Metal Ions in Life Sciences

# Exosomal microRNAs as Diagnostic Biomarkers and Gene Therapy Vehicles in Precision Medicine: A Translational Molecular Approach

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Abstract

The field of miRNA-based therapies is constantly expanding as a result of substantial research conducted across the world. Exosomal origin must be addressed for the use of exosomal miRNA in cancer diagnostics. A uniform procedure for exosome separation and detection should be devised, as current approaches have various limitations. More research on maximizing the benefits of target variety while avoiding off-target impacts is needed. miRNAs are involved in a number of cancer-related pathways, as well as developmental and regulatory processes. miRNAs control a large number of genes. The possibility of miRNA treatments having an off-target impact is a serious worry. Various techniques, including viral, nonviral, and chemical alterations, are recommended to improve target delivery. Nanoparticle-based delivery is being studied extensively, and attempts are being made to reduce toxicity and cellular accumulation. Next-generation sequencing of miRNAs is being used to study the functions that miRNA can play as a biomarker for diagnosis, detection, and prognosis. Several miRNA signatures unique to cancer types have evolved, with some of them now being tested in therapeutic studies. Antisense oligonucleotides that block miRNIs, tumor and CSC-targeted nanoparticle treatment, and combination treatment with chemotherapeutic agents are all promising clinical strategies for cancer personalized medicine.

## Introduction

MicroRNAs are tiny noncoding RNAs that influence gene expression post-transcriptionally (miRNAs). They are usually 20–22 nucleotides long and are indigenous to the cell. (3) It has now been demonstrated via different experimental research that miRNA dysregulation has a significant impact on the genesis and progression of cancer in people. They regulate a wide range of biological activities, including cancer, by activating oncogenes through transcription. MiRNAs govern diverse biological processes such as cell differentiation, proliferation, and death through feedback mechanisms by detecting the complementary area in the 3′ untranslated region (UTR) of multiple target RNAs. (5)

For the first time, Ambros et al. discovered a miRNA termed lin-4 in Caenorhabditis worms (C. elegans) that controls lin-14 protein production, laying the groundwork for miRNA study.

(6) Following that, Reinhart et al. (7) discovered that let-7 inhibits lin-14 protein production via an RNA–RNA sequence-specific interaction with the heterochronic gene lin-41's 3′ UTR. These short noncoding RNAs attach to a sequence-specific target mRNA and change its expression, according to this research. The expression pattern of a large pool of mRNAs has been demonstrated to be profoundly affected by deregulation of a single or small fraction of miRNAs. (8), (9) As a result, multiple additional investigations have shown that miRNAs are substantially conserved throughout all domains of life, indicating that miRNAs have a broad post-transcriptional regulatory role. (10-12) Through unique interactions with epigenetic modifiers, proteins, transcription factors, and RNP complexes, all of this research has established miRNAs as a crucial regulator of cellular processes. (13-15)

Calin et al. (16) used B-cell chronic lymphocytic leukaemia (CLL) cells to demonstrate for the first time the function of miRNA in human cancer. In CLL cells, two miRNA genes, miR-15a and miR-16-1, are usually observed to be deleted. Mir-15 and mir-16-1 genes were also discovered to operate as tumor suppressors by inhibiting the bcl-2 protein and triggering apoptosis. (16) The importance of miRNAs in cancer was proven in this study. Since then, multiple studies have confirmed the role of miRNA in cancer formation and progression. (17, 18)

The development of next-generation sequencing and miRNA profiling techniques has substantially aided our understanding of miRNAs for cancer detection, classification, diagnosis, and prognosis. The importance of miRNAs in cancer and their increasing relevance as therapeutic targets are discussed in this study. Finally, we talk about the difficulties of miRNA research and its clinical applications.

Biogenesis/biosynthesis of miRNA and regulatory mechanisms

MiRNA biogenesis is well conserved. MiRNAs are encoded in the genome in a variety of ways, including clusters of numerous precursors or production of intergenic transcripts, each of which encodes just one strand of pre-miRNA (which then adopts a hairpin-like secondary structure). (19) RNA polymerase II is primarily used for pri-miRNA transcription, but RNA polymerase III is also used in rare cases. (20, 21) Pri-miRNA is subsequently translocated into the nucleus, where endonuclease enzymes such as DGCR8 (RNA-binding protein) and DROSHA (a type III RNase) cleave the transcribed sequence into an 80–100 nucleotide long pre-miRNA sequence. (22, 23)

The pre-miRNA is subsequently exported from the nucleus to the cytoplasm by the Ran/GTP/Exportin-5 complex. (24) Dicer, a cytoplasmic ribonuclease (RNase III) enzyme, cleaves the pre-miRNA into a double-stranded mature miRNA strand in the cytoplasm. (25)

The released mature single strand miRNA attaches to Argonaute 2 (AGO 2) as a result of this processing step, forming the RNA-induced silencing complex (RISC). This complex has the ability to attach to 3′UTRs that are particular to their cytosolic mRNA targets on their own. Binding to mRNAs is based on base-pairing complementarity at the 5′ end of the mature miRNA or open reading frame and the cytosolic mRNA molecule, with the seed region, which is approximately 6–8 bp long from the 5′ end of the miRNA, being approximately 6–8 bp long from the 5′ end of the miRNA. Because the binding site is so small, the miRNA may target a huge number of distinct mRNAs. (26-28) Methyltransferases like 3 govern miRNA synthesis by methylating pri-miRNAs, marking them for DGCR8-based detection and processing, finally resulting in a mature miRNA. (29)

