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REVIEW ARTICLE **OPEN ACCESS**

MicroRNA as Potential Therapeutic Targets to Improve Immunotherapy

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ABSTRACT
MicroRNAs (miRNAs) are non-coding RNA molecules originating from cellular processes, playing critical roles in cancer development and immunomodulation. This article explores the complex interaction between miRNAs, cancer, and immunotherapy. Initially transcribed as primary transcripts (pri-miRNAs), miRNAs undergo precise processing by proteins like Drosha and Dicer, resulting in functional miRNA molecules. These molecules regulate diverse cellular processes, including differentiation, proliferation, and apoptosis. In the context of cancer, miRNAs exhibit both pro-tumour and anti-tumour immunomodulatory functions. Certain miRNAs promote cancer by suppressing tumour suppressor genes and disrupting cell communication, while others enhance immune responses by targeting immune checkpoint proteins and signaling pathways. miRNAs hold significant therapeutic potential in cancer treatment, offering the ability to suppress oncogenes or enhance immune responses. Synthetic miRNAs can be designed and delivered using methods like viral vectors and nanoparticles. These miRNA-based therapies offer promise in boosting immunotherapy effectiveness. However, further research and clinical investigations are necessary to fully harness miRNAs' therapeutic potential in cancer treatment, particularly in combination with conventional therapies.
Keywords: *microRNA, cancer, immunotherapy, immunomodulatory effects, immune responses*

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INTRODUCTION

MicroRNA (miRNA) is a class of RNA originally from inside the cell. These non-coding areas are the results of the transcription and translation processes. MiRNAs are removed from the RNA strand as introns by one of the posttranscriptional modification processes known as splicing since they do not code for proteins. In its initial form, miRNA is a 100–120 nucleotide molecule that was first discovered from the L-4 genes in the nematode [1-5]. MiRNA serves significant roles in a variety of cellular processes, including differentiation and stem cell maintenance, metabolism, and immunotherapeutic activities, despite the fact that they do not code for proteins. The potential for miRNA to supplement traditional cancer treatments including surgery, radiation, and chemotherapy is quite high. Because miRNA's regulatory functions and the processes that lead to cancer proliferation are similar, miRNA is useful in suppressing and growing tumours. As a result of a mutation in the p52 genes, a key regulator of the cell cycle, a protoncogene can transform into an oncogene, which causes the cell to grow out of control and develop into cancer [6-12]. More than 60% of human protein-coding genes are anticipated to be subject to selection pressure to be controlled by miRNAs in complex cellular processes as development, proliferation, differentiation, apoptosis, and stress response. MicroRNA can function as an oncogene by altering how RAS proteins function to disrupt cellular processes that result in cancer, such as the cell cycle, or they can function as tumour suppressor genes by reversing the process by targeting oncogenes. Because there are several cancer types and stages of growth, researchers were unable to calculate precise percentages. Since there are many types of cancer and different stages of proliferation, it was unable to pinpoint the exact ratio between miRNA-mediated oncogenes and miRNA tumour suppressor genes [48]. There have been additional miRNAs, or tumour suppressor genes, discovered recently. Cancer is one of the deadliest illnesses in the world, particularly in the United States, where it has been reported that 1,918,030 new cases and 609,360 deaths have occurred [35]. Several recent miRNAs have been identified, including miR-320a in gastric cancer [25], miR-497-5p in breast cancer [26], carcinoma [58], miR-16-5p in hepatocellular [12], and miR-143-3p in bladder cancer [5]. MiRNAs orchestrate key cellular processes such as differentiation, proliferation, and apoptosis. Das et

al. [7] suggested that microRNAs (miRNAs) have shown promise as predictors of bladder cancer recurrence. Within the realm of cancer, miRNAs exhibit a dual persona—some drive malignancy by suppressing tumour suppressor genes and disrupting cellular communication, while others bolster immune responses by targeting immune checkpoint proteins and signaling pathways. This review explores the intricate involvement of microRNAs (miRNAs) in cancer progression and immunotherapy. By elucidating miRNA biogenesis, immunomodulatory effects, and therapeutic potential, the article aims to provide insights into harnessing miRNAs for enhancing cancer treatment strategies [8].

