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Non-coding RNAs and potential therapeutic targeting in cancer

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Abstract

Recent advances have begun to clarify the physiological and pathological roles of non-coding RNAs (ncRNAs) in various diseases, including cancer. Among these, microRNAs (miRNAs) have been the most studied and have emerged as key players that are involved in the regulation of important growth regulatory pathways in cancer pathogenesis. The ability of a single ncRNA to modulate the expression of multiple downstream gene targets and associated pathways, have provided a rationale to pursue them for therapeutic drug development in cancer. In this context, early data from pre-clinical studies have demonstrated that synthetic miRNA-based therapeutic molecules, along with various protective coating approaches, has allowed for their efficient delivery and anti-tumor activity. In fact, some of the miRNA-based cancer therapeutic strategies have shown promising results even in early-phase human clinical trials. While the enthusiasm for ncRNA-based cancer therapeutics continue to evolve, the field is still in the midst of unraveling a more precise understanding of the molecular mechanisms and specific downstream therapeutic targets of other lesser studied ncRNAs such as the long-non-coding RNAs, transfer RNAs, circular RNAs, small nucleolar RNAs, and piwi-interacting RNAs. This review article provides the current state of knowledge and the evolving principles for ncRNA-based therapeutic approaches in cancer, and specifically highlights the importance of data to date and the approaches that are being developed to overcome the challenges associated with their delivery and mitigating the off-target effects in human cancers.

Keywords

non-coding RNAs; microRNAs; long non-coding RNAs; piRNAs; snoRNAs; cancer; therapy

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1. INTRODUCTION

Decades of accumulating research indicates that dysregulated expression of certain genes in critical growth regulatory pathways is a major driver of oncogenesis in human malignancies. Although the prevailing consensus is that altered gene expression is causally related to cancer pathogenesis, the underlying mechanisms driving the neoplastic growth of cancer cells are far more complex. Extensive investigations in the context of genetic causes of cancer have revealed that aberrant gene expression is not only a consequence of protein-coding genes, but to a large extent is also mediated by the regulatory actions of non-coding genomic elements in the human genome. The Encyclopedia of DNA Elements (ENCODE) transcriptome project concluded that only ~1.2% of the genome comprises protein-coding genes, whereas ~80% of it is actively transcribed into a variety of non-coding RNAs (ncRNAs), some of which have been characterized, and some of which are under active interrogation [1]. Although ncRNAs were initially deemed as “transcriptional noise,” “junk DNA,” or “dark genomic matter,” research in the past two decades has provided convincing and irrefutable evidence favoring biological roles for various types of ncRNAs in various diseases, including cancer [2]. Broadly speaking, all ncRNAs can be divided into two categories based on size: small ncRNAs (sncRNAs), which are shorter than 200 nucleotides and long ncRNAs (lncRNAs) that are longer than 200 nucleotides. The sncRNA category includes microRNAs (miRNAs), transfer RNAs (tRNAs), piwi-interacting RNAs (piRNAs), small nucleolar RNAs (snoRNA) [3]. Although specific biological functions for some sncRNAs continue to be realized and appreciated, a fascinating theme that has emerged to date is that hierarchically, ncRNAs represent a higher-level gene regulatory domain, and a single ncRNA is theoretically capable of controlling the expression of many downstream gene (mRNA) targets.

In view of the increased recognition of the biological roles of ncRNAs in various diseases, it is not surprising that recent years have seen a concerted effort to evaluate the translational and clinical significance of sncRNAs in cancer and other diseases [4–10]. Given that a single sncRNA can control the expression of several mRNA targets in distinct cancer-associated pathways, an early hypothesis was that using a ncRNA-based therapeutic approach would address the issue of the multi-faceted nature of cancer pathogenesis and resultant tumor heterogeneity present in various cancers. Indeed, numerous studies and clinical trials have already been initiated to leverage this aspect of ncRNAs, and ncRNA-based anti-cancer drug development has gained significant momentum and is potentially ripe for breakthroughs [11]. Based upon the evidence gathered to date, this review evaluates the advantages and challenges associated with ncRNA-based cancer therapy, and summarizes the knowledge surrounding emerging therapeutic strategies for the application of ncRNAs in cancer treatment.

2. MICRORNA (MIRNA)-BASED THERAPY IN CANCER

While the evidence for miRNA-based cancer therapy in cancer is still in relative early stages, burgeoning body of literature and scientific evidence indicates that this concept has merit, while additional research is needed to overcome existing challenges as we improve our understanding for their functional downstream targets.

2.1 miRNAs in Cancer

miRNAs are endogenous single-stranded sncRNAs that are 18–25 nucleotides in length and are present in animals, plants, and some viruses. miRNAs bind to the 3'-untranslated regions of target genes that regulate cellular processes including the cell cycle, apoptosis, cellular development, differentiation, and metabolism. miRNAs were first discovered in 1993 in *C. elegans* [12, 13], but the first evidence for aberrant miRNA expression and its biological consequences in human cancer were not revealed until 2002, when Calin and colleagues identified genomic alterations in the miR-15a/16 cluster in leukemia [14]. Publication of this seminal study paved the way for a plethora of investigations describing miRNA dysregulation in cancer. Moreover, microarray profiling has since demonstrated dysregulated expression of various miRNAs in a variety of tumor types, highlighting the functional relevance of these sncRNAs in oncogenesis [15]. Today, miRNAs are by far the most studied ncRNAs in cancer, with more than 80,000 publications catalogued in PubMed involving miRNAs and cancer.

A single miRNA has the potential to modulate the expression of multiple genes and influence various biological systems in a specific manner. Cancer-associated miRNAs are generally classified into one of two subcategories: tumor suppressor miRNAs (or "tumor-suppressor-miRs") and oncogenic miRNAs (or "onco-miRs"). Examples of well-characterized tumor-suppressor-miRs include miR-34a, miR-145, and the let-7 family; well-established onco-miRs include miR-21 and miR-155. Interestingly, several miRNAs appear to possess dual functionality, acting as both as a tumor suppressor and as an oncogene. For instance, although miR-200c inhibits epithelial-to-mesenchymal transition (EMT) and blocks initiation of cancer metastasis, it is also frequently overexpressed in late-stage cancers and involved in promoting distant metastasis [8, 16, 17]. Therefore, miR-200c appears to have both tumor suppressor and oncogenic functions, which manifest in a context-dependent manner, and relate to specific stages of carcinogenesis. While the enthusiasm continues to grow, presently, the ncRNA-based cancer research still is not as mature and well-established as classical protein-encoding genes. This highlights the need for continued research in developing a better understanding of the role of ncRNAs in cancer, identification of signaling pathways and the specific downstream genetic targets, as this will all be pivotal in a better realization of their therapeutic potential.

2.2 Clinical Application of miRNAs in Cancer Therapy

Many miRNAs inhibit cellular signaling pathways by suppressing the expression of multiple genes within a single growth regulatory pathway. Additionally, due to crosstalk between various signaling pathways, miRNAs can theoretically affect the functionality of multiple interconnected growth regulatory pathways all at once – which, provides an attractive rationale for the development of miRNA-based cancer therapeutics. Cancer development is a heterogeneous process that evolves by negating the impact of various environmental stressors. Most cancer cells acquire resistance to therapeutic drugs by activating survival signals, evading immune responses, and blocking programmed cell death or apoptotic pathways [18]. Not surprisingly, majority of therapeutic agents that target a single gene or pathway are effective for only for a limited time period, until the cancer cells figure out alternate mechanisms to evade the efficacy of a specific drug – a concept that has been the

Achilles heel of most anti-cancer modalities to date. Cancer therapeutic strategies that modulate the expression of miRNAs in tumors act by restoring miRNA expression, replenishing endogenously depleted miRNAs, or inhibiting overexpressed miRNAs through the application of small-molecule antagonists. Because a number of miRNAs are epigenetically silenced due to hypermethylation of their promoter regions, clinically-approved hypomethylating agents such as 5-azacytidine and decitabine were initially considered as potential therapeutic options [19]. However, these drugs are non-specific and cause global demethylation of all genomic DNA, which leads to the upregulation of many other epigenetically silenced miRNAs and protein-coding genes. To overcome this challenge, recent technological advancements have allowed for the development of novel miRNA mimics and inhibitors that can regulate the expression of specific miRNAs for precise therapeutic application in cancer.

