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REVIEW

MicroRNAs in the regulation of Wnt/β-Catenin, NF-kB, PI3K/AKT, STAT3, p53, and Hedgehog pathway

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Abstract

Background and aim: There are two significant challenges in cancer treatment: malignancy and resistance to anti-cancer drugs. As a result, a thorough understanding of cancer etiology is essential for developing new cancer treatments. There is a crucial role for micro-RNAs in physiological processes as well as pathological processes. Cancer pathogenesis is strongly influenced by miRNAs, which play a crucial role in neoplastic disease pathophysiology. They can be used to diagnose, prognosticate, and treat a wide range of cancers. Also, they play an important role in metastasis and resistance to treatment and the stamens of cancer stem cells by regulating several signaling networks. A better understanding of the miRNAs that play a role in cancer's signaling pathways could lead to new cancer diagnostic, prognostic, and treatment options. This study focuses on miRNAs, which play a vital part in regulating cancer-related signaling networks and pathogenic signaling pathways in cancer.

Relevance for patients: This study highlights the relevance of microRNAs (miRNAs) in cancer, as they have a significant role in cancer development, metastasis, treatment resistance, and cancer stem cells. Understanding the role of miRNAs in cancer signaling pathways could lead to improved diagnostics, prognostics, and treatment options for patients.

Keywords: miRNAs, Wnt/β-Catenin, NF-kB, PI3K/AKT, STAT3, p53, Hedgehog pathway

1. Introduction

While significant efforts have been made to enhance cancer detection and treatment, up to 90% of cancer-related deaths result from the spread of the disease rather than the original tumor itself [1]. Invasion and metastasis are essential hallmarks of cancer. The primary carcinoma cells are dispersed into local tissues, then infiltrate into the adjacent circulation and travel through the hematogenous system to the capillaries of distant organs [2]. "Cancer colonization" is the development of overt and clinically identifiable macrometastases that result from the expansion of micrometastatic colonies in the parenchyma of distant tissues. Complex molecular processes are involved in these metastatic phases, underscoring the importance of examining the issue from a different perspective. Cancer was thought to be a hereditary disease but this is still debatable [3]. Mutations in various important genes are associated with cancer development and metastasis. The most important signaling pathways involved in tumor metastasis are Wnt/β-Catenin [4], NF-kB [5], PI3K/AKT [6], STAT3 [7], p53 [8], and Hedgehog [9]. Nevertheless, evidence suggests that epigenetic modulation is as important as possible regulatory mechanisms in cancer metastasis and may shed light on novel cancer metastatic techniques [10,11].

miRNAs have gained much attention in cancer research. Tumor genesis, development, invasion, and metastasis have been linked to abnormalities in miRNA expression. Many new miRNAs have been discovered in the last few years, which have helped us better understand the contribution of miRNAs in cells. Competing endogenous RNA networks is an important aspect of cancer, which include microRNAs, long non-coding RNAs (ncRNAs), and circular RNAs (circs) [12]. Genome-wide association analyses of tumor samples have linked miRNAs to cancer. Alterations in lncRNA expression and mutations in these genes aid tumorigenesis and metastasis. miRNAs may exhibit tumor-suppressive and cancer-promoting (oncogenic) activities. It is possible that miRNAs could be used as new cancer biomarkers and therapeutic targets because of their tissue- and genome-specific expression patterns [13,14]. The microRNAs have been found in B-cell CLL (Chronic lymphocytic leukemia), but the gene responsible for them has not been

identified. miR-15 and miR-16 genes were not the cause of the disease, but rather the genes that produced miRNAs [15]. The role of miRNAs as tumor suppressors [16] or oncogenes [17] has been established repeatedly.

miRNAs have also been extensively researched for their potential as biomarkers in diagnosing GC (Gastric cancer) [18]. Many types of cancer, such as BC (Breast cancer) [19], CRC (Colorectal cancer) [20], and liver cancer [21], are aided by the actuation of the Wnt/β-catenin signals. The development of GC tumors is intimately linked to the actuation of the Wnt/β-catenin pathway [22]. A better understanding of how miRNAs affect the Wnt/β-catenin, STAT-3, p53, NF-kB, PI3K/AKT, and Hedgehog signaling pathways may lead to earlier detection of GC, as well as the development of new treatment options. miRNAs' role in modulating several cancers-associated signaling pathways has been reviewed in this study.

2. miRNA biosynthesis

Following RNA polymerase II transcription of pri-miRNA precursors, an endonuclease enzyme, such as DROSHA or DGCR8, produces pre-miRNA sequences of about 80–100 nucleotides[23,24]. A recent study found that exportin-5 plays an important role in transporting pre-miRNA from the nucleus to the cytoplasm [25]. In the cytoplasm, Dicer cleaves the miRNA into mature, double-stranded molecules [26]. miRNA duplexes bind to Argonaute (Ago) proteins after maturation, forming RNA-induced silencing complexes (RISCs), which regulate messenger RNA (mRNA) translation. miRNA recognizes complementary sequences in its target mRNAs' 3′ untranslated regions (UTRs). Recent studies indicate miRNA binds to target mRNAs' 5′UTR or open reading frame (ORF) [27,28]. Because miRNA regulation does not require high complementarity, a single miRNA can regulate up to several hundred mRNAs, resulting in aberrant miRNA expression that profoundly impacts cancer-related signalling pathways.

3. miRNAs in cancer

s several studies found that half of the miRNA genes are located in cancer-related genomic regions or fragile sites. The aberrant expression of miRNAs is a standard rather than an exception in cancer tissues/cells based on microarray data. Multiple reports have involved miRNAs in many types of cancers, such as breast, colon, gastric, lung, prostate, and thyroid [29,30]. In March 2015, about 15,943 PubMed hits indicated that miRNAs have massive peer-reviewed scientific literature. Their role in cancer is very diverse in terms of the disease and experimental approaches used. Despite the overwhelming majority of published papers focusing on single mRNA targets, many miRNAs act by targeting multiple mRNAs, some of which may reside in the same cellular pathway. Several studies have also shown that similar mRNAs are repressed by redundant distinct sequences [31]. A causal relationship has been established between miRNA expression and cancer development in mouse models using miRNA overexpression or downregulation[32,33].

4. Sample preparation techniques and analytical approaches used for mRNA analysis

mRNA analysis plays a crucial role in understanding gene expression patterns, identifying biomarkers, and studying various cellular processes. To analyze mRNA, researchers employ specific sample preparation techniques and utilize various analytical approaches. Here are some commonly used techniques and approaches in mRNA analysis:

4.1 Sample preparation technique:

a. RNA Extraction: The first step in mRNA analysis is to extract RNA from the biological sample. Total RNA extraction methods, such as phenol-chloroform extraction or column-based purification kits, are commonly employed to isolate RNA from cells or tissues [34].

b. mRNA Enrichment: Since mRNA constitutes only a small fraction of the total RNA in a sample, enrichment techniques are used to selectively isolate and enrich mRNA molecules. Poly(A) tail selection, where oligo(dT) beads are used to capture mRNA through hybridization with the poly(A) tail, is a widely employed method for mRNA enrichment [35].

c. cDNA Synthesis: Once mRNA is enriched, it needs to be reverse transcribed into complementary DNA (cDNA) for downstream analysis. Reverse transcription converts the mRNA into cDNA using reverse transcriptase and a primer, often oligo(dT) or random hexamers [36].

4.1 Analytical approaches

a. Quantitative PCR (qPCR): qPCR is a widely used technique to measure mRNA expression levels. It uses fluorescently labeled probes or DNA-binding dyes to monitor the amplification of cDNA derived from mRNA. The fluorescence signal is recorded in real-time during each amplification cycle, allowing quantification of mRNA levels [37].

b. Reverse Transcription Polymerase Chain Reaction (RT-PCR): RT-PCR is similar to qPCR but lacks real-time monitoring. It is used for qualitative or semi-quantitative analysis of mRNA expression levels. The amplified PCR products can be visualized on an agarose gel or further analyzed by techniques like Sanger sequencing [38].

c. RNA Sequencing (RNA-Seq): RNA-Seq is a high-throughput sequencing technique that enables comprehensive analysis of the entire transcriptome, including mRNA. It involves converting mRNA into a complementary DNA library, followed by sequencing using next-generation sequencing platforms. RNA-Seq provides information about gene expression levels, alternative splicing events, novel transcript discovery, and more [39].

d. Microarrays: Microarray technology allows the simultaneous analysis of thousands of mRNA molecules. The mRNA is reverse transcribed into labeled cDNA, which is then hybridized to a microarray chip containing immobilized probes representing specific mRNA sequences. The intensity of the hybridization signal indicates the abundance of mRNA in the sample [40].

e. In situ Hybridization (ISH): ISH is a technique used to visualize mRNA molecules in fixed cells or tissues. It involves the hybridization of labeled RNA or DNA probes complementary to specific mRNA sequences. The probes can be labeled with fluorophores or enzymes for detection [41].

f. Northern Blotting: Northern blotting is an older, yet reliable, technique for mRNA analysis. It involves the separation of mRNA molecules by gel electrophoresis, followed by transfer to a membrane and hybridization with labeled probes. Northern blotting provides information about mRNA size, abundance, and alternative splicing patterns [42].

5. miRNAs in the regulation of Wnt/β-Catenin pathway

The Wnt/β-catenin pathway is not only controlled by lncRNA-mediated mechanisms but also by specific miRNAs, which have direct regulatory effects. For example, scientists have discovered that miR-214 suppresses GSK-3 expression. Genes downstream of GSK-3a, such as GSK-3b, have been considerably increased, therefore promoting cell proliferation and reducing the death of GSK-3b-positive cells [43]. Additionally, miR-501-5p suppresses the expression of DKK1, NKD1, and GSK-3 [44]. Several human cancers have been associated with WNT ligands, including breast, colon, and prostate cancers [45]. In addition, Wnt1 and Wnt2 work together to trigger the Wnt/β-catenin signaling pathway [46].