Biogenesis and Regulations of miRNA

The transcription of a gene into a long primary transcript (pri-miRNA), which has a 3′ polyadenylated structure and a 5′ cap, is the initial step in miRNA production. Although RNA polymerase III generates some pre-miRNAs, RNA polymerase II typically facilitates transcription. The RNA-binding protein DGCR8 and type III RNase Drosha form a microprocessor complex that cleaves the pri-miRNAs into precursor miRNA (pre-miRNA), an 85-nucleotide stem-loop structure. The Ran/GTP/Exportin 5 complex moves pre-miRNAs from the nucleus to the cytoplasm, where the RNase III enzyme Dicer processes them to create a duplex of 20–22 nucleotides known as miRNA/miRNA. At several steps, including transcription, Drosha and Dicer processing, transportation, RISC binding, and miRNA decay, miRNA synthesis is strictly controlled. For instance, it has been proposed that SMAD protein and DEAD-box RNA helicases participate in Drosha-mediated miRNA maturation. By functioning as a part of the Drosha and Dicer complexes, the KH-type splicing regulatory protein (KSRP) regulates the production of a subset of miRNAs in mammalian cells. In the genome's protein-coding genes' intergenic regions, introns, or exons, miRNAs are encoded. Mature miRNAs are typically transported from the nucleus to the cytoplasm for processing, cleavage, and loading into the RNA-induced silencing complex (RISC). MiRNA mediates target mRNA degradation or ribosome detachment by forming base pairs with the 3′ untranslated region (UTR) of the target mRNA. However, there are a few exceptions, such as miR-10a, which can interact with miRNAs' 5′ untranslated regions to improve their translation [9-11, 28]. **(**Error! Reference source not found.)

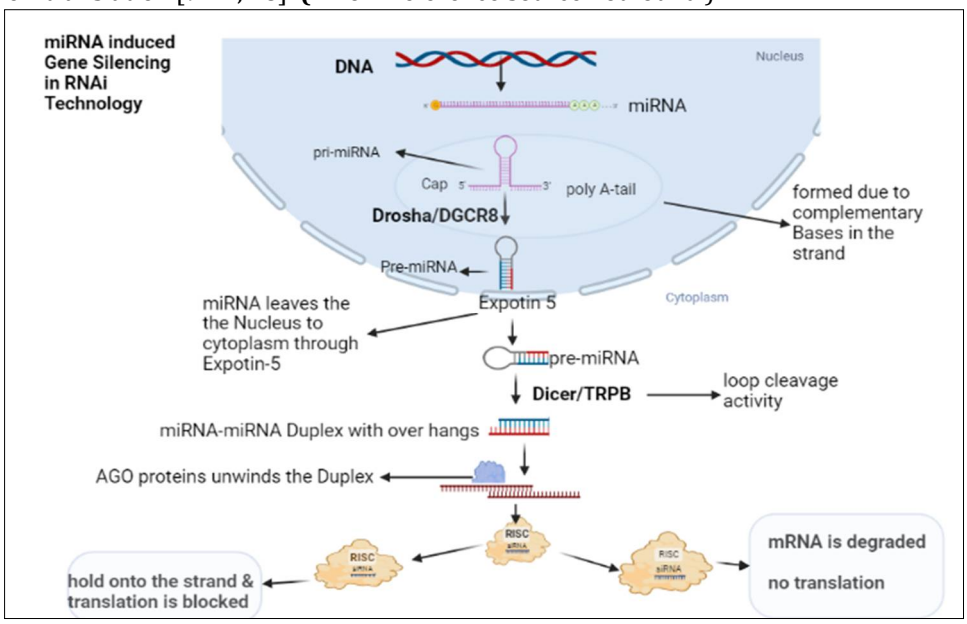

Figure 1: synthesis of microRNA: After splicing, microRNA detaches from the strand as a double strand with loop, poly-A-tail, and 5'cap and is called pri-microRNA with approximately 100 to 120 nucleotides long. The poly-A-tail and 5'cap will be cleaved off the pri-microRNA by Drosha and DGCR8 complex, now it called pre-miRNA with 65-70 nucleotides long. Pre-microRNA leaves the nucleus and enters the cytoplasm by a protein known as expotin -5 and another protein known as Dicer from the RISC complex cleaves out the loop resulting in a shorter miRNA-miRNA*duplex (double strand with 18-25nt). Argonaut, which is another protein from the RISC complex also cleaves out of strands from the miRNA-miRNA*duplex. As all nucleotides of the remaining strands get exposed, they become cohesive and have the potential to bind to nearby molecules. miRNA inhibits the translation of structural genes because translation also occurs in the cytoplasm

Overview of immunotherapy and its potential as a disease treatment

On the basis of this, we will talk about the pro- and anti-tumour effects of immunomodulation.

