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REVIEW

BDNF and its signaling in cancer

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Abstract

Purpose Brain-derived neurotrophic factor (BDNF) belongs to the family of neurotrophic factors that can potentially increase cancer cell growth, survival, proliferation, anoikis, and migration by tyrosine kinase receptors TrkB and the p75NTR death receptor. The activation of BDNF/TrkB pathways leads to several downstream signaling pathways, including PI3K/Akt, Jak/STAT, PLCγ, Ras-Raf-MEK-ERK, NF-kB, and transactivation of EGFR. The current review aimed to provide an overview of the role of BDNF and its signaling in cancer.

Methods We searched a major medical database, PubMed, to identify eligible studies for a narrative synthesis.

Results Pathological examinations demonstrate BDNF overexpression in human cancer, notably involving the prostate, lung, breast, and underlying tissues, associated with a higher death rate and poor prognosis. Therefore, measurement of BDNF, either for identifying the disease or predicting response to therapy, can be helpful in cancer patients. Expression profiling studies have recognized the role of microRNAs (miR) in modulating BDNF/TrkB pathways, such as miR-101, miR-107, miR-134, miR-147, miR-191, miR-200a/c, miR-204, miR-206, miR-210, miR-214, miR-382, miR-496, miR-497, miR-744, and miR-10a-5p, providing a potential biological mechanism by which targeted therapies may correlate with decreased BDNF expression in cancers. Clinical studies investigating the use of agents targeting BDNF receptors and related signaling pathways and interfering with the related oncogenic effect, including Entrectinib, Larotrectinib, Cabozantinib, Repotrectinib, Lestaurtinib, and Selitrectinib, are in progress.

Conclusion The aberrant signaling of BDNF is implicated in various cancers. Well-designed clinical trials are needed to clarify the BDNF role in cancer progression and target it as a therapeutic method.

Keywords BDNF · Biomarker · Cancer · microRNA · Pan-Trk inhibitors · Therapeutic targeting · TrkB

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Background

Neurotrophic factors (NTFs) are a specific family of proteins that play a role in the growth and differentiation of mature and immature neurons (Binder and Scharfman 2004). In 1982, researchers discovered a substance that affected the survival of a group of nerve roots (Barde et al. 1982). Then they extracted and purified it from the pig brain, the so-called brain-derived neurotrophic factor (BDNF). Although most neurons in the brain remain unchanged after birth, some of our neurons can grow and differentiate in a neurogenesis process, which importantly involves BDNF (Kowiański et al. 2018).

The human *BDNF* gene is located on chromosome 11 and encodes BDNF protein synthesis in the endoplasmic reticulum of nerve cells that requires transport vesicles for traveling throughout the cell. Several studies have examined the relationship between BDNF and different diseases in humans. Decreased BDNF expression most notably occurs in psychiatric, neurodevelopmental, and neurodegenerative diseases (Piepmeier and Etnier 2015; Mojtabavi et al. 2020; Rahmani et al. 2019; Saghazadeh and Rezaei 2017), although the expression of BDNF and its receptors are also altered in non-neural diseases. Particularly, there is evidence of increased levels of BDNF in cancer patients and the existence of the modified form of tropomyosin receptor kinase B (TrkB) that, in interaction with BDNF, is involved in different stages of tumorigenesis, from the growth and maturation of tumor cells to their migration and invasion (Simon et al. 2017). It has led to a great interest in using BDNF as a diagnostic/prognostic biomarker for cancer (Smeele et al. 2018) and developing agents that selectively target TrkB and its downstream processes, such as first-generation TrkB inhibitors (Cocco et al. 2018). Here, we review the possible role of BDNF in cancer pathogenesis.

BDNF and TrkB in cancer pathogenesis

Expression

In physiological conditions, BDNF and TrkB are widely distributed in central and peripheral tissues (Box 1). In cancer conditions, despite their normal distribution, BDNF and/or TrkB are upregulated. Particularly, this upregulation has been reported in lung (small cell and non-small cell) cancer (Ricci et al. 2001), myeloma (Pearse et al. 2005), hepatocellular carcinoma (Lam et al. 2011), ovarian cancer (Au et al. 2009), pancreatic ductal adenocarcinoma (Miknyoczki et al. 1999), glioblastoma (Nakamura et al. 2006), head and neck squamous cell carcinoma (Kupferman et al. 2010), breast cancer (Kim et al. 2015a), gastric cancer (Okugawa et al. 2013), prostate cancer, colorectal cancer, gallbladder cancer, and cervical cancer (Li 2020).

Signaling pathways

BDNF contributes to cancer progression by increasing cancer cell survival, proliferation, migration, and invasion; decreased chemotherapy response; and increased angiogenesis. Figure 1 schematically represents BDNF signaling pathways. Primarily BDNF for signal transduction binds with lower affinity to p75 neurotrophin receptor (NTR) and also integrin α9β1, but preferably binds to TrkB with significantly higher affinity (Zhang et al. 2013; Staniszewska et al. 2008). TrkB belongs to the neurotrophic tyrosine kinase (NTRK2) receptor family, which is encoded by the *NTRK2* gene (Chao and Bothwell 2002) and can interact with other ligands such as neurotrophin 3 (NT3) and neurotrophin 4 (NT4) (Reichardt 2006). Studies point toward dose-dependent and time-dependent functions of the TrkB/BDNF axis (Pinheiro et al. 2017; Street et al. 2002). BDNF binding to TrkB causes dimerization of the receptor. Dimerized TrkB leads to auto-phosphorylation of the receptor tyrosine kinase domains. This will activate the following intracellular signaling pathways (Huang and Reichardt 2003) to mediate BDNF functions.

RAS-MAPK-ERK

After phosphorylation, TrkB activates Src homology collagen protein (SHC), a transforming protein, which, in turn, engages the growth factor receptor-bound protein 2/Son of Sevenless complex (GRB2/SOS) to induce the rat sarcoma (Ras). Activation of Ras leads to signaling through downstream pathways mediated by Raf, class I phosphoinositide 3-kinases (PI3K), and p38 mitogen-activated protein kinase (MAPK). Raf can cause phosphorylation of MEK1 and MEK2, and then these two can cause phosphorylation of extracellular-regulated kinase 1 (ERK 1) and ERK2. Also, the RAS-MAPK pathway activates transcription factors such as STAT1/3, Elk1, and Myc and translocates ERK to the nucleus. Totally, TrkB-mediated activation of RAS-MAPK-ERK results in cell proliferation, differentiation, and development. Additionally, PI3K and ERK regulate VEGF expression, a known factor of angiogenesis (Trisciuoglio et al. 2005; Karar and Maity 2011).

