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Review Article

MicroRNA Regulation in Cancer: Insights into Diagnosis, Prognosis, and Treatment

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Abstract
MicroRNAs (miRNAs) are tiny, non-coding RNA molecules that are pivotal in regulating cell growth, development, cell cycle, and programmed cell death. Alterations in miRNA expression, caused by various mechanisms such as amplification, deletion, mutation, or epigenetic changes, can lead to either an increase or decrease in their levels in cancerous cells. Since their initial discovery in 1993, a wealth of research has established miRNAs as key players in oncogenesis and tumor suppression across various human cancers. The study of miRNAs is critical for predicting cancer outcomes and aiding in its detection. Numerous miRNAs have demonstrated potential as markers for cancer prognosis and diagnosis, as well as targets for therapy. Their profound influence on tumor development and spread is becoming increasingly acknowledged. This article presents a summary of how miRNAs are synthesized and generated, and explores their dual function as tumor suppressors and oncogenes. Additionally, we delve into the promising applications of miRNAs as instruments for cancer diagnosis, prognosis assessment, and therapeutic intervention.

Keywords: Oncogenesis; microRNA regulation; molecular mechanisms; prognostic biomarkers; therapeutic targets

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INTRODUCTION

Malignancy is a significant public health disease as well as one of the deadliest diseases about 18 million novel cases worldwide in each year[1,2]. It is a complex illness distinguished by chromosome reconfigurations, magnification, genetic variances, and epigenetic modifications that result in unchecked cellular development[1]. Despite the greatest efforts of professionals to perform serious exploration to produce more efficient therapeutic procedures, several cancers have been associated with higher causes of death and mortality[1]. Surgery, chemotherapy, and radiotherapy are some of the tumor therapeutic interventions today, but they are not always effective. To improve the long-term survival and treatment rates of tumor patients, it is crucial to identify efficient detection technologies, diagnosing biomarkers, improved efficient therapy techniques, and other complementary measures[1,3]. The Small non-coding RNA having an average length of the 18–22 base pairs have been known as microRNAs (miRNAs). Numerous features of cell biology, such as metabolic reactions, stress reactions, apoptosis, as well as cancer development depend heavily on microRNAs[4]. MicroRNAs are now well-established as essential cellular molecules across both healthy and pathological conditions[5]. Well during last 10 years, the examination of miRNAs mostly has focused on tumors. Many investigations were shown the implication of microRNAs by signifying in what way they control the appearance of their target mRNAs to encourage cancer development, angiogenesis as well as resistant attack in cancer biology[5]. Tumor microRNA profiles can also identify pertinent subgroups, predict patient survival, and assess therapeutic effectiveness[6]. Furthermore, physiological fluids can be used to detect cancer related microRNA biomarkers, enabling less intrusive surveillance[7]. According to the identification of its expanded seed sequence (from 2-8 nucleotids), the miRNAs' targeting properties are divided into categories[8]. The ncRNAs called miRNAs control the transcription of genes via deteriorating mRNA or preventing translation[8]. MiRNAs also have both inhibitory and stimulatory effects on the development of cancer[9]. Whenever the balance between these two effects shifts, uncontrolled miRNAs that are abnormally dysregulated and lose body control over the development of particular malignancies. Normally, these two effects are in a state of equilibrium. Oncogene stimulation and abnormal apoptosis are two common examples of this lack of control[9]. It is extremely difficult to pinpoint desired transcripts and mechanisms that have been controlled via specific miRNAs because it was revealed that just single miRNA might interact to more than two hundered (200) target genes, having different functions, for example transcription factors, receptors, as well as transporters[10]. It is not surprising that microRNAs affect some biological processes given their ability to target many genes. In addition, different miRNAs exhibit different impacts on different types of tumors. They behave as tumor inducers in certain cancers while acting as tumor suppressors in others. Physiologically, mRNAs and miRNAs coordinate and essentially regulate all biological processes[11].The etiology of numerous cancers is substantially influenced by an overall within production of total mature miRNA in tumor cells[12]. Biologically, mRNAs and miRNAs collaborate and essentially regulate all biological processes. Furthermore, under pathological settings, miRNA levels can be dysregulated as a result of the illness as well as a cause of it, which can lead to changed conditions.

In this review, we delve into the synthesis of miRNAs, their distinct characteristics, and their potential roles as both tumor suppressors and oncogenes. We also examine the impact of miRNA dysregulation on tumor diagnosis, prognosis, and treatment. The significance of this article lies in its comprehensive consolidation of current insights into the diverse roles of miRNAs in cancer biology. Understanding these small non-coding RNAs is essential, as they play a critical role in regulating gene expression and are involved in fundamental cellular processes such as cell proliferation, apoptosis, and differentiation.

By detailing the mechanisms of miRNA synthesis and their biogenesis pathways, we provide a foundational understanding crucial for the development of miRNA-based diagnostic and therapeutic strategies. This review highlights the dual nature of miRNAs, which can act as oncogenes or tumor suppressors depending on their specific targets and context. This complexity underscores the necessity for precise therapeutic approaches tailored to individual miRNA profiles. Additionally, the article underscores the clinical importance of miRNAs. Their unique expression patterns in various cancer types and stages make them promising biomarkers for early cancer detection, disease monitoring, and personalized treatment strategies. We also discuss the challenges and advancements in miRNA delivery systems, such as nanoparticles and exosomes, which are critical for translating miRNA research into clinical practice.

Ultimately, this review aims to offer a thorough overview of miRNA biology in cancer, highlight recent research advancements, and explore the future potential of miRNAs in oncology. By doing so, it seeks to encourage further research and innovation in the field, contributing to the development of more effective cancer diagnostics and therapies.

2. ELUCIDATING THE ATTRIBUTES, DETECTION, AND GENESIS OF MICRORNAS

MicroRNAs (miRNAs), diminutive non-coding RNAs, are pivotal in gene regulatory mechanisms, targeting messenger RNA (mRNA) for degradation or translational inhibition[13]. These miRNAs are implicated in a myriad of biological functions, from cancer progression and epithelial-to-mesenchymal transition (EMT) to disease etiology[14-16]. They modulate critical signaling cascades, including the Wnt/β-catenin, PI3K/AKT/mTOR, and RAS/RAF/ERK/MAPK pathways. Furthermore, miRNAs have emerged as prospective biomarkers for various conditions, such as type 2 diabetes, gastric cancer, and adrenal hyperplasia[16-18].

