Molecular Therapy
Nucleic Acids
Review

miR-134: A Human Cancer Suppressor?

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MicroRNAs (miRNAs) are small noncoding RNAs approximately 20–25 nt in length, which play crucial roles through directly binding to corresponding 3′ UTR of targeted mRNAs. It has been reported that miRNAs are involved in numerous of diseases, including cancers. Recently, miR-134 has been identified to dysregulate in handles of human cancers, such as lung cancer, glioma, breast cancer, colorectal cancer, and so on. Increasing evidence indicates that miR-134 is essential for human carcinoma and participates in tumor cell proliferation, apoptosis, invasion and metastasis, drug resistance, as well as cancer diagnosis, treatment, and prognosis. Nevertheless, its roles in human cancer are still ambiguous, and its mechanisms are sophisticated as well, referring to a variety of targets and signal pathways, such as STAT5B, KRAS, MAPK/ERK signal pathway, Notch pathway, etc. Herein, we review the crucial roles of miR-134 in scores of human cancers via analyzing latest investigations, which might provide evidence for cancer diagnose, treatment, prognosis, or further investigations.

Cancers, the leading cause of death-related diseases in humans, have long been severe threats to human health. Multitudes of people are diagnosed with or dead from cancers every year. In America, cancers have been the second major cause of death, which is barely inferior to heart diseases. Siegel et al.[1] reported that there might be 1,658,370 newly diagnosed cancer patients and 589,430 cancer deaths in 2015. In China, Chen et al.[2] collected information of 72 cancer registries, which indicated about 12,000 new cancer cases occur every day, and it would be increased to approximately 4,292,000 new cases in 2016. Moreover, cancers lead to increases in severe disease burden and hamper economic development.[3] Therefore, it is imperative to investigate the correlation between cancers and their risk factors, especially the molecular mechanisms of cancers, which might contribute to develop novel and effective pharmaceutics or treatments.

MicroRNAs (miRNAs) are characterized as a group of small noncoding RNAs approximately 20–25 nt in length, which play key roles by binding to corresponding 3′ UTR of targeted mRNAs.[4–6] miRNAs regulate approximately 30%–50% of human gene expression.[7,8] Recently, numerous researches have reported the roles of miRNAs in several human diseases, especially in cancers. Massive evidence indicates miRNAs could function as modulators in multiple pathological and biological progressions, such as cancer cell differentiation, proliferation, apoptosis, etc. Additionally, miRNAs are described as a kind of emerging clinical, diagnostic, and prognostic biomarker, as well as treatment approach.[9,10] Sun et al.[11–15] have explored the association between miRNAs and non-small cell lung cancer (NSCLC), revealing miR-139-5p, miR-187, miR-206, miR-326, and miR-329 were downregulated in lung cancer cell lines and tissues and played tumor-suppressive roles by targeting specific 3′ UTR of mRNAs for several oncogenes. However, there are also scores of miRNAs overexpressed in various cancers, including gastric cancer, bladder carcinoma, NSCLC, breast cancer, and so on, which might promote cancer development and malignancy.[16–20] Moreover, investigations suggested that miRNAs functioned as vital modulators in DNA damage with ionizing irradiation engendered, and, what's more, a subset of miRNA's signature has been verified that could respond to radiotherapy in head and neck squamous cell carcinoma (HNSCC).[21] Chen and colleagues[22] found few miRNA-based treatments were applied for clinical trials, but they were not appropriate to glioblastoma. However, we suppose that miRNA-based medicine might be a novel and promising method against various tumors in the future, when the roles and mechanisms of miRNAs in cancer are clearly discovered.

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Table 1. miR-134 Deregulates in Various Cancers and Their Target Genes

Cancer Type	Target Gene	Reference
miR-134 Down		
lung cancer	DPD gene	90
NSCLC	oncogenic CCND1	34
NSCLC	FOXM1	69
NSCLC	EGFR	35
gliomas	KRAS	39
gliomas	—	79,91
glioblastomas	KRAS, STAT5B	40
glioblastomas	Nanog	41
breast cancer	C/EBPα	46
breast cancer	HER2	47
breast cancer	—	111
renal cell carcinoma	KRAS	29
renal cell carcinoma	—	112
colorectal cancer	EGFR, PIK3CA	43
colorectal cancer	—	44
gastric cancer	—	94,95
hepatocellular carcinoma	KRAS	72
hepatocellular carcinoma	ITGB1	70
HNSCC	—	83
endometrial cancer	POGLUT1	30
osteosarcoma		92
miR-134 Up		
lung tumors	—	110
NSCLC	YKT6	88
HNSCC	WWOX gene	64
pancreatic cancer	—	62
colon cancer	—	42
prostate cancer	—	45
uveal melanoma	—	78
SCC of tongue	—	80

