Review | Received 9 December 2025; Revised 11 February 2026; Accepted 18 March 2026; Published 24 March 2026
https://doi.org/10.55092/exrna20260001

# Crosstalk between KRAS and miRNA in cancer

**Ruoming Shen[1], Yixuan Zhao[1], Qin Sheng[1], Ying Sun[2,*] and Yanbo Wang[1,*]**

[1] State Key Laboratory of Pharmaceutical Biotechnology and Department of Physiology, Jiangsu Engineering Research Center for MicroRNA Biology and Biotechnology, NJU Advanced Institute of Life Sciences (NAILS), School of Life Sciences, Nanjing University, Nanjing 210023, China

[2] Department of Urology, Nanjing Drum Tower Hospital, Affiliated Hospital of Medical School, Nanjing University, Nanjing 210008, China

* Correspondence authors; E-mails: dg1930037@smail.nju.edu.cn (Y.S.); ybwang@nju.edu.cn (Y.W.).

## Highlights:

- Bidirectional regulation of KRAS and miRNA in cancer.
- MiRNA directly targets KRAS to inhibit tumour growth.
- KRAS mutations reshape miRNA expression profiles.
- KRAS hijacks miRNA processing pathways.
- Clinical potential of the KRAS-miRNA axis.

**Abstract:** Kirsten RAS viral oncogene homolog (KRAS) is one of the most frequently mutated oncogenes in human cancers. Its mutations result in constitutive activation of the protein, which drives the mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3K) signaling pathways and promotes tumor progression. Meanwhile, microRNAs (miRNAs), as key post-transcriptional regulators, can directly or indirectly modulate the activity of the KRAS signaling network, forming a bidirectional regulatory axis. This review summarizes the complex interplay between KRAS and miRNAs: on one hand, specific miRNAs suppress oncogenic signaling by targeting KRAS or its upstream/downstream effectors; on the other hand, mutant KRAS actively hijacks miRNA biogenesis, processing, and function, leading to a global reprogramming of miRNA expression that drives tumor progression, immune evasion, and drug resistance. In-depth dissection of this dynamic regulatory mechanism not only offers novel insights into the biology of KRAS-driven tumors, but also establishes a theoretical foundation for developing miRNA-based therapeutic interventions.

**Keywords:** KRAS; miRNA; oncogenic KRAS signaling; MAPK signaling; colorectal cancer; post-transcriptional regulation

## 1. Introduction

Rat sarcoma (RAS) was the first oncogene identified in human tumors and remains one of the most commonly mutated gene families, detected in over one-third of all cancers [1]. This family comprises

Copyright©2026 by the authors. Published by ELSP. This work is licensed under Creative Commons Attribution 4.0 International License, which permits unrestricted use, distribution, and reproduction in any medium provided the original work is properly cited.

three members: kirsten RAS viral oncogene homolog (KRAS), neuroblastoma RAS viral oncogene homolog (NRAS), and harvey RAS viral oncogene homolog (HRAS) [2]. Among them, KRAS is the most frequently mutated isoform, particularly in solid tumors, accounting for approximately 20% of all cancer cases. Its mutation prevalence is especially high in specific malignancies: about 90% in pancreatic cancer, 50% in colorectal cancer, and 30% in lung adenocarcinoma. Nearly all KRAS mutations occur at codons 12, 13, or 61, with codon 12 being the most common hotspot. In pancreatic cancer, the predominant subtypes are G12D (41%), G12V (32%), and G12R (16%), whereas in colorectal cancer, G12D (45%) and G12V (30%) represent the major variants [3,4].

KRAS mutations occupy a central role in tumor initiation and progression. At the molecular level, these amino acid substitutions lock the protein into a GTP-bound conformation, disrupting the cycling between active GTP- and inactive GDP-bound states. Sustained GTP loading leads to constitutive activation of downstream signaling axes, notably the rapidly accelerated fibrosarcoma (RAF)-mitogen-activated protein kinase kinase (MEK)-Extracellular signal-regulated kinase (ERK) and phosphoinositide 3-kinase (PI3K)-protein kinase B (AKT) pathways, which regulate key cellular processes including proliferation, survival, metabolic reprogramming, and invasive potential [5]. By maintaining these oncogenic outputs, mutant KRAS drives tumor cells through each stage of progression and reinforces their malignant phenotype.

In parallel, microRNAs (miRNAs) have emerged as critical post-transcriptional regulators of gene expression. These evolutionarily conserved non-coding RNA molecules, typically 20–25 nucleotides in length [6], are deeply involved in nearly all fundamental cellular processes and contribute to every hallmark of cancer [7]. Depending on context, miRNAs can function as tumor suppressors or oncogenes. Their dysregulation is a frequent event in cancer development, influencing a broad spectrum of processes including proliferation, apoptosis, metastasis, and immune evasion [8].

A growing body of evidence has revealed a complex bidirectional regulatory interplay between KRAS mutations and miRNAs, establishing a pivotal axis in cancer biology. This crosstalk operates through two fundamental mechanisms: multiple miRNAs precisely modulate KRAS activity through direct targeting or regulation of its signaling cascades; conversely, mutant KRAS orchestrates extensive reprogramming of the miRNA landscape via transcriptional control and disruption of miRNA biogenesis machinery. Although previous studies have uncovered various facets of this relationship, this review synthesizes current understanding of how KRAS-miRNA interactions cooperatively drive tumorigenesis. We delve into their roles in tumor initiation and progression and critically evaluate the therapeutic potential of targeting this dynamic regulatory network.

## 2. KRAS and miRNA

MiRNAs, which serve as crucial post-transcriptional regulators of gene expression, are highly evolutionarily conserved and ubiquitously expressed in eukaryotes [9]. KRAS, as a central oncogenic driver, exerts its biological effects within a dynamic regulatory network shaped by tissue microenvironment, mutation subtype, and therapeutic pressures. This complexity is particularly evident at the level of miRNA regulation. The miRNA expression profile does not merely accompany KRAS mutations but acts as a key mediator of tissue specificity, subtype dependency, and adaptive resistance.

*2.1. A regulatory network woven by tissue and mutation subtype*

The miRNA response triggered by KRAS mutations exhibits significant tissue-context specificity, which partly explains why identical mutations lead to distinct biological behaviors in different organs. For instance, in pancreatic ductal adenocarcinoma, KRAS mutations frequently drive overexpression of miR-21, which enhances survival signaling by suppressing targets like phosphatase and tensin homolog (PTEN) [10]. Conversely, in colorectal cancer, widespread downregulation of the let-7 family miRNAs directly removes inhibition on KRAS itself, thereby amplifying oncogenic signaling [11]. This specificity is further fine-tuned by specific KRAS mutation subtypes, with distinct miRNA dysregulation patterns observed. Alterations in c- myelocytomatosis oncogene (MYC)-dependent miRNA expression are commonly associated with the G12D variant [12], while G12C mutations are linked to dysregulation of miRNAs related to invasion and immunity [13]. These observations suggest that a shared oncogenic signaling hub, combined with subtle signal nuances unique to each mutation subtype, collaboratively weaves a complex miRNA regulatory network.