By promoting the synthesis and activity of regulatory proteins like cytokines and chemokines to trigger responses, miRNA regulates the actions of malignant cells. About 30% of human genes are regulated by

miRNAs of which 50% are linked to tumours. Based on this, the immunomodulatory effects of miRNA are discussed here as pro-tumour and anti-tumour therapeutic agents [13-18].

Pro-tumour immunomodulatory effects of miRNAs

Dysregulation of certain microRNAs (miRNAs) is a fundamental aspect of cancer progression and development. Various factors, including mutations, epigenetic modifications, environmental influences, and dysregulation of transcriptional factors, can lead to the down-regulation of tumour suppressor genes such as p53, while other oncogenes are overexpressed. Several miRNAs including miR-10b, miR-155, miR-17-92, miR221/222, miR-21, and miR-34a, play a role in driving this process. According to Sheedy and Medarova [40], miRNAs regulate gene expression post-transcriptionally by pairing with mRNA sequences through the RNA-induced Silencing Complex (RISC). This can either promote or suppress the formation and progression of cancerous tumours. For instance, Liu et al., [26-28] noted that miR-155 is capable of degrading Tp53INP1 by binding to its 3' untranslated region (3'UTR) and altering specific nucleotide sequences primarily located at positions 2-8. Further research using RNA sequencing (RIP-seq immunoprecipitation) has identified potential mRNA targets of miR-155 [30]. Inhibiting cytokines (SOCS1) and phosphate signaling molecules including SH2-containing inositol-5'-phosphatase-1 (SHIP1), miR-155 prevents cell communication and protein synthesis [31]. Mendell [31] reported that miR-17-92 promotes cell proliferation, suppresses apoptosis of cancer cells, and induces tumour angiogenesis. The PI3K/Akt pathway, which generally promotes proliferation and important metabolic processes, as well as the control of B cell signaling and the regulation of innate immune responses, are all affected by this imbalance.

Anti-tumour immunomodulatory effects of miRNAs

This is where the immune system becomes stimulated, enhanced, and able to detect and deter the growth and development of cancerous cells through an immune surveillance system made up of various cells, proteins (cytokines), and antibodies that cause non-self-cells to apoptosis, with recent studies showing that microRNAs have immunotherapeutic effects in the silencing of tumour-causing genes. It is interesting to note that the majority of miRNAs that support cancer development are also capable of suppressing it [4-6]. These microRNAs include let-7 family members, miR155, miR146a, miR21, and miR150 [19, 20].

By specifically targeting the two important molecules IRAK1 and TRAF6, the miR-146a prevents the activation of the NF-B signaling pathway [36]. Park et al. [36] reported pro-inflammatory cytokines like IL-1 and TNF- are less expressed, which suppresses the inflammatory response and could have an impact on the proliferation and spread of cancer cells. Let-7 genes play a role in inhibiting oncogenes involved in cancer development and enhancing immunotherapy. Wang et al. [50] confirmed that the Let-7 miRNA regulates gene expression in cells. They also identified novel factors and feedback loops involved in let-7 synthesis and discovered additional target genes. Let-7 targets RAS/MYC oncogenes and can regulate the expression of co-stimulatory molecules, such as PD-1 and CTLA-4, which are involved in inhibiting T-cell activation. Intlekofer and Thompson [17] explained that CTLA-4 and PD-1Rs are two T cell-inhibitory receptors with distinct mechanisms of action. Preclinical studies have shown that CTLA-4 enforces an activation threshold and suppresses the proliferation of tumour-specific T lymphocytes. This regulation prevents the overwhelming inhibition of T-cell activation by PD-1/CTLA-4, potentially enhancing immune responses against cellular abnormalities (

Table 1)

Table 1. Represents containing some recently researched microRNAs, their mechanisms of immune-checkpoints modulation, the protein targeted in cancer cells, and the type of cancer involved

No.	miRNA	Mechanism in modulating immune-checkpoints	Target proteins on cancer cell	Cancer cell type	Reference
1.	Mir-21	Upregulates PD-L1 expression	PD-L1	Various types	Exposomal PD-L1 confers chemoresistance and promotes tumourigenic properties in esophageal cancer via upregulating STAT3/miR-21 [49]
2.	miR-21	Downregulate PD-L1 expression	PD-L1	Non-smal cell lung cancer	**[4]**
3.	miR-200c	Modulates TIM-3 expression	TIM-3	Colorectal cancer	**[20]**
4.	miR-155-5p	Suppress PD-L1	PD-L1	Lung adenocarcinoma	MicroRNA-155-5P surpress PD-L1 expressing in lung adenocarcinoma [16]