Helwak et al. employed an unbiased methodology called CLASH to gain a better understanding of how miRNA-mRNA base-pairing influences gene expression. They discovered a new noncanonical binding cluster that was unaffected by seed region or interaction complexity. Imperfect complementarity leads to translational repression, whereas complete complementarity leads to mRNA destruction once the mRNA and miRNA contact is formed. (30, 31)

miRNA has been demonstrated to behave as a ligand in tumors, upregulating a variety of signaling pathways. The manipulation of a nuclear factor-kB signaling pathway by miRNA was discovered to influence Toll-like receptor I in natural killer cells. (32) MiR-21/miR-29a, for example, is released by tumor cells and is signaled to immune cells through TLR8, causing a pro-metastatic inflammatory response that may contribute to tumor development and metastasis. (33) As a result, every change in miRNA biogenesis has a profound impact on a variety of cancer-related processes and pathways.

The role of microRNA (miRNA) in cancer

MiRNAs have been identified as a unique cell component that is variably expressed in sick and normal cells in recent years of research. (34) The relevance of miRNAs in cancer biology has recently been proven through their modulation of gene expression. MiRNA aids tumor invasion, proliferation, immunological invasion, and angiogenesis by acting as a facilitator. (35, 36) These studies have highlighted potential miRNA-based cancer biomarkers that may be identified in a variety of bodily fluids, allowing for less invasive cancer detection and surveillance. (37) When a cluster of miR-15 and miR-16 was discovered at 13q14.3, which is usually deleted in CLL, it was the first indication of altered miRNA levels in malignancy. (16) By researching the ‘tumour microenvironment,' Hanahan and Weinberg (38) demonstrated the significance of miRNA as a characteristic in numerous forms of cancer. Different types of tumors have distinct miRNA signatures that aid in the classification of cancer kinds. (39) Various cancer-related targets and their corresponding miRNAs have been well-characterized via different research.

The homeostatic maintenance of gene regulation, which is extremely cell-type dependent, and (2) cell destiny specification and the preservation of cell identity through feedback mechanisms are the two fundamental roles of miRNAs. (34) Changes in miRNAs help cells adapt to changing circumstances in their microenvironment in response to stress. (19) This has been found in glioblastoma, where low miR-451 levels are linked to low glucose levels. MiR-451 controls the activation and repression of the AMP-activated protein kinase pathway, which controls cell survival and mammalian target of rapamycin-activated cell proliferation. (40) Cancer cells have microRNA-specific genetic mutations that lead to changes in target binding, processing, and post-transcriptional modifications in the 3′UTR of mRNA. Due to loss of the 3′UTR, single nucleotide polymorphisms, and mutations, microRNA control of mRNA is lost in cancer cells during mRNA splicing. (42) Mutations that cause the miRNA processing machinery to be less efficient result in a considerable drop in the overall quantity of mature miRNA in the cell. Low amounts of mature miRNA are frequently seen in tumors, which can be caused by genetic loss, epigenetic silencing, alterations in the biogenesis route, or transcriptional repression. (43, 44) Some tumors with microsatellite instability have the same pattern. Mutations in exportin-5 (XPO5) cause pre-miRNAs to be trapped inside the nucleus, blocking miRNA processing. (45)

DICER expression has been discovered to be reduced in a variety of human carcinomas, including lung cancer, ovarian cancer, and CLL. (46-48) Binding of BCDIN3D (Bicoid-interacting 3, domain-containing) influences O-methylation of 5' monophosphate, which affects miRNA processing since that methyl mark is necessary for effective DICER cleavage and hence adversely regulates miRNAs. (49) Reduced Dicer expression, for example, is linked to a drug resistance sign and poor drug therapy results in ovarian cancer. (50) Overexpression of DICER, in contrast to these findings, has been linked to prostate cancer development. (51) Furthermore, oesophageal cancer is associated with Drosha locus amplification. (52) These findings imply that determining the frequency of these mutations as well as changes in the miRNA expression profile in a variety of cancer types is critical.

### Mechanisms of cancer-related miRNA dysregulation

In human cancers, there is a lot of variation in the degree of miRNA expression in malignant cells compared to normal ones.

### Genes encoding miRNAs are amplified or deleted.

Gene amplification, deletion, or translocation are hypothesized to produce changes in miRNA expression levels in malignant cells. In lung cancer and B-cell lymphomas, for example, amplification of the gene encoding miR-17-92 clusters has been found. (17, 18) In B-cell CLL patients, on the other hand, there is a loss of miR-15a/16-1-related genes on the 13q14 chromosome. (16) Similarly, lung cancer patients had miR-143 and miR-145 deletions in the 5q33 locus. (53) However, translocations have been seen, such as the translocation of miRNA-17-92 in T-cell acute lymphoblastic leukemia, which induces overexpression of this miRNA. (54) These findings were verified in 227 specimens representing human breast cancer, ovarian cancer, and various melanomas using an array-based comparative genomic hybridization approach. (55)

In addition, whole-genome sequencing of these samples revealed that a large number of miRNA genes are found in cancer-associated genomic areas, such as tumour suppressor genes, oncogenes, and common breakpoint areas. As a result of the deletion, amplification, and translocation of certain genomic locations, various areas in the genome are responsible for changing miRNA expression patterns.

