Cancer Cell International

REVIEW

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Nuclear-activating miRNAs: unveiling the intricacies of subcellular miRNA function and regulation in cancer and immunity disease

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Abstract

MicroRNAs (miRNAs) are small non-coding RNAs that traditionally recognized as negative regulators of gene expression through post-transcriptional regulation in the cytoplasm. However, recent discoveries have unveiled some novel miRNA functions in the cell nucleus, where a subset of miRNAs, termed nuclear-activating miRNAs (NamiRNAs), play pivotal roles in gene activation and transcriptional regulation for cancer and immunity disease. The discovery of NamiRNAs demonstrated a complementary regulatory function of miRNA, showing their differential activities in the nucleus and cytoplasm. This review aims to explore the biogenesis, mechanisms, and regulatory functions of NamiRNAs, deciphering their involvement in NamiRNA-gene network for gene expression modulation, and emerging significance as drug targets against cancer.

Keywords Nuclear activating MiRNAs, Promoter, Enhancer, Cancer, Immunity, COVID-19

Introduction

The first discovery of microRNAs (miRNAs) can be dated back to the early 1990s, where lin-4 was identified by Victor Ambros and colleagues in the nematode Caenorhabditis elegans [1]. In 2000, Ruvkun lab discovered and reported a second miRNA, let-7, in C. elegans [2]. However, the conservation of let-7 across species underscored the importance of miRNAs in evolution and development of biology. Subsequent research in the early 2000s revealed that miRNAs are widespread in nature, and not restricted in peculiarities of C. elegans. Researchers gradually find out that miRNAs act as a fundamental component of gene regulation in many organisms, including humans [3]. The canonical pathway of miRNA biogenesis involves transcription and production of primary miRNA (pri-miRNA) with further cleavage into a precursor miRNA (pre-miRNA). The pre-miRNA is exported to the cytoplasm to process into a mature miRNA. The mature miRNA is incorporated into the RNA-induced silencing complex (RISC) and interact with target mRNA to repress gene expression [4]. miRNAs play crucial roles in various biological processes, including cell proliferation, differentiation, apoptosis, and metabolic regulation [4].

The functional divergence of miRNAs into cytoplasmic and nuclear roles underscores the importance of RISC assembly and nuclear import mechanisms in determining

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their functional outcomes [5, 6]. These distinctions highlight a complex regulatory interplay that is both conserved and diversified across species, reflecting the evolutionary adaptation of RNA-based regulatory pathways. For example, RNA interference (RNAi) and RNA activation (RNAa) serve as essential regulatory mechanisms in eukaryotic systems, though their processes exhibit significant differences between mammals and plants. In plants, RNAi primarily involves small interfering RNAs (siRNAs), which guide the RISC complex to degrade complementary mRNAs, thus ensuring robust antiviral defense and precise gene regulation. In mammals, RNAi is typically mediated by miRNAs in the cytoplasm, where they mainly repress translation or promote mRNA degradation.

Since Rovkun elucidated the theoretical mechanism of miRNA-mediated negative regulation, the notion of miRNAs functioning as cytoplasmic negative regulators has become widely accepted within the scientific community [2]. However, numerous studies have revealed that miRNAs can also positively regulate target genes under specific circumstances. These positive effects are often mediated through transcription factors or other regulatory elements, enabling miRNAs to activate target genes [7–15]. Emerging evidence further suggests that miRNAs are not confined to the cytoplasm; they are also found in the nucleus and other organelles [16], where they play significant roles, such as influencing tumor drug resistance. In 2017, Yu and colleagues systematically analyzed the ENCODE database and identified over 300 miRNA precursors, out of 1,594 examined across seven cell lines, that exhibited significant overlap with genomic enhancers. Notably, enhancers are marked by classic epigenetic signatures, including H3K27ac and H3K4me1. These nuclear-localized miRNAs, termed *nuclear-activating miRNAs* (NamiRNAs), activate nearby target genes [7, 15]. NamiRNAs interact with key regulatory elements of genes, such as promoters, enhancers, or even gene bodies, modulating gene expression at the transcriptional level. Unlike the traditional role of miRNAs in gene silencing, NamiRNAs engage in gene activation by recruiting transcription factors or altering the chromatin's epigenetic state to promote transcription [17–20].