Research has revealed that miRNAs possess specificity to particular tissues and cell types and are conserved across diverse species[19]. These robust molecules, found in bodily fluids, are considered promising candidates for clinical biomarkers[20]. Additionally, miRNAs have been linked to a range of pathological states, including colorectal cancer, uveal melanoma, and pancreatic ductal adenocarcinoma[21-23]. Distinct miRNA profiles have been discovered for various illnesses, contributing to early diagnosis and prognostic evaluations. The modulatory influence of miRNAs in the Epithelial-to-Mesenchymal Transition (EMT) is noteworthy, as they engage with transcription factors such as ZEB, SNAIL, and TWIST to influence cellular differentiation. Additionally, miRNAs have been implicated in the compaction of the Golgi apparatus and are associated with the advancement of neoplasms[15]. Within the realm of oncology, miRNAs are recognized for their role in enhancing tumor cell proliferation, metastasis, and invasiveness[24].

RNA sequencing technologies have revealed the existence of over 100,000 distinct RNA entities within mammalian species. These RNA molecules are categorized into two groups: coding RNAs and noncoding RNAs (ncRNAs). NcRNAs are further classified by their transcript size. Small noncoding RNAs, which comprise less than 200 nucleotides, include various types such as microRNAs, PIWI-interacting RNAs, small nucleolar RNAs, among other native RNA forms[1]. Small non-coding RNAs (ncRNAs) were initially discovered in nematodes and plants through external RNA interference (RNAi). It was later found that these molecules are endogenous and primarily function as gene regulators in both animals and plants by targeting specific genes and controlling their post-transcriptional functions. Among these, single-stranded RNAs known as microRNAs (miRNAs) play a crucial role in the post-transcriptional regulation of target genes, influencing various biological and pathological processes[25]. It was immediately realized how micro-RNAs possess a stable machine with wide-ranging

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functional importance throughout the plant and animal kingdoms once they have been first exposed and discovered in 1993 in investigations on Caenorhabditis elegans[26]. Currently, miRBase, an accessible database of reported microRNAs and their annotation[27], has approximately 2,500 possible human microRNAs cataloged. Exons, introns, and intergenic spaces are there, wherever microRNA encoding sequences are found in protein-coding genes. They might have unique promoters or co-regulate along with the host genes they are found in. The miRNA encoded regions are translated by RNA polymerase II and/or III to create primordial miRNAs (pri-miRNAs), that can be made up of few thousand nucleotides long as well as have a hairpin structure. This process is called biogenesis, and it has been well discussed elsewhere[28-30]. The Drosha-DGCR8 microprocessor complex subsequently does the processes for pri-miRNAs inside the nucleus to produce a pre-miRNA that is about 70 nucleotides long, which is the progenitor to miRNA. Pre-miRNAs (mirtrons) with intron-encoding may be immediately digested by spliceosomes in noncanonical biogenesis together with the co-encoding transcripts. The exportin-5 protein exports pre-miRNA hairpin to cytoplasm, wherein it's broken down via the RNase Dicer as well as double-stranded RNA binding enzyme TRBP producing a mature miRNA that is about 22 nucleotides long. The ribonucleoprotein complex (RISC) is then modified to contain single miRNA strands, which enables the ribonucleoprotein complex to interact with target sequences. The seeding sequence, which is typically found at 2 to 7 nucleotides of the miRNA's 5' ends, serves as a site for reverse complementary binding. As a consequence of this binding, the translation process is inhibited or stopped as shown in (Figure1). According to estimation, about 60% of all protein-coding genes and genetic factor have been regulated post-transcriptionally by miRNAs[31]. As a result, miRNAs are major controllers of cellular signaling with a significant effect on practically all physiological processes[32]. Recent research has shown that miRNAs might transfer to the nucleus to control the transcript effectiveness of particular genes, thus increasing the miRNA's influence on cell signaling cascades[33] and this is enhancement to their actions on the post-transcriptional level.

3. DECIPHERING THE MULTIFACETED ROLES AND MECHANISMS OF MICRORNAS

MicroRNAs (miRNAs), diminutive non-coding RNAs, are pivotal in modulating gene expression subsequent to transcription. These entities partake in a multitude of biological functions, encompassing cellular growth, differentiation, programmed cell death, and metabolic processes. The roles and intricacies of miRNAs are manifold, playing a substantial part in maintaining cellular equilibrium and the genesis of diseases. MiRNAs exert their function by attaching to the 3'-untranslated region (3'-UTR) of target messenger RNAs (mRNAs), which results in either translational inhibition or mRNA disintegration. This mode of regulation permits miRNAs to precisely calibrate gene expression and orchestrate cellular activities. Furthermore, miRNAs are capable of concurrently targeting multiple mRNAs, thereby impacting a range of signaling cascades and biological operations, as noted by Kabłak-Ziembicka[34].

The interaction between miRNAs and essential cellular pathways is vital for the preservation of cellular balance. For example, research indicates that miRNAs can control the expression of hypoxia-inducible factor-1α (HIF-1α), influencing conditions such as acute kidney injury (AKI)[35]. The reciprocal regulatory interactions between miRNAs and HIF-1α are instrumental in the development of AKI, underscoring the complex relationship between miRNAs and pivotal cellular pathways.

In conditions such as Alzheimer's and cancer, miRNAs have surfaced as promising targets for therapy owing to their role in regulation. These molecules partake in the post-transcriptional governance of gene expression, either inhibiting or decomposing target mRNAs. Altering miRNA levels via physical activity or pharmacological measures can affect the trajectory and outcomes of diseases[36,37]. Moreover, miRNAs have been associated with a variety of cellular functions across different tissues and illnesses. In the case of chronic lymphocytic leukemia, miR-150 impacts B-cell receptor signaling through the regulation of gene expression, including genes such as GAB1 and FOXP1[38]. This influence on gene expression by miRNAs highlights their significance in cellular communication and the development of diseases. It is estimated that microRNAs regulate over 60% of human genes[39]. It's interesting to note that just the single miRNA monomer could interact to several target mRNAs (up till 2019, over 2300 distinct miRNAs were defined within humans[40]. Distinct miRNAs may each block multiple mRNA molecules. Depending on bond complementarity and the degree of miRNA and/or mRNA production, bindings that link target mRNA units have different effects[40]. It has been demonstrated that numerous diseases, especially cancer, might lead to miRNA expression, which manifests in the absence of a particular miRNA's expression[41]. According to their role in the growth of cancers, miRNAs have been divided into two groups: suppressor miRNAs (which prevent appearance of oncogenes and/or other genes that can cause apoptosis) as well as oncogenic miRNAs (which either activate oncogenesis and/or prevent the appearance of suppressor genes). The influence of few miRNAs, such as, miR-155 as well as miR-125b, depends on the overall function of regulatory genes, thus it must be noted that this classification is significantly simplified[42].