NSCLC, non-small cell lung cancer; HNSCC, head and neck squamous cell carcinoma; SCC of tongue, squamous cell carcinoma of tongue.

miR-134 belongs to chromosome 14q32 miRNAs clusters, and it has been reported that DLK1-DIO3 that appears in a differentially methylated region leads to abnormal expression of 14q32 gene clusters.[23,24] miR-134 was found to regulate dendritic spine development through targeting Limk1 mRNA in rat hippocampal neurons.[25] Recently, it has been reported that miR-134 also plays a crucial role in enhancing hippocampal memory and synaptic plasticity through 2,3,5,4′-tetrahydroxystilbene-2-O-β-D-glucoside treatment in normal mice.[26] Fiore et al.[27] discovered miR-134 acted as a vital regulator in homeostatic synaptic repression by targeting Pumilio-2. Furthermore, miR-134 was monitored for involvement in epilepticus, as evidenced by the fact that miR-134 protected neurons and decreased epilepticus seizure.[28] Recently, miR-134 has been reported to participate in a majority of carcinomas and tumors. Upregulation of miR-134 was observed in lung tumor, pancreatic cancer, colon cancer, and prostate cancer, whereas downregulation of miR-134 was also found in a variety of cancers, including NSCLC, glioblastomas, breast cancer, renal cell carcinoma, colorectal cancer, hepatocellular carcinoma, osteosarcoma, etc. (Table 1). These findings suggested miR-134 might present some characters in tumor progression. Consistently, it has been reported that miR-134 played a critical role in cancer cell proliferation, apoptosis, invasion and metastasis, drug resistance, as well as cancer diagnosis, treatment, and prognosis. For instance, Liu et al.[29] found miR-134 markedly decreased in renal cell carcinoma cells and tissues, and restoration of its expression was able to refrain cell proliferation by silencing G0/G1 phase. Overexpressed miR-134 could also refrain cell metastasis in endometrial tumor.[30] Furthermore, miR-134 could also regulate drug resistance through targeting ABCC1 in breast cancer cells; meanwhile, it also participated in drug resistance in ovarian carcinoma and SCLC cells, suggesting the mechanisms of miR-134 in different carcinomas might be diverse. In addition, miR-134 targeted multiple genes in tumors, such as KRAS, STAT5B, Nanog, FOXM1, EGFR, etc. (Table 1). Despite functioning as a modulator in cancers, miR-134 affected abundant and complicated signal pathways, including MAPK/ERK signal pathway, EGFR pathway, Notch pathway, etc.

In this review, we synthesize the roles and mechanisms of miR-134 in cancer cell proliferation, apoptosis, invasion and metastasis, drug resistance, cancer diagnosis as well as patients' survival and prognosis, to provide intuitionistic evidence for clinical applications and further investigations in the future.

miR-134 in Cell Proliferation

Increasing evidence indicates miR-134 associates with various genes mediating cancer cell proliferation. Cyclin D and CDK4 have been discovered to be upregulated in a variety of human cancer cells.[31] P21 gene, a cell growth regulator, is found to involve in cancerous cell-cycle arrest at G1 phase.[32,33] Sun et al.[34] disclosed that miR-134 increased p21 expression and suppressed cyclin D1, cyclin D2, and CDK4 proteins expression in SPC-A1 and A549 cells, which indicated miR-134 could repress NSCLC cell proliferation. In another study, increasing miR-134 expression suppressed lung cancer cell proliferation by downregulating EGFR.[35] It has been reported that EGFR possessed effect of resistance to cancer procession and development.[36] MiR-134 was also found to associate with cancer treatment as well as trigger numerous pathways, such as the MAPK pathway and PI3K-AKT-mTOR pathway.[37] Qin et al. found EGFR was an appropriate target of miR-134 in NSCLC cells, and upregulation of miR-134 inhibited the EGFR-correlated signal pathway. After transfection with miR-134 mimics, the protein level of p-Akt was downregulated in H1299, H520, as well as A549 cell lines; pERK1/2 yield was reduced in A549, H520, and H1975 cell lines; p-STAT3 expression was decreased in H1299 and H520 cells. These data suggested miR-134 repressed NSCLC cell proliferation via targeting EGFR and activating corresponding pathways.[35] Consistently, that evidence uncovered

that mutant KRAS played a critical modulator in the EGFR signaling cascade through repressing miR-4689 to modulate both PI3K/AKT and RAS/MAPK pathways in colorectal cancer.[38]