2.3. miRNA Mimics in Cancer Therapy

To date, preclinical studies using ectopically overexpressed miRNAs far outnumber those that suppress miRNA expression. Expression vectors and oligonucleotide-based mimics are currently the most commonly used methods to synthetically overexpress target miRNAs. The miRNA mimics are typically double-stranded synthetic oligonucleotides that, upon entering cancer cells, are processed by the cellular machinery to form active, single-stranded molecules. These synthetic oligonucleotides subsequently incorporate into the RNA-induced silencing complex (RISC) and acquire phosphorothioate backbone modifications. However, during this process, a significant portion of backbone modifications are lost before the molecules can reach their target locations, which presents a challenge for their effective therapeutic clinical application [20]. Furthermore, because double-stranded RNAs that are not formulated for stable durability within the body, degrade quickly within biological fluids, emphasizing the need for unique protective delivery systems that must be designed to maintain a sufficiently effective dosage [21]. Such well-recognized inefficiencies of synthetic oligonucleotides are not unique to miRNA-based therapeutics, and essentially overlap with those of other conventional molecular therapeutic drugs. To overcome these technical impediments for effective drug delivery, chemical modifications for a newer generation of molecular mimics are generally designed to optimize RNA oligonucleotide stability, while limiting potential off-target effects. Collectively, these recent technological advancements have significantly advanced the use of miRNA-based molecules in cancer therapeutics, but more research is needed—and is currently underway—to address the enduring challenges associated with their delivery.

Nonetheless, a number of well-characterized miRNAs have already passed the initial litmus test and are now in early-phase clinical testing. One such example is MRX34, a synthetic mimic of the highly studied tumor suppressor miR-34a that suppresses metastasis and stemness in various cancers, which was tested in lung cancer patients [22]. While the clinical trial with MRX34 was halted due to immune-related adverse effects in a small group of patients, it did exhibit antitumor activity in a subset of patients with refractory advanced solid tumors [23]. Considering that a single miRNA modulates the expression of multiple genes, side effects observed during the MRX34 trial were not entirely surprising. Regardless, this study suggested that some miRNA mimics might require combinatorial

administration along with another drug to minimize their side effects and provided an important proof-of-concept, confirming findings from previous preclinical experiments and demonstrating promise for clinical application of miRNA mimics as cancer therapeutics.

2.4. miRNA Inhibitors as Cancer Therapeutic Agents

As for miRNA mimics, suppression of onco-miRs through the use of miRNA inhibitors is of significant research interest. In contrast to miRNA mimics, which are predominantly created using oligonucleotide-based technologies, several distinct methods are used to generate miRNA inhibitors. It is also easier and more practical to design miRNA inhibitors compared to miRNA mimics, due to the specific structural and pharmacokinetic properties of miRNA inhibitors [24]. The Figure 1 illustrates various strategies to inhibit, as well as promote, the expression of miRNAs in cancers, hence providing a rationale for their clinical application as cancer therapeutic agents.

2.4.1. Oligonucleotide-based Approach: Antisense oligonucleotides (ASOs) are single-stranded RNAs that are complementary to sense segments of target mRNA sequences [25] and function as competitive inhibitors to suppress the expression of target miRNAs. Locked nucleic acids (LNAs) are ASOs substituted with several bicyclic RNA analogues that form a “locked” conformation, which provides high intrinsic target affinity and suitability for inhibiting short RNA and DNA segments [26]. The locked ribose conformation ideally targets Watson-Crick binding and significantly improves hybridization to oligonucleotides for targeting miRNAs [27]. Currently, ASO is the most commonly used method for targeting specific miRNAs. In addition, recently heteroduplex oligonucleotide antimir has been developed and demonstrated that structural modification resulted in substantial improvement of target suppression efficiency [28].

2.4.2. miRNA Sponges: Similar to ASO, miRNA sponges are typically DNA plasmids or transcribed RNAs, that contain multiple miRNA binding motifs [29]. miRNA sponges are designed to contain binding sites complementary to heptamers in the seed sequences of target miRNAs; thus, a single miRNA sponge can block an entire family of miRNAs containing the same target binding sequence [30]. Although *in vitro* studies have demonstrated that miRNA sponges inhibit specific miRNAs and downregulate their respective downstream targets, significantly higher concentrations (i.e. much higher than for ASO-based inhibitors) are required to achieve effective target mRNA inhibition, which can potentially increase unwanted off-target effects [31].

2.4.3. CRISPR/Cas9 Genome Editing: Clustered regularly interspaced short palindromic repeats (CRISPR) is a novel adaptive immune system found in many prokaryotes that encounter invading foreign genetic elements. These unique sequences in the genomic loci, discovered 30 years ago in *Escherichia coli*, serve as a defense mechanism against viruses. CRISPR sequences, along with associated enzymes such as CRISPR-associated protein 9 (Cas9), can cut nucleic acids and disable viruses. In the type II CRISPR system, the Cas9 protein partially complexes with repeat sequences in a spacer-containing RNA and transactivating CRISPR RNA (tracrRNA). The CRISPR/Cas9 complex cleaves foreign genetic material upon recognition of target gene sequences. The use of this system of

cutting and inserting nucleic acids has recently become a popular method for editing the genome [32]. To date, the CRISPR/Cas9 system has been exploited to knock out various ncRNAs, including miRNAs, lncRNAs, and small nucleolar RNAs (snoRNAs) [33–35]. CRISPR is efficient, specific, and cost-effective. However, because liposome or nanoparticle-based systems are not very proficient at delivering CRISPR/Cas9 machinery to cells, this system requires viral vector delivery to achieve high delivery efficacy and therefore is not currently very popular in therapeutic settings [36]. Nevertheless, as CRISPR becomes the foremost genome-editing strategy, its integration into clinical applications may eventually replace the use of oligonucleotide-based inhibitors.

2.5. Delivery Strategies

Despite the availability of various mimics and inhibitors, it is difficult to modulate the expression of ncRNAs in tumors without first improving specific pharmacological barriers. Synthetic ncRNA mimics and inhibitors generally degrade rapidly in biological fluids, absorb poorly into the intracellular space, and often may fail to reach specific target locations [37]. Chemically modifications of RNA backbones prolongs the half-life of ncRNAs *in vivo* and could significantly alter intracellular interaction with target ncRNAs [38]. Furthermore, artificial protective coatings, such as nanoparticles and polymer-based formulations, are popular methods that protect fragile synthetic ncRNAs [39]. In the following section, we describe various delivery systems and their potential advantages and disadvantages.

2.5.1. Liposomes—Liposomes are lipid-bilayer compounds composed of aqueous cores surrounded by hydrophobic membranes. They are commonly used in various manufactured products, from dietary supplements to cosmetics and recognized as a relatively safe delivery method. Therefore, it is not surprising that liposomes are the most commonly used delivery vehicles for miRNA mimics and inhibitors [21]. Through years of compositional and structural optimization, the current generation of liposome-based delivery systems offer highly efficient delivery to a target cell while maintaining high loading capacity [40].

2.5.2. Cationic polymers—The cationic polymer polyethylene imine (PEI) is another popular delivery technology commonly used for the transfer of plasmid DNA and small interfering RNA (siRNA) [41, 42]. Polymer PEI coating provides a net cationic charge, which shields molecules from enzymatic degradation, while enhancing the interaction with anionic cell membrane polysaccharides [31]. Although the delivery efficiency of polymer PEI coating is high, a cationic-based delivery system is often hampered by excessive interactions with serum proteins [43].

2.5.3. Peptide based transmembrane structures—Certain structural modifications can stabilize miRNA mimics and inhibitors for improved delivery. One standard structural modification used for drug delivery attaches a peptide with a low pH-induced transmembrane structure (pHLIP) to miRNA inhibitors [44]. This peptide forms a transmembrane alpha-helix when it is exposed to acidic conditions, such as those normally found in tumors. The pHLIP structure can then translocate molecules such as anti-miRs

across the cell membrane through a non-endocytic route, resulting in high drug delivery efficiency [45, 46].