PI3K/Akt pathway

SHC can also recruit GRB2-associated-binding protein 1 (Gab1), which leads to the activation of the phosphatidylinositol-3-kinase (PI3K). PI3K activates many pathways and proteins (Huang and Reichardt 2003), playing a key role in cell survival and mitogenic signaling (Song et al. 2005).

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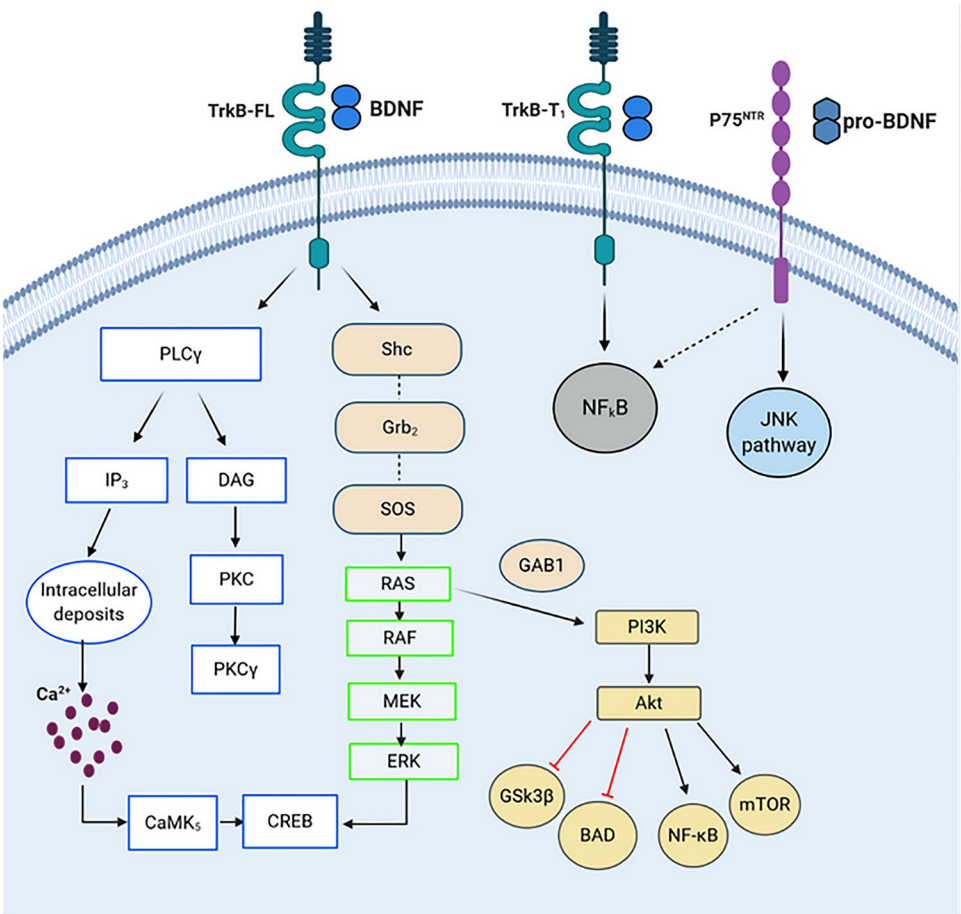

Fig. 1 BDNF signaling pathways

Protein kinase B (Akt) is one of these proteins attached to the inner side of the cell membrane through its interaction with the PI3K phospholipid products. The PI3K-Akt pathway leads to pro-survival, anti-apoptotic, and pro-migratory effects (Mohammadi et al. 2018; Xia et al. 2016a; DeWitt et al. 2014). Of note, Akt can exert these effects through inhibition of Bcl-2-associated death promoter (BAD), glycogen synthesis kinase (GSK-3beta), and Forkhead box protein O1 (FOXO1) transcription factor. Also, the PI3K-Akt pathway activates the mammalian target of rapamycin complex 1 (mTORC1), which phosphorylates its effectors directly, such as eIF4E-binding proteins (4E-BPs), to end binding to eIF4E and S6 kinase1 (S6K1), again resulting in increased cell survival and protein synthesis (Navé et al. 1999; Aoki et al. 2001). Finally, this pathway can transduce to reinforce hypoxia-inducible factor 1-alpha (H1F1a), which activates TrkB expression. This positive feedback loop further increases BDNF/TrkB's effect on tumors (Meng et al. 2019).

PLCγ pathway

The phospholipase C-gamma (PLCγ) pathway causes activation of the inositol trisphosphate (IP3) receptor to facilitate the release of the Ca2 + from intracellular stores. High intracellular calcium levels cause an increase in neuron synaptic plasticity by increasing the CaMK activity (Berridge and Irvine 1989). Also, PLCγ allows the generation of diacylglycerol (DAG). Calcium release and DAG formation regulate plenty of cell activities with the indirect activation of PI3K and MAPK pathways and direct activation of protein kinase C (PKC) (Reichardt 2006). Moreover, phosphorylation of PLC by the TrkB receptor drives another path that eventually regulates transcription factors, such as cAMP response element-binding protein (CREB). This axis also increases VEGF expression and angiogenesis (Lin et al. 2014; Usui et al. 2014).

Miscellaneous

In addition to the pathways mentioned above, TrkB has been shown to promote metastasis through suppression of Runt-related transcription factor 3 (*RUNX3*) and Kelch-like ECH-associated protein 1 (*KEAP1*) (Kim et al. 2016). TrkB receptor also affects the Janus kinase 2/signal transducer and transcription 3 (JAK2/STAT3) pathways and

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Table 1 Main BDNF signaling pathways involved in cancers

BDNF signaling pathways	Cancer
PI3K/Akt	Breast Cancer
PI3K/Akt	Neuroblastoma
Ras-Raf	Lung cancer
PAR2	Bone cancer
STAT3	Colorectal cancer
BDNF/TrkB	Oral cancer
BDNF/TrkB	Ovarian cancer

activates Twist-1 and -2, which are considered key regulators of epithelial-mesenchymal transition (EMT) (Kim et al. 2015a). Autocrine and paracrine regulation of TrkB by BDNF has also been implicated in breast cancer cell migration (Tsai et al. 2017).

