Role of miRNA-122 in cancer (Review)

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Abstract. MicroRNAs (miRNAs) are small non-coding RNAs that serve key roles in cell proliferation, migration, invasion and apoptosis by regulating gene expression. In malignant tumors, miRNA-122 serves either as a tumor suppressor or oncogene, influencing tumor progression via downstream gene targeting. However, the precise role of miRNA-122 in cancer remains unclear. miRNA-122 is a potential biomarker and modulator of radiotherapy and chemotherapy. The present review aimed to summarize the roles of miRNA-122 in cancer, its potential as a biomarker for diagnosis and prognosis and its implications in cancer therapy, including radiotherapy and chemotherapy, alongside strategies for systemic delivery.

Contents

1. Introduction

According to Global Cancer Statistics from 2018, there were 18.1 million new cancer cases and 9.6 million deaths attributed to cancer (1). Cancer ranks as the second leading cause of death globally, following ischemic heart disease (2). Current research on cancer diagnosis, treatment and prognosis primarily focuses on genetic and epigenetic factors, such as microRNAs (miRNAs). The first miRNA was discovered in nematodes, leading to further exploration of similar endogenous miRNAs across species using RNA interference (3). miRNAs not only translate proteins but also regulate gene transcription, influencing processes such as cell differentiation and organism development (3,4). Initially transcribed by RNA polymerase II in the nucleus, primary miRNAs are processed into precursor miRNAs by the Drosha enzyme-Dgcr8 complex. After translocating to the cytoplasm, these precursor miRNAs are cleaved into ~22-nucleotide-long double-stranded miRNAs by the enzyme Dicer (5). The double strands are then unwound, and the mature miRNA strand forms an RNA-induced silencing complex, which binds to the 3'-untranslated region (3'-UTR) of target mRNA to degrade or inhibit its translation, thereby negatively regulating gene expression (6). To date, >1,000 miRNAs have been identified in humans (7). Dysregulation of miRNA, such as miRNA-122, is associated with various diseases, particularly cancer (8). miRNA-122 constitutes ~72% of the total miRNAs found in the liver (9). Its expression is altered in multiple diseases. For example, elevated levels of miRNA-122 are associated with bronchiolitis. which may progress to asthma (10). miRNA-122 is also implicated in promoting diabetic retinopathy (11). Additionally, high levels of miRNA-122 suppress the release of inflammatory factors in osteoarthritis, suggesting potential therapeutic applications (12). Numerous studies have reported abnormal expression of miRNA-122 in various types of cancer, where it modulates tumor development by targeting specific genes (8,13). However, the exact role of miRNA-122 in cancer remains elusive.

The present review aimed to summarize how miRNA-122 influences various aspects of tumor cell behavior, including proliferation, migration, metastasis, invasion, angiogenesis and apoptosis, the role of miRNA-122 in modulating responses to radiotherapy and chemotherapy in tumor cells, as well as strategies for its systemic delivery and potential utility as a biomarker.

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2. miRNA-122 and cancer

miRNAs are classified as oncogenic or tumor-suppressive based on their effects (14). miRNA-122 is derived from a single genomic locus on human chromosome 18 (15). miRNA-122 regulates tumor cell processes such as proliferation, angiogenesis, invasion, migration and apoptosis by targeting downstream genes. Due to its ability to target a diverse array of downstream genes, including both oncogenes and tumor suppressors, miRNA-122 exerts varied roles in cancer development, serving as either an oncogene or tumor suppressor, and may exhibit dual roles in certain types of cancer (16-34). Table I summarizes the role of miRNA-122 in various types of cancer.

Non-small cell carcinoma (NSCLC). Lung cancer includes small cell carcinoma and NSCLC, with NSCLC being the predominant form, constituting 80-85% of cases and associated with 2-year relative survival rate of ~42% (35). NSCLC cells do not express endogenous miRNA-122. miRNA-122 inhibits the PI3K/AKT signaling pathway through suppression of its target gene insulin-like growth factor 1 receptor (IGF1R). This suppression blocks PI3K and AKT phosphorylation, enhances E-cadherin expression and decreases N-cadherin and vimentin expression. This disruption impedes epithelial-mesenchymal transition (EMT), thereby inhibiting migration and invasion of NSCLC cells (17).

Long-term exposure of NSCLC cells to gefitinib leads to emergence of gefitinib-resistant A549/GR cells. As a target of miRNA-122, peroxiredoxin II (Prx II) inhibition suppresses the self-renewal and EMT of A549/GR stem cells, which is characterized by an increase in E-cadherin and decrease in vimentin expression following miRNA-122 knockout. This process involves inhibition of Hedgehog, Notch and Wnt/β-catenin signaling pathways following Prx II targeting by miRNA-122. Knockout of miRNA-122 reverses these effects (Fig. 1) (18).

Nasopharyngeal carcinoma (NPC). NPC arises from the nasopharyngeal crypt, originating from mucosal epithelium of the nasopharynx, and is characterized by high malignancy (36). NPC cells exhibit significantly decreased expression of miRNA-122. miRNA-122 suppresses PI3K and AKT phosphorylation, inhibits the PI3K/AKT signaling pathway and decreases the expression of E-cadherin, metastasis-associated gene 1, MMP2 and tissue inhibitor of metalloproteinase 2 by targeting tripartite motif-containing protein 29. This inhibition suppresses the proliferation, migration and invasion capabilities of NPC cells (20). Moreover, the long non-coding RNA (lncRNA) DRAIC (downregulated RNA in cancer) upregulates special AT-rich binding protein 1 (SATB1) expression by binding to miRNA-122, thereby alters the configuration of the miRNA-122 binding site on SATB1 and suppressing miRNA-122 expression. This promotes the proliferation, migration and invasion of NPC cells; these effects are reversed by miRNA-122 overexpression (Fig. 2) (21).

