Targeting the BDNF/TrkB pathway for the treatment of tumors (Review)

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Abstract. Neurotrophins are a family of growth factors that regulate neural survival, development, function and plasticity in the central and the peripheral nervous system. There are four neurotrophins: nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3) and NT-4. Among them, BDNF is the most studied due to its high expression in the brain. Over the past two decades, BDNF and its receptor tropomyosin receptor kinase B (TrkB) have been reported to be upregulated in a wide range of tumors. This activated signal stimulates a series of downstream pathways, including phosphoinositide 3-kinase/protein kinase B, Ras-Raf-mitogen activated protein kinase kinase-extracellular signal-regulated kinases, the phospholipase-C-γ pathway and the transactivation of epidermal growth factor receptor. Activation of these signaling pathways induces oncogenic effects by increasing cancer cell growth, proliferation, survival, migration and epithelial to mesenchymal transition, and decreasing anoikis, relapse and chemotherapeutic sensitivity. The present review summarizes recent findings to discuss the role of BDNF in tumors, the underlying molecular mechanism, targeting Trk receptors for treatment of cancers and its potential risk.

Contents

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1. Introduction

Neurotrophins are a family of proteins that regulate neuron differentiation, survival, dendritic pruning, patterning of innervation, synaptic function and plasticity in the central and the peripheral nervous system (1,2). There are four neurotrophins: nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3) and NT-4. They have two types of receptors: the p75 neurotrophin receptor and tropomyosin receptor kinases (Trk) (2). P75 is the receptor for all four neurotrophins. Regarding Trk receptors, NGF binds TrkA; BDNF and NT-4 bind TrkB; and NT-3 mainly binds TrkC (2) (Fig. 1).

Initially, neurotrophins and their receptors were thought to be expressed only in nervous system but further studies showed they are also expressed by macrophages, endocrine cells, immune cells, smooth and striated muscle fibers (3,4). Recently, neurotrophins and their Trk receptors, especially BDNF and TrkB, were found to be highly up-regulated and play a vital role in various cancers, including breast, lung, colon-rectum, pancreas, prostate, liver, myelomas and lymphoid tumors (5). Activation of these Trk receptors elicits a series of downstream signalings, including PI3K/Akt, Ras-Raf-MEK-ERK, PLCγ pathway, transactivation of EGFR, etc. As a result, these pathways exhibit oncogenic effects by promoting cancer cell's growth, proliferation, survival, migration, epithelial to mesenchymal trasition, anoikis, relapse and chemotherapeutic sensitivity (6-12). Drugs targeting these Trk receptors have been put into clinical trials for cancer therapy and promising results have been achieved with moderate side effects (13).

This review will summarize all recent findings about the role of BDNF/TrkB in tumor and its underlying downstream pathways. We will also conclude and discuss clinical trials of targeting Trk receptors for treatment of cancers and the potential risk.

2. BDNF and TrkB receptor

Among the 4 neurotrophins, BDNF is the most abundant growth factor in the brain, which plays an important role in sustaining physiological processes of the brain. For example, BDNF regulates dendritic branching and dendritic spine morphology (14,15), as well as synaptic plasticity and long-term potentiation (LTP) (16). BDNF also modulates hypothalamic metabolic function, further reflecting the diversity of its role in the brain (17,18).

It has been revealed that BDNF is important in the developmental and mature taste system, by supporting survival of taste cells and geniculate ganglion neurons, and maintaining and guiding taste nerve innervations (19-21). These results demonstrated BDNF exhibits crucial effects in both of the central and peripheral nervous system. Another study also showed that BDNF/TrkB pathway may be involved in maintaining adult hippocampal neurogenesis by promoting survival, proliferation, and neural differentiation of neural stem cells (22,23). This function and underlying mechanism is comparable to BDNF's role in cancer (23-25).

Recently, lots of evidences showed BDNF and its receptor TrkB play a vital role in tumor pathology (26-28). TrkB is a type of receptor tyrosine kinases (RTKs) and some RTKs were characterized as oncogenes (29). Preclinical trials of target therapies on these RTKs showed promising results (13). Recent reports indicate that BDNF/TrkB pathway has an important function in neural tumors, such as neuroblastoma (30). Further studies have shown that BDNF/TrkB is oncogenic not only in neurogenic original tumors (31), but also in other tumors outside of the neural system (32,33).