Biogenesis of canonical MiRNA and NamiRNA

Biogenesis of canonical MiRNA

The biogenesis of canonical miRNAs is a complex, multistep process that occurs sequentially in the nucleus and cytoplasm of eukaryotic cells (Fig. 1a) [5, 6]. Initially, miRNA genes are transcribed by RNA polymerase II (RNA pol II) to produce pri-miRNAs. These pri-miRNAs are then processed by the DiGeorge syndrome critical region 8 (DGCR8) protein and the Drosha microprocessor complex, which ensure precise cleavage into

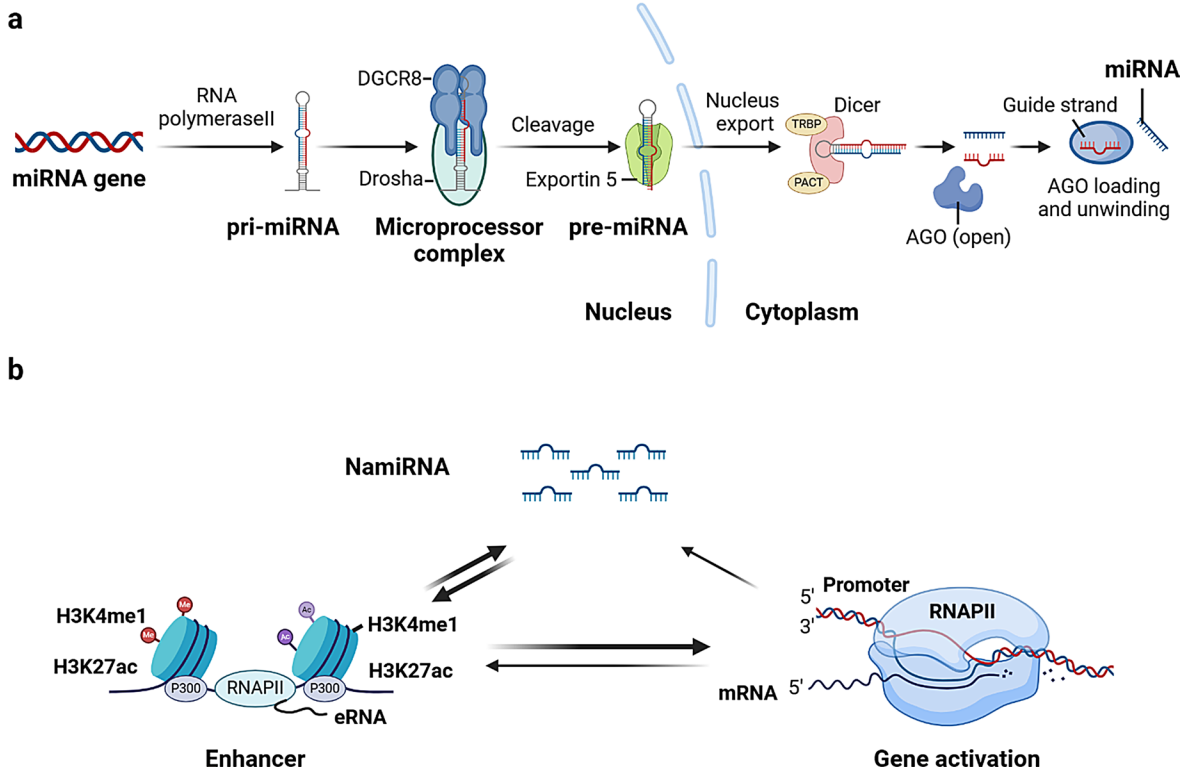

Fig. 1 Schematic illustration of the biogenesis of canonical miRNA **(a)** and the network for NamiRNAs, enhancers, and gene activation **(b)** [15]

pre-miRNAs [4]. Pri-miRNAs are characterized by an unstructured hairpin loop and flanking sequences at their 5′ and 3′ ends. In contrast, pre-miRNAs possess distinct structural features, including a hydroxyl group (OH) at the 3′ end, two nucleotides forming a 3′ overhang, and a phosphate (P) group at the 5′ end. The pre-miRNA is then transported from the nucleus to the cytoplasm by the nuclear export receptor Exportin-5 in a process that depends on the small GTP-binding protein Ran-GTP [21].