Prostate cancer. Prostate cancer is a prevalent malignancy in male patients, accounting for ~26% of newly diagnosed cancer cases (35). Tumor cells obtain their energy supply through relatively low-yield glycolysis, which does not involve oxygen or mitochondria (37). Pyruvate kinase M2 (PKM2) serves as a key rate-limiting enzyme in glycolysis, driving tumor cell proliferation (38). In docetaxel-resistant prostate cancer cells, miRNA-122 expression is notably decreased. This leads to increased PKM2 expression, enhancing glycolysis, promoting proliferation and reducing apoptosis in these resistant cells. The mechanism involves miRNA-122 targeting and inhibiting PKM2 to suppress prostate cancer progression (39).

miRNA-122 inhibits the proliferation of prostate cancer cells by downregulating Rho-associated protein kinase 2 (ROCK2) expression (22). ROCK2, a member of the Rho family, promotes invasion and metastasis in prostate cancer (40). Additionally, silencing ROCK2 expression counteracts enzalutamide resistance in enzalutamide-resistant prostate cancer cells, leading to inhibition of cancer cell proliferation (Fig. 3) (41).

Bile duct cancer (BDC). BDC is a malignant tumor of the epithelial cells of the bile ducts; it is insidious and the 5-year survival rate drops to 2% if distant metastasis occurs (42). Expression of miRNA-122 is notably decreased in BDC compared with normal bile duct tissue. Overexpressed miRNA-122 in BDC cells significantly inhibits tumor cell proliferation and invasion while promoting apoptosis. However, the specific mechanism by which miRNA-122 inhibits BDC progression has not been fully elucidated (43). Wu *et al* (44) demonstrated that overexpression of miRNA-122 in BDC cells upregulates P53 expression, thereby suppressing tumor cell proliferation and invasion while promoting apoptosis. Additionally, miRNA-122 also inhibits BDC cell migration and invasion by targeting the downstream target gene chloride intracellular channel 1 (CLIC1). lncRNA urothelial cancer associated 1 (UCA1) regulates CLIC1 expression through sponging miRNA-122 to promote BDC metastasis (Fig. 4) (19).

Bladder cancer. In 2018, 549,393 patients were diagnosed with bladder cancer worldwide and 199,922 died from the disease (1). Angiogenesis is key for tumor development, making its inhibition a potential treatment strategy. Vascular endothelial growth factor (VEGF) is associated with tumor progression (45). miRNA-122 expression is downregulated in human bladder cancer tissue. By binding to the 3'-UTR of VEGFC, miRNA-122 significantly decreases VEGFC expression, inhibiting AKT and mTOR phosphorylation. This inhibition ultimately suppresses angiogenesis, invasion, migration and proliferation of bladder cancer cells (8). Furthermore, miRNA-122 overexpression enhances sensitivity of bladder cancer cells to cisplatin and promotes cancer cell apoptosis (8).

Prior research (16) has established that the cAMP-response element-binding protein (CREB) 1 serves as a downstream target of miRNA-122. miRNA-122 directly inhibits CREB1 to suppress proliferation and invasion in bladder cancer cells (Fig. 5) (16).

Breast cancer. Breast cancer is the most common cancer in female patients and the leading cause of cancer mortality in female patients worldwide (46). lncRNA ribonuclease P RNA component H1 (RPPH1) is highly expressed in breast cancer tissue. lncRNA RPPH1 promotes the expression of

Table I. Role of miRNA-122 in different types of cancer.

Cancer	Upstream regulator	Expression	Site	Target	Biological function	Role	(Refs.)
Bladder	-	Downregulated	Tissue and cell	VEGFC	Inhibit tumor proliferation, angiogenesis, migration and invasion	Tumor suppressor	(8)
	-	Downregulated	Tissue	CREB1	Inhibit cell proliferation and invasion	Tumor suppressor	(16)
Non-small cell carcinoma	-	Not detected	Cell	IGF1R	Inhibit tumor proliferation, invasion, and migration	Tumor suppressor	(17)
	-	Downregulated	A549/GR Cell	Prx II	Inhibit tumor progression	Tumor suppressor	(18)
Bile duct	lncRNA UCA1	Downregulated	Tissue and cell	CLIC1	Inhibit cell invasion and migration	Tumor suppressor	(19)
Nasopharyngeal carcinoma	-	Downregulated	Tissue and cell	TRIM29	Inhibit tumor proliferation, migration and invasion	Tumor suppressor	(20)
	lncRNA DRAIC	Not detected	Not detected	SATB1	Inhibit cell proliferation, migration and invasion	Tumor suppressor	(21)
Prostate	-	Downregulated	Tissue and cell	ROCK2	Inhibit cell proliferation	Tumor suppressor	(22)
Breast	-	Upregulated	Radiation-resistant breast cancer cells	ZNF611	Promote radiation resistance in breast cancer cells	Oncogene	(23)
	lncRNA RPPH1	Upregulated	Tissue	PKM2 and IGF1R	Inhibit cell proliferation	Tumor suppressor	(24)
Liver	-	Downregulated	Tissue	LMNB2	Inhibit tumor proliferation, migration and invasion	Tumor suppressor	(25)
Colorectal	-	Upregulated	Colorectal cancer liver metastatic tissue	CAT1	Promote colorectal cancer metastasis to the liver	Oncogene	(26)
	-	Downregulated	Oxaliplatin-resistant cells	XIAP	Promote colorectal cancer cell sensitivity to oxaliplatin	Tumor suppressor	(27)
Esophageal	-	Not detected	Not detected	KIF22	Inhibit cell proliferation and migration; promote apoptosis	Tumor suppressor	(28)
Glioma	-	Downregulated	Tissue and cell	RUNX2	Inhibit cell proliferation; promote apoptosis	Tumor suppressor	(29)
	CircRNA PTN	Downregulated	Cell	SOX6	Inhibit glioma cell proliferation; promote apoptosis	Tumor suppressor	(30)

Table I. Continued.

