Perspectives on miRNAs directly targeting BDNF for cancer diagnosis and treatment (Review)

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Abstract. MicroRNA (miRNA), a non-coding single-stranded RNA molecule with a length of 21-25 nucleotides transcripts, has been identified to play important roles in tumorigenesis and shows great potential applications in cancer diagnosis, prognosis and therapy. Brain derived neurotrophic factor (BDNF) is a member of the nerve growth factor family and usually serves as a biomarker in neurological and neuropsychiatric diseases for diagnosis and treatment by regulating its high-affinity receptor TrkB (Tyrosine Kinase Receptor B). Abnormal expression of BDNF is also closely related to the development of cancer, cancer-related pain and depression. However, little significant progress has been made in the application of BDNF in cancers. Recent studies have shown that the expression of BDNF is directly regulated by a cluster of miRNAs. This review concluded and discussed the role and mechanism of miRNAs targeting BDNF in cancers, and provided novel insights into the diagnosis and therapy of cancer in the future.

Contents

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1. Introduction

Brain-derived neurotrophic factor (BDNF), an important member of the nerve growth factor family, mainly activates downstream signaling by binding with two receptors, namely high-affinity receptor TrkB (Tyrosine Kinase Receptor B) and low-affinity receptor p75NTR (p75 neurotrophin receptor) (1-3). BDNF gene contains eleven exons (I-V, Vh, VI-VIII, VIIIh, IX), which include functional promotors and alternative splice sites. The sequence that encodes precursor of BDNF (proBDNF) is located within exon IX (4). proBDNF can be processed into mature BDNF by protease. ProBDNF and BDNF exert opposing effects by regulating different signaling: proBDNF often promotes cell apoptosis and inhibits growth and migration through p75NTR/sortilin, while BDNF increases cell proliferation, invasion and migration through TrkB (5-8). BDNF rs6265 (G196A) single nucleotide polymorphism (SNP) is an A→G substitution at nucleotide position 196 that directly results in a valine (Val) changing to methionine (Met) at amino acid position 66 (Val66Met) of the preprotein, and this SNP is significantly associated with the variability of BDNF activity (9,10). More than that, epigenetic regulation of BDNF, particularly DNA methylation and non-coding RNA (ncRNA), has been widely studied and often regulates the mRNA or/and protein expression of BDNF. BDNF methylation often happens in CpG island at promoter regions within BDNF exon I, IV and IX, and is significantly associated with BDNF expression (11,12). ncRNAs include long non-coding RNA (lncRNA), microRNA (miRNA), circular RNA (circRNA), rRNA and tRNA. In recent years, multiple studies have proved that ncRNA, mainly including miRNA, lncRNA and circRNA, could directly target BDNF and regulate the expression of BDNF.

Generally, BDNF regulates a variety of cellular processes by binding and activating TrkB, then results in the activation of a variety of downstream kinases, i.e., PI3K/Akt (Phosphoinositide

3-kinase/protein kinase-B), MAPK (mitogen-activated protein kinase) and PLC-γ (Phospholipase C-γ) (1-3,13). BDNF and its downstream signaling pathways are involved in the development of neurological and neuropsychiatric diseases and can serve as a biomarker in their adjuvant diagnosis, prognostic monitoring and therapeutic effects (14-16). The abnormal expression of BDNF is also found in numerous cancers. BDNF can regulate tumor cell proliferation, invasion and metastasis, anoikis and drug resistance, and often acts as cancer suppressor or cancer promoter in context-dependent signaling pathways and tumor microenvironment (1-3). However, little progress has been made in the application of BDNF in cancer diagnosis and treatment.

miRNA is a non-coding single-stranded RNA molecule with a length of 21-25 nucleotides transcripts and regulates gene expression by degradation or translation inhibition of target mRNAs. miRNAs have been identified to play important roles in tumorigenesis and showed great potential applications in cancer diagnosis, prognosis and therapy (17-19). Recent studies from PubMed, Web of Science, Scopus, Willy, EBSCO have shown that the expression of the BDNF was regulated by a cluster of miRNAs (20-51). In the present review, the role and mechanism of miRNAs directly targeting BDNF in cancers was summarized and their potential applications in cancer diagnosis and treatment were discussed.

2. Multiple miRNAs directly targeting BDNF were identified in human cancers

The expression of miRNAs directly targeting BDNF in cancers. miRNA regulates the expression of BDNF at the transcriptional level by pairing with the base of 3'-untranslated region (3'-UTR) of BDNF mRNA. At present, 20 miRNAs were found to directly regulate the expression and functions of BDNF in 16 cancers, i.e., miR107, miR191 and miR-204 in breast cancer, miR-1-3p in bladder cancer, miR-10a-5p in cervical carcinoma, miR-210-3p, miR-489-3p and miR-577 in glioblastoma, miR-103 in gliomas, miR-107, miR-206 and miR-613 in gastric cancer, miR-15a-5p and miR-584 in hepatocellular carcinoma (HCC), miR-204 and miR-10a-5p in renal cell carcinoma (RCC), miR-10a-5p in laryngeal cancer, miR-107 and miR-16 in neuroblastoma, miR-107, miR-147b and miR-496 in non-small cell lung cancer (NSCLC), miR-10a and miR-204 in ovarian cancer, miR-496 and miR-646 in osteosarcoma, miR-10a-5p in pancreatic cancer (PAAD), miR-191 and miR-382 in retinoblastoma, and miR-497 in thyroid cancer (20-51) (Fig. 1 and Table I).