### Epigenetic changes

Cancer cells have abnormal epigenetic changes such as hypermethylation of tumor suppressor genes, variations in histone modification patterns, and global DNA hypomethylation. (56) A large number of miRNA loci are linked to CpG islands, suggesting that DNA methylation-based epigenetic control of miRNA production is important. (57) AML1/ETO (AML fusion protein) epigenetic suppression of miR-223 expression via CpG methylation is one example. (58) In DNA methylation and histone acetylation inhibitor-treated T24 bladder cancer cells, seventeen miRNAs were elevated more than. MiR-127 (embedded in CpG Island) was dramatically increased in treated cancer cells relative to normal cells, downregulating the proto-oncogene BCL6 at the same time. These findings imply that DNA methylation and histone acetylation inhibitor therapy can be used to reduce tumors depending on miRNA expression. (59) Moreover, several investigations have shown that DNA hypomethylation-mediated overexpression of putative carcinogenic miRNA occurs. (60, 61)

MiR-29 expression inhibits the expression of DNMT3A and DNMT3B, (62) genes necessary for DNA methylation regulation, indicating that miRNA and epigenetic processes have a significant link to cancer. In NSCLC (nonsmall-cell lung cancer), restoring miR-29 levels results in the expression of CpG island methylation-silencing tumour suppressor genes. MiR-101 targets EZH2, a kind of histone methyltransferase that affects cancer cell survival and metastasis by silencing target genes. (63) The miR-200 family targets SUZ12, a polycomb repressor complex 2 component that has the propensity to produce cancer stem cells (CSCs). Increased expression and binding of SUZ12, H3-K27 tri-methylation, and E-cadherin gene suppression result from the loss of miR-200 expression. (64)

Lujambio et al. (65) found miR-148a and miR-34b/c as a hypermethylation-specific suppressor of cancer cells with reduced tumor development and metastatic development. All of these instances highlight the function and significance of epigenetic control by miRNAs, as well as their potential to modify DNA methylation and histone acetylation levels of the genes in question, demonstrating their relevance as cancer diagnostic or prognostic biomarkers.

miRNA transcriptional control

Almost half of the miRNA genes are found in the introns of protein-coding genes or in long noncoding RNA genes, and they have promoters and enhancers linked with them. (66) RNA polymerase II is responsible for the transcription of genes that only encode miRNAs. Because the miRNA gene is present in a clustered form, miRNAs are generally translated as a polycistronic message. A single factor controls many miRNA genes via a complicated circuit of feedback and feed-forward loops, which is governed by a multitude of RNA polymerase II-associated transcription factors.

Multiple studies have shown that transcription factors like c-Myc and p53 regulate miRNA expression in various malignancies. c-Myc is often elevated as a result of the activation of the miR-17-92 cluster, which regulates apoptosis and cell proliferation in malignant cells. c-Myc also inhibits the transcriptional activity of tumor-suppressive miRNAs from the miR-15a, miR-26, miR-29, miR-30, and let-7 families. (43) This is hypothesized to be due to a feedback loop in which c-Myc controls miR-122 by binding to its promoter, while Tfdp2 and E2f1 are indirectly blocked by miR-122, resulting in c-Myc transcription being repressed. As a result, the significance of this feedback loop in the development of carcinoma is highlighted. (68) In nonsmall cell lung cancer, the hepatocyte growth factor receptor c-MET regulates the production of miR-221/miR-222 clusters, which in turn regulates the transcriptional factors AP1 and ELK-1, resulting in a negative feedback loop with miR-27a. (70, 69) The miR-148a-5p/miR-363-3p gene promoter is directly targeted by c-Myc, inhibiting its expression in a similar loop. These also help the cell cycle advance, particularly from the G1 to the S phase. As a result, miR-148a-5p inhibits c-Myc production and miR-363-3p destabilizes it via targeting a ubiquitin-specific protease directly. (71)

Between p53 and miR-34, there is a synergistic sort of loop that confers a tumor-suppressive effect. (72) It has been demonstrated that p53 attaches directly to the promoter of the mir-34a gene and initiates the apoptotic process. (73, 74) As a feedback mechanism, miR-34a downregulates SIRT1, which in turn negatively regulates p53 via deacetylation and hinders p53-dependent transcriptional apoptosis. However, there is a rise in p53-mediated apoptosis that is not transcriptionally reliant. (75) p53 regulates the expression of miR-107, miR-605, and miR-1246, ( Dicer1 transcription can be regulated by p63, a member of the p53 family. Dicer1 expression is particularly low in tumors with a p63 deficit, which leads to low levels of mature miRNAs, which leads to an increased susceptibility to metastasis. (79)