Cancer	Upstream regulator	Expression	Site	Target	Biological function	Role	(Refs.)
Renal cell carcinoma	-	Upregulated	Tissue	Dicer	Promote cell migration, invasion and metastasis	Oncogene	(31)
	-	Upregulated	Tissue and cell	FOXO3	Promote cell proliferation, migration and invasion	Oncogene	(32)
Osteosarcoma	-	Not detected	Cell	CCNG1, Bcl-w and ADAM10	Inhibit cell proliferation, migration and invasion	Tumor suppressor	(33)
Cervical	-	Not detected	Not detected	RAD21	Inhibit cell proliferation; promote apoptosis	Tumor suppressor	(34)

IGF1R, insulin-like growth factor 1 receptor; Prx II, peroxiredoxin II; CLIC1, chloride intracellular channel 1; lncRNA UCA1, long non-coding RNA urothelial cancer associated 1; TRIM29, tripartite motif-containing protein 29; DRAIC, downregulated RNA in cancer; SATB1, special AT-rich binding protein 1; ROCK2, rho-associated protein kinase 2; VEGFC, vascular endothelial growth factor C; CREB1, CAMP-response element binding protein 1; ZNF611, zinc finger protein 611; PKM2, pyruvate kinase M2; RPPH1, ribonuclease P RNA component H1; LMNB2, lamin B2; CAT1, cationic amino acid transporter protein 1; XIAP, X-linked inhibitor of apoptosis protein; KIF22, kinesin superfamily protein 22; circ PTN, circular RNA pleiotrophin; FOXO3, forkhead box O3; CCNG1, cyclin G1; ADAM10, a disintegrin and matrix metalloproteinase-10.

Figure 1. miRNA-122 targets IGF1R and Prx II to inhibit invasion and migration and stem cell proliferation, metastasis and angiogenesis of non-small cell lung cancer cells. miRNA, microRNA; IGF1R, insulin like growth factor I receptor; Prx II, Peroxiredoxin II; p-, phosphorylation; Hh, hedgehog; EMT, Epithelial mesenchymal transition.

Figure 2. Targeting of TRIM29 and STAB1 by miRNA-122 inhibits proliferation, invasion and migration of nasopharyngeal carcinoma cells. TRIM29, Tripartite motif-containing protein 29; SATB1, Special AT-Rich Binding Protein 1; miRNA, microRNA; p-, phosphorylation; MTA1, Metastasis-associated gene 1; TIMP2, Tissue inhibitor of metalloproteinase 2.

downstream genes, such as PKM2 and IGF1R, by sponging miRNA-122, which further promotes proliferation of breast cancer cells; by contrast, miRNA-122 overexpression reverses

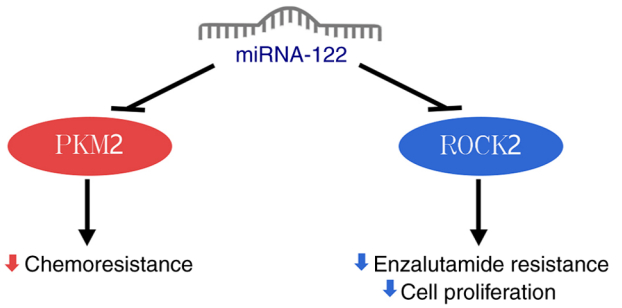

Figure 3. miRNA-122 inhibits proliferation of prostate cancer cells and ameliorates chemoresistance and enzalutamide resistance by targeting PKM2 and ROCK2. miRNA, microRNA; PKM2, Pyruvate kinase M2; ROCK2, Rho-associated protein kinase 2.

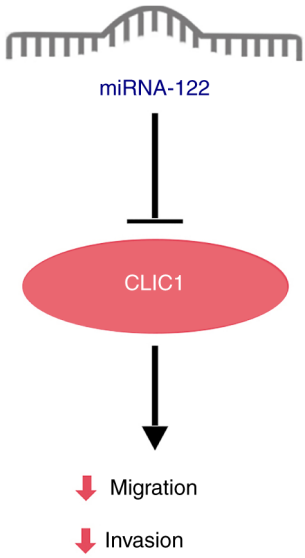

Figure 4. miRNA-122 inhibits Bile duct cancer cell invasion and migration by targeting CLIC1. miRNA, microRNA; CLIC1, chloride intracellular channel 1.

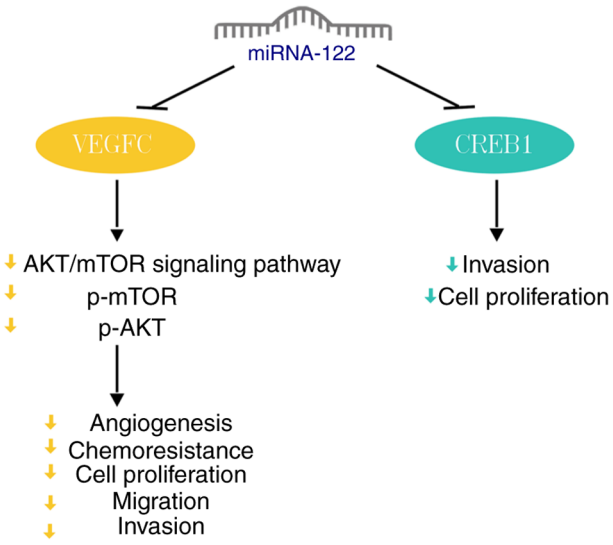

Figure 5. miRNA-122 targets VEGFC and CREB1 to inhibit proliferation, invasion, migration, chemoresistance, and angiogenesis of bladder cancer cells. miRNA, microRNA; VEGFC, vascular endothelial growth factor C; CREB1, CAMP-response element binding protein 1; p-, phosphorylation.

this process (24). miRNA-122 overexpression enhances sensitivity of breast cancer cells to radiotherapy, thereby inhibiting tumor cell survival (23). Radioresistant breast cancer cells show significantly increased miRNA-122 expression, whereas miRNA-122 knockout decreases the survival of these cells. This mechanism may involve miRNA-122 oncogenic potential through targeting zinc finger proteins 611 (ZNF611) in radioresistant breast cancer cells (23). Therefore, in primary breast cancer cells (before radiation therapy and without radioresistance), elevated miRNA-122 expression inhibits cancer progression and serves as a tumor suppressor. Conversely, in radiotherapy-resistant breast cancer cells, elevated miRNA-122 expression can promote radiotherapy resistance, demonstrating its dual role as both a tumor suppressor and oncogene depending on the cellular context (Fig. 6).