*2.2. Dynamic feedback and resistance remodeling under therapeutic pressure*

Therapeutic targeting of the KRAS pathway, such as direct inhibition of G12C [14] or downstream MEK [15], rapidly disrupts the existing regulatory equilibrium. This triggers adaptive feedback networks in which miRNAs serve as key mediators. For example, MEK inhibitor treatment can lead to upregulation of miR-30c [16], which subsequently inhibits the negative regulator RAS p21 protein activator 1 (RASA1) [17] thereby diminishing drug efficacy. This indicates that the therapy itself becomes a selective pressure reshaping the miRNA-KRAS regulatory axis. These rapidly responsive miRNA feedback loops are a significant reason for the transient effectiveness of many targeted therapies.

*2.3. MiRNA functional hubs constituting the core regulatory axis*

In KRAS-driven tumors, a core regulatory axis is formed by opposing groups of miRNAs. On one hand, inhibitory miRNAs, represented by let-7 [18] and miR-34a [19], act as fundamental molecular brakes by directly targeting KRAS mRNA or its adaptor proteins. Their loss is a common basis for the hyperactivation of KRAS signaling. On the other hand, oncogenic miRNAs, such as miR-21 [20] and miR-155 [21], provide synergistic amplification and bypass activation opportunities for KRAS signaling by suppressing pathway negative regulators like PTEN [22] This axis is not static but undergoes dynamic shifts during tumor evolution and therapeutic intervention. Its balance profoundly influences the malignant phenotype of the tumor and its therapeutic vulnerabilities.

## 3. KRAS-targeting miRNA

KRAS, a pivotal oncogene in tumorigenesis, was historically considered an “undruggable” target, which has spurred extensive scientific investigation into its molecular mechanisms in cancer [3]. A substantial body of research has focused on the regulatory roles of miRNAs on KRAS. miRNAs modulate KRAS activity through multi-layered mechanisms. Some act as tumor suppressors by directly targeting KRAS, while others exert anti-tumor effects indirectly by regulating its upstream or downstream signaling pathways.

### *3.1. MiRNAs directly targeting KRAS*

MiRNAs can directly target KRAS by binding to complementary sequences within the 3′-untranslated region (3′-UTR) of KRAS mRNA, leading to translational repression and a consequent reduction in KRAS protein synthesis. Relevant miRNAs are listed in Table 1.

**Table 1.** MiRNAs that regulate KRAS cited in this research highlight.

| MiRNA | Regulatory Function | Cancer Type | Polymorphic Site | Data Source | References |
|---|---|---|---|---|---|
| let-7 miRNA | Tumor Suppressor | OPC | LCS6 | Clinical Data | [23] |
| | | CRC | LCS6 | Clinical Data | [24] |
| | | CA | LCS6 | Clinical Data | [25] |
| | | GC | rs712 | Clinical Data | [26] |
| | | HNC | LCS6 | Clinical Data | [27] |
| | | NSCLC | LCS6 | Clinical Data | [28] |
| | | BC | LCS6 | Clinical Data | [29] |
| miR-134 | Tumor Suppressor | RCC | - | *In Vitro* Cell Assays | [30] |
| hsa-miR-557 | Tumor Suppressor | OS | - | *In Vitro* Cell & *In Vivo* Animal Experiments | [31] |
| miR-16 | Tumor Suppressor | CRC | - | *In Vitro* Cell & *In Vivo* Animal Experiments | [32] |
| miR-193a-3p | Tumor Suppressor | LC | Nucleotide positions 302–308 & 1073–1079 in 3′-UTR | *In Vitro* Cell & *In Vivo* Animal Experiments, Clinical Data | [33] |
| | | NSCLC | - | *In Vitro* Cell & *In Vivo* Animal Experiments | [34] |
| miR-873 | Tumor Suppressor | BC | - | *In Vitro* Cell & *In Vivo* Animal Experiments, Clinical Data | [35] |
| miR-101-3p | Tumor Suppressor | NSCLC | - | *In Vitro* Cell & *In Vivo* Animal Experiments, Clinical Data | [36] |
| miR-18a | Tumor Suppressor | CRC | - | *In Vitro* Cell Assays | [37] |
| miR-143 | Tumor Suppressor | CRC | - | *In Vitro* Cell Assays | [38] |
| miR-206 | Tumor Suppressor | PDAC | - | *In Vitro* Cell & *In Vivo* Animal Experiments | [39] |

#### 3.1.1. The let-7 miRNA family

Let-7 is one of the earliest identified miRNA families. miRNAs typically bind to conserved sequences within the 3′-UTR of target genes to inhibit translation. A T-to-G transversion in the sixth let-7 complementary site (LCS6) of the KRAS 3′-UTR creates a single nucleotide polymorphism (SNP) that impairs binding by let-7 family miRNAs, consequently reducing their repression of KRAS expression [40].

In various cancers, downregulation of let-7 is frequently accompanied by upregulation of KRAS protein, underscoring a key mechanistic link between let-7 dysregulation and tumorigenesis.

In oropharyngeal carcinoma (OPC), let-7 serves as a critical negative regulator of KRAS. The LCS6 polymorphism (G allele) in the KRAS 3′-UTR disrupts this regulation, leading to KRAS protein overexpression, enhanced tumor aggressiveness, and poorer patient prognosis [23].

Studies in colorectal cancer (CRC) demonstrate that the LCS6 polymorphism in the KRAS 3′-UTR weakens the binding of tumor-suppressive let-7, resulting in elevated KRAS protein expression. This polymorphism has been identified as an independent prognostic marker associated with adverse outcomes in CRC [24].

In gallbladder cancer (GBC), the KRAS LCS6 polymorphism, by interfering with the tumor-suppressive function of let-7, is associated with increased cancer risk and shorter survival in populations from Northern India [25].

The rs712 polymorphism (T allele) within the let-7 binding site of the KRAS 3′-UTR is significantly correlated with an elevated risk of gastric cancer (GC), suggesting KRAS rs712 as a potential genetic marker for GC susceptibility [26].

Research on head and neck cancer (HNC) indicates that the KRAS-LCS6 variant may serve as a candidate biomarker for predicting lymph node metastasis. In non-small cell lung cancer (NSCLC), the LCS6 variant allele is significantly associated with increased risk among moderate smokers, representing a novel paradigm for let-7 miRNA in lung cancer susceptibility [28].