In the miR-34 study, tumor suppressor depletion is linked to the activation of carcinogenic pathways. P53 is directly downstream of the Wnt and EMT genes targeted by miR-34, such as WNT1, WNT3, AXIN2, β-catenin, and LEF1. miR-34/UTR lacks p53 function, which increases Wnt activity and Snail-dependent EMT in the absence of p53. There is a decrease of miR-34 in the oncogenic pathway that affects TCF/LEF transcriptional signatures in clinical samples. These findings support a continuum model of human cancer since preserving cancer stem cell characteristics and developing the metastatic program when wt-p53 is lost or Wnt is hyper-activated [47]. One of the most common cancer-related genes, PTEN, is targeted by miR-188-5p. Wnt/β-catenin signaling is activated by miR-188-5p, which inhibits PTEN, causing metastases and a poor prognosis [48]. According to the research, miR-19 levels in GC clinical samples are consistently

lower than in normal stomach tissue. Researchers have shown MEF2D (Myocyte Enhancer Factor 2D) to be one of the targets of miR-19. High MEF2D expression enhances Wnt/β-catenin signaling and encourages cancer cell development. This study further showed that MEF2D's effects are reversed by MiR-19 [49]. Overexpression of miR381 and 489 together could reduce cell motility, invasion, and EMT by targeting cullin 4B synergistically [50]. A better knowledge of the role of miRNAs in modifying Wnt/β-catenin signaling pathways in cancer is critical to its success (Fig. 1).

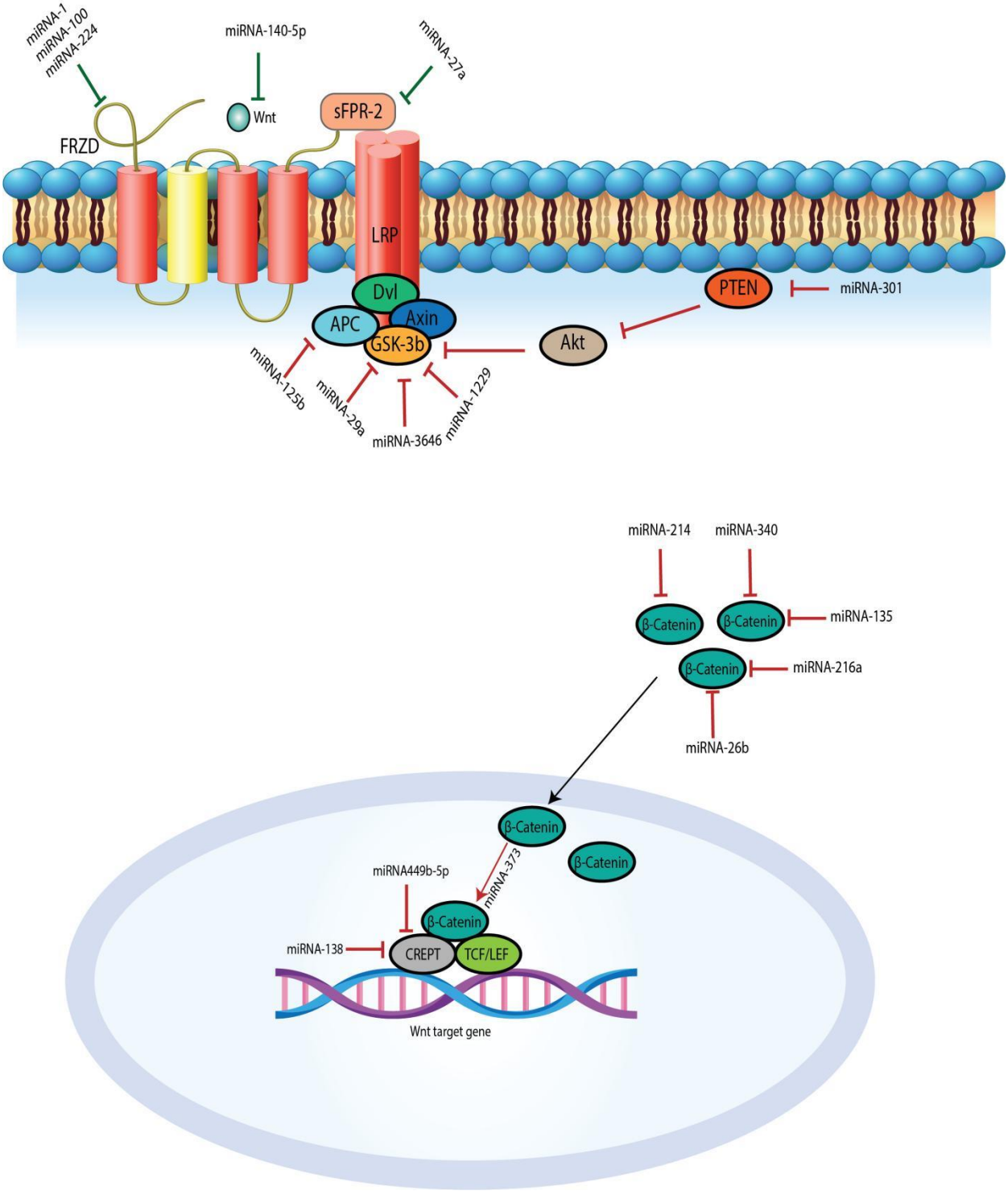

Fig. 1 Some miRNAs, including miR-1229, miR-125b, miR-3646, miR-29a, and miR-301, may be overexpressed, resulting in abnormal Wnt/β-catenin signaling. A number of tumor suppressors are targeted by these miRNAs, including GSK-3, APC, and PTEN. In breast cancer patients, Wnt signaling downstream

target genes were consistently increased, resulting in tumor growth, metastasis, and resistance to therapy. In contrast, tumor suppressor miRNAs such as miR-26b, miR-135, miR-214, miR-216a, and miR-340 are downregulated in breast cancer patients. It has been proven that these miRNAs act tumor-suppressing by inhibiting the growth of cancer cells through β-catenin. Combining these findings with previous research indicates that unregulated activation of oncogenic Wnt/β-catenin signaling is linked to poor prognosis and aggressive behavior in breast cancer patients.

6. miRNAs in the regulation of NF-kB Pathway

There are approximately 2600 miRNAs have been discovered [51]. According to current estimations, there are an estimated 45,500 miRNA-targeted sites in the human genome based on current estimations, which means that over 60% of genes are affected by miRNA regulation [52]. miRNAs are involved in cancer progression as they activate abnormally the NF-kB pathway. Increasing evidence indicates that miRNAs and their target genes play a critical role in carcinogenesis and cancer progression through the NF-kB signaling cascade. When NF-kB is bound and sequestered by IkBs in the cytoplasm, the signal-triggered breakdown of IBks drives nuclear translocation, and NF-kB is released from the IkBs. Researchers do not know how cancer cells break this negative feedback loop, which supports the production of its inhibitors, IkBs, which maintain NF-kB activity in the cytoplasm. A previous study has demonstrated that miR-30e binds the IB 3'-UTR, deactivates NF-kB hyper-activation, and triggers glioma cell invasion and angiogenesis by modulating NF-kB expression [53]. A new epigenetic mechanism that interrupts the IB-NF-kB loop is mediated by miR-30e. miR-30e has been found to suppress tumor invasion and neo-vessel creation in gliomas, providing new information for developing therapeutic interventions.

Cancer of the digestive tract, known as esophageal squamous cell carcinoma (ESCC), is highly aggressive. NF-kB signaling disorder contributes to ESCC [54]; downregulation of miR-138 in squamous cell carcinoma is linked to an increased risk of disease progression. TRAF2 (TNF receptor-associated factor 2) and RIP1 (Receptor-Interacting Protein 1) poly-ubiquitination are increased when miR-138 is inhibited, resulting in prolonged activation of NF-kB. These findings reveal a new method for ESCCs to activate NF-

kB and a possible therapeutic target [55]. The ubiquitin-proteasome system regulates NF-kB signaling by destroying IBks [56]. An unexpected feature of human cancer is abnormal ubiquitin conjugation. CYLD (conserved cylindromatosis), A20, and Cezanne deubiquitinate NF-kB [57]. Inflammatory glioma cells are more aggressive when miR-486 is present [58].

NF-kB signaling is positively influenced by ubiquitin conjugation [59]. Tumor development is stimulated by TGF-β/Smad signaling. According to Song et al., overexpression of miR-182 in gliomas directly inhibits CYLD, a negative regulator of NF-kB activation [60]. Cellular aggressiveness is increased when the components of NF-kB signaling pathways are ubiquitinated. To enhance NF-kB signaling, TGF-induced miR-182 is activated. As TGF and miR-182 are linked in clinical glioma specimens, so is the activation of nuclear factor-kB. miR-182 targets TCEAL7 (Transcription Elongation Factor A Like 7), an NF-kB negative regulator. The deletion of miR-182 slows the growth of endometrial cancer cells. NF-kB is activated in glioblastoma using a novel pathway [57].

Overexpression of miR-892 reduced tumor development, metastasis, and angiogenesis, whereas miR-892b inhibits NF-kB signaling by targeting TRAF2, TAK1, and TAB3 [61]. PPF (propofol _ effectively reduces bacterial translocation in the intestines by preserving intestinal mucosal barrier function in CRC surgery model mice. By decreasing the expression of miR-155, PPF may prevent the actuation of the NF-kB pathway, hence decreasing the production of cytokines. According to this study, PPF anesthesia during clinical CRC surgery protects the intestinal mucosa barrier [62].

NF-kB activation appears to be regulated by miRNAs in different cancers. Furthermore, the relevance of posttranscriptional control of miRNAs in modifying NF-kB signaling is underscored because these miRNAs target gene regulators in the NF-kB signaling network. Therefore, anti-cancer treatments targeting a miRNA-based regulatory system will benefit from a deeper understanding of whether this mechanism is crucial for NF-kB signaling oncogenic involvement in cancer.

According to research, increasing the expression of tumor-suppressor miRNAs and reducing NF-kB activation in cancer patients may be possible with the administration of anti-tumor medicines. As a result, it is vital to thoroughly investigate the relationship between miRNAs and NF-kB signaling in cancer (Fig. 2).