Defects in the mechanism that produces miRNA

Dysregulation of enzymes and/or cofactors involved in the biogenesis pathways, such as Dicer, Drosha, DGCR8, and exportin 5, has a major impact on total mature miRNA levels. When Dicer1 and Drosha were largely deleted in both in vitro and in vivo models, accelerated carcinogenesis was found in several kinds of tumors. (80) Drosha processing has been discovered to be an important stage in the control of miRNAs in cancer and embryonic development. (81) Dicer1 dysfunction has been linked to increased tumor metastasis and initiating potential in colorectal cancer cells. (82) Furthermore, ovarian cancer patients with high mRNA levels of Dicer and Drosha have a longer median survival. (83) On the other hand, decreasing Dicer expression levels are linked to a worse patient survival rate. (47, 84)

Argonaute proteins (AGO) are important regulators of RNA silencing, and their dysregulation can lead to cancer. Wilms' tumor of the kidney has been shown to lack the human EIF2C1/hAgo1 gene. (85) Melanomas have lower levels of AGO2 expression than primary melanocytes. In primary gastric cancer patients, on the other hand, significant AGO2 expression has been detected. (87) Lin28, a highly conserved RNA-binding protein that regulates miRNA let-7 processing, has been linked to cancer, cell pluripotency, and developmental timing. (88) Exportin 5 (XPO5) is a dsRNA-binding protein that helps pre-miRNA leave the nucleus and enter the cytoplasm. Pre-miRNA is stuck in the nucleus because a shortened form of the XPO5 gene is unable to export it from the nucleus, resulting in poor mature miRNA processing. (45) Interestingly, restoring the XPO5 function normalizes miRNA processing while simultaneously acting as a tumor suppressor. It's worth noting that a variety of different miRNAs can control miRNA processing. The miR-103/107 family of miRNAs targets DICER in aggressive breast tumors, lowering the global miRNA level. In summary, chromosomal abnormalities, transcriptional alterations, nuclear receptors, and errors in miRNA synthesis are the primary processes connecting miRNAs to cancer.

Tumors with altered miRNA expression

Tumours develop the capacity to resist apoptosis, avoid growth inhibitors, sustain proliferative signaling, enable replicative immortality, stimulate angiogenesis, and commence invasion and metastasis. (38) Because miRNA profiling of these tumors revealed aberrant expression when compared to normal tissues, it's thought that dysregulated miRNAs act as tumor suppressors or oncogenes, depending on the gene target, influencing any of the above-mentioned hallmarks. The cell cycle is controlled by the balance of extracellular signaling molecules and intracellular activities. MiRNAs have been found to be integrated into several cell proliferation pathways, hence prolonging proliferation and evading growth control in malignant cells, according to recent research.

The E2F proteins are important cell proliferation regulators that are controlled by miRNAs in a cell cycle-dependent manner. E2F1-mediated gene transcription induction has been seen during the G1 to S transition stage. (89) E2F1-/- mice developed a variety of cancers, indicating that E2F1 functions as a tumor suppressor. The MiR-17-92 cluster inhibits E2F1 translation after c-Myc activation. (67) The miR-17-92 cluster also regulates E2F2 and E2F3 translation. (90) To accomplish cell cycle progression in normal cells, a feedback mechanism controls the expression of the miR-17-92 cluster and E2F. (91) Overexpression of the miR-17-92 cluster in tumors causes a break in the feedback loop, which leads to cell growth. (92) MiRNAs also control cyclins, cyclin-dependent kinases (CDKs), and CDK inhibitors, all of which are required for cell cycle advancement.

The deletion of Dicer-1 in Drosophila germline stem cells prevented the transition from G1 to S phase, revealing the relevance of miRNAs in this process.(93) Furthermore, elevated expression levels of CDK inhibitors (Dacapo) from the p21/27 family were identified in this setting, indicating that miRNA-mediated downregulation of the protein might promote cell cycle advancement. In glioblastoma cells, the Cdk inhibitor p27kip1 is specifically targeted by miR-221/222. (94) High levels of miR-221/222 in malignant cells promote cell growth, whereas low levels cause G1 cell cycle arrest. Both primary tumor samples and cancer cell line investigations corroborate these findings. (95-97) Furthermore, overexpression of miR-221/222 has been reported in a variety of human tumors, corroborating previous results that Cdk inhibitor p27kip1 regulation is part of an oncogenic pathway. Other than p27Kip1, the miRNA family comprising miR-302, miR-663, and miR-24 controls p21CIP1 and p16INK4a. (98, 99) MiR-663 and p21CIP1 establish a molecular loop that is responsible for nasopharyngeal cancer cell growth. (100) MiRNAs also affect the expression of cyclins and Cdks, as miRNA-545 reduces the production of CDK4 and cyclin D1 in lung cancer cells as a result of cell cycle arrest. (101)

MiRNAs also control cell growth by regulating a range of signaling pathways. MiR-486, for example, affects cell proliferation and migration by targeting the PI3K and insulin growth factor (IGF) signaling pathways 85, IGF1, and IGF1R.(102) As a result, altered miRNAs have been linked to cancer in a number of ways, making them a potential target for cancer treatment.

