Roles and regulatory mechanisms of miR-30b in cancer, cardiovascular disease, and metabolic disorders (Review)

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Abstract. MicroRNAs (miRNAs) are non-coding RNAs 21-23 nucleotides in length that regulate gene expression, and thereby modulate signaling pathways and protein synthesis in both physiological and pathogenic processes. miR-30b inhibits cell proliferation, migration, invasion and epithelial-mesenchymal transformation in multiple types of cancer. In addition to its role in several types of neoplasias, miR-30b has been shown to exhibit essential roles in cardiovascular and metabolic diseases. In the present review, an overview of the biological functions of miR-30b and its role in the pathogenesis of neoplastic, cardiovascular and metabolic diseases is provided. miR-30b is a potential candidate for clinical development as a diagnostic and prognostic biomarker, therapeutic agent and drug target. However, further research is required to elucidate its role in health and disease and to harness its potential clinical utility.

Contents

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Abbreviations: AMI, acute myocardial ischemia; CRC, colorectal cancer; EGFR, epidermal growth factor receptor; EGFR-TKIs, EGFR tyrosine kinase inhibitors; EMT, epithelial-mesenchymal transformation; miRNA, microRNAs; NAFLD, non-alcoholic fatty liver disease; NSCLC, non-small cell lung cancer; PAI-1, plasminogen activator inhibitor-1; RISC, RNA-induced silencing complex

Key words: miRNA-30b, tumor, cardiovascular diseases, metabolism, biomarker

1. Introduction

MicroRNAs (miRNAs) are endogenous short-chain RNAs 21-23 nucleotides in length that regulate posttranscriptional gene expression (1). A series of biogenetic processes convert transcripts into mature miRNAs (2). Briefly, miRNA-encoding genes are first transcribed into pri-miRNAs that are digested by Drosha and Dicer enzymes to produce mature miRNAs (3,4). Subsequently, mature miRNAs are assembled into RNA-induced silencing complexes (RISC) (5). RISC recognize complementary bases, and either degrade the target mRNAs or inhibit their expression depending upon the degree of complementarity (6,7). miRNAs regulate translation through both direct and indirect mechanisms (8).

miRNAs serve important roles in cell proliferation, differentiation, apoptosis and other biological processes (2,9). Furthermore, miRNAs affect various metabolic pathways, including lipid, glucose and bone metabolism (10-12), and pathophysiological dysregulation of miRNAs may result in oncogenesis and tumor progression (13). miR-30b, a member of the miR-30 family, has been implicated in the pathogenesis of multiple diseases, including various types of cancer, diabetes, and cardiovascular, renal and neurological disorders (14-19). In the present review, the current body of literature regarding the role of miR-30b in diverse range of diseases, particularly cancer, cardiovascular diseases and metabolic disorders is summarized.

2. Biological function of miR-30b

In this section, the biological function of miR-30b in the physiology of cell differentiation and development, autophagy and inflammation is summarized. miR-30b is an important modulator of cell differentiation and development. miR-30b was shown to downregulate chondrogenic differentiation induced by TGF-β3 in murine embryonic stem cells (C3H10T1/2) by targeting SOX9 (20) and promoted the growth of retinal ganglion axons by inhibiting the expression of Semaphorin3A in a murine model of optic nerve injury (21). During angiogenesis, miR-30b overexpression stimulated the TGF-β2 signaling pathway, thus inhibiting capillary formation; whereas miR-30b inhibition promoted angiogenesis (22).