The variant allele (rs61764370 T > G) in the KRAS 3′-UTR, which disrupts a let-7 miRNA binding site, is found to be enriched in patients with hereditary breast cancer (BC). Functional studies confirm that this variant promotes increased KRAS expression *in vitro* [29].

#### 3.1.2. Other miRNAs

Numerous studies have identified additional miRNAs that directly target KRAS to modulate tumor progression.

MiR-134 acts as a tumor suppressor in renal cell carcinoma (RCC) by targeting KRAS, inhibiting cell proliferation and epithelial-mesenchymal transition. Luciferase reporter assays confirm its direct binding activity to the KRAS 3′-UTR [30].

Has-miR-557 significantly suppresses the proliferation of osteosarcoma (OS) cells and reduces tumor size and weight *in vivo*. Further mechanistic studies demonstrate that has-miR-557 directly targets the 3′-UTR of KRAS and regulates the phosphorylation of downstream proteins [3].

Experimental validation confirms that miR-16 directly recognizes the 3′-UTR of KRAS transcripts and regulates KRAS expression. In vitro, miR-16-mediated suppression of KRAS inhibits proliferation and invasion while inducing apoptosis in CRC cells. In vivo, miR-16 exerts tumor-suppressive effects by negatively regulating KRAS in xenograft mouse models [32].

Two functional binding sites for miR-193a-3p within the KRAS 3′-UTR have been identified, sufficient to mediate KRAS downregulation. Investigations into the impact of miR-193a-3p on KRAS-driven tumor formation and metastasis in both *in vitro* and *in vivo* lung cancer (LC) models highlight its promising clinical translational potential [33]. KRAS is validated as a direct target of miR-193a-3p via dual-luciferase reporter assays. Reduced expression of miR-193a-3p is observed in NSCLC tumor tissues, and its enforced expression suppresses tumor formation, cell proliferation, and migration [34].

MiR-873 is shown to directly bind the 3′-UTR of KRAS mRNA and inhibit its expression, leading to suppressed KRAS signaling and tumor growth in pancreatic ductal adenocarcinoma (PDAC) and triple-negative breast cancer (TNBC) models [35].

MiR-101-3p directly interacts with the 3′-UTR of KRAS mRNA. KRAS levels are regulated by the circular RNA mediator of cell motility 1 (circ-MEMO1) /miR-101-3p axis, and silencing circ-MEMO1 inhibits NSCLC tumor growth *in vivo*[36].

MiR-18a specifically targets KRAS, but not other RAS family members. Inhibition of miR-18a increases KRAS expression, promoting proliferation and anchorage-independent growth in A431, HT-29, and WRL-68 cells. Luciferase reporter assays confirm its binding activity to the KRAS 3′-UTR [41].

In CRC tumor tissues, miR-143 expression is inversely correlated with KRAS protein levels. Luciferase reporter assays in CRC Lovo cells confirm that miR-143 directly targets the 3′-UTR of KRAS transcripts. Furthermore, miR-143-mediated suppression of KRAS inhibits ERK1/2 phosphorylation [37].

MiR-206 exerts tumor-suppressive functions in PDAC cells by directly targeting both KRAS and annexin A2 (ANXA2), thereby inhibiting cell proliferation, migration, and invasion. Overexpression of miR-206 in PDAC cells suppresses angiogenesis and lymphangiogenesis, leading to inhibited tumor growth [39].

### *3.2. MiRNA-mediated indirect targeting of KRAS*

Research indicates that miRNAs can exert tumor-suppressive effects not only by directly targeting KRAS itself but also, more broadly, through the indirect regulation of its upstream activators or downstream effector molecules. This enables fine-tuning of KRAS signaling network activity at the post-transcriptional level. These multi-layered, multi-node regulatory mechanisms reveal the complex role of miRNAs within the KRAS signaling network and provide potential non-coding RNA targets for the precise intervention of KRAS-driven tumors.

#### 3.2.1. Upstream indirect regulation of KRAS by miRNAs

Numerous miRNAs effectively inhibit the activation status of KRAS by targeting its upstream activators. Specific pathways and functions involved are summarized in Table 2.

MiRNAs indirectly influence KRAS signaling pathway activity by targeting the expression of receptor tyrosine kinases (RTKs). miR-7 has been shown to directly target epidermal growth factor receptor (EGFR) mRNA, while simultaneously targeting downstream rapidly accelerated fibrosarcoma 1 (RAF1), a direct effector of KRAS. Therefore, restoring miR-7 expression can effectively suppress the EGFR/KRAS/RAF/ mitogen-activated protein kinase (MAPK) signaling axis, demonstrating therapeutic potential in glioblastoma [42].

Growth factor receptor bound protein 2 (GRB2), CT10 regulator of kinase (CRK), and src homology 2 domain containing (SHC) are crucial adaptor proteins linking upstream receptor tyrosine kinases (RTKs) to downstream KRAS activation. By regulating the expression of these adaptors, miRNAs can efficiently modulate the signal flux strength of the RTK → KRAS signaling pathway. In hepatocellular carcinoma (HCC) studies, miR-433 was confirmed to directly bind the 3′-UTR of GRB2 mRNA and inhibit its expression. Downregulation of GRB2 significantly attenuated EGF-induced ERK1/2 phosphorylation (indicating MAPK pathway activation), directly demonstrating that inhibiting GRB2 via miRNA can suppress RAS-MAPK signal output [43].

GEFs catalyze the transition of KRAS from its inactive GDP-bound state to the active GTP-bound state. In glioblastoma, miR-124 and miR-137 have been shown to directly target the 3′-UTR of son

of sevenless homolog 1 (SOS1). Overexpression of these miRNAs significantly reduces SOS1 protein levels, thereby inhibiting EGF-induced KRAS-GTP loading and downstream ERK/MAPK pathway activation, leading to cell cycle arrest and differentiation [44].

**Table 2.** Pathways for indirect upstream regulation of KRAS by miRNAs.

| Pathway Level | Key Molecules | Function |
|---|---|---|
| RTKs | EGFR, Mesenchymal-epithelial transition factor (MET), Erb-B2 receptor tyrosine kinase 4 (ERBB4), Insulin-like growth factor 1 receptor (IGF1R) | Autophosphorylation upon ligand binding, recruiting adapter proteins. |
| Adapter Proteins | GRB2, CRK, SHC | Link RTKs to SOS1. |
| GEFs | SOS1, SOS2 | Catalyze RAS-GDP → RAS-GTP conversion. |

3.2.2. Regulation of downstream KRAS signaling pathways

MiRNAs themselves do not directly regulate KRAS to influence its downstream pathways. Instead, they achieve a multi-pronged attack on the KRAS-driven signaling network by simultaneously inhibiting multiple key downstream nodes. This approach can amplify inhibitory effects and overcome feedback activation or drug resistance. Beyond targeting the KRAS oncogene itself, certain miRNAs function by regulating downstream signaling pathways such as the MAPK and PI3K pathways (Table 3).