Except for miR-10a-5p in pancreatic cancer and miR-191 in breast cancer, the vast majority of the miRNAs directly targeting BDNF serve as suppressors in numerous cancers (Table I). For example, in gastric cancer, 4 miRNAs of miR-107, miR-206, miR-613 and miR-744 are downregulated and act as tumor inhibitors by suppressing BDNF expression (20-24); and in NSCLC, the expression of 3 miRNAs of miR-107, miR-147b and miR-496 are also decreased to inhibit the expression of BDNF (25-27). In addition, the expression of the same miRNA regulating BDNF has been discovered in different cancers. For example, miR-107 was downregulated in gastric cancer, NSCLC, breast cancer and neuroblastoma (20,21,25,28,29); and the expression level of miR-204 was reduced in ovarian cancer, breast cancer and RCC. The varied expression patterns of miRNA directly targeting BDNF suggested that BDNF regulated by miRNA is a very complex regulation network.

The miRNA families directly targeting BDNF in cancers. At present, ~772 miRNA families have been identified (https://www.targetscan.org/cgi-bin/targetscan/mirna_families.cgi?db=vert50, Release 5.2: June 2011). Normally, the members of miRNAs in the same miRNA family share a common seed sequence. The known 21 miRNAs targeting BDNF belong to 15 different miRNA families including miR-1/206, miR-10, miR-15/16/195/424/497, miR-103/107, miR-147/147b, miR-191, miR-204/211, miR-210, miR-382, miR-489.h, miR-496, miR-577, miR-584, miR-646 and miR-744 (20-51). The details of miRNA families are shown in Table I.

The members of miRNA family also have similar physiological functions. For example, human miR-1/206 family, including miR-1-3p, miR-206 and miR-613, not only inhibit the cancer cell proliferation, metastasis and invasion, but also play important roles on myogenesis, oxidative stress in both heart and lung pathologies (22,23,30,52,53). miR-15a-5p, miR-16 and miR-497, belonging to miR-15/16/195/424/497 family, have been discovered to target both BDNF and Bcl2, and inhibit cell proliferation and induce cell apoptosis in HCC, neuroblastoma and thyroid cancer, respectively (31-33,41,54,55). Those findings would further provide information and help to investigate the potential roles and mechanism of members in the same miRNA family.

3. The dual roles of miRNAs directly targeting BDNF in cancers

BDNF act as a cancer suppressor or/and an oncogene. BDNF is well known to not only act as an oncogene, but also serve as a cancer suppressor (Fig. 2). BDNF always upregulates and performs its cancer-promoting function through activating TrkB and/or PI3K/Akt, Ras-Raf-MEK-ERK, EGFR (1-3,56). The dual functions of BDNF in cancer are usually significantly associated with the TrkB isoforms. TrkB is the high-affinity receptor of BDNF, and BDNF/TrkB signaling pathway plays important roles in cancer occurrence and progression (2,3,14). TrkB mainly contains two isoforms, namely the full length of TrkB (TrkB-FL) and the truncated TrkB (TrkB-T1) (2,57). In most cancers, BDNF promotes cancer cell proliferation, invasion and metastasis by binding to TrkB, actually it is TrkB-FL isoform. TrkB-T1, lacking the intracellular tyrosine kinase domain, is a natural antagonist of TrkB-FL and also can stimulate cancer cell growth; However, its tumor-promoting effect is not dependent on BDNF but is associated with Nfe2l2 response, retinol metabolism, and hedgehog signaling (57,58). More than that, the downstream signaling of RhoA (a small G protein belonging to the Ras superfamily) is also involved in the dual function of BDNF in cancers. For example, BDNF increases cancer cell metastasis in HCC by stimulating the activity of RhoA, which is activated by TrkB-FL; while in glioma, BDNF reduces cancer cell migration by inhibiting RhoA through the truncated TrkB-T1 receptor (57,59). The regulatory mechanism is that BDNF binds with Rho GDI1 (Rho guanine nucleotide dissociation inhibitor 1) and then