3.1 MicroRNAs the Oncogenic Architects in Cancer Progression

MicroRNAs (miRNAs), diminutive non-coding RNAs, are instrumental in the dynamics of cancer biology, functioning as oncogenes that facilitate the inception, advancement, and spread of tumors. These miRNAs can assail tumor suppressor genes, oncogenes, and pivotal cellular pathways, thereby contributing to the perturbation of cellular functions in cancer. Numerous investigations have pinpointed specific miRNAs that act as oncogenes across diverse cancer types. For example, miR-423-5p is known to modulate cellular progression in prostate cancer by interacting with FRMD3, thereby underscoring its oncogenic role in this disease, as reported by Wei et al[43]. In addition, miR-765, miR-21, and miR-144 are implicated in fostering cell proliferation, invasion, and the epithelial-mesenchymal transition in renal cell carcinomas through their influence on LHPP, signifying their roles as oncogenes[44].

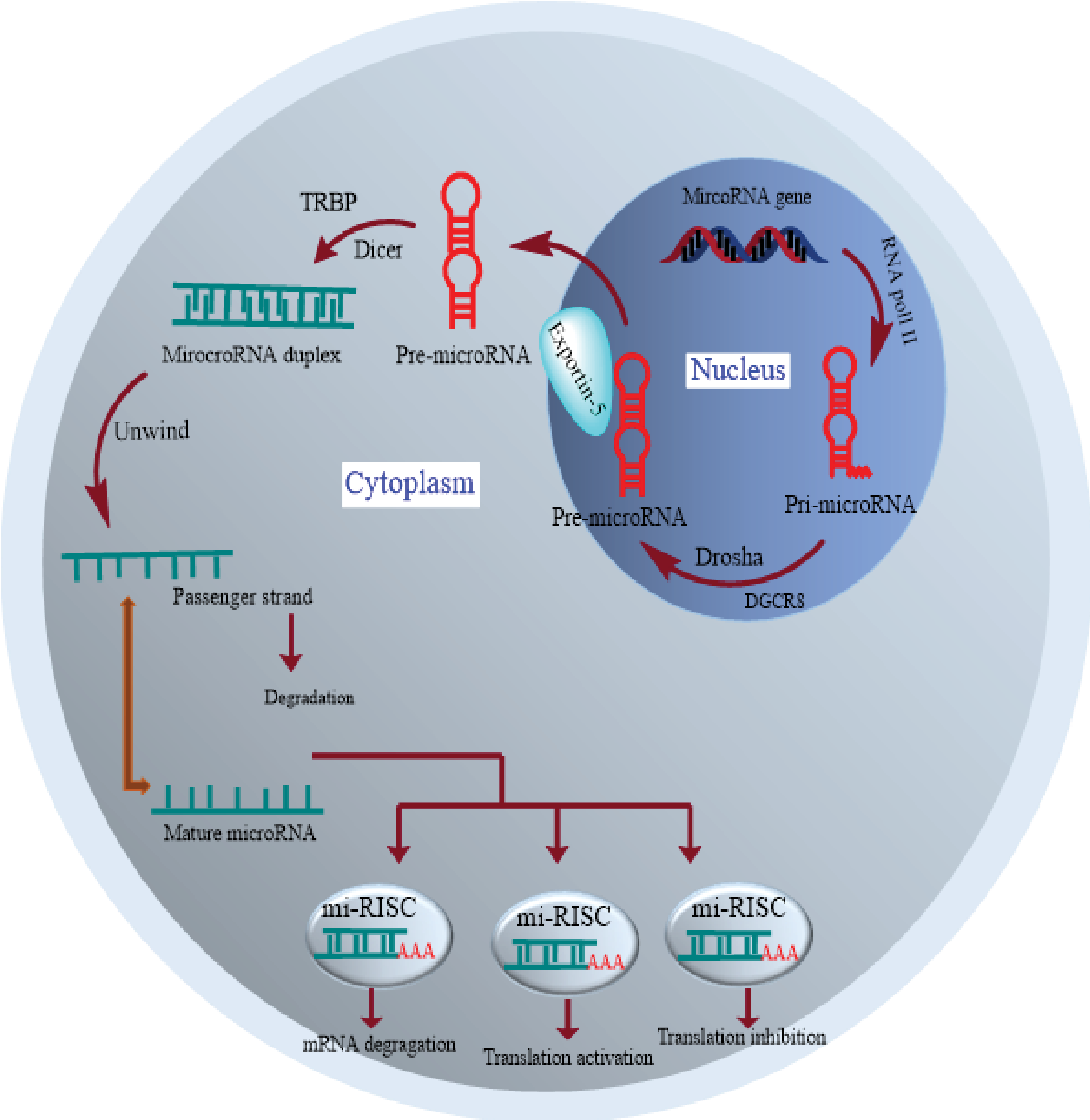

Figure 1. MicroRNAs biogenesis within nucleus. The miRNAs genetic traits are copied via RNA polymerase II to create miRNA transcript (prior miRNA), that is cut into pre miRNA (miRNA transcript precursor) inside nucleus through the microprocessor complex Drosha DGCR8. The exportin 5 translocate then further pre miRNA into the cytoplasm, where Dicer as well as its communication partner, TRBP, translate it into a duplex structure of miRNA. After that, the dublex of miRNA is unraveled into binary single stranded miRNAs. Although the passenger segment of the matured miRNA is devastated, the active component uploads on RNA-induced silencing complex (RISC) as well as undesirably controls gene expression, and try to target mRNA devastation or translational stimulation and suppression.