In the cytoplasm, Dicer processes the pre-miRNAs by recognizing the 5′ phosphate, 3′ overhang, and loop structure [5, 6]. It then cleaves the pre-miRNAs to produce ~ 22 bp miRNA duplexes, each with a 5′ phosphate and a 3′ two-nucleotide overhang on both strands. This catalytic process is modulated by interactions between Dicer and accessory proteins, including TAR RNA-binding protein 2 (TARBP2) and protein activator of the interferon-induced protein kinase (PACT). The resulting miRNA duplex is subsequently loaded onto Argonaute (AGO) proteins with the assistance of heat shock cognate protein 70 (HSC70) and heat shock protein 90 (HSP90), which maintain AGO in an open conformation to ensure successful loading [22]. After the duplex is loaded, the passenger strand (or miRNA) is expelled, leaving the guide strand retained within AGO. This guide strand directs the assembly of the RNA-induced silencing complex (RISC), enabling interaction with target mRNAs to suppress gene expression. miRNAs were originally characterized as post-transcriptional regulators of gene expression, mediating silencing by binding to complementary sequences on target mRNAs.

Biogenesis of NamiRNA

NamiRNAs, like other miRNAs, undergo initial transcription and processing within the nucleus [7, 14, 15]. Functionally, they play a role in gene activation by recruiting transcription factors or modifying the chromatin epigenetic state to facilitate gene transcription. Recent studies have revealed that NamiRNAs can be transcribed from miRNA genes by RNA polymerase II into primary transcripts. These transcripts are subsequently processed by RNA processing factors, such as cleavage and polyadenylation specificity factor 1 (CPSF1) and cleavage and polyadenylation specificity factor 3 (CPSF3). These factors remove intronic sequences and generate precursor miRNA (pre-miRNA) species in the nucleus [23]. In the nucleus, pre-miRNA is processed by Dicer and other RNA processing enzymes to generate double stranded miRNA. The double stranded miRNA unwinds and releases single strand miRNA to create RISC like structure. This structure guides the NamiRNA based pairing on enhancers and promoters of targeted gene to realize activation.

Certain NamiRNAs, initially synthesized through a pathway similar to canonical miRNAs, can shuttle back to the nucleus to mediate gene activation. Following their maturation in the cytoplasm, these NamiRNAs associate with a similar RISC-like complex, enabling their functional activation. This process is facilitated by Fragile X mental retardation syndrome-related protein 1 (FXR1), which plays a crucial role in their nuclear re-import. Once inside the nucleus, NamiRNAs engage with target genes and enhancers, promoting transcriptional activation [7, 14].

Mechanisms of NamiRNAs function

Mechanisms of NamiRNA-enhancer interaction

NamiRNAs and enhancer share several unique characteristics, including specific histone modification (e.g., H3K27ac and H3K4me1), binding of the P300/cAMP response element-binding protein (CREB) coactivator, DNase I hypersensitivity, and enhancer RNA (eRNA) production [15, 24–26] (Fig. 1b). Among 1,594 human miRNA precursor loci, 303 show partial overlap with enhancer regions enriched for H3K27ac [7]. For example, miR-24-1 has been shown to unconventionally activate gene transcription by targeting enhancers. This activation was completely abolished when the enhancer sequence was deleted using TALEN technology [7]. NamiRNA-enhancer interactions can modulate enhancer properties, such as influencing transcription and chromatin looping via nuclear AGO2 and RNA polymerase II (Pol II) and recruiting p300 to catalyze H3K27ac at activated enhancer sites. However, gene activation requires the interaction of active and intact enhancers with NamiRNAs. This suggests that inactive enhancers are unable to interact effectively with NamiRNAs.

Suzuki et al. reported that super-enhancers play a critical role in the biogenesis of master miRNAs essential for maintaining cell identity by enhancing both transcription and Drosha/DGCR8-mediated processing of primary miRNAs (pri-miRNAs). Together with broad H3K4me3 domains, super-enhancers establish a tissue-specific and evolutionarily conserved miRNA expression and functional landscape [8].