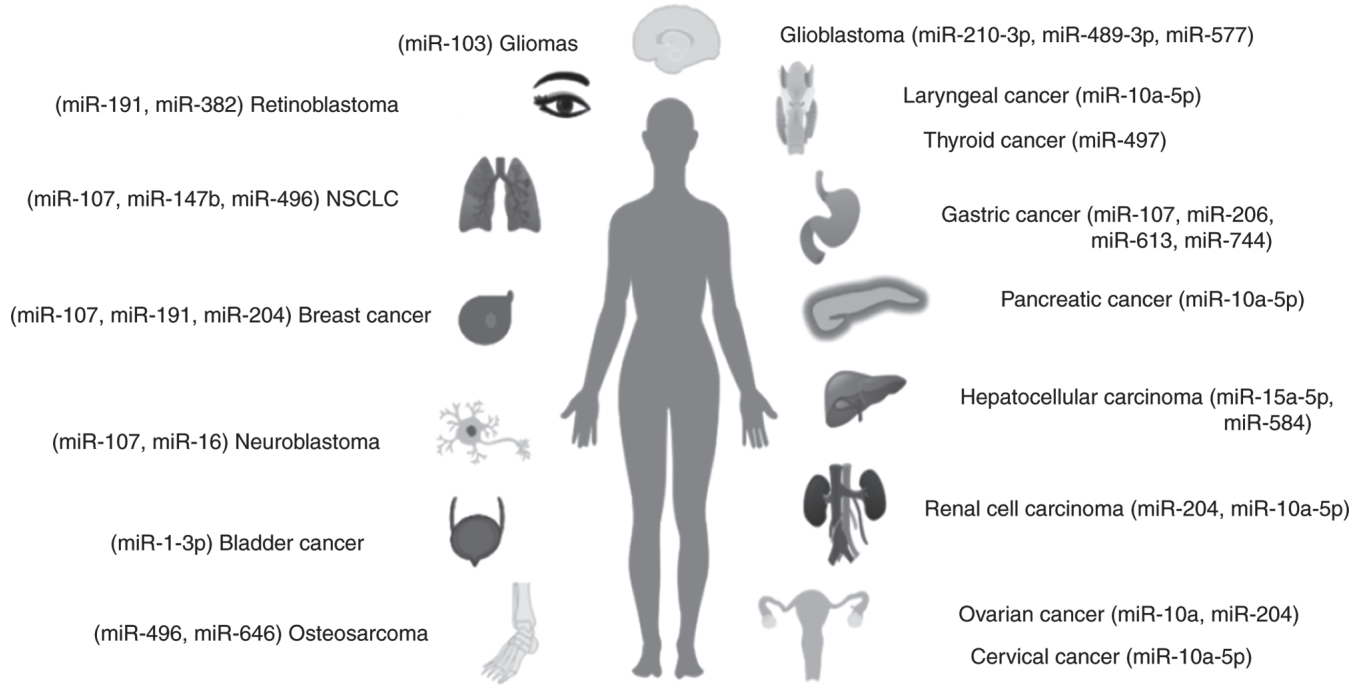

Figure 1. The miRNAs directly targeting brain derived neurotrophic factor in different cancers. HCC, hepatocellular carcinoma; NSCLC, non-small cell lung cancer.

causes Rho GDI1 to dissociate from the COOH-terminal tail of TrkB-T1, which leads to inhibiting the activity of RhoA (59,60).

The cancer microenvironment, including tumor cells, fibroblasts, endothelial cells, immune cells and extracellular components, exerts a significant impact on cancer occurrence, development and therapy (61,62). Previous studies have revealed that cancer microenvironment affects the function of BDNF in cancer (2,60,63-65). For example, in melanoma, colon, glioma and breast cancer, BDNF is upregulated by enriched environment and reduces the malignance development, which is associated with obesity and the immune system. However, these findings are only reported in the cancer models of mice (60,63-65).

miRNAs directly targeting BDNF also serve as cancer suppressor and cancer promoter. miRNAs directly targeting BDNF are also found to have both pro-cancer and anti-cancer effects in cancer (Fig. 2). The majority of miRNAs act as suppressor in cancer by downregulating BDNF and/or its downstream signal pathways, which include TrkB and PI3K/Akt. These miRNAs contain miR-1-3p, miR-10a-5p (except in pancreatic cancer), miR-103, miR-107, miR-147, miR-15a-5p, miR-16, miR-191 (in Retinoblastoma), miR-204, miR-206, miR-210, miR-382, miR-489-3p, miR-496, miR-497, miR-577, miR-584, miR-613, miR-646 and miR-744 (Table I and Fig. 2). In laryngeal cancer, miR-10a-5p binds with the 3'-UTR of BDNF and protects cancer cells from apoptosis and promotes cell proliferation by inducing the expression of TrkB (34). miR-1-3p is downregulated in bladder cancer and affects the cell viability, proliferation, invasion and apoptosis via targeting BDNF to inhibit TrkB phosphorylation (30). PI3K/Akt is a well-known signaling pathway and has been considered as an important target for cancer therapy. In most cancers, PI3K/Akt signaling pathway can modulate cancer cell proliferation, apoptosis, invasion and metastasis. Previous studies showed that miRNAs affected the PI3K/Akt signaling pathway by directly downregulating the expression of BDNF in cancer. For example, by downregulating the expression of BDNF and its downstream signaling of PI3K/Akt, the increased expression of miR-204 leads to ovarian cancer cells acquiring more sensitivity to anoikis and presenting decreased invasive and metastatic behavior (35). Another example is miR-147b, it blocks epithelial-mesenchymal transformation and inhibits the cell activity and metastasis of NSLC by downregulating of BDNF and inhibiting the phosphorylation levels of PI3K and Akt (26). Furthermore, the miRNA/BDNF/PI3K/Akt signaling pathway is also clearly confirmed by the studies on the effect of miR-107, miR-206 in gastric cancer, miR-496 in NSCLC, and miR-382 in retinoblastoma (20,22,27,36).

