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Review

The Versatile Role of microRNA-30a in Human Cancer

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Key Words
microRNA-30a • Cancer • Oncogene • Onco-suppressor

Abstract
MicroRNAs (miRNAs) are a group of noncoding RNA molecules of 20-23 nucleotides length that negatively regulate gene expressions in numerous cellular processes. Through complementary paring with target mRNAs, miRNAs have frequently emerged as dual regulators of cancer development by acting on multiple signaling pathways, thereby act as novel biomarkers for cancer diagnosis, prognosis, and prediction of response to treatment. As one of them, miR-30a has been found to act as an onco-suppressor of tumorigenesis pathways through inhibition of cellular proliferation, migration and invasion. Simultaneously, miR-30a plays a progressing role in several types of cancer, determined by relevant target genes as well. In the present review, we summarize recent research regarding miR-30a, including its biological function, expression and regulation, especially focusing on its role in cancer development and progression. Clinically, miR-30a may serve as a potential target in the diagnosis and therapy of human cancer.

Introduction

MiRNAs, a set of non-coding RNAs encoded by the genome with about 20-23 nucleotides in length, play important roles in various biological processes, including cellular proliferation, differentiation and apoptosis [1, 2]. By complete or incomplete complementary paring to the 3'-untranslated region (UTR), miRNAs promote degradation or translational repression of targeted mRNAs and act as negative post-transcriptional modulators [3, 4]. Each miRNA targets approximately 200 mRNAs, while each mRNA can be targeted by couple of miRNAs [5].

Most of the genes encoding miRNA are located in fragile sites or in cancer-associated genomic region, implying that miRNAs are extensively involved in cancers [6]. In the last decade, abnormal expression of miRNAs has increasingly been documented in the progress

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of human cancer, involving oncogenesis, invasion and metastasis, functioning as oncogene or tumor suppressor [7-9]. Therefore, miRNAs have provided a promising insight into strategies of diagnosis and prognosis in various types of human cancers [10-13]. Moreover, the diagnostic and prognostic characteristics of miRNAs could open new opportunities in the field of cancer therapy [14-18].

To data, miRNA30a has been demonstrated to be involved in development of several types of tumors [19-21]. This article reviews the current research of the physiology of miR-30a with a focus on its function in different types of cancers.

Biological function of miR-30a gene

The miR-30 family consists of five highly conserved and mature members (miR-30a, -30b, -30c, -30d and -30e), which lie in different chromosomes or neighboring sites (Fig. 1). Among the members, miR-30a is located on chromosome 6q13, and is derived from an intron transcriptional unit [22]. MiR-30a has usual functions of many miRNA species, and participates in a wide spread of biological processes, including cellular differentiation and development. In osteoarthritis, significantly upregulated miR-30a promoted extracellular matrix degradation by modulating Sox9 and downstream effectors [23]. In the myogenic regulatory activity, overexpression of miR-30a resulted in expanded apoptosis and altered somite morphology by controlling Sine oculis homeobox 1 (Six1) expression[24]. In mesenchymal stem cells (MSCs), miR-30a presented to be biomarker and novel regulator on the osteogenic differentiation other than proliferation by inhibiting bone morphogenetic protein 9 [25, 26]. Furthermore, the over expression of miR-30a promoted chondrogenic differentiation via down-regulating the expression of Delta-like 4 (DLL4, a ligand of the Notch signaling family) [27]. In addition, miR-30a stimulates arteriolar branching by abrogating endothelial DLL4, consequently controlling endothelial tip cell behavior [28]. As demonstrated, glioma cell invasion could be boosted by miR-30a through repressing neural cell adhesion molecule (NCAM) [29].