In addition to TrkB, p75 is a receptor for a precursor form of BDNF (pro-BDNF), which can be cleaved to form the mature form by metalloproteinases (34). Unlike TrkB, which is the receptor for the mature form of BDNF (35), the role of p75 is not well established in tumors. It is found to be overexpressed in glioblastoma (34,36), melanoma (37,38) and breast cancer (6), implying it may exhibit an oncogenic role. However, it also displays an oncolytic role by suppressing tumor cell proliferation and migration in bladder (39), hepatocellular (40) and gastric cancers (41). Considering p75's controversial role in tumor, we will only summarize the oncogenic role of BDNF/TrkB pathway for the following sections.

3. Oncogenic role of BDNF in tumor

As said above, BDNF's oncogenic role in cancer has initially been characterized in neuroblastoma, a type of cancer in nervous tissue (30). It has ever been demonstrated Tyro3, Axl and Mertk (TAM) receptor tyrosine kinases promote neurogenesis by supporting neural stem cell survival, proliferation and neuronal differentiation (22,42). Removal of TAM receptors leads to a significantly-reduced level of neurogenesis and BDNF expression, indicating TAM receptors support neurogenesis by activating BDNF pathway (23). Some scientists also concluded BDNF mediates development, migration, differentiation and survival of newborn neurons (43). Further on, high levels of BDNF were found in neuroblastoma cells and were discovered to be linked with better prognosis of neuroblastoma (44). An increase of BDNF and TrkB signaling in neuroblastoma cells may represent an autocrine system to support tumor growth, invasion and metastasis. Mover, BDNF/TrkB pathway was implied to induce angiogenesis in neuroblastoma. It was found that BDNF could stimulate neovascularization through recruitment of TrkB-expressing endothelial progenitor cells (45,46). Lastly, this signaling was also demonstrated to promote resistance to chemotherapy in neuroblastoma cells (47).

As evidence is accumulated, BDNF/TrkB signaling is universally considered to have oncogenic consequences. It has been found BDNF/TrkB are up-regulated in countless types of cancers, such as breast cancer, carcinoid, cervical, colorectal, glioma, liver, lung (6-12). Some studies even revealed BDNF might be an important prognostic factor for cancers (12,48-50). Recently, BDNF/TrkB pathway has been demonstrated to transactivate EGFR, a growth factor receptor commonly up-regulated in many cancers (43,51). This transactivation is important for proliferation and migration of embryonic cortical neurons, lung cancer cells and ovarian cancer cells (43,51,52). Administration of BDNF prevents the oncolytic role of EFGR inhibition in colon cancer. Besides, BDNF and EGFR seems to compensate for each other so that dual inhibition of the two pathways works effectively to suppress colon cancer cell proliferation (53).

BDNF/TrkB can also decrease a cancer cell's sensitivity to chemotherapy. It has been reported that BDNF increases the survival of neuroblastoma cells from cisplatin, etoposide and vinblastine in a dose-dependent manner (54,55). Treatment with antibodies against BDNF made mice more susceptible to chemotherapy in models of breast cancer (6), uterine sarcoma (56), and neuroblastoma (57,58). BDNF administration was demonstrated to cause chemotherapeutic resistance in head and neck squamous cell carcinoma (59). This protective role of BDNF from chemotherapy was possibly due to its ability to support proliferation and survival of cancer cells (55).

In addition, BDNF/TrkB pathway promotes resilience against the programmed death of anchorage dependent cancer cells. This programmed death of cancer cells, known as anoikis, is important to fight against many types of cancers. As solid tumors metastasize from the original sites and migrate to other regions with plentiful nutrients, tumor cells may undergo anoikis (60). However, some tumor cells can have a mesenchymal transition from an epithelial nature so that they survive short travel through the blood to distant organs (61). Interestingly, BDNF/TrkB has been reported to regulate the resistance to anoikis of several cancers since up-regulation of BDNF/TrkB was found in metastatic tumor cells. Nevertheless, no activation of BDNF/TrkB pathway was observed in non-metastatic tumor cells or tumor cells that fail to survive through metastasis (60,62,63). This supports how BDNF/TrkB signaling may perhaps play a crucial role in the progression and invasion of malignant tumors.