Pathways, which are involved in mediating tumorigenic effects of the BDNF-TrkB axis, are briefly listed in Table 1 and illustrated in Fig. 2.

Box 1. BDNF and TrkB distribution in normal tissues and cells

BDNF is expressed highly in the CNS (Hing et al. 2018). Studies in mice, rats, and pigs showed the detection of BDNF transcripts and proteins in the hypothalamus, hippocampus, amygdala, cerebral cortex, and adrenergic nuclei of the brain stem in both newborns and adults (Cacialli et al. 2016). Also, BDNF mRNAs were detected in different human brain regions such as the hippocampus, the septum, and the amygdala (Murer et al. 1999; Quartu et al. 2010). There are more studies on different animals, such as amphibians, songbirds, and zebrafishes. In songbirds, BDNF expression occurs in the brain nuclei involved in song learning and sensorimotor integration (Tang and Wade 2013). BDNF mRNAs and immunoreactivity were detected in the hypothalamus and optic tectum in amphibians (Duprey-Díaz et al. 2002; Wang et al. 2005). The zebrafish study showed that BDNF expression has the same distribution in adult zebrafish and larvae, with most expression in the dorsal telencephalon, dorsal thalamus, synencephalon preoptic area, hypothalamus, posterior tuberculum, and optic tectum. It reported that cells expressing BDNF mRNA were in the parenchyma and identified as neurons. Also, it suggested that BDNF is not expressed in glial cells under physiological conditions (Cacialli et al. 2016). However, its expression in glial cells has been reported in mammals under pathological conditions specifically around amyloid plaques or brain lesions (Murer et al. 1999; Tokumine et al. 2003; Burbach et al. 2004). BDNF expression was also reported in peripheral tissues and cells, including the lachrymal gland, macrophages, lymphocytes, salivary glands (Lomen-Hoerth and Shooter 1995; Aloe et al. 1986), testis, ovary, thyroid gland, and adrenal gland (Li and Zhou 2013; Cacialli et al. 2018; Szekeres, M.r,, et al. 2010; Ceccanti et al. 2013). BDNF and its receptor TrkB were detected in human testes, and the localization of BDNF protein was in the adult Sertoli and Leydig cells. Strong immunoreactivity of TrkB was detected only in Leydig cells, while there were just some levels of its immunoreactivity in the spermatids of some tubules and Sertoli cells (Mutter et al. 1999). Both BDNF and TrkB mRNAs and proteins were found in ejaculated bull sperm. The BDNF protein was detected in the tail, neck,

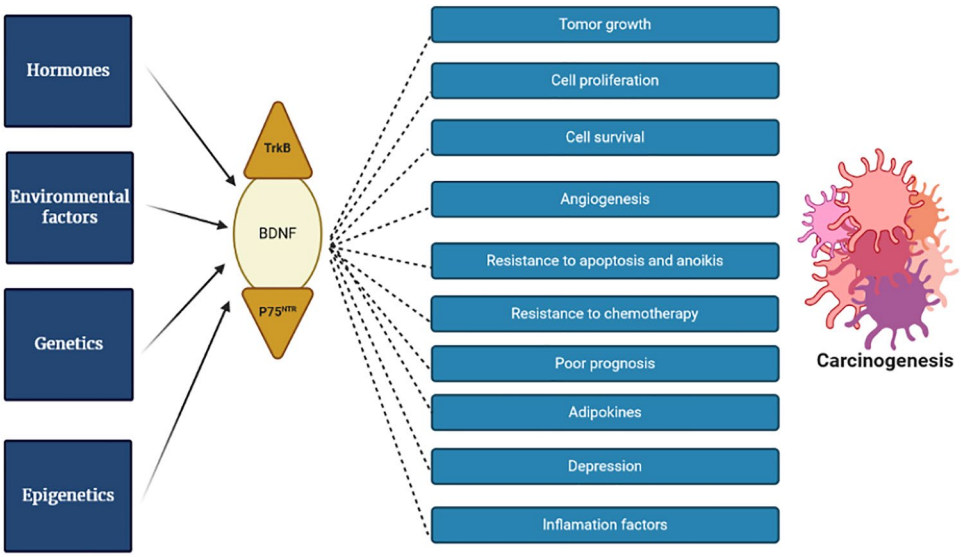

Fig. 2 The role of BDNF in cancer

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and head of the sperm cells, and TrkB was concentrated in the acrosome (Li et al. 2012). The decrease in BDNF protein and its mRNA can be related to the pathogenesis of some types of infertility in men (Zheng et al. 2011). BDNF expression was reported in the ovary of several species of mammalians, including humans (Cacialli et al. 2018). In the normal ovary, TrkB activation in oocysts by BDNF assists extrusion of the first polar body and prepares zygotes' development into preimplantation embryos (Kawamura et al. 2005). Also, it has a role in follicles' early development by providing proliferation signals for granulosa cells (Paredes et al. 2004). In the rat's adrenal gland, it has been reported that expression of the TrkB protein and mRNA occurred in the chromaffin cells in the medulla of the adrenal (Kondo et al. 2010), and expression of the BDNF was localized to the subcapsular region in the cortex of the adrenal (Szekeres et al. 2010).

MicroRNAs as mediators of the role of BDNF in cancer

microRNA (miRNAs) serve as non-coding and short-length RNA, which interact in the gene expression process by binding to the 3′-untranslated region of target genes. It has been indicated that miRNAs have a controversial role in cancer progression. They can act as tumor suppressors or tumor initiators in different contexts (Kopp et al. 2012). The evidence (Table 2) suggests that different miRNAs target BDNF as their downstream factor. So, the miRNA/BDNF axis's exact effects on cancer inhibition or cancer progression remain to be unraveled (Hu 2016).