Notably, neuronal overexpression of miR-30a resulted in decrease of brain-derived neurotrophic factor, a crucial regulator during cortical development and maturation in prefrontal cortex [30]. After stroke, miR-30a expression was significantly reduced in cortical neurons, pretending to be a biomarker for ischemic stroke in humans, furthermore prevented neural ischemic injury by down-regulating heat shock protein A5 protein expression [31, 32]. Circulating miR-30a in human was highly expressed after acute myocardial infarction, acting as a potential indicator and providing a promising therapy strategy [33, 34]. Overexpression of glucocorticoid receptor (GR) α induced by silencing of miR-30a could inhibit podocytic apoptosis [35].

Epithelial-to-mesenchymal transition (EMT), which is recognized to be one of the key mechanisms for inducing variability in cell populations [36], is well characterized during organogenesis [37], wound healing [38], and initiating metastasis in epithelial cancer [39, 40]. With regard to EMT, miR-30a exhibited an attenuating effect after podocyte injury by inhibiting the nuclear translocation of nuclear factor of activated T cells 3 (NFATc3) [41]. Besides, miR-30a inhibited transforming growth factor (TGF)-β1-induced EMT and peritoneal dialysis related peritoneal fibrosis through down-regulating of snai1 [42].

Autophagy is a cellular process of self-degradation of double membrane-bound vesicles in which organelles or portions are sequestered into autophagosome for energy production [43]. Overexpression of miRNA-30a could restrain the beclin-1 expression induced by Hepatitis B virus X protein (HBx), wherefore modulating autophagosome formation in hepatic cells [44]. Through inhibiting beclin-1, miR-30a was proved to activate autophagy during myocardial injury induced by angiotensin II [45], thereby eased pressure overload-mediated cardiomyocyte hypertrophy [46]. As demonstrated, miR-30a affected autophagy via modulating Beclin-1 expression [47], thereby played a pivotal role in rheumatoid arthritis [48] and cancer development and treatment [49].

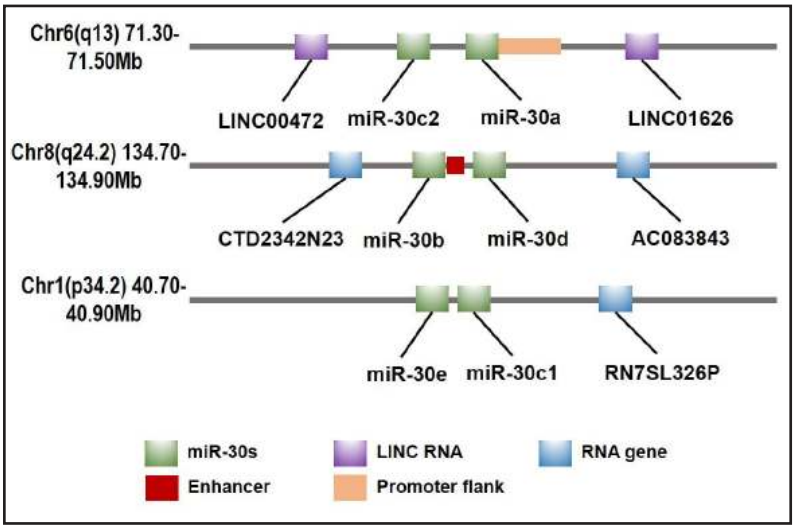

Fig. 1. Architecture of the miR-30 family. The miR-30 family members lie in different chromosomes or neighboring sites.