Additionally, miRNAs such as miR-21, miR-155, and the miR-17-92 cluster are recognized as oncogenic miRNAs in a variety of cancers, including those of the breast, lung, stomach, and pancreas[45,46]. These oncogenic miRNAs can suppress the production of tumor suppressor proteins, enhance cellular proliferation and invasion, and stifle programmed cell death, thereby fueling tumor development and advancement. In the context of lung cancer, miRNAs have been documented to function as oncogenes by altering signaling pathways and fostering resistance to medication[47]. Moreover, miR-663 has been observed to support the persistence of non-small cell lung cancer by impeding mitochondrial outer membrane permeabilization, underscoring its role as an oncogene in this type of cancer[48]. Colorectal tumor cells frequently exhibit elevated transcription of specific miRNAs, indicating that they are more frequently oncogenic[49]. Augmentation of miRNA-coding genes, improved biosynthesis, the constituent action of their promoters, and/or improved stabilization of the miRNA is all possible causes and reasons of increased miRNA expression[50]. Numerous miRNA complexes are concerned in the onset, development and spread of breast cancer over the past ten years[51]. It has also been established that there is a connection among the appearance of specific miRNAs and clinical pathological characteristics of breast cancer and/or the way through which this aggressive cancer responds to causative therapy[51]. One of the first described miRNAs was MiR-155[52,53]. It is situated on chromosome 21q23 which is entrenched in a noncoding RNA of host known as B cell integration cluster (BIC)[54]. A prior investigation demonstrated that BIC as well as c-myc can perform equally to promote oncogenesis. Cell growth was enhanced when c-myc and BIC were expressed simultaneously and/or within pairs in cultured chicken embryo fibroblasts[54,55]. MiR-155 is extremely upregulated in various cancers, comprising primary mediastinal non-Hodgkin lymphoma, pulmonary cancer, breast tumor, Hodgkin disease, CLL, as well as AML. Investigations had revealed that an upregulation of the oncogene molecules miR-210, miR-21 and miR-221 within triple-negative breast cancer has been linked to a lower disease-free lifetime with a poorer prognosis[56]. The miR125-b in HER-2-positive malignancies and/or also miR-520 in the hormone reliant on cancers are two examples of molecules having decreased production and hence decreased suppressor potential[55,56]. In their studies, Singh and Mo provided miRNA groups that are crucial to the development of the carcinogenic tumor under discussion. They centered their attention on the family of miR-10, where miR-10a as well as miR-10b have a role within initiation and also spread of breast tumor. The activation of miR-10b has been linked to increased levels of TNM cancer (bigger original tumor size and lymphatic node metastases) as well as increased levels of cell development and HER-2 receptor activation or duplication[55,56]. However, this is inversely connected with the quantity of E-cadherin and the presence of steroid receptors, that seem to be intricate in the Epithelial-mesenchymal transition mechanism's suppression of the metastatic process[55,56]. The oncogenic miR-21 family is likewise linked to metastasis, a poorer prognosis, especially for ductal breast tumor, as well as the overall survival become shortened[56]. Researchers have revealed that the family of miR-200 as well as miR-205 or miR-145 as suppressive miRNAs have lower transcription in malignant mammary tissue relative to normal tissue. The EMT process related metastatic pathway is likely inhibited by miR-200, miR-205, and miR-145, whereas miR-145 has a significant impact on cell death[55,56]. On the opposite side, the pivotal carcinogenic latent of the miR-200 family has been discussed and increased levels of specific miR-200s have been linked to both chemotherapeutic resistance and the formation of distal metastasis in breast cancer[57]. Elevated miRNA production has a suppressor effect and represses many genes. Transcription of Rbl2 suppressive gene was inhibited by "oncomiR-1," a group of 6 miRNAs (miR-19a, miR-20, miR-19b miR-17-92, miR-17, miR-18, and miR-92)[58]. Through suppressing CDK inhibitors (cyclin-dependent kinases), oncogenic miRNAs including miR-24, miR-31, as well as miR-21 boost proliferation capacity of the cells[58].

3.2 MicroRNAs: Architecting the Landscape of Tumor Suppression

MicroRNAs (miRNAs) are pivotal in the realm of cancer biology, serving as tumor suppressors that hinder oncogenic pathways and bolster anti-cancer activities. These diminutive non-coding RNAs regulate gene expression at the post-transcriptional level, influencing a range of cellular functions. Distinct miRNAs have been pinpointed as tumor suppressors across various cancer types. For instance, miR-15 and miR-16-1 trigger cell death by targeting Bcl-2, an anti-apoptotic protein that is overexpressed in a variety of cancers, as noted by Peng & Croce (2016)[59]. Similarly, the miR-34 family, and miR-34 in particular, is acknowledged as a tumor-suppressive miRNA due to its altered expression in human cancers and its association with the tumor suppressor protein p53[60]. In the context of leukemia, miRNAs such as miR-15, miR-16, let-7, and miR-127 function as tumor suppressors[61]. Moreover, miRNAs such as miR-195-5p, miR-125a, miR-425-5p, and miR-466 are recognized for their tumor-suppressing roles in a spectrum of cancers, encompassing lung cancer, medulloblastoma, gastric cancer, and hepatocellular carcinoma[62-65]. These miRNAs hone in on specific genes or pathways implicated in cancer advancement, curtailing cell growth, movement, invasion, and fostering programmed cell death.

The imbalance of miRNAs in cancer can undermine their tumor-suppressing capabilities, thereby fueling the onset of cancer and its progression. Nonetheless, the reestablishment of either the expression or functionality of these tumor-suppressing miRNAs holds potential for crafting innovative therapeutic approaches for cancer care. By aiming at oncogenes or crucial cellular pathways, these miRNAs can impede tumor development, prevent metastasis, and heighten the responsiveness of cancer cells to therapies[66,67].

Whenever a healthy cell's cancerous transformation is brought on via the loss of a miRNA's function, the miRNA might behave as a tumor suppressor same as protein coding genes. Numerous factors, such as epigenetic silencing, chromosomal deletions or mutations, deletion, and/or variations within processing of the miRNA, may cause a miRNA to lose its activity[68]. Synthesis of genes necessary for tumor growth, such as antiapoptotic proteins or transcription factors, increases when suppressor miRNAs are expressed less or not at all. The miR-15, as well as miR-16 molecules' lower production within chronic lymphocytic leukemia cells, has been initially reported in 2017, inhibiting apoptosis (miR-15 as well as miR-16 control production of antiapoptotic BCL-2), thus promoting unchecked leukemic cell growth[69]. In gastric carcinoma cells, decreased synthesis of the miR-146a molecule is correlated with carcinoma development[69]. The transcription of miR-143, which can target oncogene Raf1, was found to be downregulated in an in vitro colonic tumor model[70]. The mechanism of DNA methylation is crucial in controlling the transcription of suppressor miRNAs within tumor cells[50,55]. For instance, hypermethylation of promotors of miRNAs (miR-137, miR-342, let-7, miR-345, miR-129, miR-34, miR-9) results from the decrease in its expression as well as the onset of colorectal tumor. The action of DNMT3A

(DNA methyltransferase 3A) is raised as well as tumor cell viability is boosted when miR-143 transcription is reduced in colon tumor cells[71]. It is significant to memorandum how DNA methylation is necessary for miRNA production, but as miRNA production can influence the function of epigenetic controllers, for example, DNA methyltransferases and histone deacetylases[55] are all examples of suppressor miRNAs and their biological functions.