Identifying and blocking critical cancer-related pathways

## As targets, the cell cycle and cell proliferation

MiRNAs are well-known for their involvement in modulating cell proliferation, affecting several regulatory pathways, and thus having a significant impact on carcinogenesis. Overexpression of oncogenic miRNAs allows malignant cells to enter and continue through the cell cycle. MiRNAs that inhibit tumor development are frequently lost during cancer and so play a role in cell cycle arrest. (103) The retinoblastoma (pRb) pathway is involved in a number of human malignancies and has a considerable impact on cell cycle control. (104,105) It works by suppressing the E2F transcription factor family, which regulates the expression of genes important for cell cycle progression. (106) Phosphorylation of pRb by cyclin-dependent kinases causes E2Fs to activate gene transcription. Specific kinases and cyclins form complexes with active CDKs to facilitate the cell cycle's passage through its stages. (107) Growth-restricting miRNAs operate on growth. -decreasing pathways like p53 or growth-enhancing mitogenic pathways like RAS/RAF/MAPK to target these critical cell cycle components (i.e. CDKs and cyclins). (107, 108)  MiR-20a, miR-125b, and miR-17-92 clusters, for example, inhibit tumor growth by targeting the E2F transcription factor. 67, 109, and 110

The CDK inhibitors from the cip/kip family reveal that miRNAs influence cell cycle inhibitors, which adversely control CDKs. The miR-106b and miR-17-92 families target p21, a powerful CDK inhibitor and a key modulator of the p53 gene's G1 phase arrest in the cell cycle. Using a luciferase test, Wu et al. found that roughly 28 miRNAs had the capacity to target the 3'UTR region of p21 mRNA. (111) Similarly, miRNAs regulate p27 and p57 post-transcriptionally. The miR221/222 cluster, in particular, regulates p57. (112, 96) As a result, miRNAs play an important role in cancer cell entrance and progression through the cell cycle.

## Targeting senescence

Senescence is the end of the cell cycle that can not be reversed. There are two forms of replication senescence: replicative and premature senescence. The shortening of telomeres causes replicative senescence, whereas greater oxidative stress levels, DNA damage signaling, or elevated oncogene expression levels cause premature senescence. (113) Because miRNAs inhibit cell cycle progression, they play a role in the onset of senescence. The senescence inducers p16 and p19, for example, are suppressed by HMGA2, which is the main target of miRNA let-7. (114-116) In replicative senescence, miR-24 is downregulated. (98) MiR-34a, a member of the miR-34 family, controls p53 and acts as a senescence regulator by targeting numerous locations. (75, 117, 118)

MiR-34a and the p53 de-acetylating enzyme SIRT1 create a complicated feedback loop that regulates miR-34a production and activity (75, 119, 120). It is also controlled by ELK1 of the ETS family. Hence, p53 isn't the only one who controls it. E2F1 and E2F3 also induce four separate clusters of miRNA, let-7a-d, let-7i, mir-106b-25, and mir-15b-16-2, during the transition from G1 to S phase. In fact, they stymie this transition by stymieing a variety of E2F gene targets and cell cycle promoters. (122) Senescence is a very diverse process with various regulators and elements involved in its onset, maintenance, and regulation. Because miRNAs may alter several genes and pathways, they can effectively regulate senescence, perhaps acting as a senescence promoter.

Cancer stem cells could be a target.

The CSCs theory claims that cancer is caused by a small number of cells with stem cell-like qualities. (123) A group of protein-coding genes, specifically surface markers, are involved in CSC self-renewal and asymmetrical cell division. CSCs' tumorigenicity, treatment resistance, and asymmetrical cell division are all influenced by miRNAs. (124) Its effects on CSCs are thought to be caused by the overexpression of oncogenic miRNAs and a downregulation of the tumor suppressor gene. (92) According to molecular research, oncogene-targeting miRNAs are found in vulnerable locations and are susceptible to miRNA loss or decrease, causing certain oncogenes to upregulate.Finally, these modifications have an impact on a variety of cancer-related activities, including metastasis, anti-apoptotic, tissue invasion, and treatment resistance. (125)

In recent years, a novel cancer treatment method has been developed that precisely targets CSCs. There are substantial challenges to this method, as it is critical that CSCs and other malignant cells be recognized using multiple molecular distinctions and markers. The most successful type of therapy is cell-based targeted administration of miRNA inhibitors or miRNA mimics. CSCs differ from regular stem cells in terms of CSC marker expression as well as glycosylation patterns. (126) This provides for further differentiation, and the creation of antibody-conjugated nanoparticles or liposomes targeting CSC-specific glycans will allow for selective delivery of CSC-suppressing miRNAs. As a result, miRNAs serve as functional markers for CSCs, and future research might disclose the significance of miRNAs in CSC biology, especially in diagnosis, prognosis, and therapy, thereby improving cancer treatment and minimizing side effects.