In addition, miR-134 was also demonstrated to downregulate in glioma tumor and overexpressed miR-134 inhibited glioma cell growth through targeting KRAS and activating the ERK pathway.[39] Overexpression of miR-134 significantly repressed cell proliferation and xenograft development in another investigation of glioblastoma tumor.[40] Zhang et al.[40] confirmed that miR-134 expression was remarkably decreased in glioblastoma and had an opposite correlation with MET, and other proteins, including RTKs EGFR and PDGFR. Additionally, miR-134 also functioned as a tumor suppressor via downregulating KRAS and STAT5B expression.[40] It was also verified in another study about glioblastoma that miR-134 suppressed tumor progression and proliferation in vivo and in vitro.[41] Liu et al.[29] found miR-134 expression markedly decreased in renal cell carcinoma cells and tissues compared with that of normal cells and tissues, and restoration of its expression was able to refrain cell proliferation by silencing G0/G1 phase. In addition, miR-134 expression was discovered to increase in colon cancer patients' stool,[42] whereas it was found to have an opposite outcome of expression in colorectal tumor that remarkably decreased in tumor tissues and cell lines. Overexpression of miR-134 resulted in repression of colorectal cancer cell proliferation and growth.[43,44] It has been reported that 1,25-$(OH)_2D_3$ was involved in prostate carcinoma and played an inhibitory role in tumor cell proliferation. After transfecting it into cancer cells, miR-134 expression was noticeably upregulated, which verified that 1,25-(OH)2D3/miR-134 cascade might be a novel point in therapy cancer.[45] C/EBPα gene, a tumor suppressor, was verified to crosstalk with miR-134 in breast cancer, and they were both decreased in cancer tissues, and both repressed tumor cell growth.[46] Moreover, miR-134 refrained cell growth through targeting POGLUT1 in endometrial tumor cells.[30] Another investigation revealed that epidermal growth factor receptor 2 was determined as a corresponding target of miR-134.[47] However, the role of miR-134 in breast cancer has not been further investigated.

Nevertheless, Chen et al. discovered miR-134 exerted a reverse role in SCLC cells, and, after transfecting miR-134 mimics and its negative control into H69 cell, the ability of cell proliferation was enhanced. The opposite phenomenon was observed after transfecting miR-134 inhibitor and its negative control to cells.[48] The ERK signaling pathway, a crucial downstream signal, was found to participate in cell development and progression.[49–51] Chen et al.[48] also explored the mechanisms of miR-134 in SCLC cells, observing WWOX was a qualified target of miR-134. Moreover, enhancing miR-134 expression led to lower expression of pERK,[52] which was correlated with WWOX as evidenced by the fact that elevating WWOX expression resulted in noticeably promoting expression of pERK. These findings uncovered miR-134-boosted cancer cell proliferation through targeting WWOX and triggered the ERK pathway.[48] Interestingly, another study also demonstrated that miR-134 functioned as an oncogene, which uncovered that upregulation of miR-134 contributed to elevate cell proliferation in Calu-3 and A549 cells.[53]

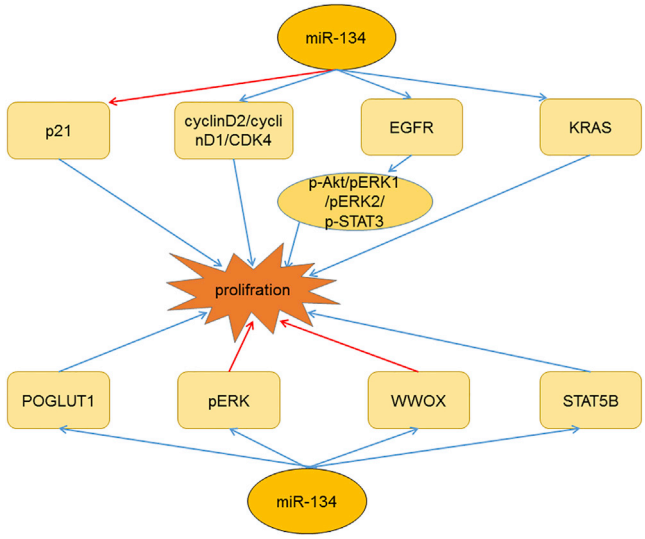

Figure 1. miR-134 Associates with Various Genes Mediating Cancer Cell Proliferation

Upregulated-miR-134 inhibits the expression of cyclin D1/cyclin D2/CDK4, KRAS, EGFR, POGLUT1, and STAT5B repressing cell proliferation, while it inhibits the expression of pERK and WWOX but with increasing proliferation. miR-134 increases the expression of p21, resulting in repressing cell proliferation. Blue arrows, suppression; red arrows, indicate promotion.