2.5.4. Adeno-associated viral vectors—Use of an adeno-associated virus (AAV) system is another intriguing technology for miRNA delivery. For example, an AAV was successfully used to deliver miRNA mimics through tail vein injections in a murine model of hepatocellular carcinoma [47]. However, safety concerns associated with any viral delivery system complicate potential clinical applications.

2.5.5. Exosomes—Exosomes were initially discovered three decades ago as cellular fragments attributed as a waste disposal mechanism; however, these small extracellular vehicles are now a topic of active interrogation due to their recognition as important mediators of cellular signalling in cancer [9, 48, 49]. Exosomes are small, 40–140 nm in size, membrane vesicles that inherit molecular cargo of their cell of origin [50–52], and contribute to cancer pathogenesis [53–55]. Intriguingly, a recent study showed that cancer exosomes contain miRNA-processing complexes that convert pre-miRNAs to mature-miRNAs, enriching cancer exosomes with miRNAs – a mechanism that is absent in normosomes (exosomes, originating from non-cancerous cells) [56]. Furthermore, knockdown of Vps4a, an exosome packaging protein frequently dysregulated in hepatocellular carcinoma, was shown to alter exosomal miRNA expression profiles [57]. This led to several studies validating the functional role of exosomal miRNAs in oncogenesis [58, 59]. By virtue of their small size, encapsulating miRNAs in exosomes is relatively simple [60]. Standard transfection methods can be used to introduce synthetic oligonucleotides into exosomes and surface ligands can be genetically modified to improve the target specificity of the exosomes. The biological origin of exosomes ensures high biocompatibility with their target tumor types and minimizes toxicity. Therefore, these tiny vesicles show significant potential as alternative delivery vehicles for ncRNAs.

2.6. Preclinical miRNA-based Cancer Therapy

As our understanding for the molecular mechanisms involving miRNAs has improved over the past decades, scientific evidence continues to build with regards to their efficacy as anti-cancer therapeutics in pre-clinical model systems.

2.6.1. Tumor-suppressor-miRs: During the last decade, use of short interfering RNA (siRNA) and short hairpin RNA (shRNA)-based pre-clinical animal studies have resulted in an improved understanding and a better characterization of the functional roles of miRNAs in cancer [61]. The results obtained from these efforts have prompted the use of miRNA mimic-based cancer therapeutics in pre-clinical settings, as summarized in Table 1.

Among various miRNAs, miR-34a is by far the most investigated miRNA in preclinical studies. miR-34a has multiple tumor suppressor-like features: it forms a positive feedback loop with tumor suppressor *TP53*; targets several key oncogenes including *BCL2*, *MYC*, *NOTCH1, CCND1*, *SNAIL1*, and *SIRT1* [62, 63]; and functions as a switch to suppress the cancer self-renewal and EMT-inducing transcription factor, Snail [64, 65]. However, miR-34a is frequently downregulated in multiple cancer types through aberrant

transcriptional regulation, genomic deletions, and promoter hypermethylation [66–68]. Therefore, in order to increase its expression, miR-34a mimics were examined in several preclinical animal models of cancer including lung, breast, pancreatic, and prostate cancer, as well as neuroblastoma – all of which, demonstrated a successful increase in its expression following introduction of miRNA mimics and eventual decrease in tumor growth [69–73]. In a multiple myeloma xenograft model, addition of lipid-particle-coated miR-34a inhibited apoptosis by suppressing Erk2 and Akt, which in turn attenuated tumor growth [74]. Another study in a mouse model of lung cancer revealed that liposome-encapsulated miR-34a suppressed an alternative apoptosis inhibitor, Birc1, and reduced tumor burden [75]. Intriguingly, results from a recent study in lung adenocarcinoma cell lines demonstrated that the miR-34a mimic MRX34 improved efficacy of radiotherapy in p53-proficient cancer through suppression of the immune response inhibitor PD-L1 [76], suggesting that miR-34a has immune-boosting potential.

Likewise, miR-143 and miR-145, a well-established putative tumor-suppressor-miR cluster, has been a focus of many studies for its role as a therapeutic target. The expression of these two miRNAs is frequently downregulated in cancer [77], and mechanistically, the miR-143/miR-145 cluster regulates the expression of key oncogenes, including the *MYC* and *FSCN1*. First investigated in 2011 in a pancreatic cancer xenograft model, treatment with miR-143 and miR-145 mimics in lipid-based nanoparticles resulted in the overexpression of the tumor suppressor gene, KRAS2, resulting in an overall attenuated tumor growth [73]. The therapeutic efficacy of a miR-145 mimic was subsequently also confirmed several years later in other mouse models of prostate and bladder cancer [78, 79]. Collectively, these results demonstrate that miR-34a, miR-143 and miR-145 mimics have effective tumor suppressor activity across multiple types of cancers.

Given that miRNAs are critical in regulating key oncogenic pathways, several miRNA mimics have the ability to block specific growth signaling pathways. EMT is a well-established mechanism in cancer, which has important implications for tumor metastasis and acquisition of drug resistance [80] – a molecular processes by which epithelial cells lose adhesion and gain mesenchymal-like migratory and invasive properties essential for the ensuing process of metastasis. miRNAs such as the miR-200 family, let-7 family and miR-34a are well-known inhibitors of EMT-inducing transcription factors [80, 81]. In particular, the miR-200 family members and miR-203 form negative feedback loops with the ZEB1 and ZEB2 transcription factors, which act to suppress the epithelial cell adhesion molecule E-cadherin, thereby potently inhibiting the process of EMT [82, 83]. A nanoparticle formulation comprising of miR-203 suppressed cellular proliferation and migration in a number of cell lines including esophageal, ovarian, lung, renal, and breast cancer [84]. Furthermore, liposomal nanoparticle delivery of miR-200c inhibited tumor angiogenesis in renal and breast cancers [17]. Collectively these studies support therapeutic targeting of oncogenic pathways using miRNAs.

Despite well-established association of some miRNAs with oncogenic pathways, an obvious challenge for developing novel miRNA-based therapeutic drugs is the requirement to replenish constitutively downregulated tumor-suppressor-miRs. Unfortunately, to date, only a handful of miRNAs, such as members of the Let-7 and miR-200 families, are accepted as

bona fide tumor-suppressor-miRs. However, their reported upregulation in some cancers raises concerns about their mechanisms of action and whether they truly are tumor-suppressor-miRs [8, 85]. Nevertheless, mimics based upon these miRNAs have exhibited significant and effective anti-tumorigenic potential in mouse models of lung, renal, and breast cancers [17, 65, 69, 86].

2.6.3. miRNA Inhibitors: Similar to tumor-suppressor-miRs, few miRNAs have now been recognized to be bona fide oncogenic miRNAs or onco-miRs. Most miRNAs have expression patterns that differ depending on the organ in which they are expressed; thus, identifying specific miRNA inhibitors that lack or have minimal off-target effects have largely proven to be a challenging task in preclinical studies. Nevertheless, a considerable number of miRNA inhibitors have been evaluated in preclinical animal models (Table 2).

For instance, miR-155 is a highly prominent, putative onco-miR involved in metastasis and tumor progression, as well as participates in fundamental biological processes such as stem cell development and inflammation [87]. miR-155 overexpression in a transgenic mice model provided the first evidence that a single dysregulated miRNA could cause a B-cell malignancy [88]. This discovery became the basis for initiating therapeutic evaluation of various miR-155 inhibitors in animal models of lymphoma and leukemia [44, 89]. Anti-miR-155 delivered in a pHLIP-based miRNA-inhibitor exhibited a significant anti-tumorigenic efficacy when overexpressed in a lymphoma mouse model [44]. Not surprisingly, therapeutic use of miR-155 inhibitor is currently being tested for hematological malignancies (Cobomarsen [MRG-106]) phase II clinical trial for cutaneous T-cell lymphoma and phase I clinical trial for adult T-cell lymphoma/leukemia [90]

Likewise, miR-21 is another well-recognized and well-established onco-miR frequently dysregulated in many cancers [91]. The overexpression of miR-21 enhances proliferation, metastasis, invasion, and drug resistance [92]. Lentiviral vector knockdown of miR-21 inhibited tumor growth in a xenograft pancreatic cancer model [93]. Similarly, miR-21 inhibitors delivered in solid lipid nanoparticles significantly suppressed cellular proliferation, migration, and invasion in human lung cancer cells [94]. Currently, anti-miR-21 oligonucleotides are being clinically tested for Alport Syndrome [95]. Considering that miR-21 is a well-established oncogene, this oligonucleotide could be used for cancer treatment in the near future.