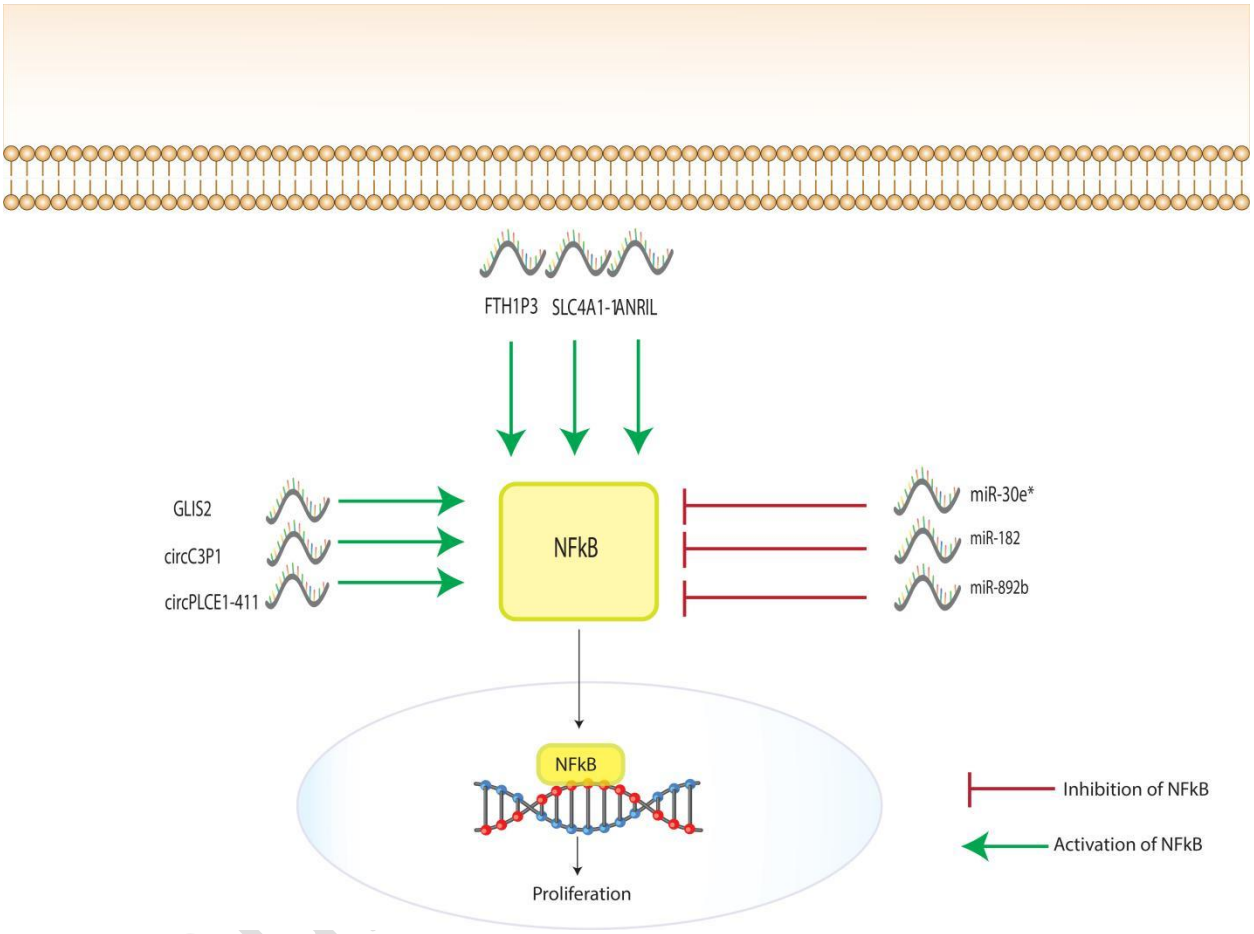

Fig. 2 In cancer, NF-kB signaling regulation via miRNAs is important. For example, GLIS2, CircC3P1, CircPLCE1-411, FTH1P3, SCL4A1, and ANRIL enhance cancer advancement by enhancing NF-kB signaling, whereas tumor-suppressing miRNAs such as miRNA30*, miRNA-182, and miRNA-892b suppress cancer progression by reducing NF-kB signaling in cancer therapy.

miRNAs in the regulation of PI3K/AKT pathway

A decrease in miR-155-5p expression was observed in Wilms' tumor (WT) patients who did not receive chemotherapy before surgery, but a higher expression was seen in those who had received chemotherapy. This miRNA inhibits PI3K/AKT/mTOR, which is linked to cell proliferation in WT tissues, which are elevated for IGF2, PI3K, AKT, and mTOR [63]. Researchers are now targeting regulatory miRNAs with specific inhibitors to reduce cancer risk. Several studies have demonstrated that tumor suppressor and oncogenic miRNAs play critical roles in cancer management because of their complicated interactions with downstream targets, suggesting that they may be used for diagnostics and prognostics (Fig.3).

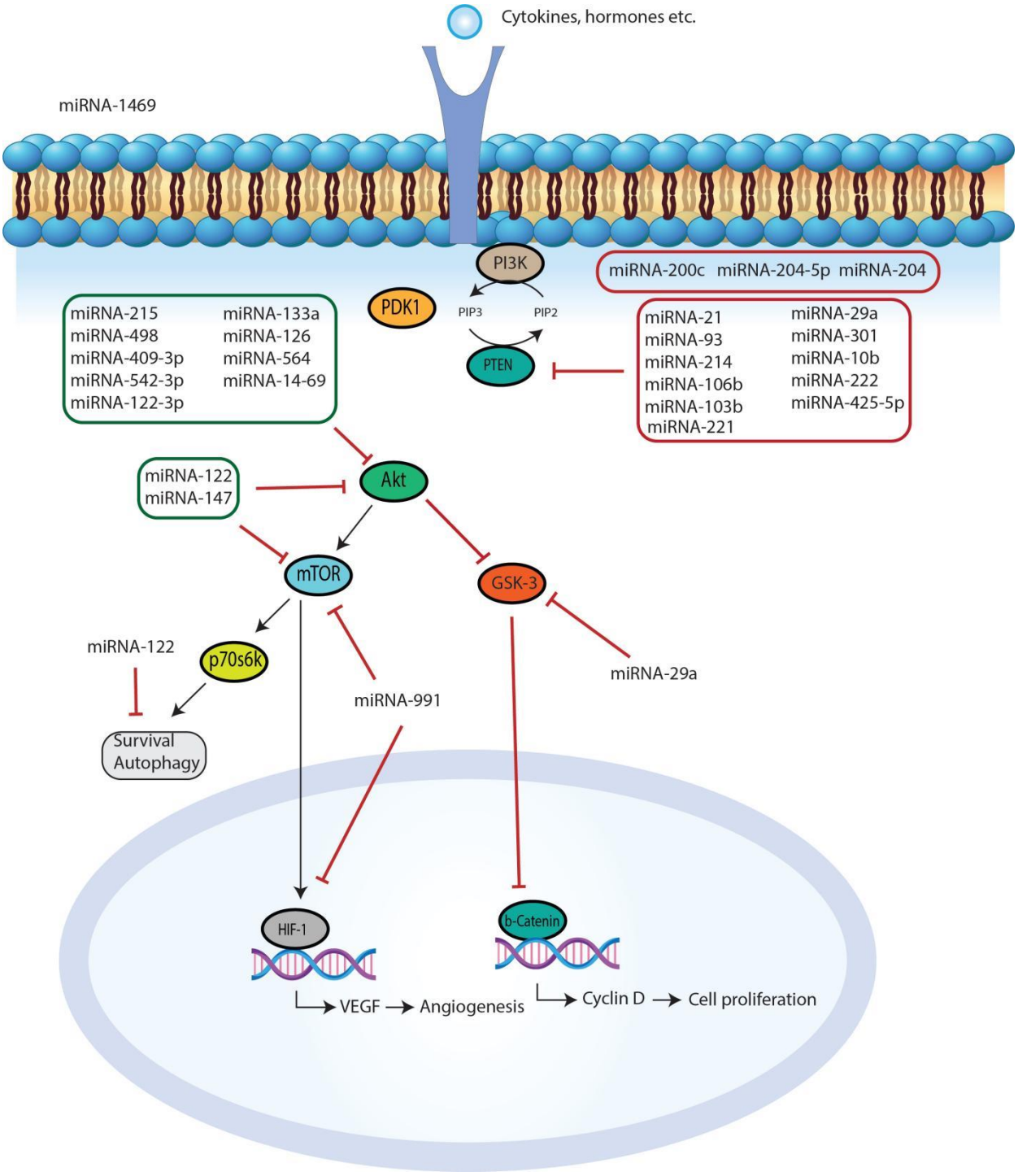

Fig. 3 The role of miRNAs in regulating PI3K/Akt pathway in cancer.

In addition, some carcinogenic miRNAs increase activity in PI3K/AKT pathways. It has been shown, for instance, that miR-182 and miR-135b are upregulated in colorectal cancer tissues compared to non-cancer

tissues. miR-182/-135b activates the PI3K/AKT pathway, which is a direct target of miR-182/-135b. A potential biomarker and treatment option for colorectal cancer patients is thus the miR-182/-135b/ST6GALNAC2/PI3K/AKT axis [64]. Colorectal cancer patients' serum specimens display lower miR-182 expression postoperatively compared to preoperatively. Those whose disease recurred had significantly higher levels of expression of this miRNA. In cancer cells, overexpression of this miRNA induces cell proliferation, colony formation, ki67 expression, and invasiveness by upregulating the expression of MMP-2 and MMP-9. Also, miR-182 inhibits the production of DAB2IP (disabled homolog 2-interacting protein) by binding to its 3' UTR. Thus, miR-182 regulates the expression of DAB2IP in colorectal cancer cells, which could activate the PI3K/Akt/mTOR and Wnt/β-catenin pathways [65]. This miRNA overexpression was associated with poor prognosis in patients with triple-negative breast neoplasms when compared with normal tissue and normal cell lines. Furthermore, miR-193 regulates the PI3K/AKT pathway and promotes cell invasion. When miR-193 is silenced, cell invasion-mediated EMT is also inhibited. [66].