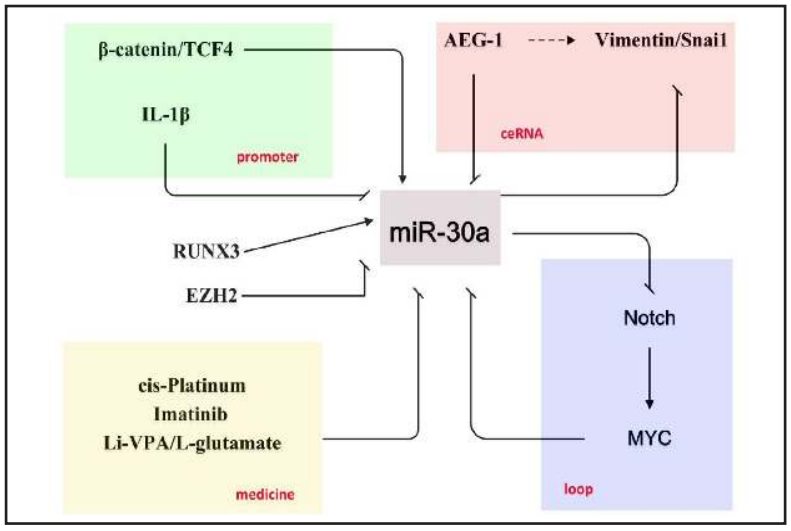

Fig. 2. Factors regulating expression of miR-30a. Expression of miR-30a is modulated in different modes.

In addition, miR-30a played a crucial role in the regulation of the autoimmune responses in rheumatoid arthritis and systemic sclerosis by blocking B cell-activating factor [50]. Moreover, miR-30a could inhibit IL-10-induced cytokine release by targeting STAT1/MD-2(a 25kDa lipopolysaccharide-binding protein) in human monocytes [51]. Besides, miR-30a inhibited the immunosuppressive effect of IL-1β by targeting transforming growth factor-β-activated kinase 1 binding protein 3 (TAB3) in MSCs [52]. The level of miR-30a was much higher in systemic lupus erythematosus (SLE) patients than in healthy, which can promote B cell proliferation and the production of IgG antibodies [53]. Interestingly, an animal experiment discovered that miR-30a produced an escalation of alcohol intake and a preference over water through the brain-derived neurotrophic factor signal pathway in mouse [54].

The expression regulation of miR-30a

Regulation of miR-30a expression occurs in several modes (Fig. 2). Accumulating evidence showed that some miRNAs have been certificated to be regulated by Wnt/β-catenin pathway, such as let-7 and miR-371-373 cluster [55, 56]. MiR-30a was also activated by Wnt/β-catenin pathway through direct binding of β-catenin/TCF4 to two sites (site1:-1206 to-1200; site2: -1145 to -1139) upstream of a canonical TATA-box (TATATTG) in the

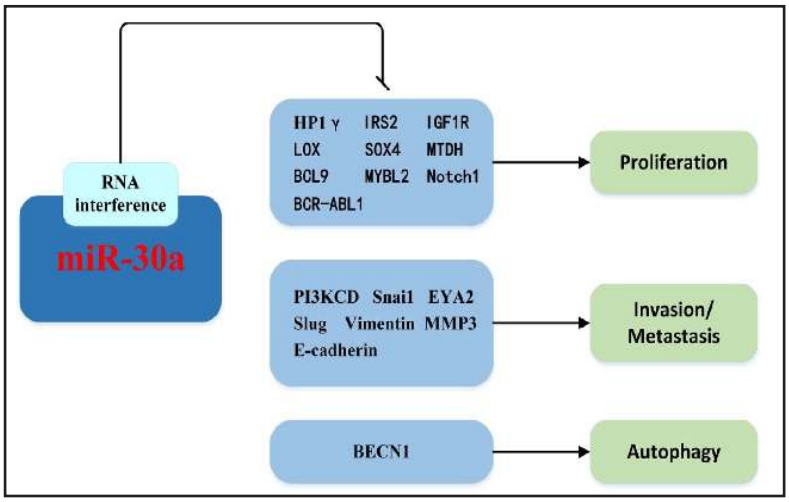

Fig. 3. The role of miR-30a in cancer. By regulating multiple targets, miR-30a participates in various of cancer processes, including proliferation, invasion, metastases and autophagy.

promoter region of miR-30a [29]. In human osteoarthritis, the proinflammatory cytokine interleukin-1β (IL-1β) could suppress miR-30a expression by recruiting the activator protein (AP-1) transcription factor c-jun/c-fos to the miR-30a promoter [57]. Enhancer of zeste homolog 2 (EZH2), a critical regulator in cell survival and EMT, could inhibit miR-30a in malignant peripheral nerve heath tumor [58]. In gastric cancer cases, overexpression of RUNX3 increased the expression of miR-30a [59].