Liver cancer. Hepatocellular carcinoma (HCC), the predominant form of liver cancer, is the fifth most common cause of cancer deaths In the United States (47). miRNA-122 disrupts mesenchymal cytoskeleton, upregulates E-cadherin and α-catenin expression and downregulates vimentin and fibronectin expression by binding to the 3'-UTR of Ras homologous gene family member A (RhoA); this triggers mesenchymal-epithelial transition, reverses EMT and thus inhibits the invasion and migration of HCC cells (48).

In a study on adriamycin resistance in HCC (49), overexpression of miRNA-122 suppressed expression of ATP-binding cassette superfamily member 2 and multidrug resistance-associated protein 1. This overexpression enhances sensitivity of HCC cells to chemotherapeutic drugs and inhibits proliferation.

Polyploidy is a balanced amplification of the genome and is common in the liver. Hepatocytes become polyploid mostly due to failure of cytoplasmic division. Approximately 30% of hepatocytes in the human liver are polyploid. Liver polyploidy prevents gene mutations in hepatocytes and decreases the formation of liver tumors (50). miRNA-122 directly targets cytoplasmic cleavage genes cut-like homeobox protein-1, RhoA, microtubule-associated protein RP/EB family member 1, IQ-containing GTPase-activating protein 1, neural precursor cell-expressed developmentally down-regulated protein 4-like and solute carrier family 25 member 34, thereby resulting in cytoplasmic cleavage failure to increase hepatic polyploidization, thus suppressing liver tumorigenesis (51). Other studies have shown that frequent ploidy reduction in polyploid hepatocytes results in predisposition to liver tumor formation, which may imply that notable reduction in hepatic polyploidy contributes to cancer development, as this leads to genetic mutations (Fig. 7) (52,53).

Colorectal cancer (CRC). CRC accounted for 9.4% of all new cases of cancer in 2020 (54). The liver is the most important target organ for hematogenous metastasis of CRC. Liver metastasis is the main cause of death due to CRC (54). Studies have found elevated miRNA-122 expression in liver cells of metastatic CRC, contrasting high expression was not detected in CRC cells. miRNA-122 correlates negatively with

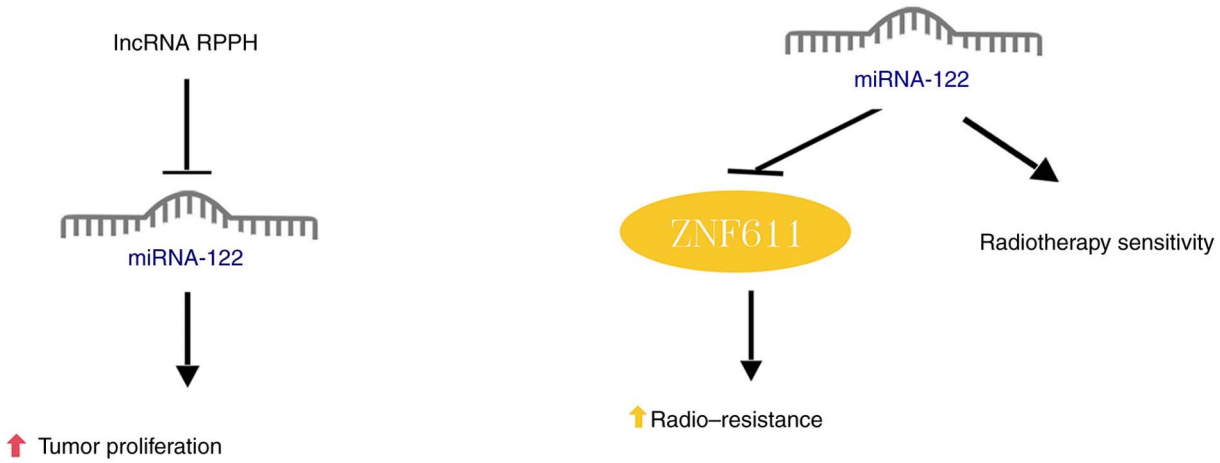

Figure 6. lncRNA RPPH sponges miRNA-122, promoting breast cancer cell proliferation. miRNA-122 promotes radiation sensitivity in breast cancer radiotherapy; miRNA-122 induces radiation resistance by targeting ZNF611. lncRNA, long non-coding RNA; RPPH, ribonuclease P RNA component H1; miRNA, microRNA; ZNF611, zinc finger proteins 611.