**Table 3.** Pathways for indirect downstream regulation of KRAS by miRNAs.

| Pathway Category | Key Target Molecules | Function |
|---|---|---|
| MAPK Pathway | RAF1, MEK1, Sprouty related EVH1 domain containing 1 (SPRED1), CRK | Activated KRAS-GTP directly binds and activates RAF kinase, initiating the RAF-MEK-ERK phosphorylation cascade, ultimately promoting cell cycle progression, proliferation, and survival. |
| PI3K-AKT Pathway | Phosphoinositide-3-kinase regulatory subunit 2 (PIK3R2), AKT2, Mechanistic target of rapamycin kinase (mTOR), IRS1 | KRAS activates PI3K directly or via IRS1, subsequently activating the AKT-mTOR axis to promote cell survival, growth, and metabolic reprogramming. |

MiR-7 inhibits the proliferation, migration, and invasion of NSCLC cells by targeting focal adhesion kinase (FAK), consequently suppressing ERK/MAPK pathway activation. These mechanisms serve as potential targets for NSCLC diagnosis and treatment [45]. In CRC cells, upregulation of miR-217 significantly downregulates MAPK1 expression. Overexpression of miR-217 in RKO cells also reduces KRAS and Raf-1 expression. miR-217 inhibits CRC tumor growth and promotes apoptosis by suppressing the MAPK signaling pathway [46].

By targeting key nodes of the PI3K-AKT pathway, miRNAs can directly impair the PI3K pathway activity relied upon by mutant KRAS, thereby inhibiting tumor growth and survival. miR-145 blocks

insulin/IGF-1 signal input into the PI3K-AKT pathway, thereby weakening KRAS-driven PI3K pathway activity and inhibiting tumor growth [47].

## 4. KRAS-regulated miRNAs

As a pivotal oncogene, KRAS activation drives cellular proliferation, survival, and invasive capabilities. Extensive studies have demonstrated that KRAS mutations can alter miRNA expression profiles and influence miRNA function through diverse mechanisms, thereby modulating tumor progression. This section systematically reviews miRNAs regulated by KRAS.

### *4.1. MiRNA expression profiles driven by KRAS mutation*

In a cohort of 55 metastatic CRC patients (15 with mutant KRAS, 40 with wild-type), a distinct miRNA expression signature associated with KRAS mutation was identified, characterized by upregulation of miR-127-3p, miR-92a, and miR-486-3p, and downregulation of miR-378. Bioinformatics analysis suggested these dysregulated miRNAs may collectively participate in processes such as NADPH regeneration and G protein-coupled receptor signaling. Furthermore, predicting their potential target genes ((including regulator of G-protein signaling 3 (RGS3) and transducer of ERBB2 (TOB1)) revealed their roles in regulating apoptosis and proliferation [48].

Research comparing miRNAs in isogenic CRC cell lines DKO-1, DKs-8, and DLD-1 (differing only in KRAS status) and their secreted exosomes found differences in miRNA expression profiles between cells and exosomes. For instance, miR-10b was specifically upregulated in exosomes from wild-type KRAS cells, whereas miR-100 was upregulated in exosomes from mutant KRAS cells. Additionally, miR-100 was found to be functional in recipient cells [49].

An analysis of miRNA expression profiles in 525 CRC tissues with KRAS or B-Raf proto-oncogene, serine/threonine kinase (BRAF) mutations revealed distinct patterns between KRAS-mutant and BRAF-mutant CRC patients. miRNAs such as miR-31-5p, miR-877-5p, miR-362-5p, miR-425-3p, and miR-31-5p showed differential expression, with the most significant fold changes. These miRNAs were significantly enriched in cancer-related pathways, including neutrophil factor signaling, general cancer pathways, wingless-related integration site (Wnt) signaling, and MAPK signaling, indicating their potential roles in CRC development [50].

Analysis of 85 NSCLC tissue samples identified miR-1253, miR-504, and miR-26a-5p as markers capable of distinguishing anaplastic lymphoma kinase (ALK)-, EGFR-, and KRAS-driven subtypes. The authors suggested further investigation into the function of these miRNAs within each driver-defined subgroup, particularly focusing on KRAS-mutant NSCLC—a subgroup currently lacking effective therapies [51].

Collectively, the data indicate that the presence of KRAS mutations can reshape the miRNA landscape within tumor tissues. Across studies, KRAS-driven cancers consistently exhibit a distinct pattern of miRNA dysregulation, highlighting the utility of these small RNAs as candidate biomarkers for this molecular subtype.

*4.2. Functional roles of key KRAS-regulated miRNAs*

KRAS-regulated miRNAs provide a clear window into the molecular mechanisms underlying tumor maintenance. They cooperatively regulate core oncogenic traits—proliferation, anti-apoptosis, local invasion, and distant metastasis. Their abundance correlates with disease stage, progression rate, and treatment response, making them promising diagnostic or prognostic indicators. However, the specific pathways linking individual miRNAs to these phenotypes are not fully elucidated. Oncogenic KRAS remodels the miRNA expression landscape, and the induced miRNAs, in turn, accelerate multiple steps of tumorigenesis, ultimately promoting tumor growth. This section enumerates current research progress on specific KRAS-regulated miRNAs and their functional contributions in various cancers.

In NSCLC, mutant KRAS constitutively activates the signal transducer and activator of Transcription 3 (PI3K-STAT3) signaling pathway; this sustained signal suppresses the expression of the tumor suppressor miR-34a. When miR-34a levels decrease, its ability to inhibit cluster of differentiationn47 (CD47) messenger RNA is lost, leading to abnormal accumulation of CD47 on the cell surface. Excess CD47 releases a “don’t eat me” signal that blocks macrophage phagocytosis, allowing tumor cells to evade innate immune surveillance and weakening natural anti-tumor responses [47].

In a tetracycline-inducible KRAS G12V model, miR-155 emerged as the most significantly upregulated miRNA following KRAS activation, and its increase strictly depended on intact MAPK and nuclear factor kappa-B (NF-κB) signaling pathways. Functionally, miR-155 directly represses forkhead box O3a (Foxo3a), thereby reducing the expression of the antioxidant enzymes superoxide dismutase 2 (SOD2) and catalase. The resulting intracellular reactive oxygen species (ROS) accumulation ultimately promotes pancreatic cell proliferation [52].