Autophagy is a cellular recycling process that is highly conserved amongst eukaryotes (23). Vesicles transport cargos to lysosomes for degradation and recycling (24). The role of miR-30b in autophagy has been investigated in several studies. In a murine model of hepatic ischemia reperfusion injury (IRI), miR-30b inhibited autophagy and attenuated the consequent severity of IRI by reducing Atg12-Atg5 conjugates (25). miR-30b was also shown to regulate autophagy in vascular smooth muscle cells; overexpression reduced the expression of autophagy-related genes such as *BECN1*, *ATG5* and *LC3b*, whereas miR-30b downregulation increased their expression (26). In an *in vitro* model of TNF-α-induced chondrocyte injury, miR-30b directly inhibited the expression of autophagy-related genes *BECN1* and *ATG5*, whereas its reduced expression increased cell survival and attenuated cartilage degradation (27). In summary, miR-30b possesses significant functions in the physiology of autophagy that should be explored in additional diseases.

miR-30b also serves a critical role in inflammation. This includes regulation of the physiological function of macrophages/dendritic cells, Fc receptor-mediated phagocytosis, antigen processing, cytokine production and related innate immune responses (28-30); as well as the regulation of cell-mediated responses by mediating T cell expression of IL-10 and Toll-like receptor 4 (31); and the control of humoral immunity by inhibitng B cell expression of kynurenine-regulated lipopolysaccharide by targeting the *Bach2* gene (32). In a rat model, the upregulation of miR-30b was shown to directly impact peritoneal fibrosis through a BMP7-mediated pathway (33). Although miR-30b function has been studied in multiple immune effector cell subtypes as described above, its role in the regulation of immune response is only partially understood and requires further study.

3. Role of miR-30b in cancer

The role of miR-30b has been studied in various malignancies, including pancreatic, gastric, and lung cancer; where it is involved in the regulation of multiple processes such as cell proliferation, differentiation, apoptosis, invasion and metastasis (Fig. 1). In addition, miR-30b serves a pivotal role in epithelial-mesenchymal transition (EMT), a phenotypic conversion that is characterized by reduced expression of epithelial markers and upregulation of mesenchymal markers in cancer stem-like cells during carcinogenesis. miR-30b inhibits Snail-mediated EMT and the consequent migratory and invasive capacity of pancreatic cancer stem cells and hepatoma cells (34,35). Paradoxically, miR-30b can function as either an oncogene or tumor suppressor gene dependent on the type of cancer, as discussed in detail in further chapters (Table I).

Role of miR-30b in gastric cancer. Gastric cancer is one of the most common malignancies and is the second leading cause of cancer-related death worldwide (36). Invasion and metastasis are major causes of mortality (37). In a 2014 study, decreased expression of miR-30b-5p was observed in gastric cancer tissue and in 4 gastric cancer cell lines, and was shown to be correlated with lymph node metastasis (38). Zhu *et al* (15) suggested that miR-30b promoted apoptosis and inhibited tumorigenesis by downregulating plasminogen activator inhibitor-1 (PAI-1). Tian *et al* (39) showed that miR-30b inhibited tumor migration and invasion in AGS and MGC803 cells, two gastric cancer cell lines, by targeting the synthesis of EIF5A2, an oncogenic protein that serves a fundamental role in EMT. Xi *et al* (40) reported that upstream regulator of miR-30b, lncRNA MALAT1, enhanced autophagy and cisplatin resistance in the gastric cancer cell line AGS/CDDP by inhibiting the miR-30b/ATG5 axis. In summary, miR-30b may act as a tumor suppressor gene in gastric cancer.

Role of miR-30b in hepatocellular carcinoma. Numerous studies have shown an association between dysregulated miR-30b expression and hepatocellular carcinoma (HCC). Huang *et al* (41) demonstrated that miR-30b expression was significantly lower in HCC compared with the para-cancerous tissue. miR-30b was also shown to regulate the expression of CD90, resulting in inhibition of HCC progression. Sun *et al* (35) found that miR-30b inhibited EMT and metastasis in HCC. Qin *et al* (42) reported that miR-30b-5p inhibited proliferation and slowed cell cycle progression of HCC by targeting *DNMT3A* and *USP37*. In addition, miR-30b influenced HCC recurrence and prognosis. Huang *et al* (41) showed there was an association between high expression of miR-30b and relapse-free survival. miR-30b expression was shown to affect hepatic metastasis; Hur *et al* (43) reported that miR-30b was upregulated in liver metastases compared with primary tumors. In addition, miR-30b may serve as a prognostic biomarker (44). miR-30b expression can accurately predict metastasis-free and hepatic metastasis-free survival (45) and the risk of recurrence (46).