These findings show that the relationship between miR-134 and cancer cell progression is complex (Figures 1 and 2). miR-134 might have a different power in various cancer cells, which requires further investigation to warrant.

miR-134 in Cell Apoptosis

Accumulating evidence discloses that dysregulation of cell apoptosis correlates with a majority of diseases, which involves multitudes of classical signal pathways and proteins. Death receptors pathway, mitochondria pathway (like Bcl-2 family), caspase pathway, and growth factors were reported to participate in cancer modulation.[54,55] Eukaryotic cell apoptosis always activates caspase-3 and caspase-7 through mitochondria- and death-receptor-induced pathways.[56–58] The Bcl-2 family exerts a key role in cell apoptosis, including three subgroups: pro-apoptosis protein such as Bax and Bak, anti-apoptosis proteins such as Bcl-2 and Bcl-xL, and BH3-only proteins.[59,60]

Recently, miR-134 has been found to promote NSCLC cell apoptosis by elevating caspase-3 and caspase-7 yield and reducing expression of Bcl2 protein.[34] In vitro, miR-134 was detected to boost cell apoptosis by inhibiting the cell cycle, while cleaved PARP as a cell apoptosis sign was elevated in vivo.[35] In glioblastoma tumor, miR-134 was found to markedly promote cell apoptosis.[40] Additionally, both STAT5B and KRAS were demonstrated as appropriate targets of miR-134, and upregulated miR-134 suppressed STAT5B and KRAS expression in

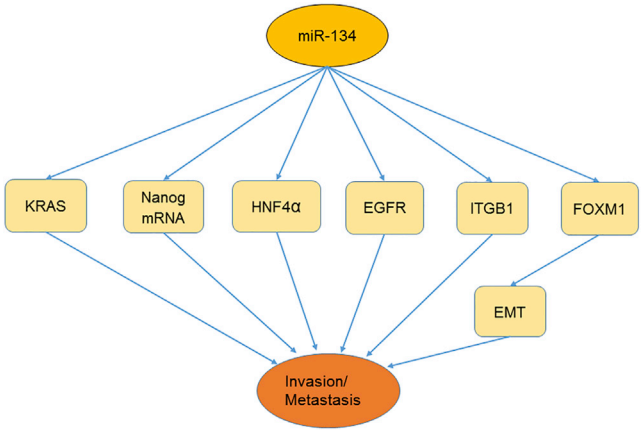

Figure 2. miR-134 Functions in Cancer Invasion and Metastasis
KRAS, Nanog mRNA, HNF4α, EGFR, ITGB1, and FOXM1 are all target genes of miR-134, and miR-134 inhibits their functions, which results in repressing cell invasion and metastasis.

glioblastoma cells.[40] The similar phenomenon was observed in another study of glioblastoma, which also confirmed miR-134 boosted cell apoptosis via flow cytometry assay.[41] As we will mention, miR-134 was remarkably upregulated in pancreatic cancer patients' serum, whereas the role of miR-134 has not been investigated in pancreatic cancer tissues or cells. Glargine was verified to boost a few tumor cells' proliferation as well as repress cell apoptosis via activating ERK and AKT pathway.[61] Li et al.[62] uncovered that after transfection with glargine, miR-134 was markedly upregulated in pancreatic cancer cells. Nevertheless, they did not further study whether miR-134 exerted the same role like glargine to improve cancer cell growth and repress cell apoptosis in pancreatic cancer. Furthermore, after transfecting EGF into A431 cells, miR-134 was detected to dysregulate, and further assays indicated it not merely targeted MYB, a resistant apoptosis gene, but also regulated BANF1 expression.[63] Nevertheless, the specific character of miR-134 in A431 cells is required for much deeper investigations.