Interestingly, the expression of miR-30a was substantiated to be altered by several kind of medicines, involving lithium/valproic acid combination (Li-VPA) and L-glutamate [60], imatinib [61] and cis-Platinum [62], although the underlying mechanism was not exclusively clear.

Another regulatory mechanism underlying is competitive endogenous RNAs (ceRNA), which indicated regulating relation between messenger RNAs through competing for the shared microRNAs [63]. It was verified that the 3'-untranslated regions of AEG-1, Snai1 and Vimentin competitively bind to miR-30a in A549 cells. Accordingly, AEG-1 indirectly regulated the expression of Vimentin and Snai1 in inducing EMT of human non-small cell lung cancer (NSCLC) via competitive combining with miR-30a [64].

As already noted in other microRNAs, the expression of miR-30a is also regulated by its own targets. It was proved that miR-30a was negatively influenced by MYC [65]. Further research confirmed that miR-30a directly inhibited NOTCH expression, which induced MYC and contributed to the pathogenesis of lymphoid malignancies. Herein, a regulatory loop was characterized, where by the MYC-mediated inhibition of miR-30a suppressed NOTCH, eventually modulating its own expression [66].

The role of miR-30a in human cancer

MicroRNA mainly performs its function via interacting with target mRNA through the seed region of nucleotide sequences. As shown in Fig. 3, most of the studies involving miR-30a have paid close attention to its function in cancers, including cellular proliferation, invasion, metastasis, and autophagy. Documents have clarified that miR-30a plays a dual role as an oncogene or onco-suppressor in different types of cancers (Table 1).

Expression and the clinical significance of miR-30a in cancer

Levels of miR-30a were found to remarkably descend in most of cancer tissues compared with those in adjacent non-tumorous tissues, such as colorectal cancer [67, 68], hepatocellular carcinoma [69, 70], breast cancer [71], renal cell carcinoma [72],

Table 1. Target genes of miR-30a verified in cancer cells

Types of tumor	Target gene	Function role	ref
Colorectal cancer	HP1γ	Inhibition of cell proliferation	[67]
	DTL	Growth inhibition, cell cycle arrest, induction of apoptosis	[91]
	PIK3CD	Inhibition of cell migration and invasion	[94]
	BECN1	Autophagy	[92]
	IRS2	Inhibition of cell proliferation, migration and invasion	[93]
	ITGB3	Inhibition of metastasis	[68]
Gastric cancer	Vimentin	Inhibition of invasion and EMT	[59]
Lung cancer		Onco-suppressor	[19]
	BCL11A	Onco-suppressor	[85]
	IGF1R	Inhibition of cell proliferation, cell cycle arrest	[84]
	Snai1	Inhibition of invasion and metastasis	[86]
	PI3K/AKT	Inhibition of invasion and migration	[115]
Glioma		Oncogene	[80]
	SEPT7	Oncogene	[101]
	SOCS3	Tumorigenecity	[100]
Renal cell cancer	BECN1	Autophagy	[72]
Chronic myelogenous Leukemia	BECN1,ATG5	Autophagy	[61]
Chondrosarcoma	SOX4	Onco-suppressor	[73]
Ewing sarcoma		Inhibition of cell proliferation and invasion	[103]
Anaplastic thyroid cancer	LOX	Inhibition of cell proliferation, invasion, and migration	[75]
Ovarian cancer		Oncogene	[81, 117, 118]
Lymphoid malignancies	Notch	Onco-suppressor	[66]
Giant cell tumor of bone	Runx2	Onco-suppressor	[109, 110]
Prostate cancer	SOX4	Inhibition of proliferation and EMT	[79]
Hepatocellular carcinoma	Snai1	Inhibition of migration, invasion and EMT	[97]
	MTDH	Inhibition of proliferation, induction of apoptosis	[98]
	Vimentin, MMP3	Inhibition of proliferation, invasion and metastasis	[70]
Multiple myeloma	BCL9	Inhibition of cellular proliferation, migration and drug resistance	[111]
Breast cancer	EYA2	Inhibition of migration and invasion	[88]
	MTDH	Inhibition of proliferation and metastasis	[21]
	Vimentin	Inhibition of invasion and metastasis	[89]
	Slug	Inhibition of metastasis and EMT	[90]
		Onco-suppressor	[71]
Acute myeloid leukemia	MYBL2	Inhibition of proliferation and maturation	[104]
Chronic myeloid leukemia	BCR-ABL1	Inhibition of proliferation	[105]
Nasopharyngeal carcinoma	E-cadherin	Promotion of invasion and metastasis	[106, 107]
Urothelial carcinoma of bladder	Notch1	Inhibition of proliferation, migration and invasion	[76]