4. GENOMIC AND EPIGENOMIC MODULATION OF MIRNAS IN ONCOGENESIS

Alterations in both genetic and epigenetic regulation of microRNAs (miRNAs) are pivotal in the onset and progression of various cancers. These small non-coding RNAs are key post-transcriptional regulators of gene expression, impacting a multitude of cellular functions. Cancer-associated disruptions in miRNA levels can stem from a variety of sources, such as gene amplification or deletion, aberrant transcriptional control, epigenetic modifications, and anomalies within the miRNA processing pathway[59]. Epigenetic mechanisms, including DNA methylation and histone modification, play a significant role in the aberrant regulation of microRNAs (miRNAs) in cancer[72]. The disruption of specific miRNA clusters, such as the Dlk1-Dio3 cluster, has been observed across various types of cancer, underscoring the influence of epigenetic changes on miRNA patterns[73]. Moreover, the dysregulation of miRNAs in cancer correlates with genomic instability, irregular transcriptional governance, altered epigenetic landscapes, and impairments in the miRNA generation process[74]. Cancer-associated miRNA dysregulation may arise from genetic and epigenetic alterations affecting miRNA genes, disrupted control over miRNA transcription, and anomalies in miRNA biogenesis[75]. Research indicates that such dysregulation can include mutations in proteins responsible for miRNA processing and maturation, as well as epigenetic modifications like histone alterations and DNA methylation irregularities[76]. Furthermore, this dysregulation can activate oncogenic pathways, suppress tumor-inhibiting genes, and ultimately facilitate the advancement of cancer[77]. Changes in the epigenome not only directly precipitate miRNA dysregulation in cancer but also indirectly instigate DNA and histone modifications via miRNAs[78]. The perturbation of miRNA regulation in cancer is multifaceted, encompassing genetic mutations, epigenetic shifts, disruptions in miRNA processing, and the misregulation of transcription factors that govern miRNAs[79]. MicroRNA production is reported to ever be dysregulated in cancer cells[80,81]. In malignancies, altered epigenetic and transcriptional regulation, anomalies throughout their miRNA synthesis process, and either higher or lower amounts of miRNAs were typically associated with genetic abnormalities[81] (Figure 2). In general, genetic abnormalities well as the deletion, amplification, and/or translocation of particular genomic neighboring microRNA genes are associated with carcinogenesis. Genomic sequence analyses revealed the prevalence of miRNA genes within chromosomal areas or fragile regions linked with malignancy, as well as in little amplified or heterozygous areas and general breakpoint regions[82]. It's well acknowledged that many transcriptional regulators tightly control the production of miRNAs. Via encouraging transcription of the pre-miRNAs, the signaling pathways may activate miRNAs. In some circumstances, while tissue or cell definite miRNA is triggered by transcription factors throughout development, such a mechanism is quite well documented. The networks among miRNA and transcription factors were exposed in tumors, and it was found that abnormalities within the articulation of major transcriptional regulators, including c-Myc, p53, and E2F, can result in completely unregulated expression of miRNA, which may encourage the growth of tumors[83]. Additionally, changes in genomic status may have an impact on miRNA expression. Such change might include distortion of the histone modification processes, abnormal DNA methylation of tumor suppressor genes, as well as hypomethylation of genomic DNA[84]. Hypermethylation of CpG islands within promoter areas may cause genetically inherited transcriptional suppression of tumor suppressor genes in various malignancies. AML1/ETO, a much more common acute myeloid leukemia related fusion protein, was shown by Fazi et al. to epigenetic changes suppress miR-223 activity via CpG methylation[85]. Furthermore, it has been shown that subsequently concurrent remedy with DNA methylation as well as histone acetylation antagonists, 17 of 313 has-miRNAs have been elevated in T24 bladder tumor cells[86]. Following the downregulation of protooncogene BCL6, miR-127, anchored inside a CpG island as well as has lower activity within cancerous cells, showed the greatest rise in transcription across all miRNAs. Those findings demonstrated that miRNA expression which may serve as a tumor suppressor was activated by histone deacetylase suppression as well as DNA demethylation. In either a related investigation, it was demonstrated that the CpG methylation was associated with miR-148a as well as miR-34b/c silencing because of hypermethylation in malignancies[87]. Overall inhibition of motility, metastasis and tumor growth in vivo has been associated well with the recovery of such miRNAs mostly in cancer. These findings, therefore, showed how epigenetic control of miRNA expression throughout cancer functions. Several enzymes as well as regulating proteins, including Drosha, Dicer, DGCR8, Argonaut proteins, and Exportin-5, are in charge of regulating miRNA biogenesis and enabling proper miRNA maturity via primary miRNA progenitors. This may result in improper expression of miRNAs that have been linked to a poor prognosis and tumor growth[88,89].

5. CLINICAL SIGNIFICANCE OF MICRORNA PROFILING IN ONCOLOGY

MicroRNAs (miRNAs) have become a focal point in cancer research due to their vital role in gene regulation and their connection to cancer's onset, advancement, and spread[90]. They are being explored as indicators for cancer detection, outcome prediction, and tracking the effectiveness of treatments[91]. The targeted packaging of miRNAs into extracellular vesicles has established them as precise indicators for identifying cancers[92]. Certain miRNAs, such as miR-143-3p, miR-375-3p, miR-451a, and miR-146a, have been pinpointed in colorectal cancer. These miRNAs are linked to reducing the spread of cancer,