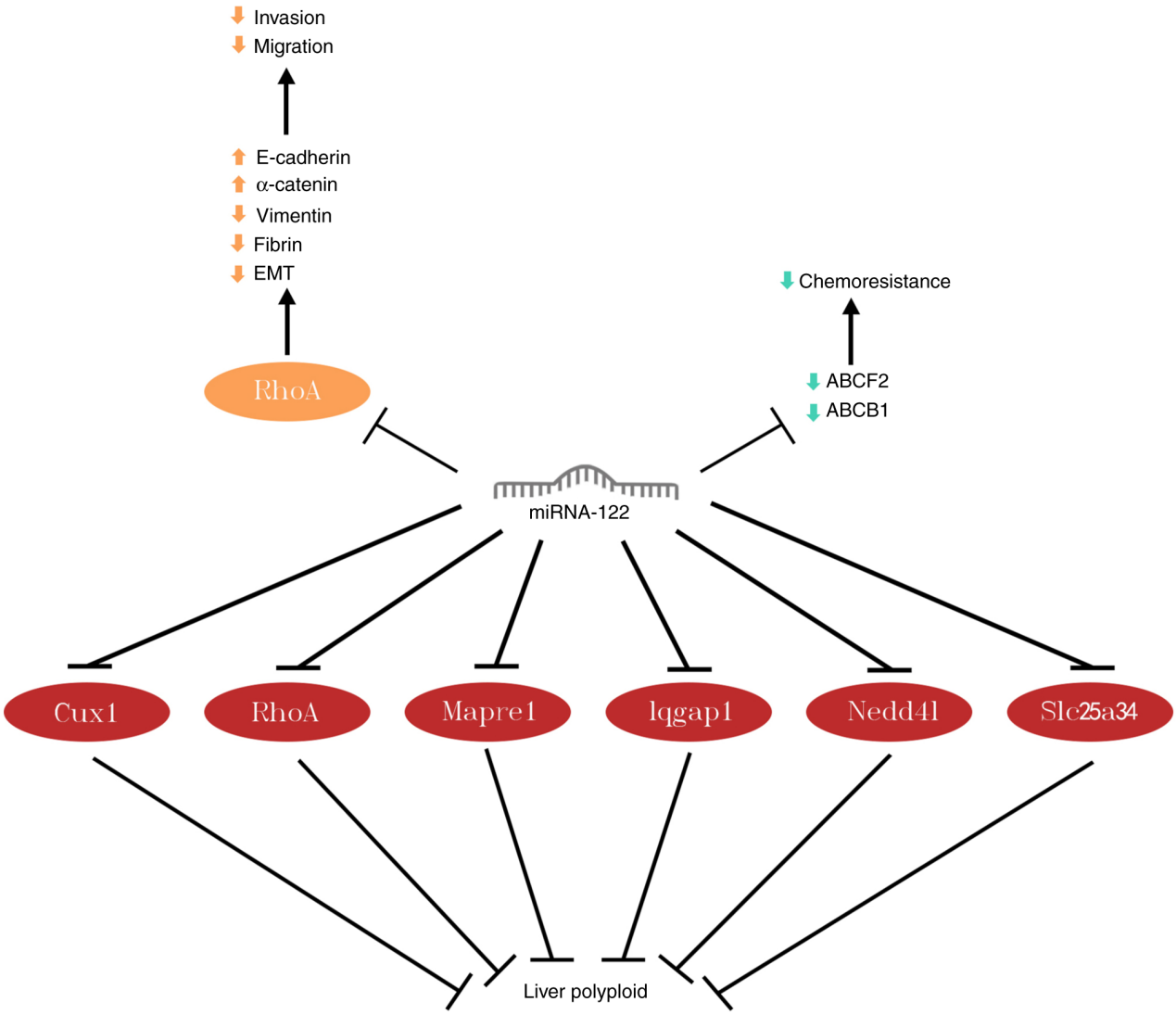

Figure 7. miRNA-122 downregulates ABCF2 and ABCB1 expression to inhibit adriamycin resistance in hepatocellular carcinoma. miRNA-122 targeting of RhoA inhibits migration and invasion of hepatocellular carcinoma cells; targeting Cux1, RhoA, Mapre1, Iqgap1, Nedd4l, and Slc25a34 promotes liver polyploidization. miRNA, microRNA; ABCF2, adenosine triphosphate binding cassette superfamily member 2; ABCB1, multidrug resistance-associated protein 1; Cux1, cut-like homeobox protein-1; Mapre1, microtubule-associated protein RP/EB family member 1; Iqgap1, IQ-containing GTPase-activating protein 1; Nedd4l, neural precursor cell-expressed developmentally down-regulated protein 4-like; Slc25a34, solute carrier family 25 member 34; EMT, Epithelial mesenchymal transition.