Inflamed tumor microenvironments are well-recognized as critical components of tumor progression, cellular proliferation, survival and migration, and inflammation in the tumor microenvironment has long been considered a key pathway in oncogenesis [96]. Recently, several inflammation-associated miRNA inhibitors have been interrogated for their therapeutic efficacy in a variety of cancers. For example, in esophageal cancer, zinc deficiency activates the miR-31 promoter region and NF-κB binding sites. NF-κB is a gene which is known to regulate inflammation and a LNA-based miR-31 inhibitor attenuated the serine-threonine kinase 40 (STK40) and NF-κB-controlled inflammation, which subsequently resulted in suppression of esophageal pre-neoplasia in zinc-deficient rats [97]. High-throughput functional screening of miRNAs in human colorectal cancer also identified miR-214 as a regulator of NF-κB [98]. In a colitis-associated colorectal cancer mouse

model, inhibition of miR-214 significantly reduced the severity of chemically induced colitis, thereby decreasing the number and size of lesions. In both of these studies, miRNA inhibitors displayed remarkable efficacy in rodent models of inflammation-associated cancers, highlighting their clinical potential.

3. Long non-coding RNA (lncRNA)-based Cancer Therapy

3.1. lncRNAs in Cancer

The lncRNAs are a class of ncRNAs that are typically longer than 200 nucleotides; despite lacking protein-coding capability, they are involved in the pathogenesis of cancer. Of the approximately 60,000 lncRNAs identified from human tumor tissues and cancer cell lines, a significant majority (more than 70%) are still awaiting appropriate annotations [99]. Nonetheless, the functional roles of numerous lncRNAs whose expression is often dysregulated in various cancers have been investigated (Table 3). Although it remains largely unclear whether dysregulation of lncRNAs is the cause or the consequence for cancer pathogenesis, this group of ncRNAs have added a new dimension to the already complex molecular architecture of carcinogenesis. Mechanistically, the majority of well-studied lncRNAs display functional similarity to typical protein-coding oncogenes and tumor suppressors involved in tumor initiation, progression, and metastasis. lncRNAs appear to play critical roles in oncogenesis and have significant potential as cancer therapeutic targets. Interestingly, a recent comprehensive genomic characterization of lncRNAs across a number of human cancers have discovered that although both lncRNAs and protein-coding genes have similar frequencies of tumor-associated dysregulation, a significantly higher proportion of altered lncRNAs were deemed cancer type-specific [100]. Furthermore, some lncRNAs display organ-specific dualities, serving as both tumor suppressors and oncogenes. In addition, recently a highly efficient RNA-seq-based method for lncRNA profiling of highly degraded FFPE fixed cancer samples has been established [101], which could accelerate lncRNA profiling in various cancers. Collectively, a thorough functional investigation of lncRNAs is needed to determine their true role in cancer, prior to their evaluation in preclinical studies as potential therapeutic targets.

3.2. lncRNAs as Potential Therapeutic Targets

Hypoxia is a major factor that contributes in a multitude of ways to cancer progression and acquisition of chemotherapeutic resistance. Therefore, targeting signaling pathways associated with hypoxia are deemed attractive for achieving tumor suppression and progression, as well as an escape mechanism from chemoresistance. Accumulating evidence indicates that NEAT1 [102], UCA1 [103], and H19 [104] are functionally relevant lncRNAs that are modulated by hypoxia during oncogenesis. Furthermore, long intergenic noncoding RNA (lincRNA)-p21 is a hypoxia-responsive lncRNA that forms a positive feedback loop with HIF-1α to drive glycolysis and promote tumor growth [105]. In breast cancer, upregulation of the HIF-1α-inducing lncRNA *EFNA3* facilitates Ephrin-A3 accumulation at cell surface to promote extravasation, and eventual metastasis [106]. Moreover, linc-RoR overexpression in the extracellular tumor environment during hypoxia in hepatocellular cancer cells has been shown to act as a miR-sponge for the tumor suppressive miR-145, which permits the self-renewal of cancer cells [107]. linc-RoR-induced upregulation of

miR-145 downstream targets p70S6K1, PDK1, and HIF-1α, genes associated with hypoxia, and resulted in the acceleration of cellular proliferation [108].

DNA damage repair (DDR) is an evolutionarily conserved process that maintains genomic integrity but is frequently dysregulated in cancer. Although this system normally protects healthy cells from tumorigenic DNA damage and replication errors, most cancer cells acquire some form of enhanced DDR that eventually results in radiotherapeutic or chemotherapeutic resistance [109–111]. Recently, several studies demonstrated that DDR dysregulation alters the expression of various lncRNAs [112, 113]. Two studies showed that a DDR-associated lncRNA, p21-associated ncRNA DNA damage-activated (PANDA), suppressed apoptosis via inhibition of p53-associated downstream genes *FAS*, *PUMA*, and *CCNB1* [114, 115]. Furthermore, another oncogenic lncRNA, the antisense ncRNA in the INK4 locus (*ANRIL*), is upregulated in an ATM-dependent manner following DNA damage [116]. *ANRIL* epigenetically represses tumor suppressor gene, *INK4B*, expression by recruiting the polycomb repressor complex (PRC) [117, 118]. Because these lncRNAs play critical roles in the DDR process, their expression can modulate the response of cancer cells to radio or chemotherapy.

Various treatment options, such as radiotherapy, chemotherapy, hormone therapy, and biological therapies exist for patients with metastatic cancer; however, responses to these treatments may differ significantly among patients. Therefore, identifying ncRNAs that become dysregulated in the metastatic process may result in the discovery of potential therapeutic targets that could be personalized to render otherwise resistant tumors responsive to conventional therapies. In particular, emerging evidence indicates that several lncRNAs are involved in the regulation of EMT, a key metastasis pathway, through epigenetic, transcriptional and post transcriptional regulation of RNA, DNA or proteins [119]. Metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) is a lncRNA that is consistently upregulated in multiple cancers [120] and its expression is associated with poor clinical outcomes in various cancers [121]. MALAT1 induces EMT through the activation of the Wnt signaling pathway and may therefore serve as a promising independent prognostic factor for early-stage metastatic non-small cell lung cancer [122]. Similarly, several other recognized oncogenic lncRNAs are dysregulated in EMT, suggesting that these lncRNAs could affect metastasis [121]. Expression of the lncRNA H19 is greater in bladder cancer tissues compared to adjacent normal mucosa, and it is even higher in metastatic tissues [123]. Mechanistically, H19 is upregulated during EMT in a positive feedforward loop, resulting in ablation of E-cadherin expression [124]. HOX antisense intergenic RNA (HOTAIR) is one of the most well-studied oncogenic lncRNAs that is involved in the EMT process in breast and gastric cancer cells, and is frequently upregulated in lymph node metastasis [125, 126]. Elevated HOTAIR expression in several cancer types is associated with resistance to chemotherapeutics, suggesting that inhibitors of HOTAIR could potentially resensitize a patient's tumor to a specific chemotherapy [127–129]. Consistent with its involvement in EMT, HOTAIR is also known to promote cancer stem cell like properties in breast and colon cancers [130, 131]. Emerging evidence indicates that lncRNAs are aberrantly expressed in diverse cancer stem cells and they appear to be involved in the regulation of cancer stem cells at different molecular levels [132]. Moreover, lncRNA MCF2L-AS1 has been recently identified as an oncogene which regulate cell migration and

invasion through sponging of miR-874–3p and its downstream target FOXM1 [133], a postulated master regulator of cancer metastasis [134]. As additional studies define the biological roles of lncRNAs in cancer, mainstream clinical use of molecular inhibitors targeting unique lncRNAs to prevent metastasis might be closer to becoming a reality for the personalized treatment of cancer patients.