miR-30b may also mediate drug resistance in HCC, although its specific role is contested (47,48). Moreover, miR-30b-mediated pathways may serve as potential novel therapeutic targets. Yeh and Huang (49) used two methods (jetPEI/anti-miR-30b complexes and a miR-30b antagonist) to deliver anti-sense miR-30b in a murine J7 tumor xenograft model of HCC and found that both methods inhibited tumor growth when compared with the controls. However, the specific roles of miR-30b in oncogenesis and drug resistance require further study.

Role of miR-30b in colorectal cancer. Colorectal cancer (CRC) is one of the most prevalent types of cancer of the digestive system in western countries and is the third leading cause of cancer-related death worldwide (50). Yilmaz *et al* (51) found that miR-30b expression was decreased in CRC tissues, and Yoon *et al* (52) showed that miR-30b suppressed the invasiveness of CRC cell lines. The inhibitory role of miR-30b in CRC may be due to targeting of *KITENIN*, *KRAS*, *PIK3CD, BCL2*, *SIX1* and *Snail* (43,53-56). Although these findings suggest a suppressor role of miR-30b in CRC, to the best of our knowledge, no studies have addressed the potential therapeutic value of miR-30b in CRC. Thus, studies investigating its therapeutic utility in CRC are required.

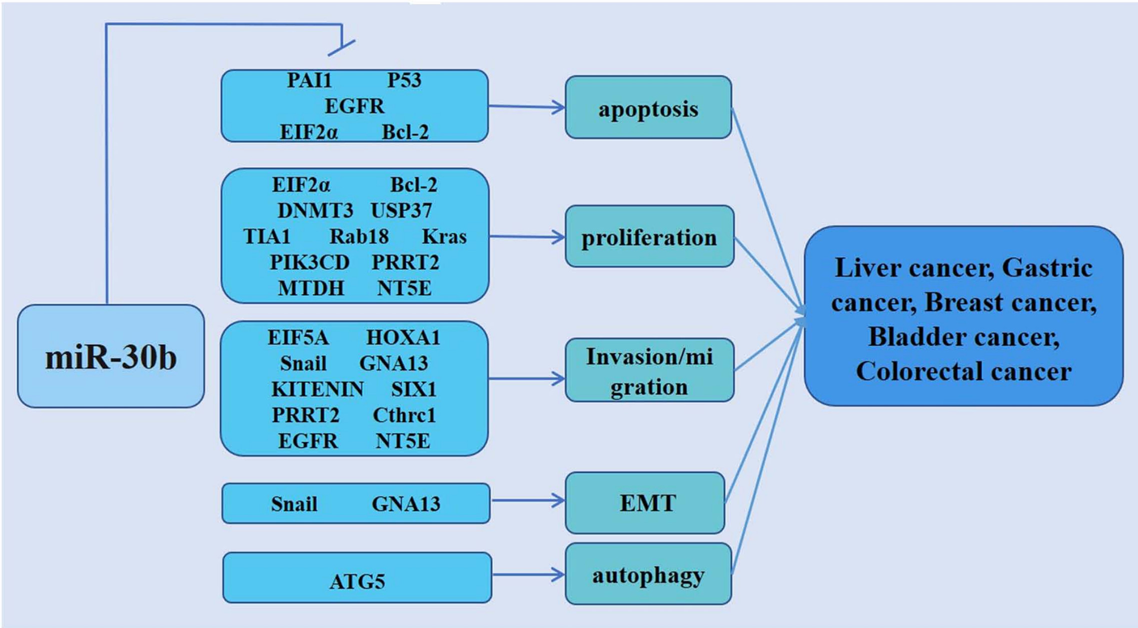

Figure 1. Roles of miR-30b in cancer. miR-30b inhibits apoptosis, proliferation, invasion, migration, EMT and autophagy by targeting numerous target genes to affect the development and progression of various neoplasms, including hepatic, gastric, breast, bladder and colorectal cancer. miR-30b, microRNA-30b; EMT, epithelial-mesenchymal transition.