Currently, only one miRNA, miR-10a-5p, has been reported to exert cancer-promoting role by targeting BDNF. Compared with healthy adjacent tissues, pancreatic cancer tissues have significantly higher expression levels of miR-10a-5p, which stimulates BDNF/SEMA4C signaling to encourage cell proliferation and invasion (37). miR-191 was also found to target BDNF and exert cancer-promoting activity in breast cancer; however, its cancer-promoting effect is not related to BDNF, but to the target SATB1 (38,39).

The sponge effect of lncRNA and circRNA on the miRNAs directly targeting BDNF. miRNAs that target BDNF in cancers are regulated by lncRNA and circRNA, such as circHIPK3, circ_0000006, LINC00152, LINC01094, lnc DLX6-AS1 and lncXIST (21,25,29,33,40-42) (Fig. 2 and Table I).

Table I. The expression, role and regulatory mechanism of miRNAs directly targeting BDNF in cancers.

	miRNAs targeting BDNF in cancers								
MicroRNA family	Seed	MiRNAs	Regulation to BDNF	Cancer type	Expression	Role in cancer	Significant with Clinicopathologic characteristics	Regulation mechanism	(Refs.)
miR-1/206	GGAAUGU	miR-1-3p	Negative	Bladder cancer	↓	Suppressor	-	BDNF-TrkB	(30)
		miR-206	Negative	Gastric cancer	↓	Suppressor	Lymphatic metastasis, local invasion, advanced TNM	BDNF/PI3K/AKT	(22)
		miR-613	Negative	Gastric cancer	↓	Suppressor	Lymph node metastasis, advanced TNM	BDNF	(23)
miR-10	ACCCUGU	miR-10a-5p	Positive	Pancreatic cancer	↑	Promoter	-	BDNF/SEMA4C	(37)
			Negative	Cervical cancer	↓	Suppressor	-	BDNF	(47)
			Negative	Laryngeal Cancer	↓	Suppressor	-	BDNF/TrkB	(34)
			Negative	RCC	↓	Suppressor	Tumor size, TNM stage, lymph node metastasis, OS	BDNF	(43)
miR-15/16/ 195/424/497	AGCAGCA	miR-15a-5p	Negative	HCC	↓	Suppressor	5-year survival rate	BDNF	(31)
		miR-16	Negative	Neuroblastoma	↓	Suppressor	Cisplatin-treatment	BDNF	(32)
		miR-497	Negative	Thyroid cancer	↓	Suppressor	-	LINC00152/miR-497/BDNF	(33)
miR-103/107	GCAGCAU	miR-103	Negative	Gliomas	↓	Suppressor	-	BDNF	(49)
		miR-107	Negative	Gastric cancer	↓	Suppressor	TNM stage	BDNF/PI3K/AKT; circHIPK3/miR-107/BDNF	(20,21)
			Negative	Breast cancer	↓	Suppressor	-	BDNF	(28)
			Negative	Neuroblastoma	↓	Suppressor	-	lncRNA DLX6-AS1/ miR107/BDNF	(29)
			Negative	NSCLC	↓	Suppressor	TNM, regional lymph node involvement, differentiation, OS, DFS	circHIPK3/miR-107/BDNF	(25,46)
miR-147/147b	UGUGCGG	miR-147b	Negative	NSCLC	↓	Suppressor	Lymph nodes metastasis, tumor stage	BDNF/PI3K/AKT	(26)
miR-191	AACGGAA	miR-191	Positive	Breast cancer	↑	Promoter	HER2, Family history of cancer	MED1/ER-α/miR-191/ SATB1	(38-39)
			Negative	Retinoblastoma	↓	Suppressor	-	XIST/miR-191/BDNF	(40)
miR-204/211	UCCCUUU	miR-204	Negative	Ovarian cancer	↓	Suppressor	-	BDNF/TrkB/PI3K/ AKT/mTOR/Rac1	(35,45)
			Negative	RCC	↓	Suppressor	-	BDNF/TrkB/AKT/mTOR/Rac1	(45)
			Negative	Breast cancer	↓	Suppressor	TNM, metastasis, OS, DFS	BDNF/TrkB/AKT/mTOR/Rac1	(45)

Table I. Continued.