chondrosarcoma [73], ovarian papillary serous carcinoma [74], and anaplastic thyroid cancer [75]. Furthermore, miR-30a expression decreased in patients with shorter overall survival and disease-free survival time in patients with NSCLC [19] and urothelial carcinoma of bladder [76], consistent with the lower expression of miR-30a in tumor tissues compared to their non-tumor lung tissues. In ovarian papillary serous carcinoma, miR-30a was remarkably negatively related with the grade, and was predicted to be an early detection and therapeutic approach, especially in high-grade cases [74]. Besides, miR-30a was significantly downregulated in the chemoresistant tissues of patients with advanced gastric cancer [77, 78].

However, miR-30a was indicated to significantly overexpressed in several types of cancers, whereby it presented to be an onco-suppressor. As demonstrated, miR-30a was

upregulated by metformin and consequently significantly inhibited proliferation and EMT of prostate cancer cells[79]. In glioma, miR-30a was overexpressed in cell lines and glioma samples, and its expression level is positively correlated with tumor grade of malignancy [80]. The upregulation of urinary miR-30a was intimately associated with early stage of ovarian serous adenocarcinoma as well as lymphatic metastasis, followed by a reduction after the surgical removal of ovarian serous adenocarcinoma [81].

Activities of miR-30a in cancer progression

Lung Cancer

Lung cancer is the leading cause of tumor mortality worldwide [82, 83]. Lung cancer is not a unique condition, but indeed a group of diseases: small cell lung cancer and non-small cell lung cancer. In NSCLC, decreased expression of miR-30a facilitated cell proliferation, G1/S, S/G2 transition through PI3K/AKT signaling pathway by targeting insulin like growth factor 1 receptor (IGF1R) [84]. Moreover, miR-30a directly targeted B-cell lymphoma/leukemia 11A (BCL11A), an independent prognostic factor for disease-free survival and overall survival [85]. Besides, miR-30a was reported to suppress *in vivo* distant metastasis to the lungs and liver by targeting Snai1 in NSCLC [86].

Breast cancer

Breast cancer is one of the most common types of malignancies and the second leading cause of cancer death among females [87]. In breast cancer patients, miR-30a expression was downregulated and negatively correlated with Eye absent protein 2 (Eya2), a promoter of cell proliferation and migration [88]. Besides, miR-30a inhibited breast cancer proliferation and metastasis by directly regulating metadherin (MTDH), and served as a prognostic marker for breast cancer [21]. By downmodulating vimentin, miR-30a inhibited breast cancer invasiveness and metastasis and was associated with the outcome [89]. The tumor-suppressive function of miR-30a reversed EMT in breast cancer by directly inhibiting Slug, a member of the Snai1 family [90].