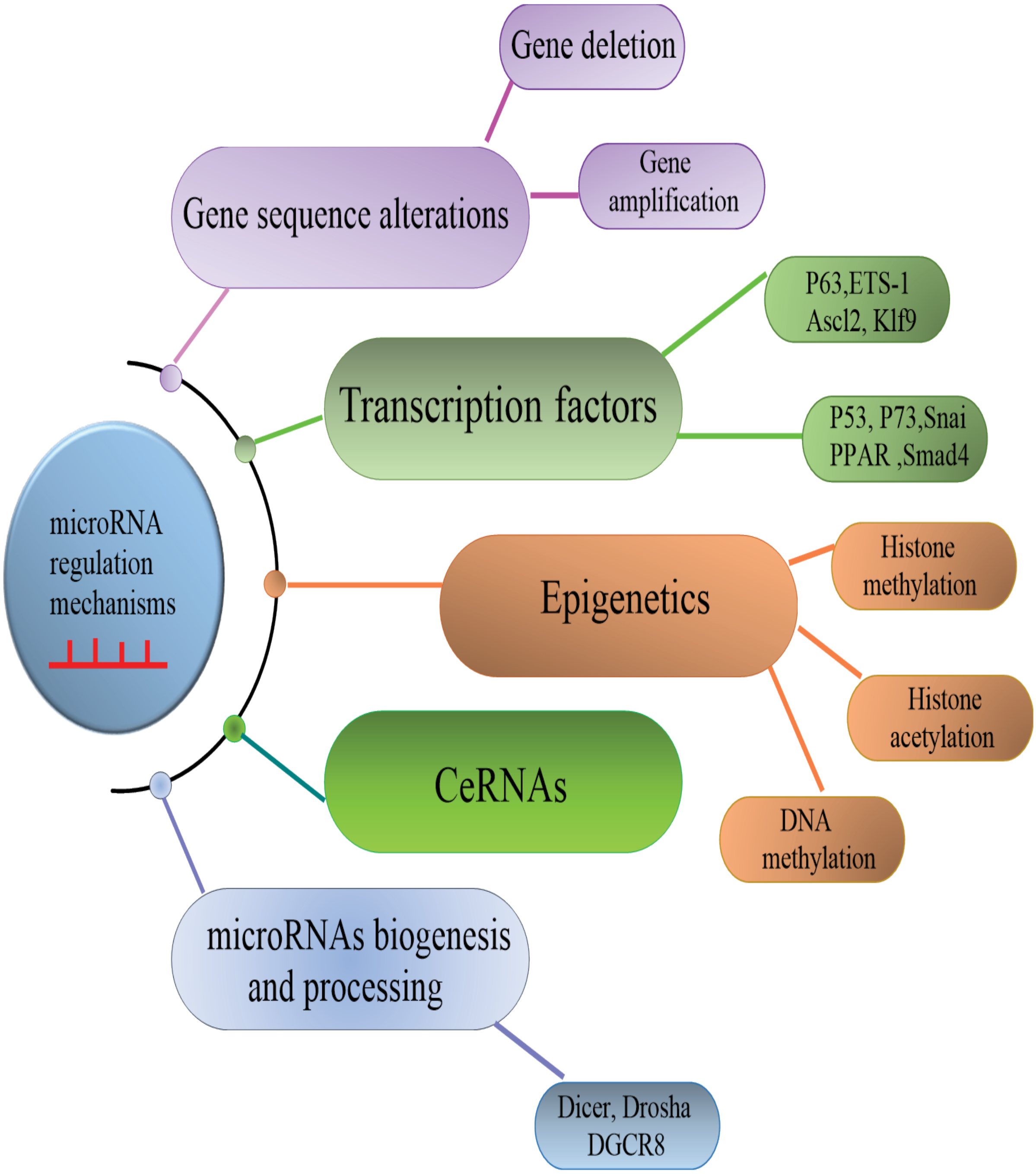

Figure 2. The deregulated mechanisms of microRNAs. Different mechanisms could inhibit and/or promote the expression of microRNAs

increasing sensitivity to chemotherapy, affecting cell growth, and blocking cancer-promoting inflammation[93].

The altered expression and mutation of miRNA biomarkers have been strongly linked to the initiation and spread of cancer, highlighting their promise as advanced markers for detecting and predicting cancer[94]. MicroRNAs have been associated with clinical and pathological features across various types of cancer, indicating their usefulness in categorizing cancer subtypes based on distinct traits[95]. Moreover, miRNAs have gained recognition as crucial markers due to their altered levels during the onset and progression of diseases, particularly in cancers[96].

Exosomal miRNAs have gained attention as potential diagnostic markers for cancer due to their stability in bodily fluids and their high levels, providing a non-invasive method for early detection of cancer[97]. Certain miRNAs, such as hsa-miR-195-5p, have been identified as indicators for assessing lung cancer risk and have also been linked to other cancers like colon, breast, and stomach cancer[98]. The identification of these circulating miRNAs in bodily fluids is expected to improve the early diagnosis of cancer[99].

A patient's diagnosis and prognostic of various malignancies could be aided by the discovery and characterization of new cancer-relevant microRNAs. Furthermore, important tumoral categories could be identified by miR profiles. As a noninvasive detection technique, we may potentially monitor miR alterations to forecast therapy responses. Last but not least, the significance of miRs in cancer has opened up new diagnostic and therapeutic possibilities[100]. The identification of melanoma cancers mainly depends on the discovery of metastatic indicators. In contrast to the serum lactate dehydrogenase, that is presently acknowledged as a biomarker for stage four while less used for stage three melanoma patients, and has been shown the efficacy of circulating cell-free miRs as possible biomarkers for the stage III and IV melanoma patients. As a result, they discovered some miRs appropriate for tracking, how well patients with metastatic melanoma respond to therapy[101].

5.1. Advancing Cancer Diagnostics and Prognostics: The Role of MicroRNA Biomarkers

MicroRNAs have emerged as promising indicators for diagnosis and prognosis in a range of conditions, encompassing both cancer and neurological diseases. These small, non-coding RNA molecules are key regulators of gene expression and have been the subject of extensive research for their potential in clinical settings. Numerous studies have underscored the value of microRNAs as non-invasive markers for detecting diseases and evaluating prognoses. In the case of bladder cancer, microRNAs such as cell-free urinary microRNA-99a and microRNA-125b have been pinpointed as diagnostic markers, highlighting the role of microRNAs in non-invasive cancer screening. In the same vein, for systemic lupus erythematosus, urinary microRNAs like microRNA-146a and microRNA-155 have proven to be effective diagnostic markers, underscoring the importance of urinary microRNAs in disease detection[102]. Moreover, microRNAs are being explored as prognostic markers in diverse medical scenarios. In mesial temporal lobe epilepsy, certain microRNAs, such as miR-27a-3p, miR-328-3p, and miR-654-3p, are being examined for their predictive value regarding surgical outcomes[103]. Furthermore, miR-1248 is being considered as a prognostic marker to identify pediatric patients with low-grade glioma who may experience disease progression[104]. The inherent stability and ease of detection make microRNAs excellent candidates for diagnostic and prognostic applications[105]. Research has demonstrated that microRNAs can act as prognostic indicators in a variety of cancers, such as gastric, colorectal, and gliomas[106,107]. Additionally, microRNAs are being investigated for their prognostic potential in specific stages of cancer, like TNM-stage II colon cancer[108]. By screening resected tumors and biopsy samples, it is possible to identify several miRNA activity profiles that can be utilized to distinguish between malignancy and benign abnormalities in various systems[109]. When matched with lymph node status and tumor size, a 97 genes expression analysis for a breast tumor is being shown to be a better strategy for classifying the histopathological grade of the illness[110]. With warmth as well as specificity of up to 100%, a 4-miRNA profile in leukemia has been able to distinguish between ALL (acute lymphoblastic leukemia) versus AML (acute myeloid leukemia)[111,112]. The miRNAs have been thought to be potential cancer indicators. First, since miRNA molecules have been found in a variety of bodily fluids, these are easily accessible for research. Second, miRNAs' great physiological stability makes it easier to find them. Third, miRNAs control every step of cancer growth and frequently express themselves within a tissue-specific method as well as appear to be especially clinically important.