Mechanisms of NamiRNA-promoter interaction

The interaction of NamiRNAs with promoters is a complicated process that involves gene regulations and cellular responses. In recent years, researchers have been endowing their efforts in digging in the precise molecular mechanisms underlying NamiRNAs-promoter interactions and their roles in various diseases, contributing to targeted therapy and diagnostic development [9, 10]. NamiRNAs bind to specific sequences of targeted promoter genes via complementary base pair between NamiRNA and the targeted DNA [15]. This process can

be facilitated by RNA-binding proteins (RBPs) as it can assist the recognition and alignment of NamiRNA and DNA. Typically, the binding of NamiRNAs to promoter region can prevent the recruitment of transcription factors and RNA polymerase to targeted genes, thus limiting gene transcription and expression [7]. Furthermore, the interactions between NamiRNAs and promoter regulate the process and stability of target mRNAs, affecting their translation and overall expression levels. In some cases, NamiRNA-promoter communication induces chromatin remodeling, resulting in varied gene accessibility and increased transcription factor recruitment [11]. This further promote the expression of key genes responsible for cell growth, differentiation and survival, and affecting signaling pathways regulation and cellular homeostasis. It may affect immune response, disease progression, cancer and drug resistance by regulating oncogene expression and drug targets.

The binding of miRNA to promoter is verified to be closely related with cancer development via the regulation of oncogene and targets. Several studies have provided examples of nuclear miRNA-promoter interaction in various cell lines. For instance, miRNA-122 can bind to the alpha-fetoprotein (AFP) promoter region, resulting in reduced AFP expression and inhibiting liver cancer cell growth [27]. miRNA-21 can interact with the Programmed Cell Death 4 (PDCD4) promoter region in breast cancer cells, decreasing PDCD4 expression and increasing cell proliferation [28]. Further research will provide insights into the precise molecular mechanisms underlying NamiRNA-promoter interaction and the role in various diseases, contributing to the development of targeted therapeutics and diagnostic markers.

Enhancement of transcription by NamiRNA association with RNA pol II

NamiRNA have been shown to enhance transcription by associating with RNA pol II. This interaction occurs in the initiation phase of transcription, where NamiRNAs help recruit RNA pol II to specific gene promoter sites [7, 14, 15]. By doing so, NamiRNAs regulate gene expression by promoting targeted gene transcription or inhibiting non-targeted gene transcription initiation.

NamiRNA can enhance transcription in several ways. One strategy is to recruit RNA Pol II to the promoters of specific genes to enhance transcription. NamiRNAs can recruit or alter the activity of epigenetic modulators such as histone acetyltransferases (HATs) or histone methyltransferases to make the chromatin more conducive for transcription, shaping a more open chromatin structure to increase gene expression [29]. Some miRNAs can interact with transcriptional co-activators and enhance the assembly of transcriptional machinery at gene promoters. For example, miRNA-200c has been shown to recruit the transcriptional activator CREB1 to promote target genes expression in cell proliferation and differentiation [12]. Moreover, NamiRNAs can influence the release of paused RNA Pol II into productive elongation, a key regulatory step in gene expression.

An example of the transcription-enhancing role of miRNAs is the action of miR-132 [30]. miR-132 can regulate neuronal plasticity by affecting the transcription of certain neuronal genes. To be specific, miR-132 interacts with transcriptional co-activator p300 and is associated with acetylation of histones at the promoters of miR-132 target genes. By promoting histone acetylation via p300, miR-132 facilitates the recruitment of RNA Pol II to the promoter regions and enhance gene transcription. miR-26a can target the enhancer of zester homolog 2 (EZH2), an essential component of the Polycom repressive complex 2 (PRC2) that is involved in H3K27me3 [30]. By downregulating EZH2, miR-26a reduces H3K27me3 marks at the promoters of certain genes, counteracting repression and promoting transcriptional levels. These examples illustrate the complex interplay between NamiRNAs and transcription machinery. NamiRNAs can serve as fine-tuners of gene expression by inhibiting mRNA as well as enhancing gene transcription with multiple mechanisms.