Colorectal cancer

Colorectal cancer (CRC) is one of the most prevalent carcinoma of digestive system and the third leading cause of cancer-related deaths in Western countries. MiR-30a arrested cell proliferation of colorectal cancer via downregulating protein levels of heterochromatin protein (HP1γ) [67]. Meanwhile, miR-30a was identified to be onco-suppressor in colon cancer cells by down-modulating of denticleless protein homolog (DTL) which was found to be overexpressed in 95.8% of human colorectal cancers [91]. Another research found that miR-30a attenuated in CRC tissues which was correlated with higher level of Beclin-1 and autophagy [92]. Taking insulin receptor substrate 2 (IRS2) as another target gene, miR-30a suppressed phosphorylation of Akt and colon cancer cell growth [93]. Extraordinary downregulation of miR-30a in metastatic CRC tissues was found to be inversely correlated with phosphoinositide 3-kinase catalytic subunit delta (PIK3CD), which dramatically assisted cell migration and invasion [94]. By targeting integrin β3 (ITGB3), miR-30a inhibited the migratory and invasive abilities and EMT of colorectal cancer cells, thereby suppressed cancer metastasis [68].

Gastric cancer

Gastric cancer is one of the most common malignant tumors and ranks the second most deadly cancer worldwide [95]. Invasion and metastasis of gastric cancer are considered to be the most ordinary cause of the death from the tumor [96]. Via modulating EMT, miR-30a was observed to increase cisplatin sensitivity of gastric cancer cells [78]. Positively mediated by RUNX3, miR-30a directly targeted the 3' untranslated region of vimentin and inhibited cell invasion and EMT in gastric cancer patients [59].

Hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is one of the most prevalent cancers and frequent causes of cancer leading death [87]. MiR-30a was positively correlated with worse disease-free survival (DFS) of HCC patients, while its downregulation promoted cancer cell migration, invasion and EMT [97]. By directly targeting metadherin (MTDH), miR-30a inhibited liver cancer cell proliferation and promoted apoptosis as a onco-suppressor through PTEN/AKT pathway [98]. Further study demonstrated that miR-30a regulated HCC cellular proliferation, invasion and metastasis by a mechanism involving reduction of vimentin and MMP3 expression and restoration of E-cadherin expression [70].

Glioma

Glioma is the most prevalent human intracranial tumor with high aggressiveness and poor prognosis [99]. Several studies have demonstrated that mir-30a served as an oncogene in glioma. In the glioma stem cells (GSCs), the overexpression of miR-30 decreased the expression of suppressor of cytokine signaling 3 (SOCS3), thereby facilitated Janus kinase/signal transducer and activator of transcription (Jak/STAT3) pathway and downstream effect of tumorigenecity [100]. Meanwhile, overexpression of miR-30a was clarified to upgrade cell growth and invasion through the repression of (SEPT7) [101].

Sarcoma

Cartilage tumors are the most common primary bone lesions, which range from benign infirmities, such as enchondromas and osteochondromas, to malignant chondrosarcoma [102]. Clinically, miR-30a expression in chondrosarcoma cases was negatively correlated with sex-determining region Y-box 4 (SOX4), which acted as an unfavorable independent prognostic factor for patients with low histological grade [73]. In Ewing sarcoma, miR-30a decreased cell proliferation and invasion, and constituted a major functional link between EWS-FLI1 and CD99, two critical biomarkers and therapeutic targets [103].

Myeloid leukemia

In acute myeloid leukemia, low expression of miR-30a was associated with overexpression of MYB proto-oncogene like 2 (MYBL2), a transcription factor implicated in cell proliferation and maturation [104]. In chronic myeloid leukemia (CML), miR-30a reduced ABL1 and BCR-ABL1 protein expression, and acted as an onco-suppressor via inhibition of cell proliferation [105].