Role of miR-30b in non-small cell lung cancer (NSCLC). Lung cancer is the leading cause of cancer death worldwide (57). Previous studies have suggested that miR-30b expression is downregulated in non-small cell lung cancer primary tumors (58) and that it inhibits proliferation, invasion and migration of NSCLC cells by targeting *Cthrc1*, *Rab18* and *EGFR* (59,60). These findings suggest that miR-30b upregulation may serve as a therapeutic strategy, and this has been attempted using radiation therapy; low-dose pretreatment was used to increase miR-30b expression, thereby inhibiting PAI-1 activity and improving the clinical response to full-dose radiation (61).

In contrast to its reduced expression in lung tumors, miR-30b levels are increased in circulating extracellular vesicles in patients with NSCLC (62), highlighting its potential use as a diagnostic and prognostic biomarker. High serum concentrations of miR-30b and miR-30c are associated with a reduction in both progression-free and overall survival (63). In addition, miR-30b expression is a useful predictor of a patient's response to first-line tyrosine-kinase inhibitors (TKIs) (64).

The role of miR-30b in drug resistance in patients with lung cancer is less clear. The targeting of the epidermal growth factor receptor (EFGR) pathway by miR-30b enhanced the *in vitro* sensitivity of NSCLC cells to EGFR-TKIs (65). However, Garofalo *et al* (66) showed an association between increased expression of EGF and hepatocyte growth factor receptors with upregulated miR-30b expression and resistance to the EGFR-TKI gefitinib. Silencing of Dicer downregulated miR-30b/c and miR-221/222 expression, increased capsase-3 expression and restored gefitinib sensitivity (67). miR-30 also serves a fundamental role in cisplatin resistance. miR-30 inhibition reduces the clonogenic survival of CisR cells *in vitro* when treated with cisplatin (68).

Role of miR-30b in bladder cancer. Bladder cancer is a common urogenital malignancy, with high mortality rates and a 70% recurrence rate (69). Wszolek *et al* (70) found that the expression of miR-30b in invasive bladder cancer was downregulated compared with normal tissues. However, Mahdavinezhad *et al* (71,72) found that 64% of bladder cancer tissues possess high levels of miR-30b compared with normal tissues. A study in the USA showed elevated expression of miR-30b in the urine of patients with high-grade urothelial carcinoma (73), whereas two other studies from the USA and the Czech Republic showed significantly reduced urine miR-30b levels in patients with bladder cancer (70,74). Therefore, the role of miR-30b in bladder cancer is unclear and should be investigated further. However, miRNAs may possess potential value as biomarkers for the early diagnosis of bladder cancer, and can also supplement histopathological diagnosis (75), and urine samples may serve as an easily accessible clinical specimen to study this biomarker (76).

Role of miR-30b in breast cancer. Breast cancer is the most commonly diagnosed cancer and the leading cause of cancer-related death in women (77). The expression of miR-30b is lower in breast cancer tissues than in normal tissues (78). However, Zhang *et al* (79) found that miR-30b levels were upregulated in the blood of patients with breast cancer, even during the very early-stages of the disease. In 2015, Ribas *et al* (80) studied 1,302 subjects from the European genomic archives and found that miR-30b expression was lower in younger patients (<35 years old) compared with the older group. miR-30b may also inhibit bone metastasis by targeting numerous genes related to osteoclast stimulation (such as *IL-8* and *IL-11*), osteoblast inhibition (*DDK-1*), tumor cell osteogenesis (*RUNX2* and *CDH11*) and invasion (*CTGF*, *ITGA5* and *ITGB3*) (81).

Table I. Function of miR-30b in different types of tumors and the possible target genes.