	miRNAs targeting BDNF in cancers								
MicroRNA family	Seed	MiRNAs	Regulation to BDNF	Cancer type	Expression	Role in cancer	Significant with Clinicopathologic characteristics	Regulation mechanism	(Refs.)
miR-210	UGUGCGU	miR-210-3p	Negative	Glioblastoma	↓	Suppressor	Histological grade, shorter OS	BDNF	(44)
miR-382	AAGUUGU	miR-382	Negative	Retinoblastoma	↓	Suppressor	-	BDNF/PI3K/AKT	(36)
miR-489.h	UGACAUC	miR-489-3p	Negative	Glioblastoma	↓	Suppressor	clinical grade	BDNF/PI3K/AKT	(48)
miR-496	GAGUAUU	miR-496	Negative	NSCLC	↓	Suppressor	-	BDNF/PI3K/AKT	(27)
			Negative	Osteosarcoma	↓	Suppressor	survival rate	BDNF	(50)
miR-577	AGAUAAA	miR-577	Negative	Glioblastoma	↓	Suppressor	-	LINC01094/miR-577/BDNF	(41)
miR-584	UAUGGUU	miR-584	Negative	HCC	↓	Suppressor	Tumor size, TNM, lymph node metastasis	BDNF	(51)
miR-646	AGCAGCU	miR-646	Negative	Osteosarcoma	↓	Suppressor	Sensitivity to DOX	circ_0000006/miR-646/BDNF	(42)
miR-744	GCGGGGC	miR-744	Negative	Gastric cancer	↓	Suppressor	Lymph node metastasis, invasive depth, TNM	BDNF	(24)

BDNF, brain derived neurotrophic factor; NSCLC, non-small cell lung cancer; HCC, hepatocellular carcinoma; RCC, Renal cell carcinoma; ↑, overexpression; ↓, decreased expression; OS, overall survival; DFS, disease-free survival.