4. Other ncRNA-based Cancer Therapeutic Targets

Successful miRNA-based cancer research has prompted further investigations to identify other ncRNA families that might serve as potential therapeutic targets in cancer. High-throughput sequencing approaches have resulted in the identification of many new classes of ncRNAs that contribute to the pathogenesis of various diseases, including cancer. We list and illustrate several families of ncRNAs known to be involved in oncogenesis with a promising therapeutic potential (Figure 2).

4.1. tRNAs:

The transfer RNA (tRNA) fragments (tRFs) are present in most organisms; are heterogeneous in size, nucleotide composition, biogenesis, and function; and are the second most abundant family of sncRNAs after miRNAs [135]. tRNAs have higher turnover rates in cancer vis-à-vis normal cells [136], become frequently overexpressed in cancers under stress [137, 138], correlate with clinical stages of cancer, and their expression levels are elevated in the serum and urine of cancer patients [139, 140]. The high abundance of tRNAs in blood makes them legitimate candidates to serve as diagnostic markers in cancer. Several tRFs bind *YBX1*, an RNA-binding protein, and in this manner stabilize multiple oncogenic transcripts that suppress cell growth and invasion [141]. While tRNAs have important roles in cancer, yet the elucidation of their functional roles in oncogenesis is in early stages; hence, we must wait for data to accumulate, before we further consider their therapeutic applications in the clinic.

4.2. circRNAs:

Circular RNAs (circRNAs) are another novel class of endogenous ncRNAs that are emerging as important molecular modulators in cancer. Initially discovered in RNA viruses in the 1970s, circRNAs, unlike conventional linear RNAs, form covalently closed loops with neither 5’ or 3’ polarities nor polyadenylated tails [142, 143]. Although the functional role of circRNAs is evolving each day, several studies have to date demonstrated that circRNAs harbor specific binding sites and primarily act as miRNA sponges or gene regulators [144]. For example, a recently identified circRNA, ciRS-7, was shown to function as a miR-7 sponge [145]. Given that miR-7 acts as a tumor-suppressor-miRNA in various cancers and regulates the expression of several oncogenes such as *EGFR*, *RAF1*, *PAK1*, and *PIK3CD* [146–148], ciRS-7 appears to be an oncogenic circRNA based on its modulation of the miRNA activity [10]. Furthermore, a recent examination of spatial expression of ciRS-7 in tumors showed that ciRS-7 is completely absent in the cancer cells, but highly expressed in stromal cells within the tumor microenvironment [149], highlighting the complex role of circular RNAs in cancer. In addition, recently functional roles of several circRNAs that are dysregulated in cancers have been clarified. circHIPK3, circWDR77 and circZFR have been

shown to regulate cancer cell proliferations [150–152]. Moreover, circMYLK and circIRAK3 were shown to regulate EMT in prostate cancer and non-small cell lung carcinoma respectively [153, 154]. The structural stability of circRNAs is particularly appealing for designing efficiently deliverable therapeutic drugs, further underscoring their therapeutic potential.

4.3. piRNAs:

The piwi-interacting RNAs (piRNAs) are sncRNAs expressed in eukaryotic cells [155]. Initially believed to be entirely absent in cancer, a growing body of evidence indicates that not only piRNAs are aberrantly expressed in cancers, but they are also involved in tumor pathogenesis [156]. Although they are 26–31 nucleotides in length, which is similar in size to miRNAs, piRNAs are distinctly different because they lack the sequence conservation present in miRNAs. Functionally, piRNAs interact with piwi regulatory proteins to form RNA-protein complexes that induce epigenetic and post-transcriptional gene silencing. Most of the mechanisms underlying piRNA function remain in their infancy but are an active area of investigation. For example, several piRNAs appear to act as tumor suppressors through the degradation of downstream messenger RNAs [157, 158]. In contrast, piR-651 [159], piR-823 [160], and piR-Hep1[161] are upregulated in gastric and hepatocellular cancers and appear to function as oncogenes. Although piRNAs appear to be functionally relevant sncRNAs in cancer, and targeting select piRNAs may have therapeutic effects, more investigations are required to clarify their fundamental roles in oncogenesis.

4.4. snoRNAs:

snoRNAs are well-conserved, metabolically stable RNAs that are 60–300 nucleotides in length and highly abundant in human and other organisms [162]. Considering that most snoRNAs localize primarily to the nucleus, it appears unlikely that their function is similar to that of other ncRNAs. For years, it was assumed that snoRNAs functioned as housekeeping genes [163]. However, accumulating evidence indicates that snoRNAs have oncogenic roles as well [164]. In 2000, dysregulation of the C/D box type snoRNA U50 was discovered in B-cell lymphoma [165], which prompted the investigation of snoRNAs in other types of cancers. These investigations led to the discovery that amplification of SNORA42 is common occurrence in many human cancers [166–168]. In lung cancer, mechanistic gain and loss-of-function experiments demonstrated that SNORA42 enhances tumor growth [166]. In colorectal cancer, high SNORA42 expression was associated with poor prognosis of patients [167]. Furthermore, SNORA50A and SNORA50B were found to be frequently deleted in cancers [33]. In a mouse model, deleting SNORA50A/B using CRISPR/Cas9 enhanced tumorigenicity by increasing the amount of active oncogene, *KRAS*, thereby hyperactivating the *RAS-ERK1/ERK2* signaling pathway. Given that snoRNAs are highly abundant and easily detectable in solid tumors and blood, and may prove functionally relevant in oncogenesis, they may become a major target for cancer therapy.

5. Potential Clinical Implications

The clinical application of ncRNAs as potential therapeutic targets in cancer can manifest in two scenarios: using ncRNAs to “replenish” suppressed or missing RNAs (replacement therapy) or to “block” the effects of over-active oncogenic RNAs. The ncRNA-based replacement therapy primarily benefits patients with reduced tumor-suppressor-miR expression or those with an overexpression of the downstream targets of these miRNAs. Replenishing downregulated miRNAs (or the use of miRNA mimics) that have multiple gene targets critical in oncogenesis could be an attractive treatment modality in cancer patients with low expression of tumor-suppressor-miRs. Furthermore, RNA-sequencing-based miRNA profiling of cancer samples could provide further insights on which specific miRNAs are dysregulated in patients and thus provide a rationale for the restoration of expression of these targets either through replacement therapy or the use of inhibitors. In addition, it is important to recognize that molecular characteristics and functional roles of miRNAs vary between tumor types. Therefore, the effectiveness of miRNA therapeutics must be tested in individual tumor types and tumor specific efficacy of these therapeutics needs to be clarified. Collectively, further understanding of the functional roles of target miRNAs and tumor specific efficacy of miRNA therapeutics will be key factors for the development of successful miRNA therapeutics.

Beyond cancer cells, the immune environment plays an important role in promoting or preventing the process of carcinogenesis. Several miRNAs appear central to various immunological responses. Therefore, administering miRNA mimics that target critical tumor-promoting immune cells may protect patients at high risk for cancer. For example, miR-568 mimics inhibit the production of the tumor-promoting cytokines TGF-β and IL-10, and induce proliferation of tumor-protecting regulatory T cells [169]. Tissue resident macrophages and stromal cells drive propagation of gastrointestinal neoplasms through inflammatory mediators. In this regard, miR-155 knockdown represses pro-inflammatory mediators (TNFα, IL-1b, and IL-6) in macrophages [170]. Therefore, inhibitors that target immune-directing miRNAs could complement existing and future immunotherapies, such as adaptive T-cell therapy and cancer vaccines.

miRNAs that counter tumor formation and progression by neutralizing tumor-promoting mutations are also enticing entities to explore for use in cancer treatment. For example, somatic *KRAS* mutations are frequently found in patients with blood and solid tumor cancers, including leukemia and colorectal cancer [171, 172]. Thus, administering a synthetic tumor-suppressor-miR that targets *KRAS*, such as Let-7, may benefit a large number of cancer patients. Indeed, in mice with *KRAS*-active non-small cell lung cancer, therapeutic delivery of synthetic Let-7 mimics reduced tumor burden [173]. As another example, approximately one-third of tumors harbor β-catenin activating mutations, which in turn upregulate miR-34a levels. In a mouse model in which β-catenin was overactivated in the liver, using miR-34a-LNA to inhibit miRNA-34a inhibited proliferation of hepatocellular carcinoma [174]. Collectively, these studies highlight the potential that miRNAs remain an attractive therapeutic targeting in cancer patients.