Increasing the sensitivity of cancer cells to medicines

Only around 12% of the human genome codes for proteins. Nevertheless, 70–80% of the genome is translated into RNA. This demonstrates the role of noncoding RNAs in protein synthesis control. (127-129) Targeting miRNAs might, in theory, change the protein levels of genes involved in cancer cell biology. For tiny compounds, low protein levels are linked to poor therapeutic effectiveness. As a result, small chemical inhibitors targeting miRNA would limit oncogenic expression. (2)

Costales et al. developed Targaprimir-515, a selective pri-miR-515 inhibitor that inhibits mature miR-515 synthesis, resulting in increased expression of the sphingosine kinase 1 (SK1) and sphingosine-1-phosphate (S1P) proteins, which are involved in cell migration and proliferation. More importantly, they observed high levels of human epidermal growth factor receptor 2 (HER2) expression in HER2-negative MCF-7 cells, demonstrating MCF-7 cell sensitization to Herceptin (HER2 targeting medication) after treatment. The specificity of this small molecule was demonstrated when 99.7% of the genes were unaffected by pri-mir-515 inhibitor treatment, and healthy breast epithelial cells named MCF-10A were unaffected since they lacked miR-515. (130)

Similarly, miRNAs have a role in improving the efficacy of anticancer treatments. In liver and kidney cancer, for example, miR-27b sensitizes a wide range of anticancer treatments. This is accomplished by boosting the levels of miR-27b, which is commonly deleted in both liver and kidney cancers. Patients with high levels of CYP1B1 or p53 wild type are more sensitive to anticancer medicines because miR-27b assists in the activation of p53-induced apoptosis and drug detoxification via CYP1B1. (131) Finally, miRNAs are appealing targets in cancer therapy because they provide nonobvious strategies to alter oncogene expression post-transcriptionally with such tiny molecules, improving treatment responsiveness and effectiveness.

As a cancer biomarker, miRNA

MicroRNAs have a high degree of stability in bodily fluids, and their differential expression has been linked to a cancer patient's prognosis or reaction to treatment. Endogenous RNase activity protects circulating miRNAs, which are released from tumorous tissue into the environment. (132) Various circulating miRNAs are being employed to help in cancer diagnosis and prognosis, as well as the differentiation of tumor subtypes. (133) Exosomes contain a large number of microRNAs, which give them stability and play a key role in cancer formation and progression. (134-136)

Exosomes (30–120 nm membrane-derived vesicles) encased in cancer-specific miRNAs have been identified in serum, plasma, and bodily fluids, allowing for easy and early cancer diagnosis. Exosomes allow for cell-to-cell communication and miRNA production, and cancer cells use this process to control the physiological and immunological responses of the cells around them. (137) Jin et colleagues demonstrated the function of overexpressed miR-181-5p, miR-361-5p, and miR-30a-3p in lung cancer using plasma exosomes (LUAD). (138) Tanaka et al demonstrated the role of gastric juice-derived exosomal hsa-miR-933 in functional dyspepsia utilizing microarray technology. Urdinez et al. (15 (39) identified miR-143/145 as a diagnostic biomarker in chondrosarcoma.

However, because miRNAs may affect the expression patterns of numerous kinds of mRNA, their specificity towards a specific medical state is debatable. The selectivity of the miRNAs towards illness was discovered using the human miRNA disease database. Many miRNAs are not cancer-specific, as seen in the graph below, although they are frequently dysregulated in a variety of cancer types, including mir-21. Although complex miRNA signatures are illness specific, they are seldom independently replicated and verified. (140) Although miRNAs have a strong diagnostic potential, there are various obstacles to overcome before miRNAs may be used in patient care. Bias in high-throughput methods, repeatability, and the degree of specificity are all major concerns. For large-scale applications, miRNA-based multiplexed testing is indicated for clinical use.

Cancer treatments based on miRNA

Tumor growth causes the production of tumor-suppressive miRNAs to decrease, advancing the oncogenic signaling pathway. As a result, replacing tumor-suppressive miRNAs at the tumor site is an appealing approach. OncomiR-dependent tumors can also be targeted using miRNA antagonists (anti-miRs). (141) MiRNAs inhibit angiogenesis and fibrosis by targeting not just tumor-promoting stromal cells, but also endothelial cells and fibroblast cells. (142 and 143) When compared to protein-based drugs and plasmid DNA-based gene therapy, miRNAs have little toxicity and immune response as natural antisense nucleotides. The RISC complex binds the double-stranded miRNAs, and the AGO2 protein cleaves the passenger strand while the guide strand attaches to the target mRNA. (144) As a result, the features of the miRNA guide are critical for creating miRNA antagonists or miRNA mimics. MiRNAs are quickly destroyed by ribonucleases due to their unprotected 3′-hydroxyl and 5′-phosphate ends, rendering their expression transitory and with a short half-life. (145) To circumvent miRNA stability issues, argonaute 2 protein or naturally occurring extracellular vesicles are commonly employed. Nanoparticle-based delivery systems have been used to deliver tumor-specific miRNA throughout the last decade. Organic lipid-based nanoparticles (LNPs), inorganic materials such as gold, silica, and polyamidoamine (PAMAM) dendrimers are just a few of the notable miRNA delivery vehicles that have evolved as a consequence of global research. Retrovirus, adenovirus, lentivirus, and adeno-associated virus-based miRNA delivery methods have also been extensively developed. (146) A miRNA mimic whose 5′ end is complementary to the target gene's 3′ UTR mimics the endogenous mature miRNA. As a result, the deleted or downregulated tumor suppressor miRNA can be restored. (147) When cationic LNPs were coupled with a miR-634 mimic (miR-634-LNPs), pancreatic tumor development was significantly reduced compared to controls (miR-LNPs). The LNP-treated group, on the other hand, had a significant rise in AST levels, indicating LNP-related toxicity. (148) There have been several attempts to employ mesenchymal stem cells for cancer treatment, based on their capacity to release a large number of chemokines and growth factors. (149)