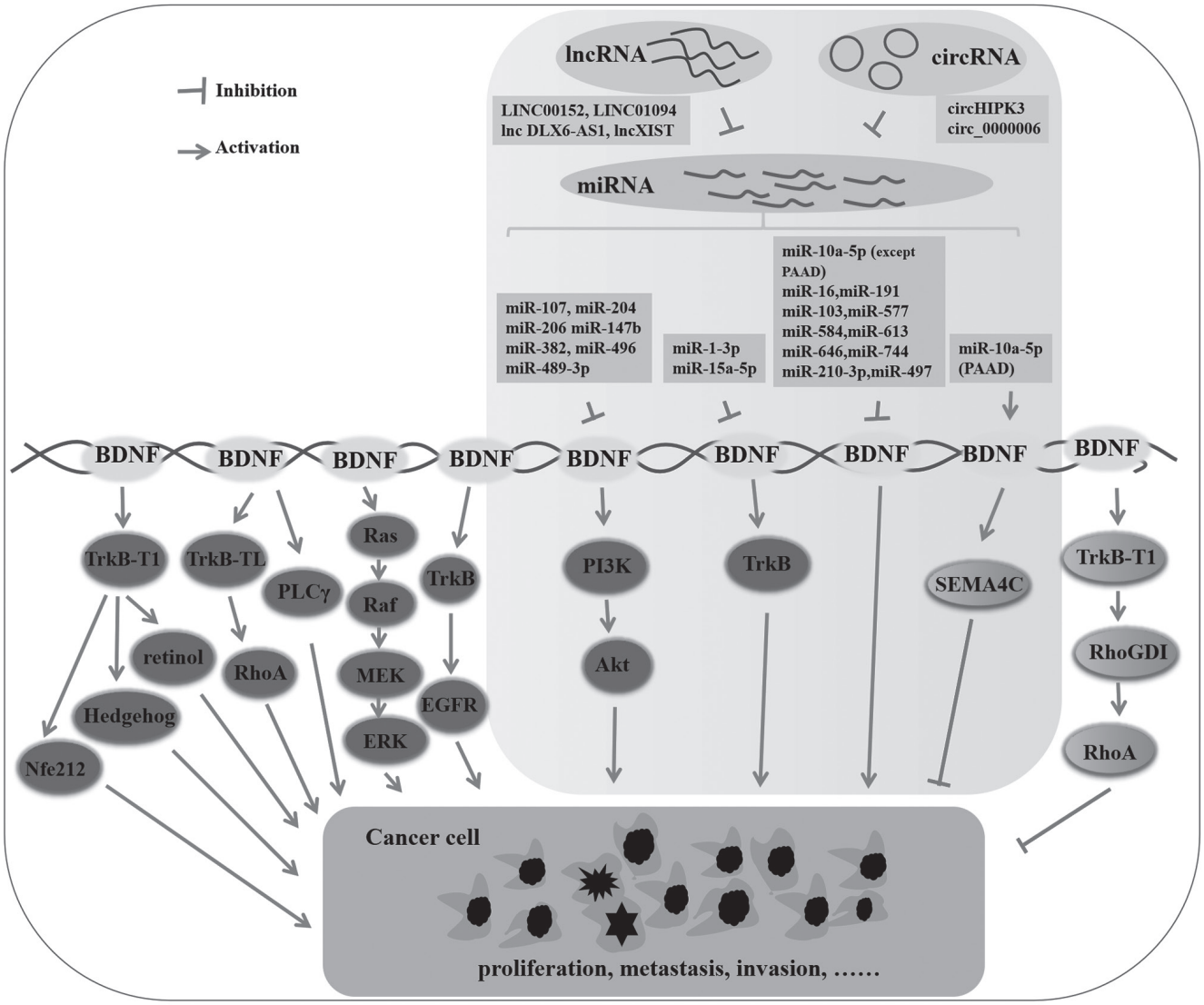

Figure 2. The role and mechanism of miRNA-BDNF regulatory network in cancer. BDNF promote cancer development always by regulating Ras-Raf-MEK-ERK, TrkB, PI3K/Akt, EGFR, TrkB-TL/RhoA, TrkB-T1/Nfe2l2, TrkB-T1/retinol and TrkB-T1/hedgehog signaling, while inhibit cancer progression mainly associated with enriched environment and TrkB-T1/Rho GDI/RhoA signaling. miRNAs can target BDNF and exert anticancer effect by decreasing BDNF expression and inhibiting TrkB and PI3K/Akt signaling pathways, and it can promote cancer development through SEMA4A in PAAD. miRNA, microRNA; BDNF, brain derived neurotrophic factor; PAAD, pancreatic adenocarcinoma.

lncRNA, with a length of more than 200 nt, accounts for 80~90% of ncRNAs and has the characteristics of the large number, low expression, poor conservation among species and cell expression specificity. lncRNAs always function as molecular decoys or sponges of miRNAs and display vital roles in regulating BDNF transcription (29,33,40,41). One example is LncDLX6-AS1, which is highly expressed in neuroblastoma tissues and cell lines, serves as a molecular sponge for miR-107 and promotes neuroblastoma cell proliferation, cell migration and invasion by positively regulating the expression of BDNF (29). Similar regulation mechanisms of LINC00152-miR497-BDNF, lnc XIST-miR191-BDNF and LINC01094-miR577-BDNF are also identified in thyroid cancer, retinoblastoma and glioblastoma, respectively (33,40,41).

CircRNA is another kind of ncRNAs, which is without 5; cap and 3' Poly (A) tail and is characterized by its covalently closed loop structures. CircRNA can target complementary miRNA response elements and is always used as competitive endogenous RNA (ceRNA) to have the sponge effect on miRNA. circRNA is also identified to participate in the initiation and progression of various cancers (1-3,14,21,25,42). At present, only two circRNAs, circHIPK3 and circ_0000006, are declared to target BDNF in cancer. circHIPK3 has been found to overexpress in NSCLC and gastric cancer cells, and the cancer-promoting effect of circHIPK3 is mainly associated with the signaling pathway of CircHIPK3/miR-107/BDNF (21,25). circ_0000006 is a newly discovered circular RNA in osteosarcoma, and the circ_0000006/miR-646/BDNF pathway is identified to be responsible for the DOX-mediated anticancer effects on osteosarcoma (42).

4. miRNAs directly targeting BDNF may be used as potential biomarker for cancer diagnosis and treatment

miRNA is involved in almost all of the important signaling pathways of tumorigenesis. The expression level of miRNA

Table II. Drugs and natural compounds exhibit anticancer effects by targeting miRNAs.

Natural compounds and Drug		Cancer type	Target miRNA	Effects on miRNA	The roles of drug on cancer	Regulatory mechanism	(Refs.)
Drug	Bortezomib	Leukemia	miR-744	Upregulate	Induce cell death	miR-744, 3154 and 3162/CEBPD	(72)
	Propofol	Colorectal cancer	miR-1-3p	Upregulate	Inhibit cell proliferation, accelerate apoptosis	miR-1-3p/IGF1/AKT/mTOR	(73)
		Breast cancer	miR-204	Upregulate	Inhibit cell invasion, migration and EMT	mir-204/MMP9	(74)
		Glioma	miR-206	Upregulate	Inhibited cell migration, invasion	miR-206/ROCK1/PI3K/AKT	(75)
		Lung adenocarcinoma	miR-210	Downregulate	Inhibit cell proliferation and metastasis	HIF-1α/miR-210	(76)
	Metformin	ESCC	miR-497	Upregulate	Induces pyroptosis	miR-497/PELP1	(77)
	Vitamin D3	Liver cancer	miR-15a-5p	Upregulate	Suppress cell proliferation, induce apoptosis	miR-15a-5p/E2F3	(78)
Natural compounds	Quercetin	Esophagus Cancer	miR-1-3p	Upregulate	Inhibit cell growth and metastasis	miR-1-3p/TAGLN2	(79)
		Oral cancer	miR-16	Upregulate	Inhibit cell viability, migration and invasion	miR-16/HOXA10	(80)
		HCC	miR-16	Upregulate	Inhibit cellular proliferation and migration	TP53/miR-15a/miR-16	(81)
	Curcumin	NSCLC	miR-206	Upregulate	Inhibit cell invasion and migration	miR-206/PI3K/AKT/mTOR	(82)
		Prostate cancer	miR-210	Upregulate	Inhibit cell proliferation, promote apoptosis	miR-210/TLR4 signaling pathway	(83)
	S-equol	Breast cancer	miR-10a-5p	Upregulate	Inhibit cell proliferation,promote apoptosis	miR-10a-5p/PI3K/AKT	(84)
	Skullcapflavone I	Colorectal cancer	miR-107	Downregulate	Suppress cell proliferation and viability	miR-107/TPM1/MEK/ERK+NF-κB	(85)
	Astragalus IV	TNBC	miR-206/613	Upregulate	Multi-Drug Resistance and glycolysis	circ_0001982-miR-206/613	(86)
	Andrographolide	Prostate cancer	miR-206	Upregulate	Inhibit cell proliferation and induce apoptosis	miR-206/STC2	(87)