6. Opportunities and Challenges

Although our understanding for the roles of ncRNAs in various cancers continues to improve, there is still much to learn. miRNAs are the most well studied among the family of ncRNAs; therefore, their presence at the forefront of ncRNA-based cancer therapeutics is not surprising. Unfortunately, to date, it has been difficult to definitively categorize the majority of miRNAs as either tumor suppressors or oncogenes. However, recent technological advancements and the increased affordability of RNA-sequencing-based profiling technologies will allow a comprehensive assessment of their functional roles in multiple organ systems. Similar approaches can elucidate the roles of other ncRNAs in cancer as well. To put it simply, the major obstacle for using ncRNA-based therapeutic strategies in cancer patients have largely been due to the lack of a clear knowledge regarding their functional roles in oncogenesis, and the specific downstream genetic targets they regulate. On the other hand, enough technological advances have been made to synthesize and manufacture most ncRNA mimics and inhibitors for utilization in pre-clinical studies and eventually in human clinical trials. In conclusion, while this field may seem to be in infancy, we are currently witnessing the bourgeoning potential of ncRNAs in cancer therapy - and, it is only a matter of time in the near future, when we may begin to successfully exploit their potential for therapeutic targeting in cancer as we embark on the journey for precision oncological treatments in cancer patients.

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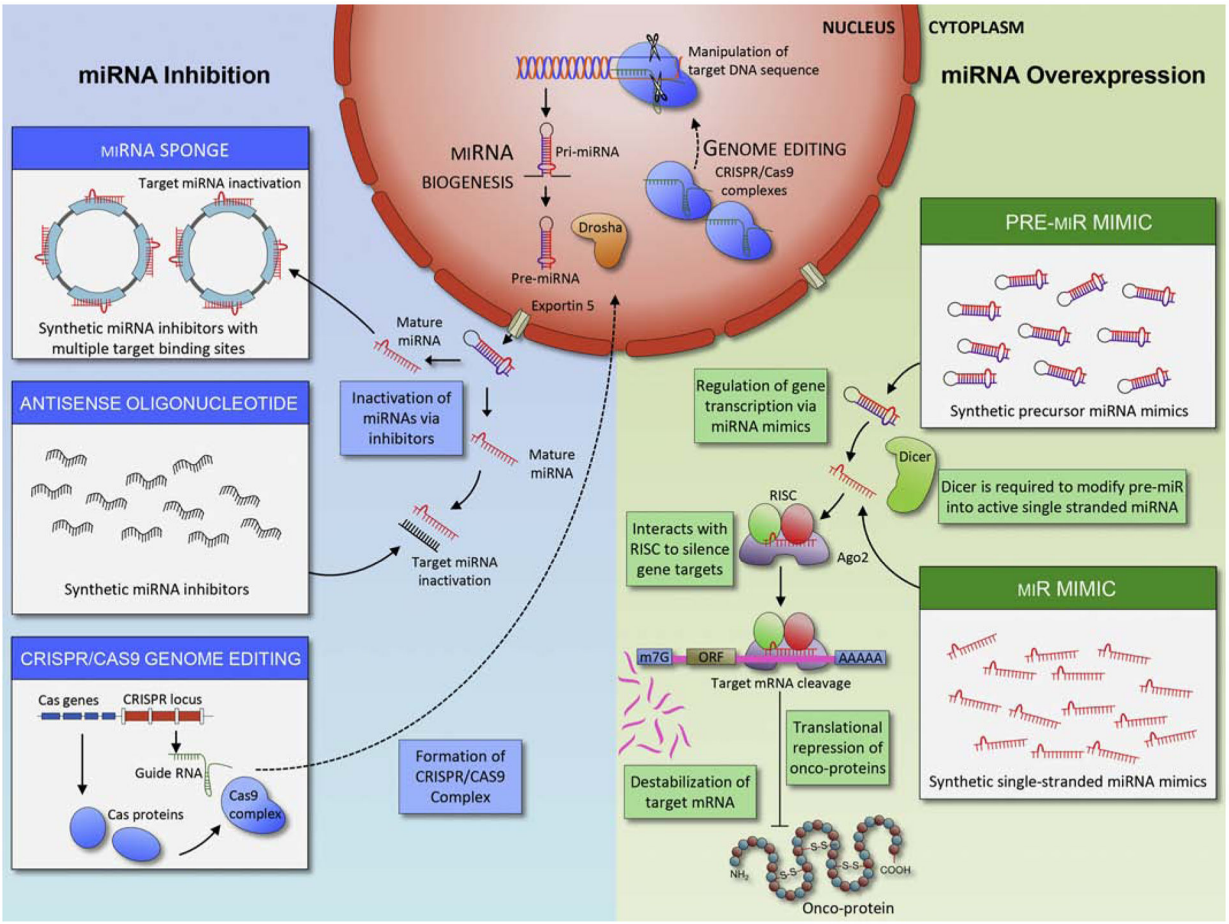

Figure 1.

Modulation of miRNA expression in a tumor. Modulation of the expression of miRNAs can occurs via several distinct strategies. To achieve overexpression of miRNAs (green), miRNA mimics enter tumor cells as “pre” (Top right) or “mature” (Bottom right) miRNA forms. Dicer cleaves pre-miRNAs into short RNA fragments. Subsequently, miRNA forms complex with RISC and Ago2 proteins and binds to DNA to suppress RNA transcription. In contrast, the suppression of miRNA expression in a tumor (blue) can occur via several methodologies, including miR-sponges (top left), and antisense oligonucleotides (middle left) and CRISPR/Cas9 genome editing (bottom left). For genome editing, CRISPR/Cas9 complex enters nucleus and changes DNA sequence of target miRNAs. Both miRNA sponge and antisense oligonucleotides bind to miRNAs and inhibit their functions.