The association between BDNF and mental health in cancer patients

Cancer is a seriously stressful life event related to emotional and physical distress, including depression and suicidal behavior (Derogatis et al. 1983; Fang et al. 2012). Also, some conditions, such as fatigue and cognitive impairment, can be associated with cancer and its treatment (Horneber et al. 2012; Cheung et al. 2012). Cancer patients are more likely to have mental disorders than healthy populations (Wang et al. 2020). Because of the crucial role of BDNF in plasticity and the development of the brain, it is an important factor in psychiatric diseases (Autry and Monteggia 2012). Animal studies showed a probable relationship between stress and low expression of BDNF mRNA in the neocortex and hippocampus of rats (Vaidya et al. 1997; Smith et al. 1995). The serum levels of BDNF are lower in patients with major depression, and it changes to normal after depression treatment (Shimizu et al. 2003; Huang et al. 2008). Stressful events are an important risk factor for depression (Kendler et al. 1999), common among patients with advanced cancers (Massie 2004). There is a relationship between increased cytosine-guanine (CpG) methylation at promoter regions of the BDNF gene and decreased BDNF synthesis in neurons (Martinowich et al. 2003). The longitudinal study on patients with breast cancer showed that the methylation status of BDNF promoter was associated with depression significantly at one week and one year after breast surgery. Also, the severity of depressive symptoms was related to the level of methylation status (Kang et al. 2015). Despite these findings, the results of another two studies were different. In a study on patients with lung cancer, there was no significant difference in BDNF serum levels between patients with depression and patients without depression (Kobayakawa et al. 2011). In another study on patients currently treated with chemotherapy for advanced metastatic cancer, BDNF did not influence clinical depression or its severity of symptoms (Jehn et al. 2015). Suicidal behavior is common among cancer patients, and cancer-related distress can lead to an increased risk of suicidality in cancer patients compared to the normal population (Fang et al. 2012; Walker et al. 2008). It has been reported that expression of BDNF was decreased in the prefrontal cortex and hippocampus of suicidal patients (Kim et al. 2015b). Moreover, serum levels of BDNF in suicidal depressed patients were lower than in non-suicidal depressed patients (Kim et al. 2007). The longitudinal study on patients with breast cancer showed that higher methylation status of BDNF promoter was significantly related to suicidal ideation one year after breast surgery (Kim et al. 2015b). Fatigue due to cancer and its treatments is a burdensome syndrome experienced by about 80% of patients undergoing cancer therapies (Horneber et al. 2012). The study on patients with prostate cancer showed decreasing concentrations of BDNF with worsening fatigue during external beam radiation therapy (EBRT); therefore, BDNF can have a role in cancer-associated fatigue (Saligan et al. 2016). Chemotherapy-associated cognitive impairment (CACI) has been widely reported among breast cancer survivors (Cheung et al. 2012). Memory, executive functions, and attention are specifically susceptible to changes induced by chemotherapy. These changes can adversely affect the patients' quality of life and their daily functioning. According to the longitudinal study on patients with early-stage breast cancer, there was statistically significant change in serum levels of BDNF over time post-chemotherapy and it was related to both self-perceived cognitive non-impaired and impaired subgroups. Thus, BDNF levels were correlated with self-perceived concentration deficit (Ng et al. 2017).

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Table 2 Ongoing clinical trials for Entrectinib, Larotrectinib, Cabozantinib, Repotrectinib, Lestaurtinib, and Selitrectinib in different types of cancers

Reference	MicroRNA	Function	Cell type	Signaling pathway	Associated cancer
Walzl et al. (2018)	miR-146b	BDNF Val66Met Polymorphism	T24 and RT4 cell lines	CRK-AKT pathway	Bladder cancer
Lin et al. (2017)	miR-624-3p	BDNF negatively regulated MiR-624-3p expression, and BDNF promoted tumor lymphangiogenesis	JJ012(S10) cell line	MEK/ERK/mTOR signaling pathway	Chondrosarcoma
Wei et al. (2020)	miR-107	CircHIPK3 is a sponge of miR-107, and as such, it regulates BDNF	MKN45, SGC-7901, BGC-823, MGC-803, and AGS cell lines	circHIPK3/miR-107/BDNF axis	Gastric cancer
Burak et al. (2018)	miR-16	It downregulates the BDNF expression	SH-SY5Y cell line	MAPK/ERK pathway	Neuroblastoma
Fei et al. (2020)	mir-10a-5p	Overexpression of miR-10a-5p regulates the BDNF expression and SEMA4C	SW1990 cell line	BDNF/sema4c axis	Pancreatic cancer
Zhao et al. (2018)	miR-214	It bounds BDNF-AS	OE19 and OE33 cell lines	PI3K/AKT pathway	Esophageal cancer
Yue and Wang (2020)	miR-424-5p	LINC00922 positively regulates BDNF expression through sponging miR-425-5p	MCF-7 and MDA-MB-231 cell lines	LINC00922/miR-424-5p/BDNF axis	Breast cancer
Dong et al. (2020)	miR-577	BDNF is a direct target of miR-577 and is positively regulated by LINC01094	U251 and T-98 cell lines	LINC01094/miR-577/BDNF axis	Glioblastoma
Zhang, et al. (2019)	miR-107	MiR-107 targets BDNF and the knockdown of miR-107 or overexpression of BDNF reversed the suppression of NB progression caused by lncRNA DLX6-AS1 silence	SK-N-SH and SH-SY5Y cell lines	lncRNA DLX6-AS1/miR-107/BDNF axis	Neuroblastoma
Sun et al. (2019)	miR-497	It downregulates the BDNF expression by LINC00152 through sponging miR-497	TPC-1 cell line	LINC00152/ miR-497/ BDNF pathway	Thyroid carcinoma
Zhai et al. (2017)	miR-10-5p	It regulates BDNF expression	HeLa and SiHa cell lines	–	Cervical cancer
Aili et al. (2016)	miR-10b	It negatively regulates BDNF	JJ012 and SW1353 cell lines	miR-10b/BDNF pathway	Chondrosarcoma
Long et al. (2016b)	miR-15a-5p	MiR-15a-5p negatively and selectively regulated BDNF	HepG2 and SNU-182 cell lines	miR-15a-5p/ BDNF pathway	Human hepatocellular carcinoma
Wang et al. (2018)	miR-103	BDNF is a direct functional target of miR-103, and there is a negative association between miR-103 and BDNF mRNA expression	U251 cell lines	miR-103/BDNF pathway	Glioma
Cheng et al. (2018)	miR-107	MiR-107 acts as a tumor inhibitor through the downregulation of BDNF expression	GC-7901 and MKN1 cell lines	PI3K/AKT pathway	Gastric cancer
Xia et al. (2016b)	miR-107	MiR-107 can suppress NSCLC metastasis by upregulation of BDNF	A549 cell line	PI3K/AKT pathway	Human non-small lung cancer
Gao et al. (2017)	miR-107	MiR-107 overexpression causes BDNF upregulation	MCF-7 and MDA-MB-231 cell lines	miR-107/BDNF axis	Breast cancer