5.	General	Inhibit protein translation	Multiple checkpoints	Various types	Immune modulators in cancer immunotherapy [51, 52]

MicroRNA and Cell cycle

Cells go through the cell cycle, which is a well-organized complicated machinery, to carry out biological operations. The cascades, a method of gradual mechanism enhancement, are used. The cycle is made up of several regulatory genes and proteins that come together to form units called checkpoints, which are used to coordinate cellular activity **(*Figure 1*).** By targeting the genes that code for these checkpoints, miRNA can employ these pathways to control gene expression by inhibiting certain miRNA molecules to halt the translation of proteins. In order to advance the cell cycle, miRNA interacts with proteins like cyclin and cyclin-dependent kinases (CDKs) by upregulating the G1 phase and downregulating the cyclin/CDK pathway to limit G1 activity. Other cycle mechanisms, like as cyclin B1 (CCNB), which controls G2/M and permits mitotic entry, can be regulated by miRNA. PLk1 for centrosome maturation, spindle fibre development, and chromosomal segregation, Aurora kinase for proper spindle fibre assembly, and Kinase 1 (CHK), which is also implicated in checkpoint activation and DNA damage [26, 30, 32-45].

MiRNA as a Therapeutic Agent

MiRNA has the potential to activate and inhibit proteins and genes, which means that it can influence the development of cancer. miRNAs can be carcinogenic, which means that their overexpression can promote the growth of cancer because it inhibits the actions of p53. However, by reducing the growth and spread of cancer through the targeting of its processes, miRNA serves a therapeutic function in the treatment of cancer. An improved treatment is needed to increase the effectiveness of miRNA; RNAi technology can be used to accomplish this [46].

In this approach, a synthetic miRNA can be utilized to block the spread of cancer via molecular methods, or a miRNA that has been isolated from the gene and boosted in vitro to target malignant cells more quickly. Two strategies must be used to achieve this:

- Direct-miRNA-mediated treatment, the structural genes are directly targeted, and their activities are inhibited.
- Indirect-miRNA mediated treatment uses these cancer cells' promoter region genes as its target genes to stop the manufacture of proteins.

Targeting the relevant tissues, proteins, and genes concurrently is possible using both strategies. Because both processes take place in the cytoplasm, miRNA interference with protein synthesis is significant. Due to the cohesive nature of miRNA, it can prevent polypeptide chains of amino acids that code for genes regulating a cellular process that favors the development of cancer from forming [47].

In order to boost stability and improve therapeutic impact, synthetic miRNA is produced. Viral systems and polymeric nanoparticles can both transport miRNA. The most common method is liposome [49-55]. The method is based on the idea that miRNA is enhanced when it is supplied into the system and degraded by a certain metabolic process in the targeted cells. The use of miRNAs as therapeutic agents is described in the following general short protocol [:

1. Determination of the miRNA target: Finding the particular miRNA involved in the target illness is the first step. Bioinformatics analysis and numerous experimental approaches can be used to achieve this.
2. Design and synthesis of miRNA mimics and inhibitors: Following identification of the target miRNA, miRNA mimics and inhibitors are created. Synthetic RNA molecules known as "miRNA mimics" can be employed to restore the production of a particular miRNA in sick cells since they closely match the mature miRNA sequence. On the other hand, miRNA inhibitors are created to selectively obstruct the function of an overexpressed miRNA.
3. Development of the delivery system: The effectiveness of miRNA molecules as therapeutic agents depends on their efficient distribution to the target tissues or cells. To guarantee efficient transport to the targeted location of action, several delivery mechanisms can be used, such as viral vectors, lipid nanoparticles, or conjugates with targeting ligands.