Finally, BDNF/TrkB pathway has been implied to mediate cancer reformation after successful treatment of cancer. Scientists overexpressed TrkB in a neural crest-derived cell line and implanted them into mice. These cells formed tumors 10 days after implantation and killed all mice within one week after tumor formation (31). Cancer stem cells are similar to neural crest-derived cells. They divide slowly but can

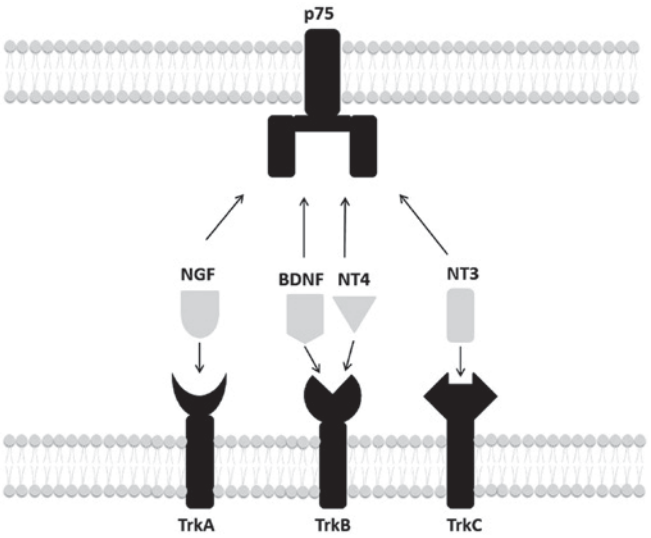

Figure 1. Neurotrophins and their receptors. NGF binds to TrkA receptors, BDNF and NT4 bind to TrkB, and NT3 mainly binds to TrkC receptors. All of these neurotrophins also bind to the low-affinity receptor p75. NGF, nerve growth factor; BDNF, brain-derived neurotrophic factor; NT, neurotrophin; Trk, tropomyosin receptor kinase.