miRNA in the regulation of STAT3 pathway

The expression of Bcl-2 increases cancer cell proliferation, whereas silencing the gene reduces cell death [67]. The glioma cells die and undergo autophagy because the let-7a-1 let-7d miRNA cluster inhibits STAT3. When Let-7 miRNA dual-luciferase reporters were used, they found STAT3 was a direct target. miRNA clusters act as tumor suppressors in glioma cell lines and animal models [68]. GBM invasion and migration depend on matrix metalloproteinase 2 expressions (MMP2). In terms of cancer metastasis, MMP2 is by far an essential factor [69]. miR-506's tumor suppressor activity directly targets STAT3. In glioma cells, motility and invasion and MMP2, cyclin D1, and Bcl-2 protein synthesis are inhibited by overexpression of miR-506 [70]. According to the Schrodinger PyMOL 2.3 molecular docking and visualization program, miR-181d directly links and binds to STAT3, STAT5A, and STAT7. Reducing STAT3 and STAT5A expression in GBM mice models lowers GBM cell motility, invasion, and tumor growth [71]. As a result, microRNAs can be effective in the therapy of GBM since they can target STAT3

directly. Temozolomide is often used to treat GBM multiforme, which is resistant to chemotherapy. However, the prevalence of TMZ resistance in clinical settings is increasing. Anti-drug resistance has lately been linked to the role of microRNAs (miRNAs) [72]. Tumor cells that overexpress miR-29b are more sensitive to TMZ treatment because it inhibits STAT3 production [73]. Specifically targeting the STAT3 transcription factor in GBM, miR-519a slows tumor growth. For the treatment of glioma, miR-519a enhances TMZ's efficacy in vitro and in vivo in naked mice. Tumor-free and overall survival are both reduced when miR-519a expression is low. The microglia/macrophage-mediated immune response relies heavily on STAT3 signaling [74,75]. miR-124 can inhibit glioma cell proliferation and increase cell death by targeting STAT3 in glioma cells. Using genetically modified mice that produce the STAT3 protein, miR-124 has been demonstrated to enhance the immunological response mediated by T cells [76]. STAT3 expression has been found to be inhibited by the overexpression of miRNA-143 in stomach cancer. Similar to the overexpression of miRNA-143, STAT3 silencing may suppress the development of AGS gastric cancer cells. STAT3 inhibition is required for the oncogenic effects of miRNA-143 on gastric cancer cells. miRNA-143 may be a primary target for treating GC [77]. miR-124-3p inhibited STAT3 activity in tumor-infiltrating immune cells, increasing cervical cancer progression. By inhibiting STAT3 signaling, microRNA-29a reduces cell growth and motility in laryngeal squamous cell carcinoma cells. This study's findings will aid in developing new cancer treatments for laryngeal squamous cell carcinoma (LSCC) [78]. PDL1 expression in CRC cells could be reduced by miR124, which could lead to a T cell-mediated anti-cancer response. The miR124 lowered STAT3 activity and its downstream pathways in CRC cells, suggesting a tumor-suppressive role in the illness [79]. The tumor suppressor miR-125b is involved in the growth and progression of CSCC cancers. By blocking the STAT3 pathway, this drug slows down the growth of cells as well as the advancement of the cell cycle [80]. In gastric cancer tissues, QRT-PCR showed a negative correlation between the expression of PD-L1 and miR-375. According to luciferase reporter tests, microRNA-375 can bind to the JAK2 (Janus Kinase 2) gene's 3′-UTR regions [81]. It's possible that miR-124 might be used as a unique target in the development of PD-L1-mediated immune response evasion strategies because blocking PD-L1 may improve the efficacy of CRC therapy.

STAT3 function is said to depend on p-STAT3. p-STAT3's nuclear entrance regulates gene transcription. It is inhibited when STAT3 is activated by the SOCS (Suppressor of cytokines signaling) and PIAS families of negative regulators. To inhibit JAK from phosphorylating STAT3, SOCS3 has an SH2 domain that can connect to STAT3's active area. SOCS3 binds to JAKs and blocks STAT3 phosphorylation [82]. miR-221 and miR-222 are oncogenes that are expressed in gliomas. However, their expression is restricted. Phosphorylation of p-STAT3 is increased due to the miR-221/222 cluster's targeting of SOCS3 [83]. GBM has also been linked to the oncogene miR-30. By targeting SOCS3, miR-30 can also induce cancer by increasing p-STAT3 protein expression [84]. To suppress the DNA binding activity of STAT3, PIAS3 attaches to the inactive STAT3 homodimer or heterodimer [85]. GSCs (glioblastoma stem cells) express miR-125b at a very high level. An inhibitor of miR-125b, which targeted PIAS3, inhibited STAT3 transcriptional activity, resulting in decreased MMP2 and MMP9 production in GSCs [86]. STAT3, SOCS3, and PIAS3 are activated by miRNAs, affecting the growth factor/cytokine receptors. Cell proliferation, development, adhesion, migration, angiogenesis, and prognosis are all affected by connective tissue growth factor (CTGF) [87]. Human glioma tissue and glioma cells express low tumor suppressor gene miRNA-133a. It binds CTGF and regulates the JAK/STAT signaling pathways as a tumor suppressor gene [88]. The TGF-beta oncogene only stimulates the Jak/Stat3 pathway when the Smad signaling pathway is present. Smad4 and the transcription factor are targets of miR-124, limiting cell proliferation by regulating STAT3 and pSTAT3 protein levels [89]. STAT3 activation is suppressed by CADM1's interactions with HER2 and Itga6b4. CADM1 gene expression and STAT3 pathway activity are controlled by miR-148a [90]. The STAT3 signaling pathway is not the only one that miRNAs can target. Kinesin superfamily 6 member 20A (KIF20A) members have been discovered to be associated with tumor genesis and progression [91]. According to functional investigations, cell proliferation, migration, and invasion are all inhibited by miR-876-3p. miR-876-3p inhibits JAK2/STAT3 signaling in naked mice by inhibiting KIF20A [92]. Intracellular communication is maintained by exosomes, including microRNAs, LNC, and other RNAs [93]. According to a new study, GBM patients' blood and CSF have higher levels of miR-1246 than individuals with low-grade glioma. It has been found that the production of miR-1246 from H-GDE

has accelerated glioma growth in both in-vivo and in-vitro. miR-1246 decreased TERF2IP expression in macrophages, activated the STAT3 signaling pathway, and reduced the NF-kB response. H-GDE miR-1246 is essential for the polarization of macrophages into M2 [94]. One of the most common types of GBM is proneural; the other two are neural and classical. Proneural GBM is the most common type of GBM [95]. GBM's current health is maintained in part by miRNAs. FZD6 and ALDH1A3 can be suppressed in prostate cancer patients by Wnt/β-catenin signaling, which results in the production of miR-125b and miR-20b.

It is becoming more and more common to see non-coding RNAs linked to a wide variety of cancers. Glioblastoma's non-coding RNAs (ncRNAs) are expected to become diagnostic and prognostic indicators and therapeutic targets. The expression and actuation of STAT3 in gliomas are also linked to the development and progression of the tumor. It's a given that STAT3, as a transcription factor, affects ncRNA formation somehow. Using the ceRNA pathway, CASC9 and miR155HG increase STAT3, and STAT3 appears to be a transcription factor in glioma cells to encourage the synthesis of CASC9 and miR155HG. Molecule expression is boosted by a positive feedback molecule. Stable STAT3 can boost the expression of cancer-causing microRNAs such as miR-182-5p, 21, and 30b-3p.

Additionally, STAT3 can block the tumor suppressor miR-218. The most typical function of a miRNA is to attach to the 3′-UTR of a target mRNA and inhibit translation. STAT3-related genes (PIAS3, SOCS3) and STAT3 upstream genes can be targeted by miRNAs in glioma, as can STAT3 mRNA. Specific miRNAs can influence STAT3 expression and activation. However, the method by which they do so is unknown. miRNAs can affect gene expression in several ways, including epigenetic regulation, transcription, and posttranscriptional regulation. Many studies, however, have concentrated on miRNAs that influence the STAT3 pathway (Fig.4).

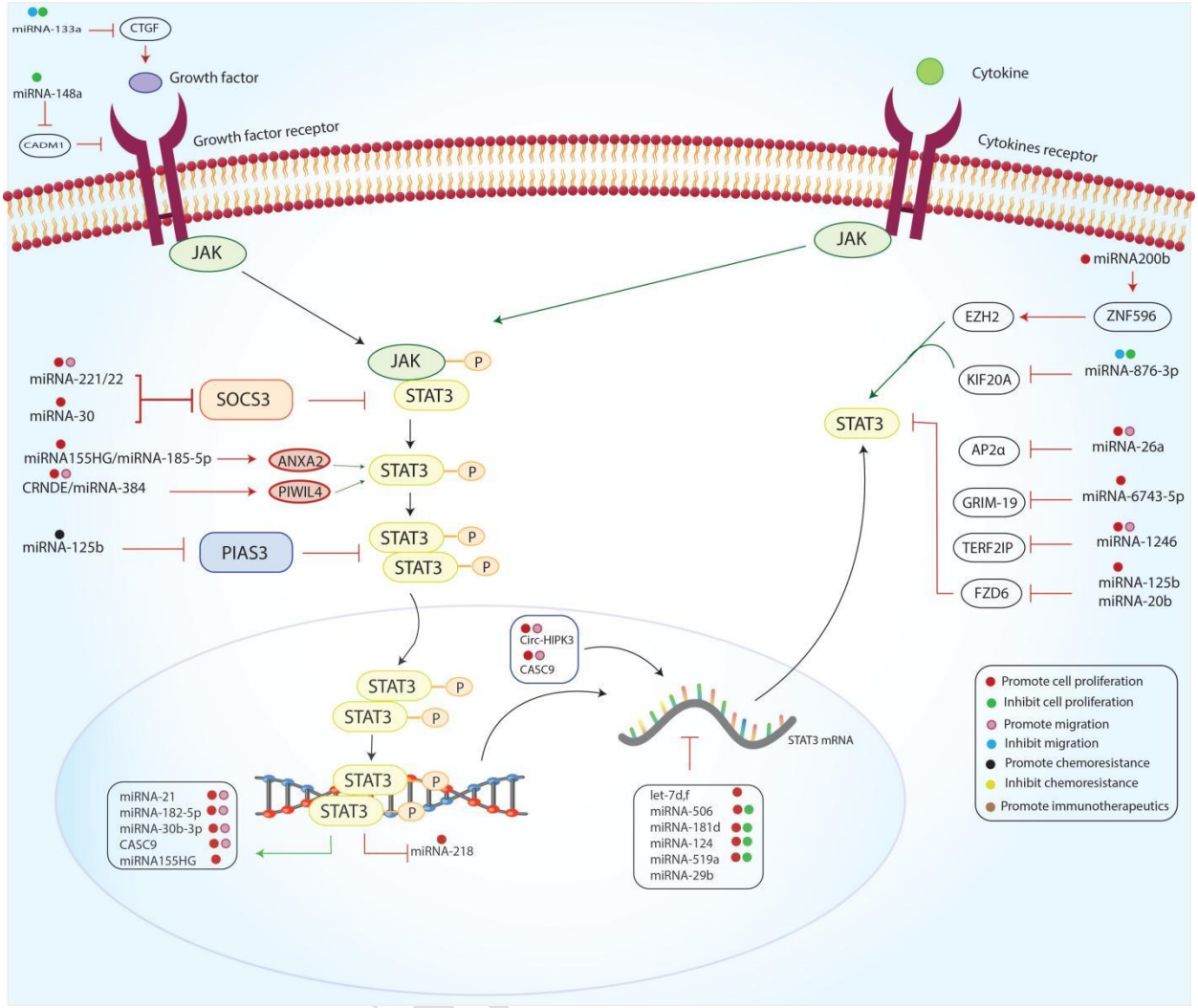

Fig. 4 miRNAs associated with gliomas and linked to the STAT3 pathway. miRNAs and their targets in the STAT3 signaling pathway are thought to regulate the formation and development of glioma. Growth factors and cytokines, can activate STAT3 in gliomas. By binding to their respective receptors, cytokines and growth factors can phosphorylate JAK. To perform its function as a transcription factor, STAT3 needs to be activated by JAKs, where it can make homodimers or heterodimers. miRNAs can influence the expression and activation of STAT3, or miRNAs can influence STAT3.