miR, microRNA; NSCLC, non-small cell lung cancer; HCC, hepatocellular carcinoma; TNBC, triple-negative breast cancer; ESCC, esophageal squamous cell carcinoma.

in serum and tissues is different in cancer patients than that in normal individuals, and thus miRNA can be used as a marker for tumor diagnosis. For example, a plasma miRNA panel (miR-21, miR-26a, miR-27a, miR-122, miR-192, miR-223 and miR-801) is applied to the clinical diagnosis of HCC and has improved sensitivity and specificity than AFP (alpha feto-protein) (66). miR-92a is a oncomir and has become a useful biomarker for early detection of colorectal cancer in stool with 89% sensitivity and 70% specificity (67,68). The great majority of studies also showed that the abnormal regulatory of miRNAs targeting BDNF were significant associated with pathogenesis and progression of cancer. These miRNAs not only regulate the cancer cell activities, but also are positively correlated with the clinicopathologic characteristics of cancer patients. For example, miR-206, miR-613 and miR-744 can inhibit the gastric cancer cell proliferation, metastasis and invasion, and their downregulation is particularly related to lymphatic metastasis and advanced TNM staging of gastric cancer (22-24). In addition, low expression of miR-10a-5p and miR-210-3p has great relevance to poorer overall survival (OS) of kidney cancer and glioblastoma patients, respectively (43,44). miR-107 and miR-204 are related to shorter OS, [progression-free survival (PFS) or disease-free survival (DFS)] in patients of NSCLC and breast cancer, respectively (45,46). In addition, cisplatin is one of the most common anticancer drugs and has been found to inhibit neuroblastoma cell proliferation by downregulating BDNF, which depends on miR-16 (32); and miR-646/BDNF is responsible for the DOX-mediated effects of Circ_0000006 on osteosarcoma development (42). Those results indicated that miRNAs targeting BDNF have the prospective to be used for cancer diagnosis and therapy.

Dysregulation of ncRNAs, primarily involving siRNA, miRNA, circRNA and lncRNA, is frequent event in a wide range of diseases. An increasing number of ncRNAs have been investigated and have made a breakthrough in drug development for their potential role as a biomarker in diseases (66-68). To date, 3 siRNA drugs, Patisiran, Givosiran and Lumasiran have been approved by FDA; there are three miRNA drugs lademirsen, MRG-201, RG-125 in phase II trials and two miRNA drugs MRG-106, MRG-110 in phase I trials; And only one miRNA drug, MRG-106, is in phase I trials for lymphomas and leukemias (69-71).

Although no BDNF-related miRNA drug has yet been identified and used in clinical trials, researchers found that certain drugs and natural compounds exhibited their anticancer effects by targeting the miRNAs regulating BDNF (72-87) (Table II). For example, Bortezomib, an anticancer drug with a significant effect in treatment of multiple myeloma, was found to induce cell death in leukemia by upregulating the signal of miR-744/3154/3162/CEPBD (CCAAT/enhancer binding protein delta) (72). In addition, the known non-anticancer drugs were also identified to possess anticancer action via regulating the expression of miRNAs, such as propofol and metformin. Propofol, a drug commonly used in anesthesia, suppressed cell proliferation, invasion and migration in colorectal cancer, breast cancer, glioma and lung adenocarcinoma by targeting miR-1-3p, miR-204, miR-206 and miR-210, respectively (73-76). Metformin, the optimal first-line drug for the treatment type 2 diabetes mellitus, was discovered to induce cell pyroptosis through activating the signal of miR-497/PELP1 in esophageal squamous cell carcinoma (77). Beyond that, the natural compounds also showed significant anticancer roles by modulating the expression of miRNAs. Quercetin, a natural flavonoid extracted from numerous plants, was found to inhibit cell proliferation, migration and invasion by targeting miR-1-3p in esophagus cancer and miR-16 in oral cancer and HCC (78-80). Curcumin, another natural phenolic compound mainly from *Curcuma longa*, exhibited its high anticancer activity via increasing the expression of miR-206 in NSCLC and miR-210 in prostate cancer (81,82). At present, however, there is no study about the anticancer effect of drugs and natural compounds associated with miRNA/BDNF signaling. Nevertheless, it was found that the aforementioned drugs and natural compounds could decrease the expression level of BDNF. For example, when treated with metformin for 6 h, the nascent and steady-state BDNF transcripts are slightly decreased in Daoy cells, a human medulloblastoma cell line (88). In addition, curcumin was demonstrated to reduce mammary cancer via increasing the expression of PPAR-gamma and decreasing the expression of BDNF in SD rats (89). Thus, the aforementioned studies strongly suggested that the drugs and natural compounds exerted their anticancer effect maybe through miRNAs/BDNF signaling. Those studies further indicated that miRNAs targeting BDNF may become new targets for cancer therapy.