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Table 2 (continued)

Reference	MicroRNA	Function	Cell type	Signaling pathway	Associated cancer
Li et al. (2020)	miR-147	MiR-147 inhibits cell proliferation, migration, and invasion in NSCLC by suppressing BDNF expression	A549 cell line	PI3K/AKT pathway	Non-small cell lung cancer
Ren et al. (2014b)	miR-206	BDNF is downregulated drastically by miR-206	SCG-7901 cell line	MEK/ERK pathway	Gastric cancer
Song et al. (2017)	miR-382	MiR-382 expression levels were negatively associated with BDNF, and BDNF was upregulated in RB tissues	Y79 and WERI-RB-1 cell lines	PI3K/AKT pathway	Retinoblastoma
Ye et al. (2020)	miR-496	BDNF is a direct target gene of miR-496 and is negatively regulated by miR-496	MG-63 and HOS cell lines	miR-496/BDNF axis	Osteosarcoma
Wang et al. (2017)	miR-497	BDNF is inversely correlated with miR-497 levels	TPC-1 cell line	PI3K/AKT pathway	Thyroid cancer
Song et al. (2019)	miR-584	BDNF level is inversely correlated with miR-584 expression	Hep3B and Huh7 cell lines	RhoA/ROCK	Hepatocellular carcinoma
Xu et al. (2017a)	miR-744	BDNF upregulates in gastric cancer tissues and is inversely correlated with miR-744 expression	SGC-7901 and BGC-823 cell lines	NM	Gastric cancer
Ding et al. (2018)	miR-1-3p	MiR-1-3p has significant effects on proliferation, viability, invasion, and apoptosis of bladder cancer cells by regulating the BDNF-TrkB pathway	UM-UC-3 cell line	BDNF-TrkB pathway	Bladder cancer
Xu et al. (2017b)	miR-101	MiR-101 inhibits ovarian carcinogenesis by repressing the expression of BDNF	SKOV3 cell line	TrkB	Ovarian cancer
Kopp et al. (2012)	miR-200c	TrkB and the transcriptional repressor Bmi1 were identified as miR-200c targets	BT474 cell line	PI3K/AKT pathway	Breast cancer
Howe et al. (2012)	miR-200c	MiR-200c targets an NF-kB upregulated TrkB/NTF3 signaling loop	MDA-231 and BT549 cell line	NF-kB /TrkB/NTF3 Signaling Loop	Triple negative breast cancer
Liu (2019)	miR-210	MiR-210 suppressed the migration and invasion of glioblastoma cells by targeting BDNF	A-172 MG, T98G, LN-229 cell lines	NM	Glioblastoma
Imam et al. (2012)	miR-204	miRNA-204 suppresses cancer cell migration and invasion by activating AKT/mTOR/Rac1 signaling and actin reorganization	HEK-293 cells	AKT/mTOR/Rac1 axis	Multiple cancers, including ovarian cancers, pediatric renal tumors and breast cancers

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Table 2 (continued)

Reference	MicroRNA	Function	Cell type	Signaling pathway	Associated cancer
Zheng and Chen (2020)	miR-489-3p	MiR-489-3p inhibits cell migration, proliferation, and invasion and induces apoptosis by targeting the BDNF-mediated PI3K/AKT pathway in glioblastoma	LN229 and U251 cell lines	PI3K/AKT pathway	Glioblastoma
Bailey et al. (2020)	miR-496	MiR-496 suppresses tumorigenesis via targeting BDNF-mediated PI3K/Akt signaling pathway in non-small cell lung cancer	H1650, H292, H1944, and A549 cell lines	PI3K/AKT pathway	Non-small cell lung cancer
Ding et al. (2018)	miR-613	MiR-613 functions as a tumor suppressor in gastric cancer by targeting BDNF	SGC-7901 cell line	NM	Gastric cancer
Hu et al. (2016)	miR-22	MiR-22 upregulates in gastric cancer cell lines and causes regulation of NTRK2 that encodes a protein, the tyrosine kinase receptor B (TrkB)	MKN-28 and SNU-719 cell lines	Wnt1, Sp1, or CDC151 signaling pathways	Gastric cancer
He et al. (2019)	miR-16	Regulator of g-protein signaling 4 (RGS4) regulates proliferation and apoptosis of NSCLC cells via microRNA-16 and BDNF	H1299 and PC9 cell lines	Downstream BDNF-TrkB signaling pathway	Non-small cell lung cancer
Zhang et al. (2018b)	miR-205	Rs6265 polymorphism in BDNF upregulates the expression of cyclin J via the inhibition of miR-205 expression, which leads to the promoted proliferation of bladder cancer cells	RT4 and T24 cell lines	NM	Bladder cancer
Bao et al. (2013)	miR-204-5p	MiR-204-5p suppresses the clonogenic growth, migration, and invasion of EC cells	HEC-1B^{shTrkB} and Ishikawa^{TrkB} cell lines	JAK2/STAT3 pathway	Endometrial carcinoma cells
Yan et al. (2015)	miR-204	MiR-204 upregulation is linked to the sensitivity of epithelial ovarian cancer cells anoikis by contributing to BDNF downregulation	HO-8910, and SKOV-3 cell lines	PI3K/AKT pathway	Epithelial ovarian cancer

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BDNF as a diagnostic and prognostic biomarker for cancer