miRNAs in the regulation of p53 Signaling Pathway

According to a number of recent studies, miRNAs play an essential role in the tight regulation of TP53 by interacting directly with its 3' UTR. Thus, these miRNAs may function as clinically important oncogenes

by acting upstream of TP53. The miR125b seed region binds to TP53 and inhibits apoptosis; inhibiting miR125b had the opposite effect [96]. In addition to PUMA (p53 upregulated modulator of apoptosis) and IGFBP3, miR125 targets other components of the p53 network, which are conserved in humans, mice, and zebrafish [97]. A higher expression of miR125b was linked to larger tumors, invasion, a poorer prognosis, and shorter survival in 89 colorectal cancer samples [98]. In human B cell precursor acute lymphoblastic leukemia (BCP-ALL), a chromosomal translocation permanently activates the mir125b gene, and animals with this gene under the control of an E-enhancer develop deadly B cell malignancies [99]. miR125b is known to negatively regulate the p53 pathway, which is in accordance with these findings. However, miR125b has been shown to suppress breast cancer growth. Perhaps this is another example of miRNAs' context-dependent function [100].

There have been several reports of miRNAs indirectly regulating p53 via downregulation of its upstream regulators. For example, SIRT1 (Sirtuin 1) was downregulated by miR34a, resulting in an increase in p53 activity, increased expression of its targets p21 and PUMA, and increased apoptosis [101]. A positive feedback loop forms between miR34a, SIRT1, and p53 due to miR34a being induced by p53. The self-activating loop in tumors may be broken by CpG methylation of mir34 genes and/or mutation of p53. Because miR200a has been proven to target SIRT1 expression [102], this induction of p53 may increase the feedback. For p53, miR34, and YY1, a miR34 target that adversely controls p53 by promoting MDM2 (murine double minute 2) ubiquitylation, a feedback loop is possible [103,104]. Both the oncogene and tumor suppressor miRNAs are represented in fig. 5, which directly or indirectly target p53 to promote or inhibit cancer progression.

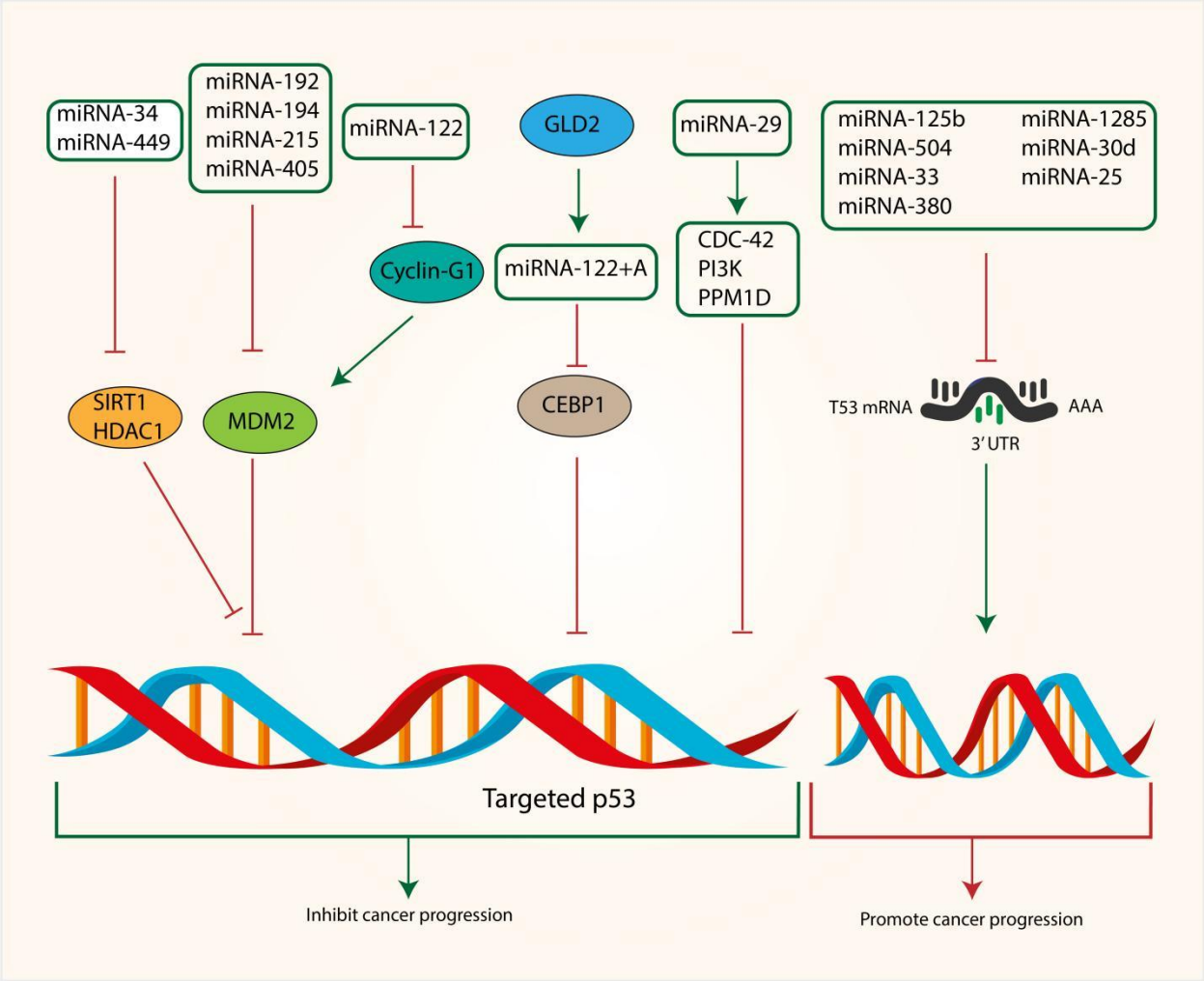

Fig. 5 The figure shows microRNA-mediated regulation of TP53's 3 untranslated regions (UTR) and miRNA-mediated downregulation of p53modifying enzymes. Some miRNAs match seed sequences in TP53's 3 UTR or miRNAs that inhibit the expression of tumor suppressors. By adding single adenosine (miR122+A in the picture), the poly(A) polymerase GLD2 can stabilize the miR122 microRNA. The adenylated miR122, in conjunction with the RNA-induced silencing complex (RISC), downregulates the expression of cytoplasmic polyadenylation element binding protein 1 (CEBP1) by binding target sites in the 3 UTR. When CEBP1 is downregulated, GLD4 poly(A) polymerase is not recruited to the 3 UTR of TP53, resulting in reduced p53 expression.

miRNAs in the regulation of Hedgehog pathway

Abnormalities in tumor stem cells' genes are common in malignant tumors; these mutations allow the tumor stem cells to grow unchecked. Skin cancer, GC, PC, BC, lung cancer, acute myeloid leukemia, and pancreatic cancer have all been connected to the Hh signaling system [105]. Tumorigenic effects of Hedgehog signaling are inhibited in HCC by contending with miR-132 for attachment to sonic hedgehog protein by TUG1 (taurine-upregulated gene 1), a competitive endogenous RNA [106]. Overexpression of miR205HG reduced cell proliferation and cell cycle progression of cells from the EAC (esophageal adenocarcinoma), which were found to be downregulated compared to cells from the NE. In mice, overexpression of miR205HG slowed the growth of xenograft tumors. Hh signaling is inhibited by miR205HG in EAC and BE tissues ($r = 0.73$), and in vitro studies showed the details of this inhibition. As part of the Hh pathway, miR205HG works as a tumor suppressor to develop both BE and EAC [107]. Among described miRNAs in MB etiology, the miR-17-92 cluster, also known as Oncomir-1, has been extensively studied for its potential role in modulating this oncogenic pathway. miR-17, miR-19a, miR-20, and miR-92, which comprise the Oncomir-1 cluster, cause increased SHH pathway activity, leading to tumorigenic consequences in MB formation, including tumorigenic consequences and Myc activation (Fig. 6).