To distinguish some tumor clients from normal people, for example, patients with breast[113], colorectal[114], gastric[115], lung[116], pancreatic[117] as well as hepatocellular[118] tumors, certain plasma/serum circulating miRNAs have been identified. This makes them resources for initial diagnosis. Two tests have been created today to assist the miRNA profile-based tumor diagnosis. Among one them is the ThyraMIR test, which could identify the kind of thyroid tumor by analyzing the production of ten (10) different types of miRNAs (miRNA-29b-1-5p, miRNA-204-5p, miRNA-551b, miRNA-375, miRNA-146b-5p, miRNA-223-3p, miRNA-146b, miRNA-31-5p, miRNA-155-5p, and miRNA-138-1-3p)[119]. For instance, increased transcription of blood-circulating miR-21 is strongly related to a expressively augmented risk of colorectal tumor[120], lung tumor[121,122], breast tumor[123], and pancreatic tumor[124]. As an example, within colorectal tumors, an intensification in miR-21 appearance is associated with confrontation to the fluorouracil treatment because of letting down appearance of the repair protein MSH2[125]. The miRNA transcription in chemo resistant tumor cells might fluctuate in cancer cells which have been sensitive to the chemotherapy[126]. Elevated overexpression of miR-224, miR-140, miR20a, as well as miR-215, has been linked to the growth of chemoresistance to oxaliplatin, fluorouracil, methotrexate, and teniposide within colorectal tumor cells[127]. Another illustration is the miRpredX-31-3p predictive diagnostic test (IVD-certified), which is applied to people with colorectal tumors who do not have K-RAS genomic mutations. Examining the activity of miR-31-3p in histopathological samples from gastrointestinal cancers. When compared to conventional chemotherapy, anti-EGFR therapy has higher medical effectiveness while miR-31-3p expression is low[128].

Numerous research is found that the miRNA expression patterns could be used to forecast the course and prognostic tool of cancer. Although the upregulation of 17 miRNAs has been linked to estrogen receptor positive phase I and/or phase II breast cancer, having a favorable medical prognosis, 31 miRNAs have been significantly related with medical variables in breast cancer[129]. Advanced risk of reappearance and a lower possibility of relapse free survival are linked to miR 210 overexpression[130]. In lung tumors as well as B cell lymphomas, miR 155 upregulation has been associated with poorer postoperative survival[112]. The non-small cell lung tumor development was revealed to be correlated to the production of the family of miR 183, that includes miR 183, miR 182, and miR 96. In colonic cancer, miR 200c expression has been linked to total survivability after surgery[131,132].

5.2. MicroRNAs Pioneering Biomarkers for Therapeutic Intervention

MicroRNAs (miRNAs) have attracted considerable interest as potential therapeutic agents due to their role in regulating a range of diseases, with a particular focus on cancer. Therapeutic approaches involving miRNAs include the use of miRNA antagonists, such as anti-miRs or locked nucleic acids, to inhibit cancer-promoting miRNAs[133]. MicroRNAs have been identified as promising targets for therapy and as biomarkers in autoimmune diseases[134]. In the realm of oncology, miRNAs have been thoroughly investigated for their involvement in disease mechanisms, and their potential for diagnosis, prognosis, and as innovative therapeutic targets[135]. They have become instrumental in the treatment, diagnosis, and monitoring of cancer[136]. MiRNAs have been investigated in a wide array of conditions beyond cancer, including psoriatic arthritis, cholangiocarcinoma, liver disorders, and viral infections[137]. These small RNA molecules have demonstrated their potential as both diagnostic and therapeutic markers across different diseases[138]. In liver health, miRNAs are pivotal, presenting possibilities for both diagnostic and therapeutic applications. Additionally, miRNAs have been associated with drug resistance in diseases such as triple-negative breast cancer, highlighting their significance as therapeutic targets to combat resistance[139]. The imbalance of microRNAs (miRNAs) is connected to a range of illnesses, positioning them as promising candidates for diagnostic and prognostic purposes, as well as therapeutic interventions[140]. Their potential as biomarkers for cancer could revolutionize early detection, outcome prediction, and monitoring of treatment efficacy[64,141]. Beyond oncology, miRNAs offer therapeutic possibilities in heart diseases, brain disorders, and pulmonary conditions, underscoring their extensive applicability. Specifically in lung cancer, miRNAs have been implicated in the development of resistance to treatments, emphasizing their importance as prognostic indicators and therapeutic agents to improve treatment responsiveness[45]. The microRNAs can independently trigger tens to hundreds (10-100) of genes. As crucial physiological route inducers that control target gene transcription via translation suppression or mRNA breakdown, these perform a vital role in tumor. The miRNAs, therefore, are desirable aspirants for tumor therapy and predictive biomarkers. Discovery of miRNAs as well as their targets, which are crucial for the growth and spread of cancer, may open up interesting treatment possibilities. Preclinical and clinical trials are right now being conducted to test some miRNA-based therapies. MiR-10b is a viable treatment target for the treatment of glioblastoma because it controls cell penetration, movement, and spread[142]. The therapeutic relevance of miR-10b comes from its involvement in tumorigenesis, where inhibition of miR-10b by antagomir inhibits spread of cancer within tumor-bearing mice by re-activating the transcription of the Hoxd10 gene[143]. The major involvement of miR-10b in diverse malignant tumors has been identified by more than 100 investigations on metastatic cancers[144]. Anti-miR-221 significantly abridged the amount as well as quantity of cancer nodules within liver of the transgenic mice model, making it another effective approach for malignant tumors[145]. The pharmacokinetic and pharmacodynamic tests were carried out and found that LNA-anti-miR-221 (LNA-i-miR-221) had half life short, ideal tissue accessibility, and little urine elimination, as well as three-week-span p27 target overexpression within xenograft cancers. In their non-human primate research, there was no evidence of LNA-i-miR-221-related toxicity[145]. A wide variety of malignancies, including NSCLC[146], prostate cancer[143], and malignant pleural mesothelioma[147], are linked to miR-16 depletion. Reid et al. demonstrated cancer progression suppression by Bcl-2 and CCND1 targeting in malignant pleural mesothelioma nude animal models by delivering miR-16 mimics using bacteria-derived minicells[143,147]. The whole earliest siRNA medicine to be approved for therapeutic usage laid the foundation for the creation of miRNA drugs[148]. The United States company Mirna Therapeutics, Inc. created anti-miRNA technologies, comprising MRX34, a liposomal nanoparticle formulation containing a miR-34 mimic (NOV40). The patients having primary liver tumor, lymphoma, NSCLC, melanoma, multiple myeloma, and or renal cell tumor, it is the initial miRNA mimic to reach clinical outcomes. Parallel to this, MRX34 treatment, either by itself or in conjunction with radiotherapy (XRT), inhibited T-cell fatigue as well as decreased p53 controlled PDL1 expression within non-small-cell lung cancers. Consequently, immune associated adverse reactions resulted in patient deaths (the cause of inflammatory responses is still unknown), which forced the comprehensive phase I study to be stopped. As more than just a result, these preliminary experiments are currently being examined to recognize well the immune correlated toxicities[148-150]. The Australian professional EnGeneIC began a phase I clinical research by means of miRNA-16 mimic (known as MesomiR-1) encumbered to bacterial-derived nano cells structure, that successfully inhibited tumor growth (NCT02369198). Individuals with highly developed NSCLC and malignant pleural mesothelioma (MPM) who had failed basic therapy have been given the miRNA-16 mimic-based EnGeneIC Delivery Vehicle (EDV) compound intravenously infusion. Layer of the EDV is covalently linked with just an EGFR-targeting antibody to make it easier to attack cancer spot. The stage II clinical trial can proceed since there were no harmful effects or negative immunological reactions at the first-dose level, loaded with miR-16 mimics[151,152]. MiRagen Therapeutics, Inc. (Boulder, CO, USA) started stage I medical test of antitumor LNA anti-miR-155 effectiveness on patients with mycosis fungoides, one of the furthermost prevalent variants of cutaneous T-cell lymphoma, as either result of encouraging preclinical results (NCT02580552). As a consequence of the trial's reported unfavorable harmful impacts, safe therapeutic dosages, and particular administering routes were optimized[143,153,154].