Various miRNA mimics, such as miR-379 and miR-146b, have been built into extracellular vesicles released from mesenchymal stem cells for systemic, oral, or intratumoral delivery. (150, 151) MSC-EV-miR-185 was tested in animal models for its ability to reduce inflammation and the occurrence of oral squamous cell carcinoma by applying it topically to the carcinoma site.(152) MiR-185 controls the AKT pathway, producing an uptick in the production of cleaved caspase 3 and 9, which promotes apoptosis. (153)

Anti-miRs inhibit the oncomiR, which affects cancer-related pathways. Anti-miR is made up of antisense oligonucleotides or locked nucleic acids (LNAs) that have the same complementary sequence as the target miRNA. MiR-21, for example, inhibits apoptosis by activating the PI3K pathway and thereby blocking PTEN. Anti-miR-21 therapy of breast cancer cells resulted in a significant activation of apoptotic factors, which inhibited cell growth. (154) Similarly, Yin et al. (155) concentrated on CSCs, which are responsible for cancer aggressiveness, metastasis, and medication resistance. It contained anti-miR-21 LNAs as well as RNA aptamer binding to the CD133 receptor using a three-way junction (3WJ) motif as a nanoparticle framework. These nanoparticles were able to target triple-negative breast cancer cells specifically, resulting in a decrease in miR-21 expression and downstream processes. (155)

Research focused on miRNA-based sensitization of tumors resistant to currently accessible cancer medicines is now being undertaken. The combination of oxaliplatin and miR-204-5p in silica nanoparticles was tried for colon cancer, and the stimulation of apoptosis resulted in a substantial reduction in tumor development. (156) Using hydrophilic polyethylene glycol in conjugation with polylactic-co-glycolic acid nanoparticles (PLGA-PEG-NPs) containing antisense-miR-21 in combination with orlistat (an anti-obesity drug), Shah et al. (157) were able to show a drastic decrease in IC50 values for TNBC when compared to monotherapy. The anti-miR-21 and miR-100 were loaded for the glioblastoma multiforme therapy combined with systemic temozolomide using gold-iron oxide nanoparticles with PEG-T7 peptide (T7-poly-GIONs), which enhanced the overall survival rate in the animals. (158) As a result, our data supports the advantages of miRNA-based cancer therapy as a monotherapy or a combinatorial therapy, paving the way for the creation of a realistic and effective therapeutic option for advanced stage cancer.

## Clinical trials based on miRNA

Several miRNAs are now being tested in clinical studies. These are being researched for use as biomarkers in illness categorization and progression, as well as for medication synergy and predictive purposes. Studies are being conducted to see if miRNA mimics and anti-microRNA constructs may be used as cancer therapeutics. MiRNAs have been studied for their ability to reduce tumor treatment resistance. For example, miR-100 has been demonstrated to exhibit chemo-resistant properties in small-cell lung cancer. (159)

MiR-199b-5p is epigenetically repressed in chemoresistant ovarian cancer. (160) Anti-miR is also being tested in advanced miRNA-based studies as a treatment for hepatitis C, and anti-miR-122 (Miravirsen) is now being tested. (161) Miravirsen possesses a complementary sequence to miR-122, and its LNA structure confers degradation resistance and strong target affinity. It not only targets mature miRNAs, but also pre- and pri-miRNAs, which aids its therapeutic impact. (162) MRX34 was the first miRNA-based cancer treatment, and it works by mimicking miR-34a, a tumor suppressor that acts downstream of the p53 gene. (163, 164)

Resistance to miRNA therapy has surfaced as a possible issue as a result of these many investigations, which can be addressed through combinatorial treatment or anti-miRNA-based therapy. (165) Despite the fact that several clinical trials are now ongoing, miRNA-based treatment is still in its early stages, and adverse effects must be assessed. Systemic side effects are also a potential that has to be researched further. Other miRNA processing changes may be noticed as a result of the external introduction of replacement miRNAs into the cell, and all of these possibilities may only be discovered in the future through clinical studies.