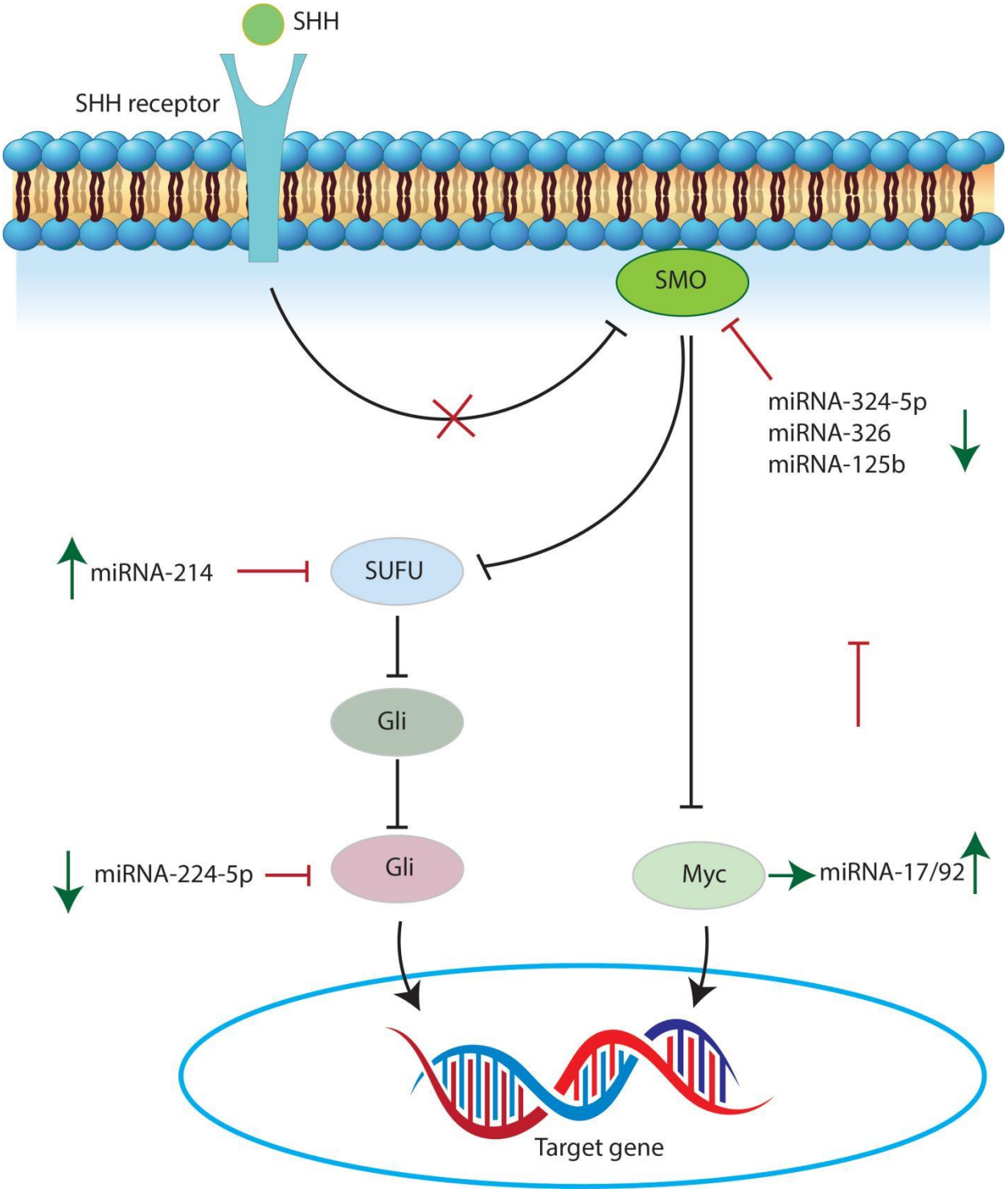

Fig. 6 In response to SHH binding to its receptor, Smoothened (Smo) is unrepressed, allowing Gli proteins to translocate to the nucleus and block SUFU repression on those proteins. A second pathway through which SHH signaling promotes proliferation is via Smo-induced upregulation of N-Myc. The deregulation

of multiple miRNAs supports the active status of this oncogenic pathway: the loss of miR-324-5p, 326, and 125b causes an increase in Smo and Gli expression. In addition, increased miR-214 expression may suppress SUFU inhibition of Gli proteins. N-Myc is upregulated when Oncomir-1, which is part of the oncogenic miR-17/92 cluster, is downregulated.

Conclusion

Understanding the role of miRNAs in cancer signaling will inspire novel research, diagnosis, and treatment avenues. Early detection of cancer patients is greatly facilitated by the aberrant expression of miRNAs, which varies as the disease advances. For example, with prostate cancer antigen 3, researchers have found that it is highly specific and sensitive in detecting prostate cancer. In addition, miRNAs could be useful therapeutic targets. Multiple techniques can be used to target the many functions of miRNAs, which can be regulated through the spatial blockage, genome editing, or inhibition of RNA-protein interactions. miRNAs can also be prevented from acting by preventing secondary structures from forming. A few years ago, researchers began considering miRNAs as cancer treatment targets. The use of miRNAs as potential targets for cancer detection and treatment holds great promise for the future of cancer care. However, utilizing miRNAs as possible therapeutic targets and biomarkers has various drawbacks. Thanks to the rapid development of biochemical tools and technological advancements in this field, it's still possible to identify new miRNA molecules. However, the rapid identification of new miRNAs offers additional problems for their definition and annotation, requiring more complete transcriptome investigations and transcription assembly. In addition, miRNAs are still challenging to study because of the intricacy and diversity of their interactions with cancer cell activities. We hope this research will help us better understand miRNAs and give us new tumor indicators that may be used in the clinical diagnosis of cancer and the prognosis of the disease.

Moreover, experimental investigations in the field of mRNA analysis aim to achieve several objectives. Researchers seek to study gene expression patterns to identify genes that are upregulated or downregulated in response to stimuli or diseases. They also aim to discover mRNA-based biomarkers for diagnostic or

prognostic purposes by comparing mRNA expression profiles between healthy and diseased individuals. Investigating alternative splicing patterns helps uncover novel splice variants and understand their roles in cellular processes and diseases. Additionally, researchers strive to comprehensively characterize the transcriptome by identifying, quantifying, and understanding the functional relevance of different mRNA transcripts. Furthermore, mRNA analysis assists in gaining insights into cellular pathways and signaling networks, elucidating the underlying mechanisms involved in various biological processes, including development, disease progression, and drug response.

Future perspectives

Future perspectives in the field of MicroRNAs (miRNAs) regulating the Wnt/β-Catenin, NF-kB, PI3K/AKT, STAT3, p53, and Hedgehog pathways hold great promise for advancing our understanding of cellular signaling and its implications in various diseases. To further our knowledge, future research should focus on identifying novel miRNA targets within these pathways using advanced computational methods and experimental techniques. Additionally, functional validation of miRNA pathway crosstalk is crucial to unravel the intricate interplay between miRNAs and these signaling pathways. Investigating the role of miRNAs in disease pathogenesis related to these pathways, such as cancer and neurodegenerative disorders, will provide valuable insights and may lead to the discovery of novel therapeutic targets. Furthermore, the development of miRNA-based therapies, exploring non-coding RNA interactions, and understanding their impact on pathway regulation are areas that hold significant potential for future exploration. These future perspectives aim to shed light on the regulatory mechanisms governed by miRNAs, expand our knowledge of disease mechanisms, and potentially open new avenues for therapeutic interventions.

Conflict of interest

There is no competing interest to declare.

References

1 Ming H, Li B, Zhou L, Goel A, Huang C. Long non-coding rnas and cancer metastasis: Molecular basis and therapeutic implications. Biochimica et Biophysica Acta (BBA)-Reviews on Cancer 2021;1875:188519.
2 Hanahan D. Hallmarks of cancer: New dimensions. Cancer Discovery 2022;12:31-46.
3 Tensen CP, Quint KD, Vermeer MH. Genetic and epigenetic insights into cutaneous t-cell lymphoma. Blood, The Journal of the American Society of Hematology 2022;139:15-33.
4 Pei Y, Zhang H, Lu K, Tang X, Li J, Zhang E, Zhang J, Huang Y, Yang Z, Lu Z. Circular rna circrna_0067934 promotes glioma development by modulating the microrna mir-7/wnt/β-catenin axis. Bioengineered 2022;13:5792-5802.
5 Kim SL, Shin MW, Seo SY, Kim SW. Lipocalin 2 potentially contributes to tumorigenesis from colitis via il-6/stat3/nf-kb signaling pathway. Bioscience Reports 2022
6 Ko E-B, Jang Y-G, Kim C-W, Go R-E, Lee HK, Choi K-C. Gallic acid hindered lung cancer progression by inducing cell cycle arrest and apoptosis in a549 lung cancer cells via pi3k/akt pathway. Biomolecules & Therapeutics 2022;30:151.
7 Lu X, An L, Fan G, Zang L, Huang W, Li J, Liu J, Ge W, Huang Y, Xu J. Egfr signaling promotes nuclear translocation of plasma membrane protein tspan8 to enhance tumor progression via stat3-mediated transcription. Cell Research 2022;32:359-374.
8 Ou A, Zhao X, Lu Z. The potential roles of p53 signaling reactivation in pancreatic cancer therapy. Biochimica et Biophysica Acta (BBA)-Reviews on Cancer 2022;1877:188662.
9 Zhu Y, Peng X, Zhou Q, Tan L, Zhang C, Lin S, Long M. Mettl3-mediated m6a modification of steap2 mrna inhibits papillary thyroid cancer progress by blocking the hedgehog signaling pathway and epithelial-to-mesenchymal transition. Cell death & disease 2022;13:1-11.
10 García-Padilla C, Dueñas Á, García-López V, Aránega A, Franco D, Garcia-Martínez V, López-Sánchez C. Molecular mechanisms of lncrnas in the dependent regulation of cancer and their potential therapeutic use. International Journal of Molecular Sciences 2022;23:764.
11 Arghiani N, Shah K. Modulating micrornas in cancer: Next-generation therapies. Cancer Biology & Medicine 2022;19:289.
12 Sanchez Calle A, Kawamura Y, Yamamoto Y, Takeshita F, Ochiya T. Emerging roles of long non-coding rna in cancer. Cancer science 2018;109:2093-2100.
13 Bhan A, Soleimani M, Mandal SS. Long noncoding rna and cancer: A new paradigm. Cancer research 2017;77:3965-3981.
14 Alexovič M, Lindner JR, Bober P, Longuespée R, Sabo J, Davalieva K. Human peripheral blood mononuclear cells: A review of recent proteomic applications. Proteomics 2022;22:2200026.
15 Calin GA, Dumitru CD, Shimizu M, Bichi R, Zupo S, Noch E, Aldler H, Rattan S, Keating M, Rai K. Frequent deletions and down-regulation of micro-rna genes mir15 and mir16 at 13q14 in chronic lymphocytic leukemia. Proceedings of the national academy of sciences 2002;99:15524-15529.
16 Witek Ł, Janikowski T, Gabriel I, Bodzek P, Olejek A. Analysis of microrna regulating cell cycle-related tumor suppressor genes in endometrial cancer patients. Human Cell 2021;34:564-569.
17 Liu X, Ma R, Yi B, Riker AI, Xi Y. Micrornas are involved in the development and progression of gastric cancer. Acta Pharmacologica Sinica 2021;42:1018-1026.
18 Zhang M, Du X. Noncoding rnas in gastric cancer: Research progress and prospects. World J Gastroenterol 2016;22:6610-6618.
19 Xu X, Zhang M, Xu F, Jiang S. Wnt signaling in breast cancer: Biological mechanisms, challenges and opportunities. Molecular Cancer 2020;19:1-35.