Patients with cancer are often diagnosed at advanced stages, and late diagnosis is partly responsible for the worse outcome. Therefore, identifying new biomarkers with diagnostic/prognostic aspects would help develop the patient's treatment process and terminate a better cancer therapy consequence (Shang et al. 2018). Several studies investigated the potential of BDNF and its receptors and signaling as a biomarker for various cancers. Patani et al., in a cohort of women with breast cancer, concluded that higher BDNF expression in patients is significantly associated with a worse death rate and poor prognosis. Also, they declared that BDNF could be utilized as a prognostic marker to help diagnose cancer in its early stages to reach better treatment outcomes (Patani et al. 2011). Another study showed that BDNF antisense (BDNF-AS) in human retinoblastoma could be a prognostic biomarker because low BDNF-AS expression correlates with patients' metastatic clinical stage and shorter overall survival; also, they utter that overexpression of BDNF-AS in Y79 and WERI-Rb-1 retinoblastoma cells inhibit cancer migration and proliferation (Shang et al. 2018). Moraes et al. investigated the BDNF/TrkB/Akt pathway effect in oral squamous cell carcinoma (OSCC) and concluded that this pathway raised in malignant cells; moreover, BDNF and Akt can be biomarkers that empower us to the prognosis of OSCC patients in earlier stages (Moraes, J.K.d,, et al. 2019). Many other studies have examined BDNF, its receptors, and signaling pathways as diagnostic markers in cancers such as gastric cancer (Ding et al. 2018), small cell lung cancer (Kimura et al. 2018), and prostate cancer (Li et al. 2018). Almost all of them confirm BDNF-related measures' potential for cancer diagnostic/prognostic purposes.

BDNF receptors and associated signaling pathways as a therapeutic target in cancer

Due to the vital role that BDNF plays in various cancers, its receptors, signaling pathways, and related molecular process have recently been studied as a therapeutic target in several investigations (Meldolesi 2017). Activation of these TrkB and p75 or LNGFR evokes downstream signaling pathways such as PI3K/Akt, Jak/STAT, PLCγ, Ras-Raf-MEK-ERK, NF-kB, AMPK/ACC, UPAR/UPA, and transactivation of EGFR (Meng et al. 2019). As a result, these signaling pathways create oncogenic impacts by promoting cancer cells' growth, survival, proliferation, anoikis, migration, epithelial to mesenchymal transition, and chemotherapeutic sensitivity (Odate et al. 2013; Yuan et al. 2018; Long et al. 2016a; Li et al. 2020; Song et al. 2017).

PI3K/Akt signaling pathway associated with the BDNF/TrkB pathway

Several studies investigated the BDNF-mediated PI3K/Akt signaling pathway as a therapeutic method (Long et al. 2016a; Li et al. 2020; Song et al. 2017; Bao, et al. 2014; Desmet and Peeper 2006). Xia et al. presented the first evidence about the miR-107 role in suppressing non-small-cell lung cancer (NSCLC) and metastasis by targeting BDNF and regulating the PI3K/AKT pathway. They also state that this approach has a potential therapeutic strategy targeting miR-107 and BDNF for human NSCLC (Xia et al. 2016a). Ma et al. showed that miR-496 might suppress tumorigenesis via this pathway in non-small cell lung cancer (Ma et al. 2019). Another study indicated that miR-382 helps as a tumor suppressor in retinoblastoma patients (Song et al. 2017).

JAK-STAT signaling pathway associated with BDNF/TrkB pathway

Activation of BDNF/TrkB pathways modulates the JAK\STAT signaling pathways (Tajbakhsh et al. 2017); this pathway has several critical functions in the body, e.g., affecting gene expression, stimulating the epithelial and mesenchymal transition, producing a pro-tumorigenic environment, increasing cancer stem cell self-revival and differentiation, and so on (Groner and Manstein 2017). Because of these effects, JAK-STAT influences tumor generation. This route can be considered in the treatment of cancers such as breast cancer (Banerjee and Resat 2016), lung cancer (Harada et al. 2014), prostate cancer (Bishop et al. 2014), glioblastoma (Kim et al. 2014), thyroid cancer (Sosonkina et al. 2014), and head and neck squamous cell neoplasm (Kupferman, et al. 2009). Chen et al. conducted an animal study on 37 informative specimens, including 33 NSCLC specimens and four noncancerous lung tissues as controls. They found that the BDNF autocrine activity stimulated by the JAK/STAT signaling pathway causes prolonged TrkB activation and intensifies NSCLC (Chen et al. 2016).

PLCγ, Ras-Raf-MEK-ERK, and other signaling pathways associated with the BDNF/TrkB pathway

Recent studies showed that PLC-γ and Ras-Raf-MEK-ERK mediated BDNF/TrkB pathway may trigger an oncogenic role (Degirmenci et al. 2020; Hajicek et al. 2019); abnormal changes in the Ras/Raf/MEK/ERK signaling pathway could lead to the human colon (Zhang et al. 2018a), ovarian (Jin 2020), and prostate cancer formation (Butler et al. 2017). For another example, NF-κB expression is activated

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by BDNF/TrkB and then, through the incitement of PLCγ, improves ovarian cancer cell survival by suppressing anoikis (Siu et al. 2009). Several other signaling pathways modulated by BDNF/TrkB, including AMPK/ACC, UPAR/UPA, and transactivation of EGFR, have notable effects on carcinogenic processes. Like the other mentioned pathways, these signal pathways can be used to treat various cancers (Meng et al. 2019; Tajbakhsh et al. 2017).

pro-BDNF/p75 receptors

Besides the TrkB, p75 is a receptor for an immature form of BDNF (pro-BDNF). The role of the p75 receptor, unlike the TrkB, is not well clarified in neoplasms (Meng et al. 2019). It is characterized by p75 being overexpressed in breast cancer (Vanhecke et al. 2011), gastric cancer (Jin et al. 2007), bladder cancer (Khwaja and Djakiew 2003), glioblastoma (Johnston et al. 2007), and melanoma (Marchetti et al. 2004) which may point to an oncogenic role. This evidence suggests that p75 has therapeutic potential as a tumor suppressor (Khwaja and Djakiew 2003).