6. CHALLENGES ASSOCIATED WITH MICRORNA IN CANCER

MicroRNAs (miRNAs) are pivotal in cancer biology, acting as either oncogenes or tumor suppressors. Their dysregulation is linked to various cancers, including those of the breast, colon, lung, prostate, pancreas, stomach, ovary, esophagus, and liver[155]. These tiny RNA entities control protein production at the translation stage, influencing key cell pathways involved in cancer development[156]. In the context of cancer, miRNAs influence abnormal cellular growth, cell death, cell differentiation, spread of cancer cells, and resistance to chemotherapy[157,158]. Furthermore, altered miRNA expression in cancer-associated fibroblasts (CAFs) affects their secretion patterns and is associated with tumor progression, invasion, spread, chemotherapy resistance, and unfavorable patient outcomes[159]. The exploration of miRNAs as diagnostic markers and treatment avenues in cancer is ongoing, yet it faces several hurdles[140,160]. The use of miRNA assays in cancer diagnosis is impeded by their short length, low presence, and fragile nature[161]. Additionally, the intricate web of miRNA interactions complicates the task of pinpointing exact miRNA-gene relationships relevant to specific cancers. A single miRNA can influence numerous genes, and one gene can be regulated by multiple miRNAs, adding to the complexity[162]. Moreover, detecting miRNAs in blood for diagnostic purposes is challenging due to their dilution amidst a myriad of molecules from different cells throughout the body[163].

In summary, miRNAs hold promise for revolutionizing cancer care with their diagnostic and therapeutic roles. However, overcoming the hurdles associated with miRNA irregularities, testing constraints, and biomarker discovery is crucial to fully harness miRNAs' capabilities in combating cancer.

7. FUTURE PROSPECTIVE OF MICRORNA IN CANCER

MicroRNAs (miRNAs) have gained significant attention in cancer research due to their potential as diagnostic biomarkers, therapeutic targets, and prognostic indicators. These small non-coding RNA molecules play crucial roles in regulating gene expression and have been implicated in various aspects of cancer biology. Studies have shown that miRNAs can serve as valuable tools for primary screening, targeted treatment, and overcoming pharmaceutical resistance in cancer. For example, miR-424(322) has been associated with improved progression-free survival in ovarian cancer patients, highlighting its potential as a prognostic marker. Conversely, high expression of miRNA-221 has been linked to poor prognosis in glioma, underscoring the significance of specific miRNAs in predicting disease outcomes.Furthermore, miRNAs have demonstrated therapeutic potential in various cancer types, including hepatocellular carcinoma (HCC). For instance, miRNA-381 has been shown to suppress cell growth and invasion in HCC by targeting specific genes involved in cancer progression. Similarly, miRNA-195-5p has been identified as a regulator of lung cancer cell proliferation and metastasis, suggesting its possible application in lung cancer treatment. Additionally, miRNAs like miR-29a have been found to enhance sensitivity to chemotherapy in lung cancer by targeting specific genes associated with drug resistance. The role of miRNAs extends beyond individual cancer types, with studies highlighting their involvement in resistance to cancer treatments, such as chemotherapy and radiation therapy. Moreover, miRNAs have been investigated as potential biomarkers for radiation exposure and tissue-specific radiation responses, indicating their promise in personalized cancer treatment approaches. The dysregulation of miRNAs can have oncogenic or tumor-suppressive effects, emphasizing their complex roles in cancer development and progression.

Overall, the future prospects of miRNAs in cancer research are promising. Advances in sequencing technologies and bioinformatics analysis are expected to enhance our understanding of the regulatory networks of miRNAs and their therapeutic implications. By elucidating the intricate roles of miRNAs in cancer biology, researchers aim to harness the diagnostic, prognostic, and therapeutic potential of these small RNA molecules for improved patient outcomes in the fight against cancer.

CONCLUSION

The global discovery that miRNA production is dysregulated in various malignancies, following the identification of miR-15a and miR-16-1 deletions in chronic lymphocytic leukemia, underscores the pivotal role of miRNAs in cancer biology. Dysregulation may arise from miRNA transcriptional activation or deletion, improper translational modulation, epigenetic misregulation, and flaws in the miRNA biogenesis system. Aberrant miRNA expression allows tumor cells to sustain proliferation signals, evade growth inhibitors, resist apoptosis, activate invasion and metastasis, and promote angiogenesis. Depending on the context, miRNAs can function as oncogenes or tumor suppressors, with their role in carcinogenesis linked to the regulation of specific targets.

Identifying key miRNA sites involved in cancer and elucidating their role in tumor development remains a significant challenge. Effective therapeutic interventions depend on advancements in miRNA delivery methods. While miRNAs are promising therapeutic targets due to their unique expression patterns and biological actions in tumor cells, challenges persist. Innovations in delivery systems such as nanoparticles, biomaterials, and electric vehicles (EVs) aim to address issues like cell-specific targeting, intracellular delivery, and miRNA stability, while minimizing toxic effects.

Exosomes and EVs offer a biocompatible delivery mechanism with specificity to tumor cell types, making them promising vehicles for targeted miRNA delivery. The development of encapsulation methods, surface engineering, and EV isolation techniques could enhance targeted therapeutic miRNA distribution. Gene expression analyses have shown that miRNA expression signatures are associated with cancer type, stage, and patient outcomes, indicating their potential as targeted therapies, diagnostics, prognostic biomarkers, and diagnostic biochemical markers. However, extensive validation through deep-sequencing and patient sample verification is essential. As research progresses, the discovery of new miRNAs, their physiological roles, and gene targets will deepen our understanding of miRNA function in carcinogenesis and support their integration into tumor prognosis, diagnosis, and therapy.

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