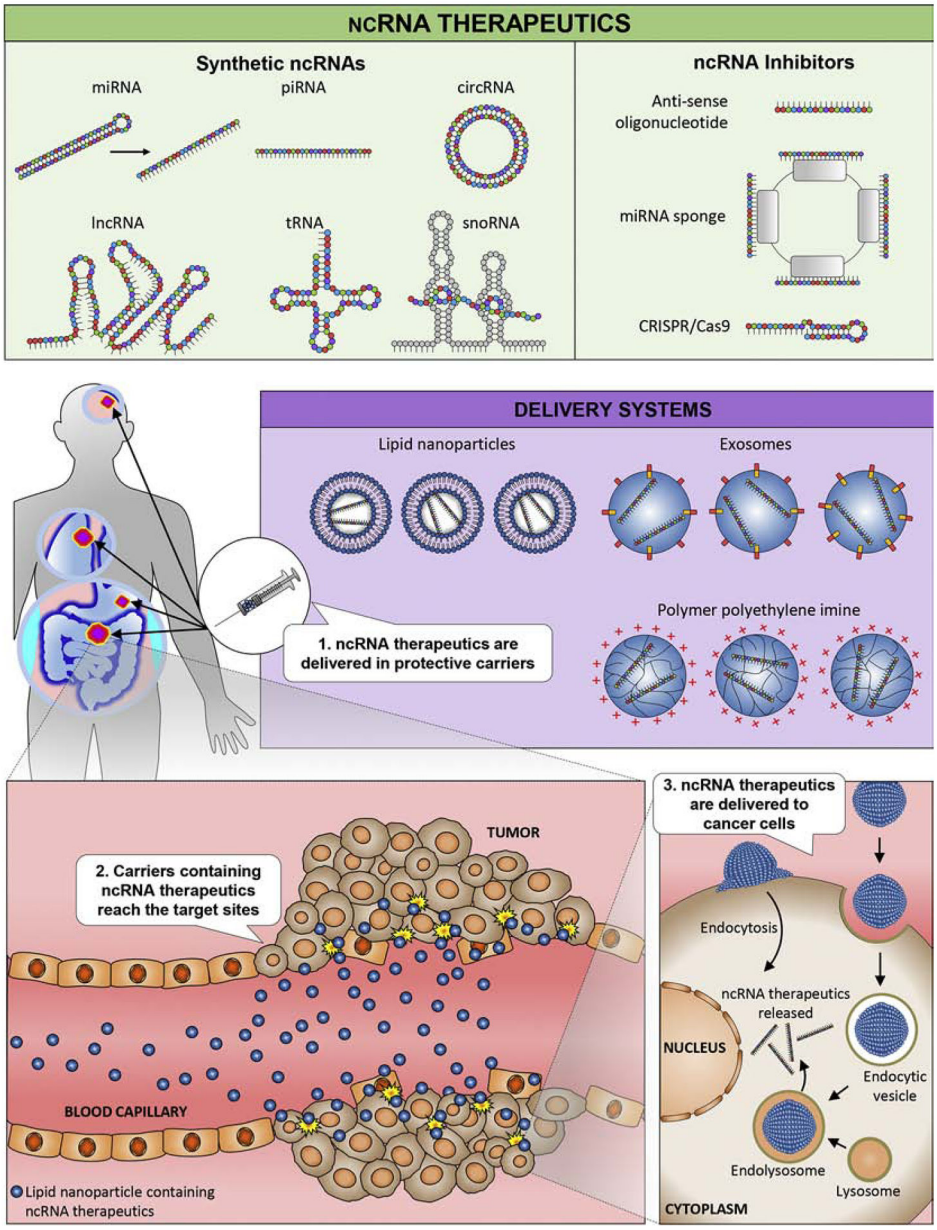

Figure 2.

Concepts in ncRNA-based therapy. (Top) Two major strategies to modulate the expression of ncRNAs in tumors. ncRNAs include miRNAs, lncRNAs, tRNAs, piRNAs, circRNAs, and snoRNAs. Synthetic generation of these ncRNAs for use in overexpression and ncRNA inhibitors such as antisense oligonucleotides, CRISPR/Cas9, or miRNA sponges can inhibit the expression of target ncRNAs. (Middle) Delivery of the mimics/inhibitors to the tumor can occur via protective delivery mechanisms including lipid nanoparticles, exosomes, or polymer polyethylene imine. (Bottom) Subsequently, the mimics/inhibitors reach the tumor site and modulate the expression of the target ncRNAs in the tumor.

Table 1.

A list of miRNA-mimics examined for their cancer therapeutic potential in pre-clinical studies *

miRNA	Year	Delivery system	Cancer	Mechanisms (Target genes)	Target genes	Model	Methodology	Ref
miR-26	2009	Adeno-associated virus	Liver	G1 cell cycle arrest	*CCND2, CCNE2*	*In vivo*	tet-oMYC;LAP-tTA	(36)
miR-34a	2010	Nanoparticles	Lung	Tumor load reduction	Survivin	*In vivo*	Intravenous	(60)
miR-34a & 143/145	2011	Nanoparticles	Pancreatic	Apoptosis enhancement	*SIRT1, CD44, ALDH1, KRAS2, RREB1*	*In vivo*	Xenograft	[73]
miR-34a	2012	Nanoparticles	Neuroblastoma	Vascularization reduction	*TIMP2*	*In vivo*	Xenograft	(58)
miR-107	2012	Nanoparticles	Head and neck	Cancer initiation cell reduction	*NANOG, OCT3/4, SOX4*	*In vivo*	Xenograft	(68)
miR-155	2012	Nanoparticles	Ovarian	Immunosuppressive mediator suppression	-	*In vivo*	Orthotopic	(126)
miR-5, 10, 7	2012	Adeno-associated virus	Retinal	Endogenous VEGF suppression	*VEGF*	*In vivo*	Intramuscular	(70)
Let-7a	2013	Nanoparticles	Lung	Proliferation reduction	*RAS*	*In vitro*	3D tumor growth assay	(62)
miR-29b	2013	Nanoparticles	Leukemia	Growth reduction	*DNMTs, CDK6, SP1, KIT, FLT3*	*In vivo*	Intravenous	(125)
miR-200c	2013	Nanoparticles	Ovarian, Lung, Real Breast	Tumor angiogenesis reduction	*IL-8 and CXCL1*	*In vivo*	Intrapulmonary	(10)
miR-203	2013	Nanoparticles	Esophageal	Proliferation and migration reduction	*Ran, ΔNp63*	*In vitro*	Cell lines	(65)
miR-1	2014	Nanoparticles	Glioblastoma	GBM sphere reduction	*MET, EGFR*	*In vitro*	Patient derived stem cells	(69)
miR-16	2014	Nanoparticles	Gastric	Apoptosis enhancement	-	*In vivo*	Xenograft	(123)
miR-34a	2014	Stable lipid particles	Multiple myeloma	Apoptosis enhancement	*ERK2, AKT*	*In vivo*	Orthotopic	(59)
miR-34a	2014	Nanoparticles	Breast	Migration reduction	*NOTCH 1*	*In vivo*	Xenograft	(57)
Let-7b	2015	Neutral lipid emulsion	Lung	Tumor growth reduction	*MYC*	*In vivo*	Kras; P53 model	(55)
miR-34a	2015	Neutral lipid emulsion	Lung	Proliferation reduction	*MET, MYC*	*In vivo*	Kras; P53 model	[69]
miR-34a	2015	Nanoparticles	Prostate	Non-canonical autophagy enhancement	*MET, AXL, MYC*	*In vivo*	Femur	(56)
miR-145	2015	Lipofectamine RNAi max	Bladder	Apoptosis enhancement	*MYC, SOCS7, FSCN1, CDH1*	*In vivo*	Xenograft	[79]
miR-145	2015	PEI nanocarrier	Prostate	Proliferation reduction	*FSCN1, MYC, IGFIR*	*In vivo*	Xenograft	[78]
miR-495	2015	Neutral lipid emulsion	Lung	Tumor burden and Proliferation reduction	-	*In vivo*	Xenograft	(122)
miR-514-3p	2015	Nanoparticles	Neuroblastoma	Apoptosis enhancement	*Survivin*	*In vivo*	Xenograft	(124)

miRNA	Year	Delivery system	Cancer	Mechanisms (Target genes)	Target genes	Model	Methodology	Ref
Let-7g	2016	Nanoparticles	Liver	Cell survival enhancement	*MYC*	*In vivo*	Orthotopic	[175]
miR-542	2016	Nanoparticles	Breast	Apoptosis enhancement	*P53 activation*	*In vitro*	Cell lines	[176]
miR-34a	2017	Nanoparticles	Colon	Apoptosis enhancement	*BCL-2*	*In vivo*	Xenograft	[177]
miR-542	2017	Nanoparticles	Gastric	Apoptosis enhancement	*P53 activation*	*In vivo*	Xenograft	[178]
miR-7	2018	Nanoparticles	Ovary	Chemosensitization enhancement	*EGFR/ERK pathway*	*In vivo*	Xenograft	[179]
miR-20a	2018	Nanoparticles	Colon	Liver metastasis reduction	*ARHGA P1 and E2F1*	*In vivo*	Liver metastasis model	[180]
miR-27a	2018	Nanoparticles	Liver	Proliferation reduction	*FOXO1, PPAP-γ*	*In vivo*	Xenograft	[181]
miR-375	2018	Nanoparticles	Liver	Autophagy and Proliferation reduction	-	*In vivo*	Xenograft	[182]
miR-27	2019	Nanoparticles	Liver	Apoptosis enhancement	*FOXO1, PPAR*	*In vivo*	Xenograft	[183]
miR-122	2019	Nanoparticle	Liver	Apoptosis enhancement	*ADAM17*	*In vivo*	Xenograft	[184]
miR-125b	2019	Nanoparticles	Ovarian	Increased Macrophage repolarization	-	*In vivo*	Orthotopic	[185]
miR-139-5p	2019	Nanoparticles	Colon	Proliferation and migration reduction	-	*In vivo*	Xenograft	[186]
miR-143	2019	Nanoparticles	Prostate	Proliferation reduction	*UPAR*	*In vivo*	Xenograft	[187]
miR-212	2019	Nanoparticles	Pancreas	Chemosensitization enhancement	*USP9X*	*In vivo*	PDX	[188]
miR-660	2019	Nanoparticles	Lung	Growth reduction	*MDM2, p-53*	*In vivo*	PDX	[189]
miR-873	2019	Nanoparticles	Pancreas, breast	Growth reduction	*KRAS*	*In vivo*	Xenograft	[190]
miR-34a	2020	Nanoparticles	Breast	Tumor growth reduction	-	*In vivo*	Xenograft	[191]

*Chronologically listed

Table 2.