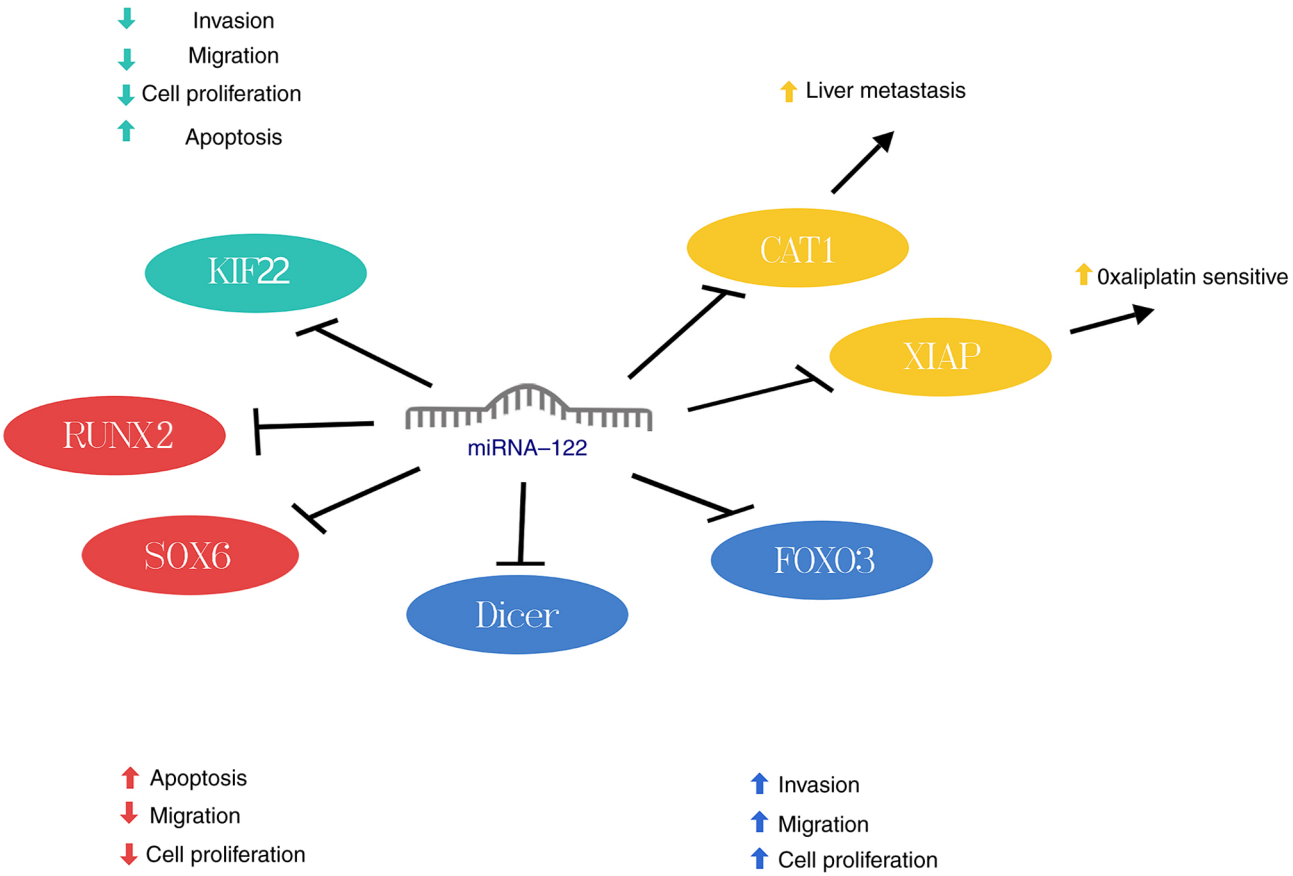

Figure 8. Role of miRNA-122 in cancer. miRNA-122 promotes colorectal cancer liver metastasis by targeting CAT1. miRNA-122 promotes colorectal cancer sensitivity to oxaliplatin by targeting XIAP (yellow). miRNA-122 inhibits esophageal cancer cell proliferation, invasion, migration and promotes apoptosis by targeting KIF22 (green). miRNA-122 inhibits glioma cell proliferation, migration and promotes apoptosis by targeting RUNX2 and SOX6 (red). miRNA-122 promotes cell proliferation, migration and invasion in renal cell carcinoma by targeting FOXO3 and Dicer (blue). miRNA, microRNA; KIF22, kinesin superfamily protein 22; XIAP, X-linked inhibitor of apoptosis protein; CAT1, Cationic amino acid transporter protein 1.

cationic amino acid transporter protein 1 (CAT1) expression and can enhance liver migration by targeting CAT1 (26). In oxaliplatin-resistant CRC cell lines, miRNA-122 expression is reduced while X-linked inhibitor of apoptosis protein (XIAP) expression is increased. miRNA-122 downregulates XIAP to restore oxaliplatin sensitivity in resistant cells, thereby suppressing CRC progression (27). Thus, elevated miRNA-122 levels in untreated CRC cells may indicate potential liver metastasis, suggesting an oncogenic role. Conversely, decreased miRNA-122 expression in oxaliplatin-treated CRC cells may indicate drug resistance, highlighting its role as a tumor suppressor. In summary, miRNA-122 exhibits dual roles as both a tumor suppressor and an oncogene in CRC (Fig. 8).

Esophageal cancer. Due to changes in dietary habits and genetic factors, esophageal cancer is a significant health challenge worldwide, with overall 5-year survival rate of ~10% and a propensity for early metastasis (55). KIF22, a kinesin-like DNA-binding protein, can promote cancer progression. Kinesin superfamily protein 22 (KIF22) is prominently expressed in esophageal squamous carcinoma tissue and cells, correlating significantly with poor prognosis (28); miRNA-122 negatively regulates KIF22, downregulates the expression of cyclin G1 (CCNG1), Cyclin dependent kinase 2, N-cadherin and vimentin and upregulates p21, p27 and E-cadherin expression; this induces S phase arrest and apoptosis of esophageal squamous carcinoma cells and inhibits EMT (28) (Fig. 8). Additionally, the response elements of miRNA-122 and miRNA-143 mediated by adenoviral vectors cause tumor necrosis factor-associated apoptosis-inducing ligand (TRAIL) to be highly expressed in esophageal cancer, but not in normal cells; this selectively induces apoptosis in esophageal cancer cells and protects against the toxicity of TRAIL to the liver (56). This may be an effective approach to treat esophageal cancer and prevent liver toxicity.

Glioma. Glioma is the most common primary malignant tumors of the brain. Glioma grows invasively and often involve surrounding normal brain tissue. RUNX2, part of the RUNX transcription factor family, regulates gene expression and enhances tumor cell proliferation by binding to specific DNA sequences (57). Additionally, miRNA-122 is downregulated in glioma compared with normal tissues (29). By targeting RUNX2, miRNA-122 inhibits proliferation and migration of glioma cells (29). Moreover, miRNA-122 induces cell cycle arrest, promotes apoptosis, and decreases proliferation in transglioma cells by targeting SOX6. However, this inhibitory effect on glioma cells can be reversed by circular RNA pleiotrophin, which serves as a miRNA-122 sponge (Fig. 8) (30).

Table II. Application of microRNA-122 as a biomarker.

Cancer	Expression	Indication	(Refs.)
Acute myeloid leukemia	Downregulated	Shorter recurrence-free and overall survival in response to low expression	(60)
Colorectal	Upregulated	High expression suggests poor prognosis for colorectal cancer with liver metastasis	(63)
Glioma	Downregulated	Glioma diagnosis and poorer prognosis	(64)
Liver cancer	Downregulated	Significant increase in expression following sorafenib treatment suggests liver cancer is sensitive to sorafenib	(65)
Clear cell renal cell carcinoma	Upregulated	Diagnosis of clear cell renal cell carcinoma	(66)
Gastric	Downregulated	Low expression is associated with poorer prognosis	(67)

Renal cell carcinoma (RCC). RCC, is a prevalent form of kidney cancer, constituting for 2 to 3% of all adult malignancies, with 1.8% mortality rate (1). Fan *et al* (31) observed elevated miRNA-122 expression in RCC cells, correlating with poor prognosis. miRNA-122 induces EMT by suppressing Dicer, a downstream target gene, thereby enhancing migration and invasion of RCC cells (31). Similarly, Nie *et al* (32) found increased miRNA-122 expression in RCC cells, which promotes cell proliferation, migration and invasion by targeting FOXO3. Thus, miRNA-122 plays an oncogene role in RCC (Fig. 8).