## Conclusions

The field of miRNA-based therapies is constantly expanding as a result of substantial research conducted across the world. As a result, gaining a deeper understanding of miRNA function and biogenesis will aid in the development of miRNA-based therapeutics. More research on maximizing the benefits of target variety while avoiding off-target impacts is urgently needed. Many firms are now investigating the prospect of using miRNA-based medicines to treat cancer. Exosomal origin must be addressed for the use of exosomal miRNA in cancer diagnostics, as tumor-generated exosomes must be distinguished from exosomes originating from other bodily fluids. Second, a uniform procedure for exosome separation and detection should be devised, as current approaches have various limitations, including contamination by other biological molecules and aggregation. Third, the normalization procedures must be well-established and universally accepted so that data from different research can be easily compared. (166) The results of different research differ, raising doubts about the reliability and repeatability of miRNA-based treatments in people, according to the literature study. (167) The results' anomalies can potentially be due to differences in sample size, sampling period, miRNA quantification and normalization process, and comorbid conditions. (168) When compared to their healthy counterparts, cancer patients have higher amounts of miRNAs in their bloodstream. As a result, for a good detection investigation, it is advised to utilize an identical volume of sample rather than the same amount of total RNA. Furthermore, housekeeping transcripts coming from cells or tissues, such as SNORD and U6, are commonly employed for normalization. However, their validity is called into question since these transcripts are extremely vulnerable to RNase activity. (169) In most of these investigations, unaffected people with no history of early or late-stage illness are utilized as controls. Validation studies, on the other hand, imply that dysregulation of miRNAs is more common in advanced stages of illness. (170)

As a result, confounding variables such as the patients' age and gender must be considered, as they have been shown to affect miRNA expression. (171) To deal with such difficulties, a meta-analysis can be used; however, the above-mentioned parameters must be kept constant, and a standard operating method must be followed.Data collection at different time periods should also be investigated, as this might reveal important information about potential confounders.

MiRNA-based treatments have a number of drawbacks, including (1) nuclease degradation, (2) insufficient cell membrane transport, (3) endosomal entrapment, and (4) insufficient target tissue delivery.(5), stimulation of innate immune responses, (175). (6) Unwanted off-target and harmful effects (175), as well as (7) low binding affinity for adjacent sequences. (176) Tissue-specific delivery is one of the most significant issues with miRNA therapies in vivo. Furthermore, significant cellular absorption of synthetic oligonucleotides is necessary for long-term target inhibition. (177) In body fluids or tissues, unaltered ‘naked' oligonucleotides are unstable and sensitive to cellular and serum nucleases. (177) The oligonucleotides' size and negative charge prohibit them from passing through the cell membrane, resulting in poor cellular absorption. (177) Given that miRNAs control a large number of genes, the possibility of miRNA treatments having an off-target impact is a serious worry, since they may do more harm than good. MiRNAs are involved in a number of significant cancer-related pathways, as well as developmental and regulatory processes. As a result, they have the potential to create catastrophic unintended consequences.

Various techniques, including viral, nonviral, and chemical alterations, are recommended to improve target delivery. However, while these changes considerably enhanced oligonucleotide target delivery, they simultaneously lowered biological activity and raised toxicity. (178) Nanoparticle-based delivery is being studied extensively, and attempts are being made to reduce their toxicity and cellular accumulation. Future research on the pharmacokinetics and pharmacodynamics of miRNA-based cancer treatment is also needed in order to design treatments that attain the optimal therapeutic concentration in target cells and tissues.

The development of innovative delivery techniques with enhanced antisense and miRNA mimic chemical design is the next step in miRNA-based cancer treatment. The development of different drug-specific miRNA maps is enabled by miRNA profiling of control and drug-treated individuals. These maps can be used to create therapy plans for reprogramming the miRNAome of cancer patients. Using miRNAs to sensitize already available chemotherapeutic drugs is also a promising method. Exosomes, nanoparticulate formulations, and novel miRNA delivery vehicles can all be employed to get around the present limitations of miRNA-based treatments. Targeting miRNAs to restore normalcy to the cancer patient's disrupted miRNA network appears to be a sensible and dependable method with a high chance of success. It will be feasible to build distinct miRNA antagonists or mimics based on the patient's miRNAome in the future, allowing for individualized cancer treatments.

## Finally, some thoughts

Since the finding that the deletion of miRNAs is associated with CLL, (16), researchers all over the globe have been looking into the function of miRNAs in other cancers and the source of miRNA expression dysregulation. This highlighted the significance of numerous processes, such as miRNA gene deletion or amplification, (16), 17, epigenetic factors, abnormal gene transcription control, and altered miRNA biogenesis.MiRNAs have a large number of targets, but they are hypothesized to cause tumors by modifying particular targets and functioning as either an oncogene or a tumor suppressor. Several miRNA inhibitors and miRNA mimics are currently being studied in clinical trials, with the potential to be used as therapeutics. The importance of noncoding RNAs such as circular RNAs and long noncoding RNAs is being studied in order to better understand the underlying processes of cancer disease.

The numerous functions that miRNAs can play as a biomarker for diagnosis, detection, and prognosis are being studied with the development of technologies such as next-generation sequencing. Several miRNA signatures unique to cancer types have evolved, with some of them now being tested in therapeutic studies. The majority of our knowledge of miRNA activities is based on cell culture models, which have their own set of constraints. As a result, research involving a large number of patients is required for better understanding and use as a cancer therapy method.

Antisense oligonucleotides that block miRNAs, tumor and CSC-targeted nanoparticle treatment (126), and combination treatment with chemotherapeutic agents (158) are all promising clinical strategies for cancer personalized medicine (159-274).

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