Therapeutic potentials of NamiRNA in cancer

NamiRNAs represent a promising frontier in therapeutic interventions for a variety of cancers due to their fundamental roles in regulating oncogene expression. The ability of NamiRNAs to modulate key processes such as cell differentiation, proliferation, metabolism, and stress responses makes them attractive targets for drug development [15]. NamiRNAs can interact with multiple components of the gene expression machinery, including transcription factors and tumour suppressor genes (TSGs). This allows NamiRNAs to regulate the expression of numerous genes involved in diverse can cell processes.

In breast and ovarian cancer, the transcription factor myc oncogene is widely expressed and regulates biological processes such as cell cycle, proliferation and tumor progression [13, 31, 32]. Typically, the high myc, low p27 and high phospho-Rb level is associated with poor prognosis of breast and ovarian cancer [33]. Combining the screening data of miRNAs library of cell lines and cancer patients, researchers have discovered five miRNA candidates, miR-124, miR-365, miR-34b*, miR-18a and miR-506, can suppress tumor progression and reverse p27/myc/phospho-Rb expression. Among these miRNAs, miR-124 can bind to p27 promoter region to increase p27 protein expression and induce subsequent G1 arrest, which leads to phospho-Rb loss and myc protein decrease. In vivo studies demonstrated that

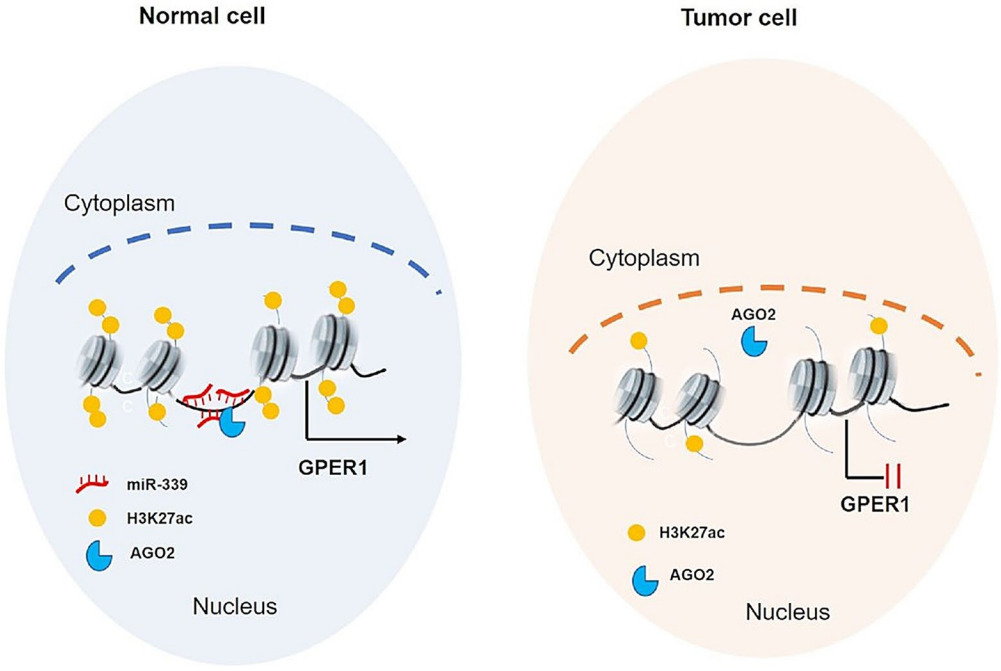

Fig. 2 The model illustrated that how tumor suppressor gene GPER1 is silenced in breast cancer [34]

nanoparticle-mediated delivery of miR-124 could reduce tumor growth and sensitize cells to etoposide, suggesting clinical applications of miRNAs as therapeutics to target myc functions on breast and ovarian tumor growth.