First author/year	Tumor type	Target gene	Expression and function of miRNA	(Refs.)
Xiong *et al*, 2018	Pancreatic cancer	Snail	Inhibits EMT	(34)
Guo *et al*, 2019		-	Reverses EMT, reduces migration and invasion, and inhibits the tumorigenicity	(85)
Zhu *et al*, 2014	Gastric cancer	PAI1	Promotes apoptosis	(15)
Tian *et al*, 2015		EIF5A2	Inhibits migration and invasion	(39)
Qiao *et al*, 2014		-	Inhibits migration	(38)
Li *et al*, 2017	Esophageal cancer	HOXA1	Inhibits growth, migration and invasion	(86)
Xu *et al*, 2019		ITGA5, PDGFRB, PI3K/Akt	Inhibits migration and invasion	(87)
Liu *et al*, 2017	Renal cell carcinoma	GNA13	Inhibits proliferation, invasion, migration and EMT	(88)
Reddemann *et al*, 2015	Malignant lymphoma	-	Downregulated	(89)
Oduor *et al*., 2017		-	Upregulated	(90)
Croset *et al*, 2018	Breast cancer	-	Inhibits bone metastasis	(81)
Zhang *et al*, 2017		-	Upregulated	(79)
Luo *et al*, 2014		-	Downregulated	(82)
Hafez *et al*, 2012				(78)
Mahdavinezhad *et al*, 2015	Bladder cancer	-	Upregulated	(71)
Mahdavinezhad *et al*, 2015				(72)
Wszolek *et al*, 2009		-	Downregulated	(70)
Park *et al*, 2014	Colorectal cancer	KITENIN	Inhibits migration and invasion	(53)
Liao *et al*, 2014		KRAS, PIK3CD and BCL2	Inhibits proliferation in vitro and tumor growth in vivo	(54)
Zhao *et al*, 2014		SIX1	Inhibits migration and invasion	(55)
Wu *et al*, 2014		Snail	Inhibits invasion and migration	(56)
Xu and Li, 2016	Malignant glioma	EFGR	Related to microvascular proliferation	(91)
Li *et al*, 2018		PRRT2	Promotes proliferation, migration and invasion	(92)
Zhang *et al*, 2018		MTDH	Inhibits proliferation	(93)
Jian *et al*, 2019		RECK	Inhibits proliferation, invasion and migration	(94)
Hu *et al*, 2018	Parathyroid carcinoma	-	Downregulated	(95)
Li and Wang, 2014	Laryngeal carcinoma	p53	Promotes apoptosis	(96)
Sun *et al*, 2017	Liver cancer	Snail	Inhibits EMT, migration and invasion	(35)
Qin *et al*, 2017		DNMT3A, USP37	Inhibits proliferation and cell cycle	(42)
Yeh and Huang, 2016		TIA1	Promotes growth in tumor models	(49)
Li *et al*, 2018	Non-small cell lung cancer	-	Upregulated	(62)
Hu *et al,* 2016		-	Downregulated	(58)
Zhong *et al*, 2014		Rab18	Inhibits proliferation	(59)
Chen *et al*, 2015		Cthrc1	Inhibits invasion and migration	(60)
Qi *et al*, 2018		EGFR	Inhibits proliferation, migration and invasion, induces apoptosis	(65)
Park *et al*, 2019		PAI-1	Reduces phosphorylation of downstream survival signals Akt and ERK	(61)
Wang *et al*, 2018	Gallbladder carcinoma	NT5E	Inhibits proliferation, invasion and migration	(97)

EGFR, epidermal growth factor receptor; PAI-1, plasminogen activator inhibitor-1; -, unknown.

Luo *et al* (82) developed an assay for the early diagnosis of breast cancer that measured levels of four downregulated miRNAs (miR-451, miR-148a, miR-27a and mi-R-30b) and was able to distinguish patients with breast cancer from the healthy controls based on the expression of these four miRNAs.

A miRNA-mediated PI3K pathway serves a central role in trastuzumab resistance (83). PI3K pathway inhibitors resulted in reduced miR30b expression and re-sensitization to trastuzumab in the trastuzumab resistant HCC1954 cells (84).