20 Flores-Hernández E, Velázquez DM, Castañeda-Patlán MC, Fuentes-García G, Fonseca-Camarillo G, Yamamoto-Furusho JK, Romero-Avila MT, García-Sáinz JA, Robles-Flores M. Canonical and non-canonical wnt signaling are simultaneously activated by wnts in colon cancer cells. Cellular signalling 2020;72:109636.
21 He S, Tang S. Wnt/β-catenin signaling in the development of liver cancers. Biomedicine & Pharmacotherapy 2020;132:110851.
22 Koushyar S, Powell AG, Vincan E, Phesse TJ. Targeting wnt signaling for the treatment of gastric cancer. International Journal of Molecular Sciences 2020;21:3927.
23 Denli AM, Tops BB, Plasterk RH, Ketting RF, Hannon GJ. Processing of primary micrornas by the microprocessor complex. Nature 2004;432:231-235.
24 Lee Y, Ahn C, Han J, Choi H, Kim J, Yim J, Lee J, Provost P, Rådmark O, Kim S. The nuclear rnase iii drosha initiates microrna processing. Nature 2003;425:415-419.
25 Bohnsack MT, Czaplinski K, Görlich D. Exportin 5 is a rangtp-dependent dsrna-binding protein that mediates nuclear export of pre-mirnas. Rna 2004;10:185-191.
26 Bartel DP. Micrornas: Genomics, biogenesis, mechanism, and function. cell 2004;116:281-297.
27 Ørom UA, Nielsen FC, Lund AH. Microrna-10a binds the 5′ utr of ribosomal protein mrnas and enhances their translation. Molecular cell 2008;30:460-471.
28 Qin W, Shi Y, Zhao B, Yao C, Jin L, Ma J, Jin Y. Mir-24 regulates apoptosis by targeting the open reading frame (orf) region of faf1 in cancer cells. PloS one 2010;5:e9429.
29 Cummins J, Velculescu V. Implications of micro-rna profiling for cancer diagnosis. Oncogene 2006;25:6220-6227.
30 Takamizawa J, Konishi H, Yanagisawa K, Tomida S, Osada H, Endoh H, Harano T, Yatabe Y, Nagino M, Nimura Y. Reduced expression of the let-7 micrornas in human lung cancers in association with shortened postoperative survival. Cancer research 2004;64:3753-3756.
31 Tsang JS, Ebert MS, van Oudenaarden A. Genome-wide dissection of microrna functions and cotargeting networks using gene set signatures. Molecular cell 2010;38:140-153.
32 Iorio MV, Croce CM. Microrna dysregulation in cancer: Diagnostics, monitoring and therapeutics. A comprehensive review. EMBO molecular medicine 2012;4:143-159.
33 Izumchenko E, Chang X, Michailidi C, Kagohara L, Ravi R, Paz K, Brait M, Hoque MO, Ling S, Bedi A. The tgfβ–mir200–mig6 pathway orchestrates the emt-associated kinase switch that induces resistance to egfr inhibitors. Cancer research 2014;74:3995-4005.
34 Brown RA, Epis MR, Horsham JL, Kabir TD, Richardson KL, Leedman PJ. Total rna extraction from tissues for microrna and target gene expression analysis: Not all kits are created equal. BMC biotechnology 2018;18:1-11.
35 Qing T, Yu Y, Du T, Shi L. Mrna enrichment protocols determine the quantification characteristics of external rna spike-in controls in rna-seq studies. Science China life sciences 2013;56:134-142.
36 Peterson SM, Freeman JL. Rna isolation from embryonic zebrafish and cdna synthesis for gene expression analysis. JoVE (Journal of Visualized Experiments) 2009:e1470.
37 VanGuilder HD, Vrana KE, Freeman WM. Twenty-five years of quantitative pcr for gene expression analysis. Biotechniques 2008;44:619-626.
38 Rio DC. Reverse transcription–polymerase chain reaction. Cold Spring Harbor Protocols 2014;2014:pdb. prot080887.
39 Ozsolak F, Milos PM. Rna sequencing: Advances, challenges and opportunities. Nature reviews genetics 2011;12:87-98.
40 Sealfon SC, Chu TT. Rna and DNA microarrays. Biological Microarrays: Methods and Protocols 2011:3-34.
41 Lehmann R, Tautz D. In situ hybridization to rna. Methods in cell biology 1994;44:575-598.

42 Koscianska E, Starega-Roslan J, Sznajder LJ, Olejniczak M, Galka-Marciniak P, Krzyzosiak WJ. Northern blotting analysis of microrna, their precursors and rna interference triggers. BMC molecular biology 2011;12:1-7.
43 Li HL, Liang S, Cui JH, Han GY. Targeting of gsk-3β by mir-214 to facilitate gastric cancer cell proliferation and decrease of cell apoptosis. Eur Rev Med Pharmacol Sci 2018;22:127-134.
44 Fan D, Ren B, Yang X, Liu J, Zhang Z. Upregulation of mir-501-5p activates the wnt/β-catenin signaling pathway and enhances stem cell-like phenotype in gastric cancer. J Exp Clin Cancer Res 2016;35:177.
45 Willert K, Nusse R. Wnt proteins. Cold Spring Harb Perspect Biol 2012;4:a007864.
46 Alok A, Lei Z, Jagannathan NS, Kaur S, Harmston N, Rozen SG, Tucker-Kellogg L, Virshup DM. Wnt proteins synergize to activate β-catenin signaling. J Cell Sci 2017;130:1532-1544.
47 Cha YH, Kim NH, Park C, Lee I, Kim HS, Yook JI. Mirna-34 intrinsically links p53 tumor suppressor and wnt signaling. Cell cycle 2012;11:1273-1281.
48 Li Y, Yan X, Shi J, He Y, Xu J, Lin L, Chen W, Lin X, Lin X. Aberrantly expressed mir-188-5p promotes gastric cancer metastasis by activating wnt/β-catenin signaling. BMC Cancer 2019;19:505.
49 Xu K, Zhao YC. Mef2d/wnt/β-catenin pathway regulates the proliferation of gastric cancer cells and is regulated by microrna-19. Tumour Biol 2016;37:9059-9069.
50 Fang Z, Zhong M, Wang Y, Yuan X, Guo H, Yao Y, Feng M, Chen J, Xiong J, Xiang X. Mir-381 and mir-489 suppress cell proliferation and invasion by targeting cul4b via the wnt/β-catenin pathway in gastric cancer. Int J Oncol 2019;54:733-743.
51 Plotnikova O, Baranova A, Skoblov M. Comprehensive analysis of human microrna–mrna interactome. Frontiers in genetics 2019:933.
52 Niu T, Liu N, Zhao M, Xie G, Zhang L, Li J, Pei Y-F, Shen H, Fu X, He H. Identification of a novel fgfrl1 microrna target site polymorphism for bone mineral density in meta-analyses of genome-wide association studies. Human molecular genetics 2015;24:4710-4727.
53 Jiang L, Lin C, Song L, Wu J, Chen B, Ying Z, Fang L, Yan X, He M, Li J. Microrna-30e* promotes human glioma cell invasiveness in an orthotopic xenotransplantation model by disrupting the nf-κb/iκbα negative feedback loop. The Journal of clinical investigation 2012;122:33-47.
54 Guo Z, Pan F, Peng L, Tian S, Jiao J, Liao L, Lu C, Zhai G, Wu Z, Dong H. Systematic proteome and lysine succinylome analysis reveals enhanced cell migration by hyposuccinylation in esophageal squamous cell carcinoma. Molecular & Cellular Proteomics 2021;20
55 Gong H, Song L, Lin C, Liu A, Lin X, Wu J, Li M, Li J. Downregulation of mir-138 sustains nf-κb activation and promotes lipid raft formation in esophageal squamous cell carcinoma. Clinical Cancer Research 2013;19:1083-1093.
56 Hu X, Wu X. Ubiquitin proteasome system regulates biological particles interaction in particle disease (pd) via nf-kb signaling. Journal of Cellular Signaling 2020;1
57 Wertz IE, Dixit VM. Signaling to nf-κb: Regulation by ubiquitination. Cold Spring Harbor perspectives in biology 2010;2:a003350.
58 Song L, Lin C, Gong H, Wang C, Liu L, Wu J, Tao S, Hu B, Cheng S-Y, Li M. Mir-486 sustains nf-κb activity by disrupting multiple nf-κb-negative feedback loops. Cell research 2013;23:274-289.
59 Iwai K, Fujita H, Sasaki Y. Linear ubiquitin chains: Nf-κb signalling, cell death and beyond. Nature reviews Molecular cell biology 2014;15:503-508.
60 Song L, Liu L, Wu Z, Li Y, Ying Z, Lin C, Wu J, Hu B, Cheng S-Y, Li M. Tgf-β induces mir-182 to sustain nf-κb activation in glioma subsets. The Journal of clinical investigation 2012;122:3563-3578.
61 Wang X, Wang H, Zhang X, Bi C, McKeithan TW, Huang X, Meng B, Chan WC, Vose JM, Zhang H. Mir-17~ 92 promotes progression of abc-dlbcl lymphoma via regulation of canonical nf-kb signaling. 2021