Another common feature of carcinogenesis is the dysfunction of TSGs [35, 36]. TSGs participate in cell cycle regulation, DNA damage repair and cell senescence, protecting normal cells from transforming into cancer cells [37–39]. The function loss and inactivation of TSGs have been recognized as common factors of carcinogenesis. It is generally believed that promoters DNA methylation and abnormal histone modifications could down regulate TSGs in non-small cell lung cancer (NSCLC). Researchers found that DNA methylation differences are rare in promoter, whereas miR-26A1 remarkably reactivates VILL promotor in lung cancer cells and this activation could be suppressed by enhancer inhibitor JQ1 [40]. miR-26A1 functions as a tumor suppressor and inhibits lung cancer cell proliferation and metastasis. The overexpression of miR-26A1 significantly enriches H3K27ac at the enhancer regions in A549 cells, suggesting that miR-26A1 can act as key regulator and potential therapeutic target for NSCLC. Recent research revealed that TSGs dysfunction is positively related with breast cancer development [41–44]. Liang et al. reported that miR-339 reactivates tumor suppressor genes (TSGs) by enhancing enhancer activity, offering a potential therapeutic approach for breast cancer treatment [34]. In normal breast cells, miR-339 binds to the enhancer region co-localized with Argonaute 2 (AGO2), activating the TSG GPER1, which prevents malignant transformation. However, reduced miR-339 expression diminishes enhancer activity, silencing GPER1 and promoting tumorigenesis (Fig. 2). Analysis of 157 breast cancer samples revealed suppressed expression of miR-339 and GPER1 in luminal A/B and triple-negative subtypes. miR-339 upregulates GPER1 via enhancer activation, but this process is abolished with AGO2 knockdown or enhancer deletion via CRISPR/Cas9. In vivo, miR-339 inhibits tumor proliferation, while GPER1 knockdown reverses this effect. Additionally, Ki67-positive cells decrease with miR-339 upregulation and increase with GPER1 loss. Together, miR-339 and GPER1 suppress breast cancer progression, with their disruption driving tumorigenesis.

Pancreatic cancer is one of lethal malignancies in the world with the 5-year survival rate lower than 6.9% [45, 46]. Patients are usually diagnosed at higher stages of pancreatic cancer for the lack of specific and effective biomarkers [47, 48]. miR-492 was found to be upregulated in a myriad of tumor tissue and may serve as a potential therapeutic biomarker [49–53]. The activation of miR-492 genes can significantly improve transforming growth factor-β (TGF-β)/Smad3 signaling pathway in tumor cells to promote epithelial mesenchymal transition of pancreatic cancer [54]. The enhancer marker H3K27ac is enriched in the NamiRNA miR-492 region, and the expression of its neighboring genes *Nuclear Receptor Subfamily 2 Group C Member 1 (NR2C1), NADH: Ubiquinone Oxidoreductase Subunit A12 (NDUFA12)* and *Transmembrane And Coiled-Coil Domain Family 3 (TMCC3)* are upregulated in pancreatic cancer. Further studies showed that miR-492, trigger

of NamiRNA-enhancer network, can accelerate pancreatic cancer progression by activating neighboring genes (*NR2C1/NDUFA12/TMCC3*) and NR2C1-TGF-β/Smad3 pathway. In vivo studies showed that utilizing miR-492 inhibitor, antagomir-492, can inhibit tumor growth when compared with the control group. Hematoxylin and eosin (H&E) and immunohistochemistry (IHC) staining results are consistent with the quantitative analysis of NR2C1/NDUFA12/TMCC3 expression after antagomir-492 treatment, suggesting that miR-492 is as a promising NamiRNA target for pancreatic cancer diagnose and treatment.

NamiRNA is efficient in suppressing tumor growth via interrupting the interaction of cancer-associated fibroblasts (CAFs) and tumor cells. Tumor initiation, invasion and metastasis are affected by the cross-talking of CAFs and tumor cells than cancer cells alone [55, 56]. The abnormality of long noncoding RNAs (lncRNAs)-NamiRNA system can accelerate glucose metabolism of CAFs in tumor microenvironment and thus expediting cancer progression [57–61]. After applying bioinformatic and epigenomic RNA sequencing technology, lncRNA-NamiRNA profiles of normal fibroblasts (NFs) and CAFs are well studied in patients with oral squamous cell carcinoma (OSCC) [62]. To be specific, lncRNA H19 was analyzed to be the key lncRNA that upregulated in oral CAFs and OSCC cell lines synchronously. Knocking down of lncRNA H19 would affect oral CAF proliferation, migration and glycolysis. Moreover, lncRNA H19/miR-675-5p/6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3 (PFKFB3) axis was involved and can promote glycolysis pathway of oral CAFs with the application of luciferase reporter assay and miR-675-5p inhibitor. This study presents how lncRNA H19/miR-675-5p network affects glucose metabolism in oral CAFs, highlighting the potential value in developing a novel biomarker for diagnosis and promising remedy for OSCC.