A list of miRNA-inhibitors examined for their cancer therapeutic potential in pre-clinical studies*

miRNA	Year	Delivery system	Cancer	Mechanism	Target	Model		Ref
miR-10b	2012	Nanoparticles	Breast	Wound healing reduction	*RHOC*	*In vitro*	Cell line	[192]
miR-21	2012	Solid lipid nanoparticles	Lung	Proliferation and invasion reduction	-	*In vitro*	Cell line	[94]
miR-155	2012	Nanoparticles	Lymphoma	Tumor growth reduction	-	*In vivo*	Xenograft	[89]
miR-21	2013	Lentiviral vector	Pancreatic	Proliferation and angiogenesis reduction	RhB	*In vivo*	Xenograft	[93]
miR-155	2013	Polymer carrier	Leukemia	LIN28 increased and RUNX1 inhibited	*LIN28, RUNX 1*	*In vivo*	Cell line	[193]
miR-520d-3p	2013	Nanoparticles	Ovarian	Proliferation and migration suppression	*EPHB2*	*In vivo*	Orthotopic	[194]
miR-211	2014	LNA	Multiple myeloma	Tumor growth suppression	p27Kip 1	*In vivo*	Orthotopic	[195]
miR-31	2015	LNA	Esophageal	Tumor formation and proliferation suppression	*STK40*	*In vivo*	Zinc-deficient model	[97]
miR-126	2015	Nanoparticles	Leukemia	Targeting leukemia stem cells	-	*In vivo*	Tail vein	[196]
miR-214	2015	LNA	Colorectal cancer	Inflammation and tumor formation suppression	*PDLM 2, PTEN*	*In vivo*	DSS-AOM	[98]
miR-155	2015	pHLIP	Lymphoma	Tumor growth suppression	*BACH1*	*In vivo*	miR-155 transgenic mouse	[44]
miR-17	2017	Nanoparticles	Liver	Tumor growth suppression	*TGFBR 2*	*In vivo*	Xenograft	[197]
miR-21	2017	Nanoparticles	Breast	Drug resistance reduction	-	*In vivo*	Xenograft	[198]
miR-21	2018	Nanocarriers	Breast	Proliferation suppression	-	*In vivo*	Xenograft	[199]
miR-21	2018	Nanoparticles	Ovarian	Drug resistance reduction	-	*In vitro*	Cell line	[200]
miR-21	2018	Nanoparticles	Liver	Drug resistance reduction	-	*In vivo*	Xenograft	[201]
miR-21 and 10b	2018	Nanoparticles	Brain	Cell cycle arrest enhancement	-	*In vivo*	Xenograft	[202]
miR-214	2018	Exosomes	Stomach	Drug resistance reduction	-	*In vivo*	Tail vein	[203]
miR-221	2018	Nanoparticles	Leukemia	Tumorigenicity suppression	p27Kip	*In vivo*	Metastasis model	[204]
miR-21	2019	Nanoparticles/LNA	Breast	Migration suppression	*PTEN, PDCD4*	*In vivo*	Xenograft	[205]
miR-204	2019	Nanoparticles	Ovarian	Angiogenesis suppression	*THBS1*	*In vivo*	Orthotopic tumor	[206]

* Chronologically listed

Table 3.

A list of potential lncRNAs that can be therapeutic targeted in cancer

lncRNA	Function	Reported cancer type	Mechanism	REF
ANRIL	Oncogene	Bladder, lung, liver, cervical, stomach	Interacts with PRC2 and CBX7	[207]
BANCER	Oncogene	Stomach, skin	Promotes proliferation and metastasis via regulation of NF-KB1, p21, MAPK pathways	[208, 209]
CCAT1-L	Oncogene	Colon	Transcriptionally regulates MYC and promotes long-range chromatin looping	[210]
CCAT2	Oncogene	Esophagus, stomach, breast, colon	Enhances Wnt signaling pathway via TCF7L2 interaction	[211–213]
CRNDE	Oncogene	Colon	Negatively regulated by insulin and insulin-like growth factors and may regulate the expression of genes involved in metabolism	[214]
HCP5	Oncogene	Stomach	Sequesters miR-3619-5p and upregulates PPARGC1A, which Induces stemness and drug resistance	[215]
HOTAIR	Oncogene	Esophagus, stomach, colon, liver, lung, breast, ovary, bladder, prostate, glioma, melanoma	Serves as a scaffold to assemble PRC2 and LSD1 complexes to the HOXD gene cluster. Epigenetic silencing of HOXD genes in multiple tissues	[216]
HULC	Oncogene	Liver, pancreas	Modulates abnormal lipid metabolism through miR-9-mediated RXRA signaling pathway	[217, 218]
lincRNA-ATB	Oncogene	Liver, breast, colon, pancreas	miR-200 family sponge. Upregulates ZEB1 and ZEB2.	[219]
lincRNA-ROR	Oncogene	Breast	Competitive endogenous RNA for miR-145	[220, 221]
MALAT 1	Oncogene	Lung, prostate colon, liver	Forms molecular scaffolds for ribonucleoprotein complexes in the nucleus. Transcriptional regulator for genes involved in cell cycle regulation, cancer metastasis, and cell migration.	[222–224]
MCF2L-AS1	Oncogene	Colon	Enhances cell proliferation and invasion through crosstalk with miR-874-3p/FOXM1 signaling axis	[133]
PCA3	Oncogene	Prostate	Enhances cell proliferation through regulation of PRUNE2	[225]
PRNCR 1 (PCAT8)	Oncogene	Colon, prostate	Binds to the androgen receptor and enhances ligand-dependent and ligand-independent androgen-receptor-mediated gene activation and increases proliferation	[226, 227]
PVT-1	Oncogene	Breast, bladder, colon, kidney, pancreas	Regulates MYC oncogene	[228]
UCA1	Oncogene	Colon, bladder, breast, esophagus, stomach, liver, skin	Regulates CREB	[229]
GAS5	Tumor suppressor	Breast, prostate, lung	Encodes glucocorticoid response element, which binds to the DNA binding domain and blocks the activity of glucocorticoid receptor, androgen, progesterone, and mineralocorticoid.	[230]
H19	Tumor suppressor	Breast, lung, pancreas, stomach, bladder, prostate, colon, skin	Cancer metastasis tumor suppressor and generates miR-675	[231]
lincRNA-p21	Tumor suppressor	Colon	Enhances p21 activity	[232]
MEG3	Tumor suppressor	Brain, bladder, bone marrow, breast, colon, liver, lung, prostate	Interacts with the tumor suppressor p53 and regulates its target gene expression.	[233]
ncRuPAR	Tumor suppressor	Colon, stomach	Inhibits tumor progression by downregulation of protease-activated receptor-1(PAR-1)	[210]
TUG1	Tumor suppressor	Bladder, esophagus	Regulates miR-145. Suppresses epithelial-to-mesenchymal transition and radio-resistance.	[229, 234]