Other types of cancer

To data, miR-30a has been confirmed to participate in progression of several other cancers via regulating different targets. As demonstrated, miR-30a could inhibit cell proliferation, migration and invasion, by antagonizing oncogene Notch1 in invasive urothelial carcinoma of bladder [76]. Through promoting invasiveness and metastasis, miR-30a was identified to play an important role in Nasopharyngeal carcinoma (NPC) by directly binding to E-cadherin [106]. Furthermore, Insulin-like growth factor I (IGF-I) could induce EMT of NPC through IGF-IR-Src-miR-30a-E-cadherin pathway [107]. MiR-30a played a critical functional role in inhibiting LOX expression and thyroid cancer progression, including cell proliferation, invasion, and migration [75]. By targeting osteogenesis transcription factor runt-related transcription factor 2 (RUNX2), miR-30a stimulated adipogenesis during the development of adipocyte [108], influenced the osteoclast differentiation and osteolysis formation [109], and inhibited apoptosis [110] in giant cell tumor of bone. Evidence was presented that miR-30a downregulation improved expression of BCL9, a transcriptional coactivator of the Wnt/β-catenin signaling known to enhance multiple myeloma cell proliferation, migration, drug resistance, and formation of cancer stem cell [111].

Role in chemo-resistance

Chemo-resistance has frequently emerged to be the obstacle to chemo-therapy, retarding successful long-term survival. MiRNAs have been implicated in the chemo-resistance of

numerous cancers [112, 113]. As investigated, miR-30a decreased in bromocriptine-resistant prolactinoma compared with bromocriptine-sensitive prolactinoma [114]. Downregulation of miR-30a in renal cell carcinoma could abolish sorafenib-mediated apoptosis by an autophagy-dependent pathway induced by Beclin-1 [72]. In NSCLC, miR-30a was reported to play vital roles in overcoming the acquired resistance to epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) through regulating PI3K/AKT signaling pathway [115]. Up-regulated protein translation of BECN1 and autophagy associated gene 5 (ATG5) mediated by repressed expression of miR-30a promoted autophagy in CML [116], thus improved survival of CML primary stem cells and resistance to imatinib, a selective inhibitor for certain type III [61].

However, the expression levels of miR-30a in ovarian cancer chemotherapy−resistant cell lines were significantly higher than those in chemotherapy-sensitive cell lines, which was associated with ovarian cancer chemotherapy resistance [117]. Furthermore, depletion of miR-30a in the paclitaxel-resistant ovarian cancer cells increased paclitaxel sensitivity [118].

The role of other members of miR-30 family in human cancer

Emerging evidence demonstrates that miR-30a is not the only member of miR-30 family participating in cancer progression. Documents have been accumulated to investigate the expression and role of other members of miR-30 family in human cancers [119-123]. As shown in Table 2, miR-30 family members were involved in processes of cancer development, concluding proliferation, migration, invasion, EMT, metastasis, autophagy and apoptosis through distinguished targets [124-126]. Clinically, they could be useful prognostic predictors or therapeutic targets for types of cancer [127-132], or even more impacted drug sensitivity of chemotherapy [133-136].

Conclusion

Accumulating evidence has shown that aberrant expressions of miRNAs, acting as critical regulators in carcinogenesis and cancer development, prevail in many types of malignant diseases. Dysregulation of miRNA expression appears to open new opportunities in the field of diagnosis and prognosis in various cancers as a promising biomarker. MiR-30a, one of the miRNAs dysregulated in various types of cancers, has been documented to play versatile roles in pathophysiologic processes of oncogenesis, including cellular proliferation, invasion, migration and metastasis. It is now clear that dysregulation of miR-30a may interfere with the effectiveness of chemo-therapy mediated apoptosis by an autophagy-dependent pathway in prolactinoma, renal cell carcinoma, CML and ovarian cancer. Accordingly, miR-30a restores the sensitivity of cancer cells to chemo-therapy and represents to be a unique potential therapeutic target in cancer therapy. However, its significance is needed to be further evaluated in other types of cancer.