In cells expressing oncogenic KRAS (e.g., IMR90 and MCF10A), KRAS activation suppresses miR-200 expression through transcription factors jun proto-oncogene (JUN), specificity protein 1 (SP1), and zinc finger E-Box binding homeobox 1 (ZEB1) [53]. Furthermore, miR-200 overexpression can eliminate KRAS-induced apoptosis resistance by directly targeting the anti-apoptotic gene B-cell lymphoma 2 (BCL2). In CRC tumor tissues, compared to normal tissues, miR-200c expression is significantly upregulated, and its level is higher in mutant KRAS CRC than in wild-type KRAS. High miR-200c expression correlates with worse overall survival outcomes [53].

Through high-throughput screening for KRAS-specific synthetic lethal miRNA mimics, we found that miR-1298 is a potent inhibitor of KRAS-driven tumor growth. Affinity purification and mechanistic studies confirmed that the cytoskeleton regulator FAK and the laminin subunit laminin subunit beta 3 (LAMB3) are direct functional targets of miR-1298 [54].

In colorectal cancer tissues, miR-450b-5p is highly expressed, and its high expression is significantly associated with KRAS mutation. This miRNA directly targets the 3'-UTR regions of secreted frizzled related protein 2 (SFRP2) and seven in absentia homolog 1 (SIAH1), activating the Wnt/β-Catenin signaling pathway, thereby promoting tumor growth and progression [55].

## 5. KRAS hijacks miRNA regulatory pathways to drive oncogenic phenotypes

MiRNAs are key regulators integral to all aspects of cancer biology. Oncogenic KRAS alleles disrupt the normal biogenesis and activity landscape of miRNAs, thereby conferring selective advantages to emerging tumor clones. Experimental evidence indicates that KRAS mutations do not merely passively

respond to miRNA regulation; rather, they actively and globally hijack multiple independent steps in the miRNA pathway—from miRNA generation (nuclear transcription and processing) and maturation (cytoplasmic Dicer 1, ribonuclease III (DICER) cleavage) to functional execution ((RNA-induced silencing complex) RISC assembly and argonaute 2 (AGO2) activity). These disruptions synergistically accelerate tumorigenesis. This understanding provides a conceptual framework for elucidating the evolution and progression of KRAS-mutant cancers. Post-transcriptional regulation by miRNAs is an evolutionarily conserved and ubiquitous mechanism often disrupted in malignancy; indeed, mutations in core components of the miRNA machinery have been found in various tumors [56].While previous research has extensively detailed how miRNAs influence KRAS expression and function, our knowledge of how KRAS shapes the global miRNA landscape remains incomplete. KRAS mutations also lead to dysregulation of miRNA biosynthesis and global miRNA profiles [57,58].This section delineates how KRAS promotes tumorigenesis by subverting miRNA regulatory pathways.

### *5.1. Regulation of miRNA biogenesis and processing*

KRAS mutations tilt the “miRNA balance” in favor of tumor development by affecting critical steps in miRNA generation.

KRAS signaling influences the early nuclear fate of miRNAs by inducing specific long non-coding RNAs (lncRNAs). For instance, KRAS-induced metastasis-associated transcript 1 (KIMAT1) stabilizes the nuclear helicase DExH-box helicase 9 (DHX9), promoting the processing of specific oncogenic miRNA precursors (e.g., miR-27b-3p). Concurrently, it represses the expression of p21 (a co-factor for developmentally regulated RNA binding protein (DROSHA), a component of the microprocessor complex) via a MYC-dependent mechanism, thereby inhibiting the biogenesis of a subset of tumor-suppressive miRNAs (e.g., miR-34a, miR-126-3p) [59]. This dual-action regulation creates an imbalance between pro-oncogenic and anti-oncogenic miRNA expression.

After nuclear export, precursor miRNAs (pre-miRNAs) require cleavage by the DICER enzyme to become mature. KRAS exerts complex regulation on DICER via its downstream ERK signaling pathway. On one hand, ERK-mediated phosphorylation of DICER can inhibit its processing activity [60]. On the other hand, studies have linked high DICER expression to pancreatic cancer risk, identifying transcription factor Sp1 as targeting the DICER promoter region. The ERK/Sp1 signaling pathway upregulates Dicer expression in gemcitabine-resistant PANC-1 cells, thereby suppressing miRNA maturation and promoting tumor progression [61].

### *5.2. Regulation of RISC assembly and AGO2 function*

RISC is the executor of miRNA function, an indispensable vehicle for miRNA-mediated gene regulation. The assembly of RISC and its subsequent capacity for gene silencing is a highly regulated and tissue-specific process [62,63]. The KRAS signaling pathway can directly modulate the assembly efficiency and silencing potency of RISC, thereby determining the output strength of the miRNA regulatory network. Research indicates that during T-cell activation, activation of the PI3K-AKT-mTOR pathway enhances the loading of miRNAs into highly active RISC, increasing their gene-silencing efficacy [64]. In the context of tumors with constitutively active KRAS-PI3K/AKT signaling, this mechanism is hijacked to enhance

RISC loading of specific oncogenic miRNAs, enabling more effective suppression of tumor suppressor genes and promoting proliferation and survival.

AGO2 is the core catalytic component of RISC, and its functional state directly determines miRNA effector outcomes. Key modifications of AGO2 are likely crucial for RISC formation and miRNA activity. Given the essential roles of AGO2 and RISC in miRNA localization and target silencing, interactions between mutant KRAS and AGO2 may lead to dysfunctional miRNA effector mechanisms.

Studies have found that in intestinal and tumor tissues from mice harboring the KRAS G12D mutation, the expression of Casein Kinase 1α (CK1α) and CK2α is suppressed, leading to reduced phosphorylation of AGO2 at multiple critical serine sites (S825/S829/S832/S835) [65]. This hypophosphorylated form of AGO2 exhibits enhanced binding to mRNA but significantly attenuated ability to mediate target cleavage and translational repression. Using isogenic colorectal cancer cell lines, it was demonstrated that hyperactive mutant KRAS inhibits the localization of Ago2 to multivesicular endosomes (MVEs) and reduces AGO2 secretion into exosomes. Mechanistically, inhibiting MEKs I and II—but not Akt—reversed the effects of active KRAS mutation, leading to increased Ago2-MVE association and elevated exosomal secretion of Ago2 [66].

The importance of AGO2 in KRAS-driven tumors appears stage-specific. In early pancreatic cancer development, EGFR/RAS signaling alone may be sufficient to drive tumor formation, making AGO2 dispensable [67]. However, AGO2 plays an indispensable role during tumor progression and metastasis. In non-small cell lung cancer, loss of AGO2 can inhibit the proliferation of KRAS-mutant cells [68]. This suggests that KRAS, by regulating functional components like AGO2, plays a critical role primarily in late-stage malignant evolution and adaptive survival, closely associated with therapy resistance and metastasis.