However, miR-134 significantly reduced SCLC cell apoptosis, and, after the treatment of anti-miR-134, a reverse result could be observed that was through controlling the expression of Bcl-2 family.[48] Likewise, evidence shows miR-134 was upregulated in cancer tissues and cells, and it was able to facilitate cell growth as well as inhibit apoptosis, which was also verified in xenograft models. Further assays documented WWOX was a qualified target of miR-134, whereas the corresponding signal pathways demand for deeper exploration.[64] The two interesting studies indicate that miR-134 not only barely functions as a tumor repressor, but also might act as a cancer promoter; the detailed roles of miR-134 require more convincing and powerful investigations to confirm.

miR-134 in Cancer Invasion and Metastasis

Cancer invasion and metastasis are severely aggravated in patients and are involved in complex mechanisms. Epithelial-mesenchymal transitions (EMTs) are a key process in tumorigenesis and tumor development. Vimentin and E-cadherin are typical biomarkers for EMT.[65–68] Recently, it has been reported that miR-134 made sense in NSCLC cell invasion and metastasis and discovered that it repressed cell invasion and metastasis through a transwell/invasion/migration assay.[34] In addition, high expression of miR-134 decreasing cell invasion was also observed in different NSCLC cell lines, which might function through affecting EMT.[69] As it transfected miR-134 mimics into cancer cells, vimentin was markedly downregulated, whereas the E-cadherin expression was found to noticeably elevate. Furthermore, the underlying mechanism of miR-134 on repressing EMT was also explored.[69] Results show FOXM1 was an appropriate target of miR-134, and further study indicated that transfecting TGF-β1 into cell resulted in FOXM1 upregulation, miR-134 downregulation, as well as vimentin and E-cadherin dysregulation, which confirmed miR-134 targeted FOXM1, which contributed to TGF-β1-mediated EMT in NSCLC cells.[69] Interestingly, EMT was also determined to be restrained after miR-134 re-expressed in renal cell carcinoma, and further assays verified increased miR-134 could strikingly decrease cell invasion and metastasis.[29] Ultimately, miR-134 was confirmed to play a tumor-suppressive role by targeting KRAS mRNA and via affecting MAPK/ERK signal pathway in renal cancer.[29]

In glioma, after miR-134 was infected into U251 cells, cell invasion was noticeably reduced through targeting KRAS.[39] In another investigation of glioblastoma, overexpression of miR-134 significantly inhibited U87 cell invasion and metastasis through targeting Nanog mRNA in glioblastoma.[41] Besides, overexpression of miR-134 inhibited cell invasion and metastasis in colorectal tumor through affecting the EGFR pathway.[43] Moreover, EGFR was confirmed as a credible target of miR-134, and further exploration indicated that miR-134 regulated the PIK3CA/AKT/mTOR signal pathway.[43] Zha et al. found miR-134 was deregulated and inhibited carcinoma cell invasion and metastasis in hepatocellular cancer. Bioinformatics and luciferase assay demonstrated ITGB1 was a suited target of miR-134, and repression of miR-134 as well as overexpression of ITGB1 facilitated tumor cell invasion and metastasis.[70] HNF4α played a shining role in hepatocellular carcinoma malignance and development.[71] Consistently, Yin et al. found HNF4α refrained tumor procession and development by increasing miR-134 expression in hepatocellular cancer. Besides, enhancing miR-134 expression remarkably restrained malignant cell invasion and metastasis. Following investigations revealed miR-134 functioned as a tumor repressor by targeting KRAS and controlling HNF4α expression, and HNF4/miR-134 cascade might be an underlying therapy approach.[72] Moreover, it has been reported that increasing miR-134 also refrained cell metastasis in endometrial tumor.[30] However, miR-134 played an opposite role in HNSCC. High miR-134 expression not only merely enhanced HNSCC cell metastasis capability, but also boosted xenograft development and metastasis in mouse models.[64]

These series of findings indicate miR-134 functions vitally in tumor invasion and metastasis (Figure 2). Elevating expression of miR-134

is able to repress cancer invasion and metastasis. We suppose that these findings barely disclose a few parts of miR-134 in tumor invasion and metastasis. In addition, other targets and signal pathways related to miR-134 might be committed to further investigation.

miR-134 in Cancer Diagnosis

Cancers have often developed to middle and advanced stages when diagnosed; therefore, early tumor and carcinoma diagnosis or screening is crucial. Evidence suggests miRNAs are stable and couldn't be impaired easily in patients' serum.[73,74] Therefore, miRNAs might be a class of novel signs to detect diseases in the next decades. In hepatitis C virus (HCV) patients' serum, miR-134 expression was detected to be prominently high, and the area under the curve (AUC) was 0.803, which indicated it might be a suited diagnosed objection.[75,76] Wang and colleagues found that miR-134-5p might be an emerging diagnostic biomarker in early stage of acute myocardial infarction because its expression was markedly increased in patients' plasma.[77] As we earlier presented, miR-134 was found to dysregulate in a variety of human tumors (Table 1), and some of them might be promising and qualified biomarkers in terms of cancer diagnosis.