Identified microRNAs associated with BDNF receptors and signaling pathways

Many microRNAs have been identified that are involved in modulating BDNF receptors and related signaling pathways. These include miR-101, miR-107, MiR- 134, miR-147, miR-191, miR-200a/c, miR-204, miR-206, miR-210, miR-214, miR-382, miR-496, miR-497, miR-744, miR-10a-5p, miR-15a-5p, and so on; and these may be of value as therapeutic use for cancer (Xia et al. 2016a; Long et al. 2016a; Li et al. 2020; Song et al. 2017; Ma et al. 2019; Zhai et al. 2017; Wang et al. 2017; Ren et al. 2014a; Zhao et al. 2018; Xu et al. 2017a; Xu et al. 2017b). For example, Gao et al. declared that miR-107 has a tumor-suppressive effect in breast cancer, likely via regulating its reverse downstream target of BDNF (Gao et al. 2017). Ren et al. showed that in gastric cancer, miR-206 is a tumor suppressor regulating metastasis steps (Ren et al. 2014a). Li et al. stated that miR-147 targets BDNF and negatively adjusts BDNF expression in NSCLC. The upregulation of BDNF weakens the inhibitory effect of miR-147. MiR-147 inhibits migration, cell proliferation, and invasion in NSCLC by suppressing BDNF expression (Li et al. 2020). In another study, researchers found that miR-10a-5p is a cervical cancer suppressor regulating BDNF expression (Zhai et al. 2017).

Clinical trials of targeting TrkB receptors for the treatment of cancer

Although several potent TrkB inhibitors have been identified by scientists, they are not used in clinical trials to treat cancers because it seems inhibitors that target all Trk receptors and downstream signaling pathways are more effective in fighting tumors. Like TrkB, TrkA and TrkC are upregulated in several types of cancers and demonstrated to be oncogenic as well (Lange and Lo 2018). Entrectinib, Larotrectinib, Cabozantinib, Repotrectinib, Lestaurtinib, and Selitrectinib are some of the pan-Trk inhibitors utilized and investigated in several studies for cancer treatment (Bailey et al. 2020) (Table 3).

Doebele et al. recently showed that Entrectinib in metastatic NTRK fusion-positive solid tumors is a safe and effective therapeutic choice because it induces prolonged and clinically significant responses (Doebele et al. 2020). Pacenta et al., in a review study, concluded that Entrectinib acts against both ALK and TRK proteins, and it probably has a potential therapeutic role in neuroblastoma. They stated that it is currently under study in adults and pediatric patients with cancer (Pacenta and Macy 2018).

Larotrectinib received its first approval in November 2018 by the USA Food and Drug Administration (FDA) to treat adult and pediatric patients with solid tumors with an NTRK gene fusion (Scott 2019). Before that, several studies enrolled patients of different age groups in phase I/II trials; for example, Drilon et al. enrolled and treated 55 patients, ranging from four months to 76 years old, identified as TRK fusion-positive cancers. They concluded that Larotrectinib had a long-lasting antitumor effect in patients with TRK fusion-positive cancer, regardless of their tumor type and age (Drilon et al. 2018).

Cabozantinib is another TrkB receptor inhibitor that inhibits ALK, c-Met, RET, ROS1, and vascular endothelial growth factor 2 (VEGFR2). Cabozantinib was approved as an effective therapeutic intervention for prostate cancer, thyroid cancer, and renal cell carcinoma. Also, more clinical trials are currently being conducted to assess its role in CNS tumors (Meng et al. 2019).

Repotrectinib, Lestaurtinib, and Selitrectinib are other groups of pan-Trk inhibitors that have been investigated in many studies for their therapeutic potential in cancer patients. Some of these studies have presented promising results (Shulman and DuBois 2020).

Conclusions

While BDNF plays a vital role in CNS development and survival, the aberrant signaling of BDNF is implicated in various cancers (Fig. 3). Identifying related signaling pathways disturbance and gene mutations as oncogenic contributors have made possibilities for therapeutic intervention. The early clinical success of Entrectinib, Larotrectinib, Cabozantinib, and others showed that BDNF and its receptors

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Table 3 microRNAs linked to the modulation of BDNF/TrkB pathways in cancer

Drug name	Number of ongoing studies	NCT number	Phase of clinical trials	Cancer type
Entrectinib	8	NCT04302025, NCT02650401, NCT03066661, NCT02097810, NCT03330990, NCT02568267, NCT03961100, NCT02587650	Phase I: 3 Phase II: 3 Phase I and II:1 Unknown: 1	Metastatic solid tumors Non-small cell lung cancer CNS tumors Cancers with NTRK, ROS1, or ALK gene fusions Breast cancer Cholangiocarcinoma Colorectal cancer Invasive skin melanoma Etc
Larotrectinib	7	NCT02576431, NCT03025360, NCT02637687, NCT02122913, NCT03834961, NCT04142437, NCT03213704	Phase I: 1 Phase II: 3 Phase I and II:1 Unknown: 2	Solid tumors harboring NTRK fusion Central nervous system neoplasm Infantile fibrosarcoma Recurrent acute leukemia Locally advanced or metastatic solid Advanced malignant solid neoplasm Recurrent ependymoma Recurrent Ewing sarcoma/peripheral primitive Etc
Cabozantinib	146	NCT02008383, NCT03542877, NCT03316586, NCT01630590, NCT03729297, NCT02260531, NCT01428219, NCT01663272, NCT03667482, NCT01834651, NCT01441947, NCT01896479, NCT01995058, NCT04289779, NCT01588821, NCT04477512, NCT03690388, NCT03911193, NCT03867045, NCT01639508, NCT03964337, NCT04230954, NCT00704730, NCT01683110, NCT01703065, NCT01683994, NCT01522443, NCT04412629, NCT01605227, NCT01599793, NCT02132598, NCT03611595, NCT01812668, NCT01738438, NCT04446117, NCT01866410, NCT04197310, NCT01466036, NCT03425201, NCT03539822, NCT00215605, NCT04173338, NCT04131543, NCT01574937, NCT04205799, NCT03367741, NCT00940225, NCT01553656, NCT04427787, NCT01688999, NCT01347788, NCT02041260, NCT04400474, NCT03793166, NCT03170960, NCT03866382, NCT00596648, NCT01935934, NCT02036476, NCT01068782, NCT01100619, NCT04514484, NCT01835158, NCT01822522, NCT01811212, NCT04204850, NCT01708954, NCT03914300, NCT02496208, NCT01716715, NCT01954745, NCT03375320, NCT01709435, NCT02867592, NCT04022343, NCT01018745, NCT03468985, NCT04310007, NCT04322955, NCT04211337, NCT04471428, NCT03534804, NCT04164979, NCT04524208, NCT04079712, NCT02761057, NCT03824691, NCT04071223, NCT02315430, NCT02216578, NCT03468218, NCT04442581, NCT02592356, NCT03541902, NCT03634540, NCT02885324, NCT01835184, NCT04149275, NCT01866293, NCT04338269, NCT03201250, NCT01835145, NCT03967522, NCT01755195, NCT04134390, NCT02302833, NCT03937219, NCT01961765, NCT01582295, NCT00960492, NCT03612232, NCT03755791, NCT04066595, NCT04551430, NCT04220229, NCT03729245, NCT03943602, NCT03299946, NCT03428217, NCT04200443, NCT03213626, NCT01865747, NCT04300140, NCT01908426, NCT01700699, NCT04116541, NCT03798626, NCT02795156, NCT02243605, NCT01979393, NCT04416646, NCT03963206, NCT04316182, NCT03635892, NCT04454762, NCT03354884, NCT02101736, NCT04472767, NCT03957551, NCT04413123, NCT03744585, NCT04510688, NCT04497038, NCT04147143, NCT03370718, NCT03149822	Phase I: 24 Phase II: 86 Phase III: 15 Phase IV: 2 Phase I and II: 10 Unknown: 9	Colorectal cancer Breast cancer Prostate cancer Salivary gland cancer Metastatic brain tumor Pancreatic cancer Head and neck squamous cell cancer Recurrent head and neck squamous cell cancer Metastatic head and neck squamous cell cancer Medullary thyroid cancer Bladder cancer Lung cancer Solid tumor (not breast or prostate cancers) Etc
Repotrectinib	2	NCT03093116, NCT04094610	Phase I and II: 2	Locally advanced solid tumors Metastatic solid tumors Lymphoma Primary CNS tumors