## 6. Conclusion

This article systematically elucidates the bidirectional and dynamic regulatory network between KRAS and miRNAs and its central role in driving malignant tumor progression. This mutual regulatory mechanism not only deepens our understanding of the pathogenesis of KRAS-driven tumors but also opens promising avenues for intervening against this historically “undruggable” target. Restoring physiological regulation of the KRAS pathway using synthetic miRNA mimics or specific inhibitors, or combining them with existing KRAS-targeted drugs to overcome resistance, has shown encouraging potential in preclinical models. Emerging single-cell and spatial transcriptomic technologies will further enable us to map detailed KRAS-miRNA interaction landscapes at cellular and anatomical resolution, providing unprecedented insights for designing personalized therapeutic strategies.

However, the path from mechanistic understanding to clinical translation remains fraught with challenges. Firstly, miRNA-based therapies face universal delivery hurdles. Achieving stable, efficient, and tumor-specific enrichment following systemic administration while avoiding degradation by serum nucleases is a critical technical bottleneck. Secondly, the inherent multi-target nature of miRNAs poses risks of complex off-target effects and potential toxicity. For instance, miR-193a-3p, intended to inhibit KRAS, may simultaneously affect other metastasis-related genes, leading to unintended consequences. This has been reflected in early clinical trials, such as the suspension of the miR-34 mimic MRX34 due to severe immune-related adverse events. Thirdly, the intrinsic heterogeneity of KRAS-mutant tumors presents a fundamental challenge. The coexistence and dynamic evolution of different KRAS mutation

subtypes (e.g., G12D *vs.* G12V) within a tumor, and the resulting intratumoral variations in miRNA expression profiles, may lead to rapid failure of single-miRNA therapies by selecting for resistant clones.

Therefore, future translational research must adopt a more integrated and pragmatic approach. On one hand, efforts should focus on leveraging clinically relevant instances—such as the miR-143 expression profile associated with KRAS status in colorectal cancer or miR-34a levels predictive of KRAS G12C inhibitor efficacy in NSCLC—to validate and optimize biomarker-guided patient stratification strategies. On the other hand, therapeutic development must be closely coupled with innovations in delivery technologies (e.g., targeted lipid nanoparticles or exosomal carriers) and a deep interrogation of tumor heterogeneity using techniques like single-cell sequencing. This is essential for designing combination strategies targeting dominant clones or key microenvironmental signals. In summary, the discovery of the KRAS-miRNA regulatory axis undoubtedly opens new avenues for precision cancer therapy. However, only by enthusiastically embracing its potential while prudently and systematically overcoming its core challenges in delivery, specificity, and tumor heterogeneity can this scientific understanding be ultimately translated into tangible clinical benefit.

## Declaration of generative AI and AI-assisted technologies

During the preparation of this manuscript, the authors used generative AI tools only to improve language and readability. The authors take full responsibility for the content of the manuscript.

## Acknowledgments

This work was supported by grants from the Starry Night Science Fund of Zhejiang University Shanghai Institute for Advanced Study (No. SN-ZJU-SIAS-008).

## Authors' contribution

Conceptualization, Y.W. and Y.S.; investigation, R.S., Y.Z. and Q.S.; resources, R.S., Y.Z. and Q.S.; writing—original draft preparation, R.S., Y.Z. and Q.S.; writing—review and editing, R.S.; visualization, R.S.; supervision, Y.W. and Y.S.; project administration, Y.W. and Y.S.; All authors have read and agreed to the published version of the manuscript.

## Conflicts of interest

The authors declare no conflicts of interest.

## References

[1] Huang L, Guo Z, Wang F, Fu L. KRAS mutation: from undruggable to druggable in cancer. *Signal Transduction Targeted Ther.* 2021, 6(1):386.

[2] Holderfield M, Lee BJ, Jiang J, Tomlinson A, Seamon KJ, *et al.* Concurrent inhibition of oncogenic and wild-type RAS-GTP for cancer therapy. *Nature* 2024, 629(8013):919–926.

[3] Singhal A, Li BT, O'Reilly EM. Targeting KRAS in cancer. *Nat. Med.* 2024, 30(4):969–983.

[4] Li S, Balmain A, Counter CM. A model for RAS mutation patterns in cancers: finding the sweet spot. *Nat. Rev. Cancer* 2018, 18(12):767–777.

[5] Liu P, Wang Y, Li X. Targeting the untargetable KRAS in cancer therapy. *Acta Pharm. Sin. B* 2019, 9(5):871–879.
[6] Lee RC, Feinbaum RL, Ambros V. The C. elegans heterochronic gene lin-4 encodes small RNAs with antisense complementarity to lin-14. *Cell* 1993, 75(5):843–854.
[7] Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell* 2011, 144(5):646–674.
[8] Lu J, Getz G, Miska EA, Alvarez-Saavedra E, Lamb J, *et al.* MicroRNA expression profiles classify human cancers. *Nature* 2005, 435(7043):834–838.
[9] Garzon R, Calin GA, Croce CM. MicroRNAs in cancer. *Annu. Rev. Med.* 2009, 60:167–179.
[10] Chu NJ, Anders RA, Fertig EJ, Cao M, Hopkins AC, *et al.* Inhibition of miR-21 regulates mutant KRAS effector pathways and intercepts pancreatic ductal adenocarcinoma development. *Cancer Prev. Res.* 2020, 13(7):569–582.
[11] Niculae AM, Dobre M, Herlea V, Manuc TE, Trandafir B, *et al.* Let-7 microRNAs are possibly associated with perineural invasion in colorectal cancer by targeting IGF axis. *Life* 2022, 12(10):1638.
[12] Knight JRP, Alexandrou C, Skalka GL, Vlahov N, Pennel K, *et al.* MNK inhibition sensitizes KRAS-mutant colorectal cancer to mTORC1 inhibition by reducing eIF4E phosphorylation and c-MYC expression. *Cancer Discov.* 2021, 11(5):1228–1247.
[13] Tirpe AA, Nutu A, Busuioc C, Pop OL, Berindan-Neagoe I. MicroRNAs and lung cancer: overview of essential pathways and somatic mutations in cancer progression. *Front. Oncol.* 2025, 15:1677471.
[14] Canon J, Rex K, Saiki AY, Mohr C, Cooke K, *et al.* The clinical KRAS(G12C) inhibitor AMG 510 drives anti-tumour immunity. *Nature* 2019, 575(7781):217–223.
[15] Hofmann MH, Gmachl M, Ramharter J, Savarese F, Gerlach D, *et al.* BI-3406, a potent and selective SOS1-KRAS interaction inhibitor, is effective in KRAS-driven cancers through combined MEK inhibition. *Cancer Discovery* 2021, 11(1):142–157.
[16] Yang S, Zhong L, Sun Y, Wang C, Ru W, *et al.* Downregulation of lncRNA SNHG16 inhibits vascular smooth muscle cell proliferation and migration in cerebral atherosclerosis by targeting the miR-30c-5p/SDC2 axis. *Heart Vessels* 2022, 37(6):1085–1096.
[17] Shi L, Middleton J, Jeon YJ, Magee P, Veneziano D, *et al.* KRAS induces lung tumorigenesis through microRNAs modulation. *Cell Death Dis.* 2018, 9(2):219.
[18] Pulliero A, Mastracci L, Tarantini L, Khalid Z, Bollati V, *et al.* Let-7a downregulation accompanied by KRAS mutation is predictive of lung cancer onset in cigarette smoke-exposed mice. *Int. J. Mol. Sci.* 2023, 24(14):11778.
[19] Hidalgo-Sastre A, Lubeseder-Martellato C, Engleitner T, Steiger K, Zhong S, *et al.* Mir34a constrains pancreatic carcinogenesis. *Sci. Rep.* 2020, 10(1):9654.
[20] Mima K, Nishihara R, Nowak JA, Kim SA, Song M, *et al.* MicroRNA MIR21 and T cells in colorectal cancer. *Cancer Immunol. Res.* 2016, 4(1):33–40.
[21] Sun J, Yang R, Fu J, Huo D, Qu X, *et al.* TGFβ1-induced hedgehog signaling suppresses the immune response of brain microvascular endothelial cells elicited by meningitic Escherichia coli. *Cell Commun. Signaling* 2024, 22(1):123.
[22] Calderaro J, Rebouissou S, de Koning L, Masmoudi A, Hérault A, *et al.* PI3K/AKT pathway activation in bladder carcinogenesis. *Int. J. Cancer* 2014, 134(8):1776–1784.