5. Discussion and conclusion

It is generally known that BDNF and its downstream signaling pathways are overexpressed in most cancers and play vital roles in cancer occurrence and development. However, little progress has been made in the application of BDNF in cancer. This may be associated with the complex epigenetics and genetic mechanism of BDNF in the same type of cancer. For example, genetic variations, particularly proBDNF and BDNF Val66Met polymorphism, play crucial biological roles in breast cancer occurrence and development. proBDNF released by breast cancer cells is identified as a mediator to induce anti-angiogenic effect in brain endothelial cells, and BDNF Val66Met gene polymorphism has a significant relation to the risk of breast cancer (90,91). In addition, Alhusban *et al* (90) declared that the ratio of proBDNF/BDNF, which is released by breast cancer cell MDA-MB-231, has significant correlation with anti-angiogenic effect. Epigenetic changes of BDNF also perform major role in breast cancer: The methylation of BDNF promoter serves as biological marker for suicidality in patients with breast cancer (92); BDNF-AS, the first identified natural non-coding antisense for BDNF, is overexpressed and significantly correlated with poor outcomes in hormone receptor-positive and triple-negative breast cancer patients (93); miR-107, miR-191 and miR-204 affect the breast cancer proliferation, metastasis and invasion by regulating the mRNA and/or protein expression of BDNF (28,39,45). Both epigenetic and genetic variations also exist in gastric cancer, HCC and RCC (5,21-23,31,43,45,94-96).

Currently, accumulating evidence has indicated that miRNAs provided a new vision to understand the occurrence and development of cancer. In the present review, the miRNAs targeting BDNF and their functions, regulatory network and clinical significance in cancers were discussed.

circRNAs and lncRNAs, often serve as cancer promoter by sponging miRNA, positively regulate the expression of BDNF, and the miRNAs targeting BDNF usually act as cancer suppressors by downregulating the BDNF/TrkB and PI3K/Akt signaling pathways. Previous studies found that decreased miR-16 and miR-107 promoted cell growth, metastasis and invasion by upregulating the BDNF expression, and increased BDNF effected cell viability and metastasis by activating the TrkB/PI3K/Akt signaling pathway in neuroblastoma (29,32,97,98). Moreover, in cervical cancer, downregulated miR-10a-5p was revealed to stimulate cell viability, division and cell cycle arrest via increasing the expression of BDNF, and overexpression of BDNF promotes cell proliferation, migration and invasion in this type of cancer through the TrkB/PI3K/AKT signaling pathway (47,99). Similar results were also identified in gastric cancer, RCC, breast cancer and glioblastoma (20,22,27,35,36,45,48,100). Thus, these published results help us confirm that miRNA directly targeting BDNF can downregulate the TrkB/PI3K/Akt signaling pathway; in other words, the regulatory network of miRNA/BDNF//PI3K/Akt is of supreme importance in cancer occurrence and development.

BDNF/TrkB and its downstream signaling PI3K/Akt are overexpressed in numerous cancers and have close correlations with poor prognosis and short survival time of cancer patients, and have become the key targets for drug development and cancer therapy. For example, TRK inhibitor Larotrectinib, has recently shown broad clinical activity in multiple tumor types with positive TRK fusion gene (NTRK1, NTRK2 or NTRK3, which encode the neurotrophin receptors TrkA, TrkB and TrkC, respectively) (101,102); multiple PI3K/Akt inhibitors, including idelalisib, copanlisib, duvelisib, linperlisib, ipatasertib, afuresertib, uprosertib, also have been widely used in cancer therapy (103-105). Although there are no studies about drugs associated with miRNAs targeting BDNF, the conclusion by the authors indicated that drugs and natural compounds exerting their anticancer effect may be obviously correlated with the miRNAs/BDNF regulatory network.

In summary, BDNF plays vital roles in cancer occurrence and development, but blocking BDNF remains a difficult task due to its complex genetic and epigenetic variation. It has been widely demonstrated that miRNAs have great potential applications in cancer diagnosis, prognosis and therapy. In the present review, the role and mechanism of miRNAs targeting BDNF in cancer was concluded and it was indicated that miRNAs targeting BDNF can be used as a potential biomarker for cancer diagnosis and treatment. However, further investigation must be conducted.

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Authors' contributions

ZX, XX and WC wrote this manuscript and created figures. LH, CK, JH and YG consulted and analyzed literature and created tables. LH, MY and SM designed, edited and revised the manuscript. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

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