In uveal melanoma, miR-134 was discovered to differentially increase compared to its counterparts, and it crosstalked with liver metastasis cases that were diagnosed with uveal melanoma, which indicated that it may be a potential biomarker.[78] In low-stage pancreatic cancer patients' serums, miR-134 level was proved to be prominently higher when contrasted to normal controls. The AUCs were 0.73–0.82, suggesting miR-134 might be an underlying diagnosis marker.[62] Furthermore, miR-134 was demonstrated to downregulate in gliomas when compared with normal tissues, and it could markedly distinguish glioblastomas from oligodendrogliomas, indicating miR-134 was a promising biomarker in terms of gliomas tumor diagnosis.[79] Wong et al. found more than 20 miRNAs expression elevated in squamous cell carcinoma of tongue that all exceed 3-fold changes compared with the non-cancerous samples, including miR-134. Nevertheless, miR-134 was not the highest expression miRNA, and its features were not explored.[80] Malignant pleural effusion (MPE) is extremely crucial for advanced lung cancer diagnosis, as emerging MPE might be a sign for unsatisfactory prognosis.[81] Thereby, investigating lung cancer with MPE is essential and significant. Some evidence shows that lung cancer patients with MPE appeared miRNAs deregulated, including miR-134.[82] Shin et al.[81] detected markedly decreased miR-134 in 87 eligible lung patients' pleural fluid compared with controls. The receiver operating characteristic (ROC) was mapped to reflect the diagnosed reliability, of which mean area was 0.721. These findings might provide clues for diagnosing terminal patients with lung cancer.[81] Additionally, it was also decreased in head and neck squamous cell cancer, and the AUC analysis showed it possessed highly distinguished ability for the tumor, which showed that miR-134 may be a possible marker for diagnosis and detection.[83] These investigations suggest miR-134 might be an emerging biomarker of cancer diagnosis. More clinical and massive investigations are needed.

miR-134 in Patient Survival and Prognosis with Cancer

With the mechanisms between miRNAs and cancer gradually disclosed, miRNA-based treatment might be a possible candidate approach in the next decades. For instance, it has been reported that miR-34 was characterized as being a tumor suppressor, which might be a promising and powerful weapon in terms of treatment or investigation of cancer, by targeting a plethora of gene mRNAs, such as CDK6, Notch, and c-MYC.[84] Additionally, sorafenib, a well-established drug for patients with advanced HCC, was validated that contributed to miR-423-5p upregulation in HCC patients' serum, and miR-423-5p was also observed that boosted hepatocarcinoma cell autophagy.[85] This part mainly summarizes the relationship between miR-134 and patient survival and prognosis in some cancers. We hope it provides evidence for further studies of cancer patients' prognosis as well as disease burden.

YKT6, a SNARE protein, was reported to correlate with breast cancer cell development,[86] and it was elevated in breast cancer patients with p53 mutation.[87] Recently, YKT6 was discovered to be a target of miR-134 and dramatically downregulated in lung cancer tissues.[88] High expression of YKT6 might contribute to unsatisfactory prognosis as it promoted emission of exosomes.[88] Consistently, YKT6 yield was studied that correlated with lung cancer patients' prognosis. Results suggested high expression of YKT6 with differential inferior disease-free and total survival compared with low expression. In NSCLC patients' plasma, upregulated YKT6 was accompanied by higher exosomes, which suggested the miR-134-YKT6 pathway might be a larvaceous candidate for lung cancer treatment and prognosis.[88] Dihydropyrimidine dehydrogenase (DPD) tightly correlates with 5-fluorouracil (5-FU), and it has about 80% of the therapeutic effect of 5-FU in cancer treatment.[89] Takeshi et al. analyzed 16 patients' specimens and demonstrated overexpression of miR-134 remarkably decreased DPD expression, and it suppressed DPD activity by targeting DPD mRNA in lung cancer, which might provide a novel idea in 5-FU-based chemotherapy.[90] Moreover, miR-134 expression apparently correlated with smoking history, tumor node metastasis (TNM) stage, tumor size, etc. Besides, low expression of miR-134 contributed to lesser total survival as compared with the higher through K-M survival analysis in NSCLC.[34] Although miR-134 was discovered to deregulate in glioma tissues and cells, its function in clinical outcome has not been investigated yet. Zhong and Li found it closely correlated with glioma progression and prognosis. Interestingly, downregulation of miR-134 related to the increase of grades of the World Health Organization (WHO) and decrease of Karnofsky scores (KPS) in glioma tumor tissues; meanwhile, cases with higher WHO scores and lower KPS grades were inclined to have conspicuously shorter survival, which demonstrated it played a vital role in glioma treatment and prognosis.[91] In osteosarcoma, miR-134 expression was downregulated in patients' tissues and cells and associated with the size of tumor and terminal pathologic grade. High expression of miR-134 presented bulky carcinoma size and terminal clinicopathological period, while the lower was inverse. Moreover, decreased miR-134 expression contributed to lower total survival, which uncovered it might be a promising biomarker and approach in