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Table 3 (continued)

Drug name	Number of ongoing studies	NCT number	Phase of clinical trials	Cancer type
Lestaurtinib	10	NCT00081601, NCT01150669, NCT00242827, NCT00469859, NCT00079482, NCT00030186, NCT00668421, NCT00557193, NCT00586651, NCT00084422	Phase I: 1 Phase II: 5 Phase III: 1 Phase I and II: 2 Unknown: 1	Prostate cancer Childhood acute lymphoblastic leukemia Childhood acute myeloid leukemia/other myeloid malignancies Acute myeloid leukemia Neuroblastoma Polycythemia vera Essential thrombocytosis
Selitrectinib	3	NCT03206931, NCT03215511, NCT04275960	Phase I: 1 Phase I and II: 1 Unknown: 1	Solid tumors harboring NTRK fusion

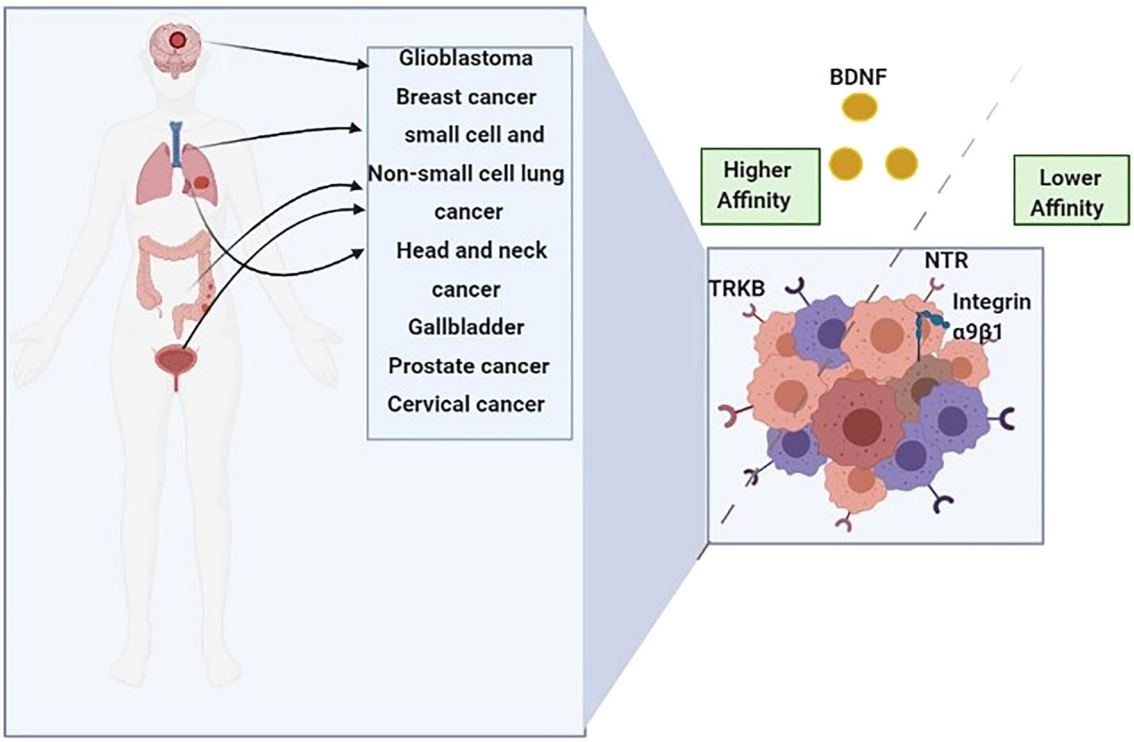

Fig. 3 BDNF and its receptors in tumorigenesis

and signaling pathways could serve as therapeutic targets. Also, some microRNAs have been recognized as linked to the modulation of BDNF/TrkB pathways, such as miR-101, miR-107, miR- 134, miR-147, and miR-191; these may be involved in tumor formation. Despite all the evidence and findings, there are still contradictions in some issues. More studies, particularly well-designed clinical trials, are needed to clarify the BDNF role in cancer progression and target it as a therapeutic method.

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