Nevertheless, research results uncovering the definite functions of miR-30a in different cancer types are inconsistent, which requires further study to specify the underlying mechanism. Downregulated miR-30a in cancer cells could function as an onco-suppressor by restraining oncogenes, alternatively overexpressed miR-30a could function as an oncogene by negatively regulating anti-oncogenes. Therefore, better understanding of gene networks regulated by miR-30a and downstream pathways may disclosure potential functions of miR-30a in regards to cancer diagnostics and therapeutics. Further studies should be conducted to establish panels of target genes distinct to each cancer type, taking into account cancer progression and response to treatment. Additionally, efforts should be made to disclose how the multiple signaling molecules collaborate through cross talk interactions to reveal the distinct role of miR-30a.

In summary, miR-30a is predicted to be a potential biomarker and provides a novel insight into diagnostic and therapeutic applications in human cancer. Undoubtedly, future

Table 2. Targets of other members of miR-30 family in human cancers

Member	Cancer types	Target gene	Function role	ref
miR-30b	NSCLC	Cthrc1	Inhibition of invasion and migration	[137]
		Rab18	Inhibition of proliferation	[138]
	Hepatocellular carcinoma	P53	Induction of apoptosis, cell cycle arrest	[139]
			Inhibition of EMT and metastasis	[140]
	Prostate cancer	AR		[141]
	Gastric cancer	EIF5A2	Inhibition of invasion and migration	[142]
		PAI-1	Induction of apoptosis	[143]
			Inhibition of migration	[144]
	Colorectal cancer	SIX1	Inhibition of invasion and migration	[145]
		KRAS, PIK3CD, BCL2	Induction of apoptosis, cell cycle arrest, inhibition of proliferation	[127]
	Laryngeal carcinoma	P53	Induction of apoptosis	[146]
	Glioma	Caspase-3, TAp63	Impairment of TRAIL-dependent apoptosis	[147]
	Breast cancer	Cyclin E2	Inhibition of proliferation, cell cycle arrest	[148]
	Melanoma	GalNAc transferases	Induction of invasion, immunosuppression	[149]
miR-30c	NSCLC	Rab18	Inhibition of proliferation	[138]
			Induction of invasion and EMT	[150]
	Glioma	Caspase-3, TAp63	Impairment of TRAIL-dependent apoptosis	[147]
	SCC of the vulva		HMGA2	[151]
	Breast cancer	NOV/CCN3	Induction of invasion	[152]
miR-30d	NSCLC	Cyclin E2	Inhibition of proliferation, cell cycle arrest	[153]
	Hepatocellular carcinoma	Galphai2	Enhancement of migration and invasion	[154]
	Prostate Cancer	Bmi-1	Inhibition of proliferation	[155]
		SOCS1	Enhancement of proliferation and invasion	[156]
		AR		[141]
	Ovarian cancer	Snail	Inhibition of EMT	[157, 158]
	Renal carcinoma	Cyclin E2	Inhibition of proliferation	[159]
		Metadherin	Induction of apoptosis	[160]
	Anaplastic thyroid carcinoma	Beclin-1	Inhibition of autophagy	[134]
		EZH2	Inhibition of proliferation and colony formation	[161]
	Melanoma	GalNAc transferases	Induction of invasion, immunosuppression	[149]
	Malignant peripheral nerve sheath tumour	KPNB1	Induction of apoptosis	[162]
miR-30e	Lung carcinoma	HOXA1	Inhibition of proliferation and migration,	[136]
	Glioblastoma	Beclin-1, AVEN and BIRC6	Inhibition of autophagy, induction of apoptosis	[163]
	Glioma	CBL-B	Enhancement of invasion	[164]
		IκBα	Induction of invasion	[165]
	Gastric cancer	Atg5	Inhibition of autophagy	[166]
	Gastrointestinal cancer	Bmi1	Inhibition of invasion, and metastasis	[167]
	Hepatocellular carcinoma	P4HA1	Inhibition of proliferation	[168]
	Colon carcinoma	caspase-3, p21WAF1/CIP1	Regulation of DNA damage-induced stress responses	[169]
	CML	BCR-ABL	Induction of apoptosis	[133]

innovative approaches will assist our ongoing molecular exploration and clinical strategy in this field.

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Disclosure Statement

All of the authors have not any conflict of interests.

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