osteosarcoma therapy and prognosis.[92] Gunawan and colleagues[93] found that deletions of chromosomal regions 14q were apt to happen in gastric carcinoma and that they were tightly related to cytogenetical evolution, while they did not apparently correlate with lesser disease-free survival. In another study, miR-134 was downregulated, and decreased miR-134 expression might lead to a worse survival rate and advancement of tumor development in gastrointestinal stromal cancer.[94] In spite of the fact that miR-134 was also demonstrated to decline in tissues and cells of human gastric cancer with lymph node metastasis, it was not verified that it affected biological behaviors or procession of this tumor.[95] We assume that further findings are warranted.

Salazar and colleagues[83] found miR-134 was downregulated through detected HNSCC patients' saliva samples. Nevertheless, Liu et al.[64] discovered an inverse result, revealing it significantly elevated in HNSCC tissues when compared with noncancerous matched tissues. The resemble phenomenon was also observed in HNSCC cell lines. Furthermore, they explored the relationship between miR-134 expression and patient survival and prognosis. Results suggested high expression of miR-134 cases were more inclined to have jeopardous prognosis and short survival.[64] This conclusion is completely converse with other investigations; whether there will be more analogous findings or not needs to be confirmed.

miR-134 in Drug Resistance

According to our current knowledge, chemotherapy is the leading approach to fight cancer, whereas it seems to appear drug resistance and has poor complications. Therefore, exploring novel, safe, and highly-effective treatment is imperative and urgent. Recently, evidence showed that miRNAs correlated with cancer drug resistance; for instance, miR-197 was found to enhance cancer cell chemoresistance,[96] whereas it was reported that miR-451 could improve NSCLC cell line sensibility to cisplatin.[97]

Consistently, miR-134 also involved in cancer drug resistance. It has been reported that miR-134 was found to deregulate in ovarian tumor tissues and cells;[98] however, its biological behaviors and mechanisms were unknown. SKOV3-TR30 cell is one of ovarian cancer cells that shows resistance to the chemotherapeutic medicine paclitaxel. Zhu and colleagues[99] found miR-134 was markedly downregulated in SKOV3-TR30 cell lines. Moreover, Shuang et al. explored the associations between miR-134 and SKOV3-TR30 cells, consistently discovering miR-134 expression was lower in drug-resistant ovarian cancer cells compared with no resistance. They also found eight potential target genes including VIM, a direct target, of miR-134 through PCR assay.[100] Regretfully, the underlying power of miR-134 in drug-resistant ovarian cancer has not been confirmed yet. Nonetheless, Wu et al.[101] demonstrated that miR-134, which activated ERK and JNK signaling pathway through targeting SDS22, not only boosted cell growth, invasion, and migration, but also decreased chemosensitivity in ovarian cancer. Furthermore, miR-134 was able to prohibit the endometrial tumor cell resistance to some drugs, including chemotherapeutic paclitaxel and cisplatin.[30] The mechanism of miR-134 was further explored to determine whether POGLUT1 was an eligible target of miR-134, and the role of miR-134 to prohibit the endometrial tumor cell resistance to drug might trigger the Notch pathway.[30] Consistently, evidence indicated POGLUT1 tightly correlated with Notch pathway in leukemia cells.[102]