62 Gao Y, Han T, Han C, Sun H, Yang X, Zhang D, Ni X. Propofol regulates the tlr4/nf-κb pathway through mirna-155 to protect colorectal cancer intestinal barrier. Inflammation 2021:1-13.
63 Luo X, Dong J, He X, Shen L, Long C, Liu F, Liu X, Lin T, He D, Wei G. Mir-155-5p exerts tumor-suppressing functions in wilms tumor by targeting igf2 via the pi3k signaling pathway. Biomedicine & Pharmacotherapy 2020;125:109880.
64 Jia L, Luo S, Ren X, Li Y, Hu J, Liu B, Zhao L, Shan Y, Zhou H. Mir-182 and mir-135b mediate the tumorigenesis and invasiveness of colorectal cancer cells via targeting st6galnac2 and pi3k/akt pathway. Digestive diseases and sciences 2017;62:3447-3459.
65 Li X, Zhang X, Zhang Q, Lin R. Mir-182 contributes to cell proliferation, invasion and tumor growth in colorectal cancer by targeting dab2ip. The international journal of biochemistry & cell biology 2019;111:27-36.
66 Xu J, Zhao J, Jiang M, Yang L, Sun M, Wang H. Mir-193 promotes cell proliferation and invasion by ing5/pi3k/akt pathway of triple-negative breast cancer. Eur Rev Med Pharmacol Sci 2020;24:3122-3129.
67 Siddiqui WA, Ahad A, Ahsan H. The mystery of bcl2 family: Bcl-2 proteins and apoptosis: An update. Arch Toxicol 2015;89:289-317.
68 Yang ZY, Wang Y, Liu Q, Wu M. Microrna cluster mc-let-7a-1~let-7d promotes autophagy and apoptosis of glioma cells by down-regulating stat3. CNS Neurosci Ther 2020;26:319-331.
69 Yu-Ju Wu C, Chen C-H, Lin C-Y, Feng L-Y, Lin Y-C, Wei K-C, Huang C-Y, Fang J-Y, Chen P-Y. Ccl5 of glioma-associated microglia/macrophages regulates glioma migration and invasion via calcium-dependent matrix metalloproteinase 2. Neuro-oncology 2020;22:253-266.
70 Peng T, Zhou L, Zuo L, Luan Y. Mir-506 functions as a tumor suppressor in glioma by targeting stat3. Oncol Rep 2016;35:1057-1064.
71 Liu H-W, Lee PM, Bamodu OA, Su Y-K, Fong I-H, Yeh C-T, Chien M-H, Kan I, Lin C-M. Enhanced hsa-mir-181d/p-stat3 and hsa-mir-181d/p-stat5a ratios mediate the anticancer effect of garcinol in stat3/5a-addicted glioblastoma. Cancers 2019;11:1888.
72 Choi S, Yu Y, Grimmer MR, Wahl M, Chang SM, Costello JF. Temozolomide-associated hypermutation in gliomas. Neuro Oncol 2018;20:1300-1309.
73 Xu JX, Yang Y, Zhang X, Luan XP. Microrna-29b promotes cell sensitivity to temozolomide by targeting stat3 in glioma. Eur Rev Med Pharmacol Sci 2020;24:1922-1931.
74 Hong L, Ya-Wei L, Hai W, Qiang Z, Jun-Jie L, Huang A, Song-Tao Q, Yun-Tao L. Mir-519a functions as a tumor suppressor in glioma by targeting the oncogenic stat3 pathway. J Neurooncol 2016;128:35-45.
75 Li H, Chen L, Li JJ, Zhou Q, Huang A, Liu WW, Wang K, Gao L, Qi ST, Lu YT. Mir-519a enhances chemosensitivity and promotes autophagy in glioblastoma by targeting stat3/bcl2 signaling pathway. J Hematol Oncol 2018;11:70.
76 Wei J, Wang F, Kong LY, Xu S, Doucette T, Ferguson SD, Yang Y, McEnery K, Jethwa K, Gjyshi O, Qiao W, Levine NB, Lang FF, Rao G, Fuller GN, Calin GA, Heimberger AB. Mir-124 inhibits stat3 signaling to enhance t cell-mediated immune clearance of glioma. Cancer Res 2013;73:3913-3926.
77 Wu Y, Wan X, Zhao X, Song Z, Xu Z, Tao Y, Sun C. Microrna-143 suppresses the proliferation and metastasis of human gastric cancer cells via modulation of stat3 expression. American journal of translational research 2020;12:867.
78 Liu Y-B, Wang Y, Zhang M-D, Yue W, Sun C-N. Microrna-29a functions as a tumor suppressor through targeting stat3 in laryngeal squamous cell carcinoma. Experimental and Molecular Pathology 2020;116:104521.
79 Roshani Asl E, Rasmi Y, Baradaran B. Microrna-124-3p suppresses pd-l1 expression and inhibits tumorigenesis of colorectal cancer cells via modulating stat3 signaling. Journal of Cellular Physiology 2021

80 Tian K, Liu W, Zhang J, Fan X, Liu J, Zhao N, Yao C, Miao G. Microrna-125b exerts antitumor functions in cutaneous squamous cell carcinoma by targeting the stat3 pathway. Cellular & molecular biology letters 2020;25:1-12.
81 Yan X-L, Luo Q-Y, Zhou S-N, Pan W-T, Zhang L, Yang D-J, Qiu M-Z. Microrna-375 reverses the expression of pd-l1 by inactivating the jak2/stat3 signaling pathways in gastric cancer. Clinics and Research in Hepatology and Gastroenterology 2021;45:101574.
82 Li C, Li H, Zhang P, Yu L-J, Huang T-M, Song X, Kong Q-Y, Dong J-L, Li P-N, Liu J. Shp2, socs3 and pias3 expression patterns in medulloblastomas: Relevance to stat3 activation and resveratrol-suppressed stat3 signaling. Nutrients 2017;9:3.
83 Xu CH, Liu Y, Xiao LM, Chen LK, Zheng SY, Zeng EM, Li DH, Li YP. Silencing microrna-221/222 cluster suppresses glioblastoma angiogenesis by suppressor of cytokine signaling-3-dependent jak/stat pathway. J Cell Physiol 2019;234:22272-22284.
84 Che S, Sun T, Wang J, Jiao Y, Wang C, Meng Q, Qi W, Yan Z. Mir-30 overexpression promotes glioma stem cells by regulating jak/stat3 signaling pathway. Tumour Biol 2015;36:6805-6811.
85 Jiao J, Zhang R, Li Z, Yin Y, Fang X, Ding X, Cai Y, Yang S, Mu H, Zong D, Chen Y, Zhang Y, Zou J, Shao J, Huang Z. Nuclear smad6 promotes gliomagenesis by negatively regulating pias3-mediated stat3 inhibition. Nat Commun 2018;9:2504.
86 Shi L, Wan Y, Sun G, Zhang S, Wang Z, Zeng Y. Mir-125b inhibitor may enhance the invasion-prevention activity of temozolomide in glioblastoma stem cells by targeting pias3. BioDrugs 2014;28:41-54.
87 Song Z-B, Yang H-P, Xu A-Q, Zhan Z-M, Song Y, Li Z-Y. Connective tissue growth factor as an unfavorable prognostic marker promotes the proliferation, migration, and invasion of gliomas. Chinese medical journal 2020;133:670.
88 Zhang P, Chen FZ, Jia QB, Hu DF. Upregulation of microrna-133a and downregulation of connective tissue growth factor suppress cell proliferation, migration, and invasion in human glioma through the jak/stat signaling pathway. IUBMB Life 2019;71:1857-1875.
89 Zhang Z, Gong Q, Li M, Xu J, Zheng Y, Ge P, Chi G. Microrna-124 inhibits the proliferation of c6 glioma cells by targeting smad4. Int J Mol Med 2017;40:1226-1234.
90 Cai Q, Zhu A, Gong L. Exosomes of glioma cells deliver mir-148a to promote proliferation and metastasis of glioblastoma via targeting cadm1. Bull Cancer 2018;105:643-651.
91 Saito K, Ohta S, Kawakami Y, Yoshida K, Toda M. Functional analysis of kif20a, a potential immunotherapeutic target for glioma. J Neurooncol 2017;132:63-74.
92 Tang J, Xu J, Zhi Z, Wang X, Wang Y, Zhou Y, Chen R. Mir-876-3p targets kif20a to block jak2/stat3 pathway in glioma. Am J Transl Res 2019;11:4957-4966.
93 Cheng J, Meng J, Zhu L, Peng Y. Exosomal noncoding rnas in glioma: Biological functions and potential clinical applications. Mol Cancer 2020;19:66.
94 Qian M, Wang S, Guo X, Wang J, Zhang Z, Qiu W, Gao X, Chen Z, Xu J, Zhao R, Xue H, Li G. Hypoxic glioma-derived exosomes deliver microrna-1246 to induce m2 macrophage polarization by targeting terf2ip via the stat3 and nf-κb pathways. Oncogene 2020;39:428-442.
95 Network CGAR. Comprehensive genomic characterization defines human glioblastoma genes and core pathways. Nature 2008;455:1061.
96 Le MT, Teh C, Shyh-Chang N, Xie H, Zhou B, Korzh V, Lodish HF, Lim B. Microrna-125b is a novel negative regulator of p53. Genes & development 2009;23:862-876.
97 Le MT, Shyh-Chang N, Khaw SL, Chin L, Teh C, Tay J, O'Day E, Korzh V, Yang H, Lal A. Conserved regulation of p53 network dosage by microrna–125b occurs through evolving mirna–target gene pairs. PLoS genetics 2011;7:e1002242.

98 Nishida N, Yokobori T, Mimori K, Sudo T, Tanaka F, Shibata K, Ishii H, Doki Y, Kuwano H, Mori M. Microrna mir-125b is a prognostic marker in human colorectal cancer. International journal of oncology 2011;38:1437-1443.
99 Enomoto Y, Kitaura J, Hatakeyama K, Watanuki J, Akasaka T, Kato N, Shimanuki M, Nishimura K, Takahashi M, Taniwaki M. Eμ/mir-125b transgenic mice develop lethal b-cell malignancies. Leukemia 2011;25:1849-1856.
100 Zhang Y, Yan L-X, Wu Q-N, Du Z-M, Chen J, Liao D-Z, Huang M-Y, Hou J-H, Wu Q-L, Zeng M-S. Mir-125b is methylated and functions as a tumor suppressor by regulating the ets1 proto-oncogene in human invasive breast cancer. Cancer research 2011;71:3552-3562.
101 Yamakuchi M, Ferlito M, Lowenstein CJ. Mir-34a repression of sirt1 regulates apoptosis. Proceedings of the National Academy of Sciences 2008;105:13421-13426.
102 Eades G, Yao Y, Yang M, Zhang Y, Chumsri S, Zhou Q. Mir-200a regulates sirt1 expression and epithelial to mesenchymal transition (emt)-like transformation in mammary epithelial cells. Journal of Biological Chemistry 2011;286:25992-26002.
103 Kaller M, Liffers S-T, Oeljeklaus S, Kuhlmann K, Röh S, Hoffmann R, Warscheid B, Hermeking H. Genome-wide characterization of mir-34a induced changes in protein and mrna expression by a combined pulsed silac and microarray analysis. Molecular & Cellular Proteomics 2011;10
104 Chen Q-R, Yu L-R, Tsang P, Wei JS, Song YK, Cheuk A, Chung J-Y, Hewitt SM, Veenstra TD, Khan J. Systematic proteome analysis identifies transcription factor yy1 as a direct target of mir-34a. Journal of proteome research 2011;10:479-487.
105 Bouscary D. Rational for targeting the hedgehog signalling pathway in acute myeloid leukemia with flt3 mutation. Ann Transl Med 2016;4:S53.
106 Li J, Zhang Q, Fan X, Mo W, Dai W, Feng J, Wu L, Liu T, Li S, Xu S, Wang W, Lu X, Yu Q, Chen K, Xia Y, Lu J, Zhou Y, Xu L, Guo C. The long noncoding rna tug1 acts as a competing endogenous rna to regulate the hedgehog pathway by targeting mir-132 in hepatocellular carcinoma. Oncotarget 2017;8:65932-65945.
107 Song JH, Tieu AH, Cheng Y, Ma K, Akshintala VS, Simsek C, Prasath V, Shin EJ, Ngamruengphong S, Khashab MA. Novel long noncoding rna mir205hg functions as an esophageal tumor-suppressive hedgehog inhibitor. Cancers 2021;13:1707.