[23] De Ruyck K, Duprez F, Ferdinande L, Mbah C, Rios-Velazquez E, *et al.* A let-7 microRNA polymorphism in the KRAS 3'-UTR is prognostic in oropharyngeal cancer. *Cancer Epidemiol.* 2014, 38(5):591–598.

[24] Smits KM, Paranjape T, Nallur S, Wouters KA, Weijenberg MP, *et al.* A let-7 microRNA SNP in the KRAS 3'UTR is prognostic in early-stage colorectal cancer. *Clin. Cancer Res.* 2011, 17(24):7723–7731.

[25] Kazmi HR, Chandra A, Kumar S, Satyam LK, Gupta A, *et al.* A let-7 microRNA binding site polymorphism in the KRAS 3'UTR is associated with increased risk and reduced survival for gallbladder cancer in North Indian population. *J. Cancer Res. Clin. Oncol.* 2016, 142(12):2577–2583.

[26] Li Z, Pan X, Han B, Guo X, Zhang Z, *et al.* A let-7 binding site polymorphism rs712 in the KRAS 3' UTR is associated with an increased risk of gastric cancer. *Tumour Biol.* 2013, 34(5):3159–3163.

[27] Ulusan M, Sen S, Yilmazer R, Dalay N, Demokan S. The let-7 microRNA binding site variant in KRAS as a predictive biomarker for head and neck cancer patients with lymph node metastasis. *Pathol. Res. Pract.* 2022, 239:154147.

[28] Chin LJ, Ratner E, Leng S, Zhai R, Nallur S, *et al.* A SNP in a let-7 microRNA complementary site in the KRAS 3' untranslated region increases non-small cell lung cancer risk. *Cancer Res.* 2008, 68(20):8535–8540.

[29] Hollestelle A, Pelletier C, Hooning M, Crepin E, Schutte M, *et al.* Prevalence of the variant allele rs61764370 T > G in the 3'UTR of KRAS among Dutch BRCA1, BRCA2 and non-BRCA1/BRCA2 breast cancer families. *Breast Cancer Res. Treat.* 2011, 128(1):79–84.

[30] Liu Y, Zhang M, Qian J, Bao M, Meng X, *et al.* miR-134 functions as a tumor suppressor in cell proliferation and epithelial-to-mesenchymal Transition by targeting KRAS in renal cell carcinoma cells. *DNA Cell Biol.* 2015, 34(6):429–436.

[31] Qiao Z, Li J, Kou H, Chen X, Bao D, *et al.* Hsa-miR-557 inhibits osteosarcoma growth through targeting KRAS. *Front. Genet.* 2021, 12:789823.

[32] You C, Liang H, Sun W, Li J, Liu Y, *et al.* Deregulation of the miR-16-KRAS axis promotes colorectal cancer. *Sci. Rep.* 2016, 6:37459.

[33] Seviour EG, Sehgal V, Mishra D, Rupaimoole R, Rodriguez-Aguayo C, *et al.* Targeting KRas-dependent tumour growth, circulating tumour cells and metastasis *in vivo* by clinically significant miR-193a-3p. *Oncogene* 2017, 36(10):1339–1350.

[34] Fan Q, Hu X, Zhang H, Wang S, Zhang H, *et al.* MiR-193a-3p is an important tumour suppressor in lung cancer and directly targets KRAS. *Cell Physiol. Biochem.* 2017, 44(4):1311–1324.

[35] Mokhlis HA, Bayraktar R, Kabil NN, Caner A, Kahraman N, *et al.* The modulatory role of microRNA-873 in the progression of KRAS-driven cancers. *Mol. Ther. Nucleic Acids* 2019, 14:301–317.

[36] Ding C, Xi G, Wang G, Cui D, Zhang B, *et al.* Exosomal Circ-MEMO1 promotes the progression and aerobic glycolysis of non-small cell lung cancer through targeting miR-101-3p/KRAS axis. *Front. Genet.* 2020, 11:962.

[37] Chen X, Guo X, Zhang H, Xiang Y, Chen J, *et al.* Role of miR-143 targeting KRAS in colorectal tumorigenesis. *Oncogene* 2009, 28(10):1385–1392.

[38] Liao W, Ye Y, Zhang N, Li T, Wang S, *et al.* MicroRNA-30b functions as a tumour suppressor in human colorectal cancer by targeting KRAS, PIK3CD and BCL2. *J. Pathol.* 2014, 232(4):415–427.

[39] Keklikoglou I, Hosaka K, Bender C, Bott A, Koerner C, *et al.* MicroRNA-206 functions as a pleiotropic modulator of cell proliferation, invasion and lymphangiogenesis in pancreatic adenocarcinoma by targeting ANXA2 and KRAS genes. *Oncogene* 2015, 34(37):4867–4878.

[40] Johnson SM, Grosshans H, Shingara J, Byrom M, Jarvis R, *et al.* RAS is regulated by the let-7 microRNA family. *Cell* 2005, 120(5):635–647.

[41] Tsang WP, Kwok TT. The miR-18a* microRNA functions as a potential tumor suppressor by targeting on K-Ras. *Carcinogenesis* 2009, 30(6):953–959.