As we have mentioned previously, miR-134/C/EBPα gene cascade exerted a tumor regulator in breast cancer. Interestingly, Lu et al. explored miR-134 possible function in drug resistance of breast carcinoma. They found it was decreased in drug-resistant MCF-7/ADR cells. While infected miR-134 mimics to cancer cells, cell growth was markedly prohibited, and cell apoptosis was significantly elevated.[103] ATP Binding Cassette C1 (ABCC1) was described as a prominent conductor of drug resistance via controlling correlative drug resistance protein MRP1.[104–106] Consistently, Lu and colleagues also affirmed that upregulated miR-134 suppressed drug-fasted tumor cell growth through diminishing expression of ABCC1.[103] In addition, miR-134 was also verified that possessed resemble power in SCLC cells. Guo and colleagues found miR-134 was markedly lowered in SCLC drug-resistant cell lines, whereas its expression and the sensibility of drug-resistant cells to the common chemotherapeutic medicine would be elevated after transfecting corresponding mimics to the cells.[107] They also investigated the possible targets, discovering miR-134 functioned through modulating ABCC1/MRP1, and whether there were other existing targets and regulated mechanisms or not that require further exploration.[107] Evidence showed EMT associated with drug resistance in NSCLC cells.[108] Likewise, Kitamura et al.[109] uncovered miR-134 led to TGF-β1-mediated EMT in lung cancer cells. Further assays confirmed that TGF-β1 modulated MAGI2 expression, while MAGI2 was an eligible target of miR-134. Interestingly, after infected miR-134 and TGF-β1 into lung cancer cell lines, they observed that elevated cancer cell resistance to gefitinib. These findings suggest miR-134 might play various characters in diverse cancer drug resistance.

Conclusions

In this review, we uncover some interesting stuff that might be beneficial for clinical applications and future studies. First, miR-134 was dysregulated in various tumors and carcinomas, whereas it may present different expression in identical cancer. For instance, miR-134 was elevated in two studies about lung cancer,[88,110] whereas it was decreased in other references about lung cancer.[34,35,69,90] Similarly, it was found to downregulate in HNSCC, while it was also upregulated in another study of HNSCC.[64,83] If every study is convincing and scientific, we assume that the difference might associate with different cancer sample sorts, histological grade, and pathological stage or detection methods. Second, the molecular and modulated mechanisms of miRNA is extremely complicated and variable, because we disclose miR-134 has diverse target genes and sophisticated signal pathways when it functions in cancer. Other targets and signal pathways of miR-134 relating to cancer might demand further investigation. Third, we suppose that miR-134 not only barely functions as a tumor repressor, but also might act as a cancer promoter. It seems to be a cancer suppressor because it repressed cancer

cell proliferation and xenograft development and boosted tumor cell apoptosis, migration, and metastasis as well as benefited patient survival and prognosis in major papers. However, it also acted as a devil for it induced tumorigenesis, cancer cell growth, prohibited apoptosis, enhanced metastasis, as well as led to poor prognosis in some investigations.[64,88,110]

Taken together, we summarize dysregulation of miR-134 in a variety of cancers, highlighting the role of miR-134 in cancer cell proliferation, apoptosis, invasion and metastasis, drug resistance, cancer diagnosis, as well as patients' survival and prognosis. Additionally, miR-134 has diverse target genes and sophisticated signal pathways when it functions in cancer. Although there are numerous investigations exploring the relationship between miR-134 and various tumors, we assume that miR-134 has more possible power in cancer biological behaviors, diagnosis, and treatment. Sincerely, we hope this review might provide some evidence for clinical applications and further investigations in the future.

AUTHOR CONTRIBUTIONS

Conceptualization, J.-Y.P., F.Z., C.-C.S., and D.-J.L.; Investigation, J.-Y.P., F.Z., C.-C.S., S.-J.L., and D.-J.L.; Writing – Original Draft, J.-Y.P., F.Z., C.-C.S., S.-J.L., and D.-J.L.; Writing – Review & Editing, J.-Y.P., F.Z., C.-C.S., S.-J.L., G.L., F.-Y.G., J.H., R.-X.H., W.-D.H., Z.-P.Y., and D.-J.L.; Visualization, J.-Y.P., F.Z., C.-C.S., S.-J.L., G.L., F.-Y.G., J.H., R.-X.H., W.-D.H., Z.-P.Y., and D.-J.L.; Supervision, C.-C.S., Z.-P.Y., X.W., Q.-Q.H., and D.-J.L.; Funding Acquisition, C.-C.S. and D.-J.L.

CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

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