Role of miR-30b in other types of cancer. miR-30b has been shown to serve as a regulatory factor in other malignancies, including pancreatic (85), esophageal (86,87) and renal cell carcinomas (88), lymphoma (89,90), glioma (91-94) and parathyroid (95), laryngeal (96) and gallbladder carcinoma (97). The role of miR-30b in these types of cancer has been evaluated in a relatively small number of studies, and the results are summarized in Table I.

4. Role of miR-30b in cardiovascular disease

Cardiovascular disease remains the leading cause of morbidity and mortality worldwide (98). In rat models, miR-30b expression was shown to be downregulated in myocardial IRI, whereas upregulation attenuated cardiomyocyte apoptosis (14,99) by targeting *KRAS* and activating the Ras/Akt pathway (14). Li *et al* (100) suggested that miR-30b reduced homocysteine-induced apoptosis in coronary endothelial cells by downregulating the expression of caspase-3. miR-30b expression was decreased in the peripheral blood of patients with acute myocardial ischemia (AMI) and in the peripheral blood and myocardial tissue in an AMI murine model (99). Based on the murine model, it was also suggested that miR-30b exerted a myocardial protective effect by targeting PAI-1 (101).

By contrast, Shen *et al* (102) reported that miR-30b expression was upregulated in a murine model of myocardial infarction and primary cardiomyocyte hypoxia models and was associated with ischemic injury. A study in the USA reported that miR-30b may promote cardiomyocyte death by targeting Bcl-2, and that inhibiting miR-30b reduced Ang II-induced myocardial cell apoptosis (103). A role for miR-30b in atherosclerosis was suggested based on the levels of miR-30b in the blood of patients with coronary artery disease (92). miR-30b may inhibit the proliferation and apoptosis of human coronary endothelial cells by targeting ITGA4 (104).

5. Role of miR-30b in metabolic disease

Numerous studies have shown an association between miR-30b and several metabolic diseases, such as obesity, diabetes and non-alcoholic fatty liver disease (NAFLD). Kim *et al* (105) found that miR-30b levels were reduced in the serum and visceral adipose tissue of obese subjects. miR-30b was downregulated in subcutaneous adipose tissue of subjects with insulin resistance (106). Stepien *et al* (107) found that miR-30b was upregulated in circulating exosomes of patients with type 2 diabetes mellitus (T2DM). Zang *et al* (108) showed reduced expression of miR-30b in the urinary exosomes of patients with T2DM and diabetic kidney disease (DKD) compared with subjects with T2DM without DKD (108). miR-30b was shown to regulate insulin sensitivity in a rat model of NAFLD by targeting SERCA2b and the serum levels of miR-30b were also positively correlated with hepatic steatosis and insulin resistance in a cohort of 165 Chinese individuals (109). A Spanish study found that hepatic miR-30b levels were upregulated in obese patients with NAFLD compared with patients with uncomplicated obesity (110). Further research is required to clarify the roles and mechanisms of miR30b in metabolic diseases, and to explore its potential clinical utility as a diagnostic analyte and drug target.

6. Conclusion

A growing body of research has shown that a range of functions are mediated by miR-30b in the pathogenesis of numerous diseases, including cancer, cardiovascular disease and metabolic disorders. These include the modulation of cell proliferation, autophagy, invasion, migration and EMT in cancer; apoptosis in myocardial ischemia, and NAFLD in insulin insensitivity. Although progress has been made, the current state of knowledge of the functions of miR-30b is still incomplete. Studies of the roles of miR-30b have yielded inconsistent results that may be related to different sample types and the demographics of the study subjects. The current body of literature suggests that miR-30b offers significant clinical potential as a diagnostic and/or prognostic biomarker, therapeutic agent and drug target. Further research is required to elucidate its role in health and disease and to harness its potential clinical utility.

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Authors' contributions

Study concept and design: YNX. Acquisition and analysis of data: QZ, SSL, JZ, XFM, MZD and BKS. The drafting and writing of the manuscript: QZ and SSL. The revision of the manuscript: YNX. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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