[42] Kefas B, Godlewski J, Comeau L, Li Y, Abounader R, *et al.* microRNA-7 inhibits the epidermal growth factor receptor and the Akt pathway and is down-regulated in glioblastoma. *Cancer Res.* 2008, 68(10):3566–3572.

[43] Xue J, Chen L, Li Z, Hu Y, Yan S, *et al.* MicroRNA-433 inhibits cell proliferation in hepatocellular carcinoma by targeting p21 activated kinase (PAK4). *Mol. Cell. Biochem.* 2015, 399(1–2):77–86.

[44] Silber J, Lim DA, Petritsch C, Persson AI, Maunakea AK, *et al.* miR-124 and miR-137 inhibit proliferation of glioblastoma multiforme cells and induce differentiation of brain tumor stem cells. *BMC Med.* 2008, 6(1):14.

[45] Cao Q, Mao Z, Shi Y, Chen Y, Sun Y, *et al.* MicroRNA-7 inhibits cell proliferation, migration and invasion in human non-small cell lung cancer cells by targeting FAK through ERK/MAPK signaling pathway. *Oncotarget* 2016, 7(47):77468–77481.

[46] Zhang N, Lu C, Chen L. miR-217 regulates tumor growth and apoptosis by targeting the MAPK signaling pathway in colorectal cancer. *Oncol. Lett.* 2016, 12(6):4589–4597.

[47] Hu H, Cheng R, Wang Y, Wang X, Wu J, *et al.* Oncogenic KRAS signaling drives evasion of innate immune surveillance in lung adenocarcinoma by activating CD47. *J. Clin. Invest.* 2023, 133(2):e153470.

[48] Mosakhani N, Sarhadi VK, Borze I, Karjalainen-Lindsberg ML, Sundström J, *et al.* MicroRNA profiling differentiates colorectal cancer according to *KRAS* status. *Genes Chromosomes Cancer* 2012, 51(1):1–9.

[49] Cha DJ, Franklin JL, Dou YC, Liu Q, Higginbotham JN, *et al. KRAS*-dependent sorting of miRNA to exosomes. *Elife* 2015, 4:e07197.

[50] Choi YW, Song YS, Lee H, Yi K, Kim YB, *et al.* MicroRNA expression signatures associated with BRAF-mutated *versus* KRAS-mutated colorectal cancers. *Medicine* 2016, 95(15):e3321.

[51] Gasparini P, Cascione L, Landi L, Carasi S, Lovat F, *et al.* microRNA classifiers are powerful diagnostic/prognostic tools in *ALK*-, *EGFR*-, and *KRAS*-driven lung cancers. *Proc. Natl. Acad. Sci. U.S.A.* 2015, 112(48):14924–14929.

[52] Wang P, Zhu C, Ma M, Chen G, Song M, *et al.* Micro-RNA-155 is induced by K-Ras oncogenic signal and promotes ROS stress in pancreatic cancer. *Oncotarget* 2015, 6(25):21148–21158.

[53] Tsunoda T, Takashima Y, Yoshida Y, Doi K, Tanaka Y, *et al.* Oncogenic KRAS regulates miR-200c and miR-221/222 in a 3D-specific manner in colorectal cancer cells. *Anticancer Res.* 2011, 31(7):2453–2459.

[54] Zhou Y, Dang J, Chang KY, Yau E, Aza-Blanc P, *et al.* miR-1298 inhibits mutant KRAS-driven tumor growth by repressing FAK and LAMB3. *Cancer Res.* 2016, 76(19):5777–5787.

[55] Ye Y, Wu P, Gu C, Deng D, Jiao H, *et al.* miR-450b-5p induced by oncogenic KRAS is required for colorectal cancer progression. *Oncotarget* 2016, 7(38):61312–61324.

[56] Kim T, Croce CM. MicroRNA: trends in clinical trials of cancer diagnosis and therapy strategies. *Exp. Mol. Med.* 2023, 55(7):1314–1321.

[57] Rachagani S, Macha MA, Heimann N, Seshacharyulu P, Haridas D, *et al.* Clinical implications of miRNAs in the pathogenesis, diagnosis and therapy of pancreatic cancer. *Adv. Drug Deliv. Rev.* 2015, 81:16–33.

[58] Ali Syeda Z, Langden SSS, Munkhzul C, Lee M, Song SJ. Regulatory mechanism of microRNA expression in cancer. *Int. J. Mol. Sci.* 2020, 21(5):1723.

[59] Shi L, Magee P, Fassan M, Sahoo S, Leong HS, *et al.* A KRAS-responsive long non-coding RNA controls microRNA processing. *Nat. Commun.* 2021, 12(1):2038.

[60] Drake M, Furuta T, Suen KM, Gonzalez G, Liu B, *et al.* A requirement for ERK-dependent dicer phosphorylation in coordinating oocyte-to-embryo transition in C. elegans. *Dev. Cell* 2014, 31(5):614–628.

[61] Su YH, Hsu TW, Chen HA, Su CM, Huang MT, *et al.* ERK-mediated transcriptional activation of Dicer is involved in gemcitabine resistance of pancreatic cancer. *J. Cell. Physiol.* 2021, 236(6):4420–4434.

[62] Bofill-De Ros X, Vang Ørom UA. Recent progress in miRNA biogenesis and decay. *RNA Biol.* 2024, 21(1):1–8.

[63] Shang R, Lee S, Senavirathne G, Lai EC. microRNAs in action: biogenesis, function and regulation. *Nat. Rev. Genet.* 2023, 24(12):816–833.

[64] Olejniczak SH, La Rocca G, Radler M, Thompson CB. Coordinated regulation of cap-dependent translation and microRNA function by convergent signaling through the PI3K/Akt/mTOR and Jak/Stat/Pim signaling pathways. *Cancer Res.* 2015, 75(15_Supplement):973–973.

[65] Shui B, Beyett TS, Chen Z, Li X, Rocca GL, *et al.* Oncogenic K-Ras suppresses global miRNA function. *Mol. Cell* 2023, 83(14):2509–2523.

[66] McKenzie AJ, Hoshino D, Hong NH, Cha DJ, Franklin JL, *et al.* KRAS-MEK signaling controls Ago2 sorting into exosomes. *Cell Rep.* 2016, 15(5):978–987.

[67] Shankar S, Tien JC, Siebenaler RF, Chugh S, Dommeti VL, *et al.* An essential role for Argonaute 2 in EGFR-KRAS signaling in pancreatic cancer development. *Nat. Commun.* 2020, 11(1):2817.

[68] Tien JCY, Chugh S, Goodrum AE, Cheng Y, Mannan R, *et al.* AGO2 promotes tumor progression in KRAS-driven mouse models of non-small cell lung cancer. *Proc. Natl. Acad. Sci. U.S.A.* 2021, 118(20):e2026104118.