Other types of cancer. Acute myeloid leukemia (AML) is a blood cancer characterized by abnormal cell proportions due to impaired differentiation of hematopoietic stem cells (58). Zhang *et al* (59) reported that patients with AML with low miRNA-122 levels in their bone marrow have poorer overall survival and lower rates of complete remission compared with those with high miRNA-122 expression (59). Yang *et al* (60) found that miRNA-122 expression is significantly reduced in AML bone marrow compared with non-malignant tissue and high miRNA-122 levels inhibit AML cell proliferation by affecting cell cycle pathways (60). However, further research is needed to understand how miRNA-122 suppresses AML progression.

Osteosarcoma, a common bone malignancy in children and adolescents, is associated with high mortality rates (61). miRNA-122 suppresses proliferation, migration, and invasion of osteosarcoma cells by decreasing the expression of CCNG1, Bcl-w and a disintegrin and matrix metalloproteinase-10 (33). However, this inhibitory effect is reversed by miRNA-122 sponging (33). Additionally, Liu *et al* (62) noted varied miRNA-122 expression between different osteosarcoma cell lines; while miRNA-122 is upregulated in HOS, Saos-2 and U2OS cell lines, it is downregulated in MG-63 cells. High miRNA-122 levels inhibit the proliferation, invasion and migration of Saos-2 osteosarcoma cells, indicating its role as a tumor suppressor despite being highly expressed in this cell line (62).

Cervical cancer is a common malignant tumor affecting female patients accounting for about 3.2% of all cancers (1). According to Yang *et al* (34), miRNA-122 targets RAD21, a component of the cohesin complex, thereby inhibiting the PI3K/AKT signaling pathway in cervical cancer cells. This inhibition suppresses cervical cancer cell proliferation and promotes apoptosis. Elevated levels of miRNA-122 are associated with improved prognosis in patients with cervical cancer (34).

3. miRNA-122 as a biomarker

With technological advancements, the quantification of miRNA-122 has become precise and convenient, highlighting its potential as a biomarker. Recent studies have indicated that miRNA-122 may be valuable for diagnosing cancer, predicting prognosis and assessing treatment response (Table II) (63-67).

Biomarker for diagnosis. The expression levels of miRNA-122 in the urine of patients with clear cell renal cell carcinoma (ccRCC) show a significant 13.9-fold elevation; alongside miRNA-1271 and miRNA-15b, this may be useful in diagnosing ccRCC (66). In prostate cancer, both tissue and serum levels of miRNA-122 are notably decreased and serum miRNA-122 levels effectively distinguish patients with prostate cancer from healthy individuals (22). Additionally, a model combining six miRNAs, including miRNA-122, has superior accuracy in differentiating patients with oral squamous cell carcinoma from healthy controls compared with serum squamous cell carcinoma antigen (68). The aforementioned studies suggest that miRNA-122 has potential to be used as an additional diagnostic marker for certain types of cancer.

Biomarker for prognosis. In CRC, miRNA-122 is associated with increased risk of tumor metastasis (69). Conversely, miRNA-122 expression is associated with improved prognosis in HCC (70), AML (59) and bile duct cancer (43). Low miRNA-122 expression also correlates with poor outcomes following radical resection in liver cancer (71). Yang *et al* (20) found that decreased miRNA-122 expression significantly correlates with advanced tumor node metastasis stage and distant metastasis in NPC. Therefore, miRNA-122 shows promise as a useful tool for predicting cancer prognosis.

Biomarker of therapeutic response. miRNA-122 expression is indicative of treatment response and aids in tailoring effective treatment plans. Elevated miRNA-122 levels predict

early resistance to transcatheter arterial chemoembolization in patients with HCC (72). Additionally, patients with HCC who are responsive to sorafenib exhibit higher miRNA-122 expression post-chemotherapy compared with non-responsive patients, underscoring its potential to predict sorafenib efficacy (65).

4. Application of miRNA-122 in chemotherapy and radiotherapy

Chemotherapy and radiotherapy are frequently utilized in cancer treatment; nonetheless, addressing drug resistance in patients with advanced and recurrent cancer remains a challenge. Enhancing the sensitivity of patients to chemotherapy and radiotherapy is key (73).

miRNA-122 targets XIAP to reverse oxaliplatin resistance in CRC cells (27) and also sensitizes colon cancer cells to 5-fluorouracil (5-FU) by targeting PKM2 (74). In prostate cancer, miRNA-122 enhances cell sensitivity to docetaxel via PKM2 targeting (39). Moreover, miRNA-122 decreases the expression of drug-resistant P-glycoprotein and multidrug-resistance proteins by inhibiting small ubiquitin-like modifier sentrin-specific protease 1, thus overcoming adriamycin and sorafenib resistance in HCC cells (75). miRNA-122 directly targets the Wnt/β-catenin pathway, leading to decreased expression of multidrug resistance proteins 1 and increased sensitivity of HCC cells to oxaliplatin (76).

In radiation therapy, miRNA-122 decreases the expression of stress response regulators such as survivin, apoptosis inhibitory proteins 1 and 2 and IGF1R. This mechanism induces DNA double-strand breaks and promotes apoptosis in NSCLC cells, thereby enhancing inhibition of NSCLC cell proliferation and invasion (77). Additionally, miRNA-122 improves the effectiveness of radiation therapy by decreasing IGF1R expression (78). Thus, adjusting miRNA-122 levels enhances the efficacy of chemotherapy and radiotherapy in specific types of cancer.

5. Systemic delivery strategies for miRNA-122

Due to the susceptibility of miRNAs to enzymatic degradation, protection from RNA hydrolases in extracellular serum is key during systemic delivery to ensure their delivery to target cells. This necessitates encapsulating miRNA in sealed carriers to prevent enzymatic hydrolysis during transportation. Therefore, effective delivery systems are essential for precise delivery of miRNA to tumor cells (79). Utilizing exosomal, viral and nanoparticle vectors for miRNA delivery can address this issue (80).