NamiRNA can suppress tumor growth via intervening the Warburg effect and energy releasing of cancer cells [63]. In the Warburg effect of solid tumor, the energy releasing of cancer cells is predominantly regulated by aerobic glycolysis that consists of glucose uptake and glycolysis, followed by lactic acid fermentation [63–65]. During this biological process, folate-binding protein (FBP) acts as a suppressive enzyme to function in the gluconeogenesis of renal cell carcinoma (RCC) and is related to poor prognosis of RCC [66, 67]. The NamiRNA, miR-24-1, with DNA locus overlapping with enhancer region, is capable to reactivate FBP1 [68]. Researcher validated that miR-24-1 can upregulate *FBP1* gene surprisingly and reactivate FBP1 expression to suppress Warburg effect, thus inhibiting the proliferation and metastasis of RCC cells. This reactivation requires the integrity of enhancer. Subsequent suppressive effects were further validated in 786-O and ACHN cell lines. miR-24-1 expression can suppress RCC tumor growth significantly in a xenograft model within 30 days. It is found that Ki-67 expression is decreased in miR-24-1 expressing group, FBP1 expression and Terminal deoxynucleotidyl transferase dUTP nick-end labeling (TUNEL) positive cells are increased with the overexpression of miR-24-1. This study highlights miR-24-1 overlapped with enhancer can activate TUNEL 1 and hinder Warburg effect of RCC progression, providing an alternative therapeutic strategy for RCC.

Conclusion and future prospect

NamiRNAs represent a fascinating and novel future of gene regulation for translational therapeutic potential. NamiRNAs have the capacity to upregulate gene expression and transcription, supplementing our understanding of inhibitory RNA interference pathway. Using NamiRNAs to target disease could provide a therapeutic means to modulate disease-associated genes and signal pathways directly from transcriptional level, offer a precision approach to cancer and immunity disease treatment.

Applying NamiRNAs technology in therapeutical areas may face some challenges in the future. The first challenge is how to ensure accurate delivery with high specificity. Typically, it is quite challenging to design effective delivery systems to transport NamiRNAs into cellular nucleus. NamiRNA carrier is supposed to traverse cell membrane and nuclear membrane with high specificity and avoid nonspecific genetic regulation. Meanwhile, introducing synthetic NamiRNAs in vivo may trigger unexpected immune response, inflammation and unwanted biological reactions. It is highly recommended to evaluate risks with patients before introducing NamiRNAs based therapies. Moreover, promoting NamiRNAs levels could bring in genes and pathways abnormal variations due to NamiRNA-gene system regulation. Finally, we have to take ethical concerns into consideration if long-term applications and potential abuse of NamiRNAs applied. Regulatory frameworks for NamiRNAs treatments are still in demand to address a wide variety of safety and ethical issues.

Future research will undoubtedly continue to illuminate the roles and functions of NamiRNAs in various biological processes and diseases. As our understanding of NamiRNAs goes deeper, NamiRNAs based therapies will be able to address specificity, delivery efficiency, and safety issues in clinic. The technology advancements will pave the way for a new generation of RNA-based therapeutics with the potential to change the landscape of disease treatment.

Acknowledgements
Figure 1 was created with BioRender.com

Author contributions
Xiang and Gang are responsible for literature study, conception and manuscript drafting. Jianping gave comments, revised the manuscript and provided funding for this work. All authors reviewed the manuscript and revised it critically before submission. All authors have seen and approved the final version of the manuscript and agreed to account for all aspects of the work.

Funding
This work was supported by Shenyang Science and Technology Project of China. (Grant number: 20-205-4-096).

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 21 April 2024 / Accepted: 19 March 2025
Published online: 15 April 2025

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