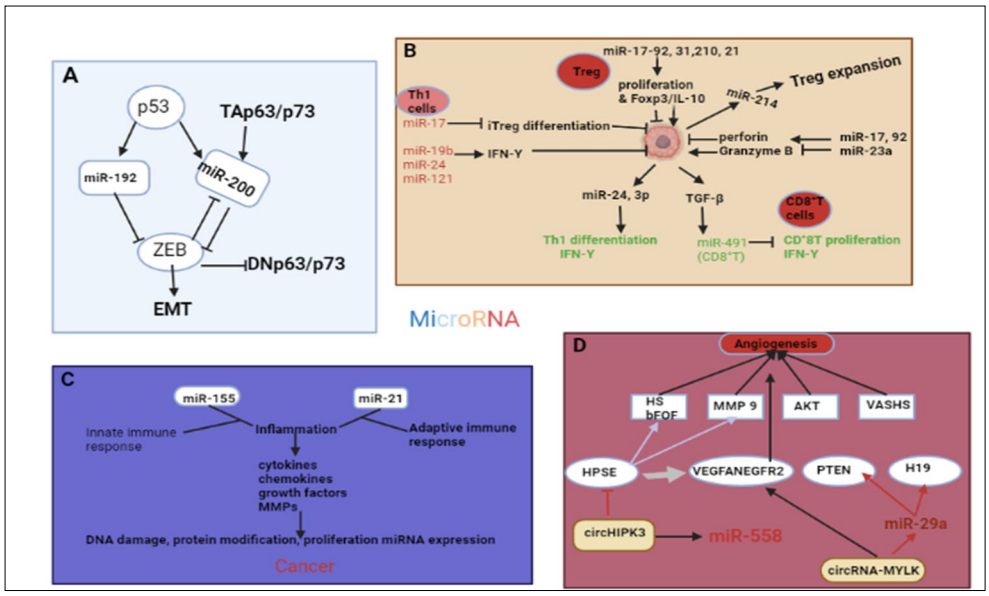

Figure 1. Role of miRNA in 4 different cancer pathways labelled A, B, C & D. (A) Epithelial-Mesenchymal Transition (EMT): MiR-192 suppresses EMT in breast cancer by enhancing p53-mediated pathways, which counteract EMT-inducing factors. MiR-200 inhibits EMT by targeting ZEB through the TAp63/p73 axis, promoting the maintenance of an epithelial phenotype and inhibiting the transition to a mesenchymal state. (B) Modulating anti-tumour activities of CTLs: Modulating anti-tumour activities of cytotoxic T lymphocytes (CTLs) involves fine-tuning the expression of co-stimulatory molecules and cytokines on CTLs, enhancing their recognition of tumour antigens and activation, including CD8+ cytotoxic T cells, to prevent collateral tissue damage. Th1 differentiation involves the maturation of helper T cells into a Th1 phenotype, promoting the release of cytokines like IFN-γ that enhance CD8+ cytotoxic T cell activation and support their anti-tumour functions within the immune response. (C) miRNA in inflammation: MiR-155 and miR-21 are microRNAs that play pivotal roles in cancer modulation by promoting tumour growth and progression. They achieve this by downregulating tumour, suppressor genes, inhibiting apoptosis, and enhancing cell proliferation, angiogenesis, metastasis and causing inflammation through the release of with cytokines and chemokines. (D) miRNA in angiogenesis regulation (linking tumour and cancer): MiRNA-29a suppresses angiogenesis by targeting the oncogenic H19 RNA, leading to increased PTEN expression and subsequent inhibition of the AKT signalling pathway in cancer cells. Conversely, miRNA-155 promotes angiogenesis by downregulating PTEN and activating AKT, facilitating tumour-associated blood vessel formation in cancer.

CONCLUSION

MicroRNAs (miRNAs) have become viable therapeutic targets for further immunotherapy. MiRNAs are essential for several biological functions, such as cancer formation and immunomodulation. They can act as tumour suppressors and oncogenes, controlling the expression of genes involved in the development of cancer and immunological responses. Targeting certain miRNAs can have pro- or anti-tumour immunodulatory effects. MiRNA dysregulation is linked to the development of cancer. Certain miRNAs have pro-tumour immunomodulatory effects, which speed up the development of cancer by suppressing tumour suppressor genes and cytokines and signaling molecules that are essential for cell communication and protein production. Alternatively, miRNAs with anti-tumour immunomodulatory activities boost immune responses against cancer cells by concentrating on immune checkpoint proteins, modifying signaling pathways, and repressing gene expression. Creating therapeutic approaches requires an understanding of the biosynthesis and control of miRNAs. To specifically target genes and proteins implicated in the growth of cancer, miRNAs can be created and administered as therapeutic agents. The effectiveness and stability of synthetic miRNAs as therapeutic agents can be improved by using a variety of delivery mechanisms, including viral systems and polymeric nanoparticles. Overall, by modifying immune responses and halting the spread of cancer, targeting miRNAs has considerable potential for enhancing immunotherapy. To fully investigate the therapeutic potential of miRNAs in cancer treatment and improve their efficacy when combined with other conventional cancer medicines, more research and clinical investigations are required.

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CONFLICT OF INTEREST
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