Exosome vectors. Exosomes are active vesicles secreted by cells to facilitate intercellular substance exchange and information transfer. They are commonly utilized as carriers for delivering miRNA (81). A recent study demonstrated that exosomes derived from adipose-derived mesenchymal stem cells effectively deliver miRNA-122 into HCC cells (82). This results in significant downregulation of CCNG1, disintegrin, MMP10 and IGF1R expression, enhancing the sensitivity of HCC cells to 5-FU and sorafenib (82).

Viral vectors. Viral vectors widely used include lentiviruses, retroviruses, adenoviruses, and adeno-associated viruses (AAVs) (83,84). In an *in vivo* mouse xenograft model, tumor growth of human HCC is notably suppressed by AAV3 along with miRNA-122 and miRNA-26a lentiviral delivery systems (85). Additionally, tumor necrosis factor-associated apoptosis-inducing ligands selectively expressed in osteosarcoma cells through adenoviral vectors of miRNA-122 and miRNA-34 promote apoptosis and inhibit cell proliferation (86). Notably, linking and cloning miRNA-21 and pre-miRNA-122 sequences into viral-like particle expression vectors and delivering them into HCC cells inhibits proliferation, migration and invasion of HCC cells and promotes apoptosis (87). While advantages such as easy cell access and high expression of introduced genes are offered by viral vectors, concerns about immunogenicity and potential promotion of gene mutagenesis have prompted a search for alternatives (88).

Nanocarriers. Nanocarriers offer advantages such as low toxicity, minimal immunogenicity, high permeability and non-integration of genes into the host cell genome, making them essential alternatives to viral vectors (89). Sendi *et al* (90) developed a galactose-targeted lipid calcium phosphate nanoformulation noted for its stability and efficient delivery of miRNA-122 to CRC liver metastatic hepatocytes. This formulation effectively prevents liver metastasis and prolongs survival in CRC mouse models without significant toxicity (90). Additionally, an ultrasound-triggered, phase-transitioning cationic nanodroplet delivers miRNA-122 to HCC cells, resulting in a significant increase in miRNA-122 expression and substantial inhibition of HCC cell proliferation, migration, and invasion (91). Zeng *et al* (92) created graphene-P-gluoprotein loaded with miR-122-InP@ZnS quantum dot nanocomposites, demonstrating effective delivery of miRNA-122 to multidrug-resistant HCC cells and induction of apoptosis (92). Furthermore, Zhang *et al* (93) utilized amphiphilic gemcitabine-oleic acid prodrug nanoparticles for encapsulating miRNA-122, effectively targeting HCC cells and significantly inhibiting proliferation in xenograft nude mice (93).

6. Clinical implications and limitations

Cell proliferation, metastasis and apoptosis are pivotal in tumor growth and development. The hallmark of cancer is aberrant cell proliferation, with the regulation of cell proliferation and survival being crucial in tumor formation (94). Thus, strategies that inhibit tumor proliferation and enhance apoptosis are key in cancer treatment. Additionally, cell metastasis significantly impacts cancer prognosis, as its occurrence signifies disease progression. Therefore, inhibiting tumor cell metastasis is a key therapeutic approach in cancer management (95).

miRNA-122 has garnered notable attention in cancer and liver disease research (96,97). Upregulation of miRNA-122 expression inhibits self-renewal, EMT and angiogenic capacity of NSCLC tumor stem cells (18). In HCC, elevated miRNA-122 levels enhance sensitivity to chemotherapy, suppress cell proliferation, metastasis and invasion and promote liver polyploidization (51,76). Conversely, as an oncogene, high miRNA-122 expression promotes migration

and invasion in RCC (31). miRNA-122 functions by targeting various genes, exerting either oncogenic or tumor-suppressive effects. Moreover, miRNA-122 serves as a biomarker for diagnosing, prognosticating and monitoring response to treatment, thereby enhancing sensitivity to radiotherapy and chemotherapy (66,69). Systemic delivery strategies for miRNA-122 circumvent enzymatic hydrolysis, ensuring precise delivery to tumor cells and enhancing its stability during cancer treatment (90). Consequently, targeting miRNA-122 presents a promising avenue for future cancer therapies, although challenges remain. Determining specific diagnostic and prognostic thresholds for miRNA-122 given its varied roles is a primary challenge. Additionally, understanding interactions between miRNA-122 downstream target genes and cancer signaling pathways requires further investigation. Furthermore, while research on miRNA-122 and cancer treatment shows potential, its clinical translation remains incomplete, necessitating large-scale controlled experiments and clinical trials to elucidate its full mechanistic role in cancer.

7. Conclusion

The present review outlines the multifaceted role of miRNA-122 in various types of cancer. Dysregulation of miRNA-122 is observed in different types of cancer, influencing pathways key to tumor cell behavior such as proliferation, angiogenesis, differentiation, metastasis and apoptosis. Mechanistically, miRNA-122 modulates complex signaling pathways by targeting various genes, although certain lncRNAs and circ RNAs may serve as upstream regulators to regulate miRNA-122 expression. This complexity underscores miRNA-122 as a promising therapeutic target for cancer treatment. However, it lacks a universal or primary pathway across different types of cancer. Furthermore, miRNA-122 shows potential as a biomarker for cancer diagnosis, prognosis and treatment response, enhancing sensitivity to radiotherapy and chemotherapy in specific types of cancer. The systemic delivery of miRNA-122 holds promise in advancing cancer therapy. These insights suggest new avenues for research in cancer diagnosis and treatment.

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Availability of data and materials

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Authors' contributions

JZ wrote the manuscript and constructed figures and tables. XD and RD revised the manuscript. ZC performed the literature review. LW conceptualized the study. Data authentication is not applicable. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

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Competing interests

The authors declare that they have no competing interests.

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