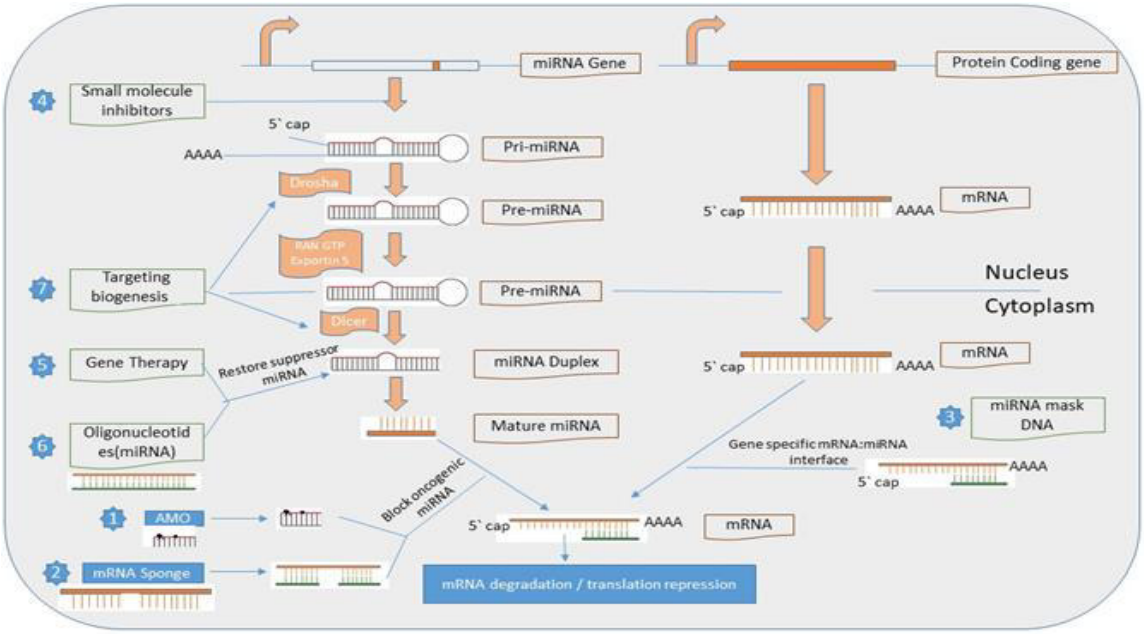

Fig 2: Schematic diagram of miRNA biogenesis and the therapeutic strategies.

9. COMPARISON OF miRNA- AND SIRNA-BASED THERAPIES

Parallel studies of siRNA in cancer therapy can be used to infer the possible therapeutic advantages of miRNA modulation. The two different kinds of tiny RNA have distinct origins and gene-targeting methods. While miRNAs are derived from genome-encoded hairpin-shaped precursors and only require a partial sequence match to repress target gene expression, siRNAs are frequently derived from synthetic/exogenous long dsRNAs and require perfect complementarity to a specific target mRNA to cleave that target[25].When siRNA is introduced in vivo, inflammatory cytokines and interferon-related genes are upregulated globally, which accounts for a significant portion of the "off-target activity." This upregulation is responsible for the therapeutic effects of siRNA and is also responsible for the potential side effects of the therapy. Therefore, it is important to consider the potential risks of siRNA therapy before administering it. This upregulation can cause unwanted side effects, such as inflammation in other tissues or organs. It can also increase the risk of other diseases, such as autoimmune diseases or cancer[26]. Therefore, weighing the potential benefits of siRNA therapy against the potential risks before administering it is important. In general, the delivery vehicle's activation of innate immunity was predominantly responsible for the interferon response. Consequently, using tumor-specific delivery mechanisms, such as viral vectors or tumor-specific nanoparticles, may prevent the concern of specific delivery.

10. CONCLUSION

Recent studies have identified miRNAs as a crucial class of regulators of the expression of protein-coding genes. It is fascinating to use our knowledge and expertise on miRNA to create therapeutic reagents for treating cancer as more and more data highlights the significance of miRNA activity during tumor growth and progression. Surgery, radio/chemotherapy, hormonal therapy, and oncogene-targeted therapy are among current anticancer therapies. The anticancer properties of piperine in Oral Cancer Therapies have been well documented, with studies showing that it can inhibit the growth of certain cancer cells, reduce tumor size, and even reduce the side effects of chemotherapy and radiation[31]. It can also reduce inflammation and activate cancer-fighting enzymes in the body, helping to reduce the risk of cancer recurrence. Additionally, piperine has been found to increase the effectiveness of certain cancer treatments, such as chemotherapy and radiation, while reducing their toxicity. Numerous clinical studies have shown that combining treatments based on the molecular profiles of patients can improve response. miRNA-mediated therapy will provide a new impetus for cancer treatment as we get a better knowledge of how miRNAs work in the development of tumors and the more sophisticated design of miRNA-modulating compounds.

11. AUTHORS CONTRIBUTION STATEMENT

P. Krubaa conceptualized and designed the whole study, including sample collection, processing, and clinically correlating the impact of miRNA on stages of Cancer Gene Therapy. Dr. Anand Mohan Jha contributed to the statistical analysis and editing of the manuscript. P. Krubaa and Dr. Anand Mohan Jha read and approved the final version of the manuscript

12. CONFLICT OF INTEREST

Conflict of interest declared none.

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