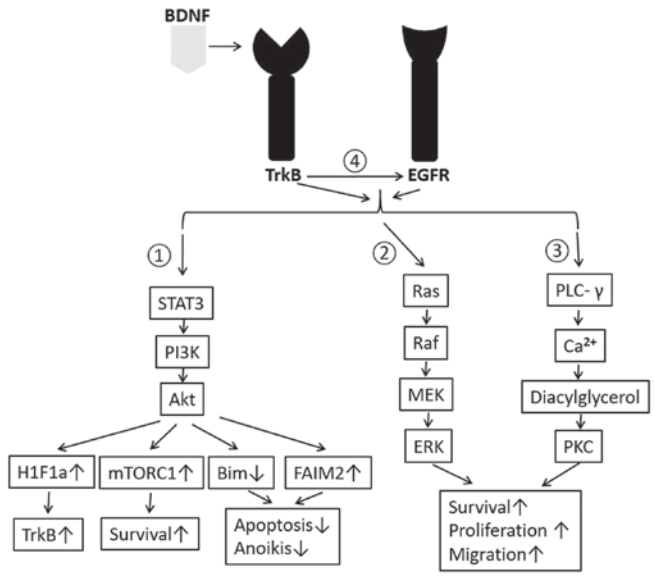

Figure 2. Summarized molecular pathway of BDNF/TrkB's oncogenic role. Four signaling pathways are discussed in the present review: i) Phosphorylation of STAT3 activates the PI3K/Akt signaling pathway, which will then amplify H1F1a to positively control TrkB expression, stimulate mTORC1 for the expression of pro-survival proteins and reduce Bim, but increase FAIM2 in order to inhibit apoptosis or anoikis; ii) Ras-Raf-MEK-ERK signaling is activated in order to promote the survival, proliferation and migration of cancer cells; iii) activated expression of PLC-γ causes the release of calcium ions from intracellular compartments and the generation of diacylglycerol. Diacylglycerol activates PKC, which exerts oncogenic effects; and iv) Transactivation of EGFR by BDNF/TrkB can also regulate cancer by activating the above 3 signaling pathways. An upwards pointing arrow after each signal protein indicates upregulation of expression level while a downwards facing arrow represents decreased expression. BDNF, brain-derived neurotrophic factor; Trk, tropomyosin receptor kinase; STAT3, signal transducer and activator of transcription 3; PI3K, phosphoinositide 3-kinase; PLC-γ, phospholipase-C-γ, mitogen-activated protein kinase. PKC, protein kinase C; H1F1a, hypoxia-inducible factor 1α; FAIM2, Fas apoptotic inhibitory molecule 2; MEK, mitogen activated protein kinase kinase; ERK, extracellular signal-regulated kinases.

turn into cancer cells under some condition. Chemotherapy can kill rapidly-dividing tumor cells but can't target these slowly-dividing cells. It has been shown that TrkB-positive cancer stem cells can cause tumor reformation after successful treatment of mice with triple-negative breast cancers (32). These findings demonstrate the importance of continuous treatment with TrkB inhibitor after successful removal of tumor cells with chemotherapy.

4. Molecular pathways of BDNF/TrkB's oncogenic role

As discussed above, it has been observed that BDNF and TrkB levels increase in many types of cancers, conferring aggressive phenotypes due to their resistance to chemotherapeutic agents (64). BDNF binds its receptor TrkB and triggers a cascade of signals, including PI3K/Akt, Ras-Raf-MEK-ERK, PLCγ pathway, transactivation of EGFR, Jak/STAT, nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB), Urokinase-type plasminogen activator (UPAR)/UPA, Wnt/β-catenin and Vascular endothelial growth factor (VEGF) pathways, etc. Among these pathways, the first 4 are mostly studied and therefore will be discussed in this review and summarized as shown in Fig. 2.

PI3K/Akt can be activated by BDNF/TrkB and then leads to production of pro-migratory, anti-apoptotic and pro-survival proteins (65,66). Some recent studies have indicated that TrkB receptor activation induces phosphorylation of tyrosine 705 of STAT3, which then activates PI3K/Akt (67). This pathway will activate the mammalian target of rapamycin complex 1 (mTORC1), resulting in increased protein synthesis and cell survival by direct phosphorylation of its effectors, such as the ribosomal S6 kinase1 (S6K1), and elF4E-binding proteins (4E-BPs) to terminate binding to elF4E and relieve the block on translation (68,69). Besides, PI3K/Akt pathway can transduce to amplify hypoxia-inducible factor 1-alpha (H1F1a), which is a transcriptional activator of TrkB expression. This positive feedback loop aggravates and extends BDNF/TrkB's effect on tumor (67,70).

As a universal attenuator of chemotherapeutic efficacy, BDNF/TrkB exhibits this role by mediating PI3K/Akt pathway, since inhibition of PI3K abrogated BDNF's ability to protect cancer cells from etoposide (55). PI3K/Akt pathway promotes resistance to extrinsic apoptosis through down-regulation of Bim, a pro-apoptotic protein that facilitates mitochondrial-mediated or intrinsic apoptosis (59,71). In addition, PI3K/Akt pathway is involved in up-regulation of Fas apoptotic inhibitory molecule 2 (FAIM2), which works to inhibit Fas-mediated Caspase-8-dependent apoptosis (72). The two possible pathways also explain how BDNF promotes resistance to anoikis through activation of PI3K/Akt.

BDNF/TrkB pathway has also been shown to transactivate EGFR even without the endogenous EGF ligand (43) (Fig. 2). *In vitro* study demonstrated administering BDNF leads to expected TrkB phosphorylation and also EGFR phosphorylation no matter if EGF is present in the culture media or not (43). Transactivation of EGFR stimulates expression of PLC-γ, which then causes the release of calcium ions from intracellular compartments and the generation of diacylglycerol. Diacylglycerol can activate protein kinase C (PKC),

which is linked to carcinogenesis and maintenance of malignant phenotype (73). Besides, EGFR can result in the progression of cancer cells through G1 phase and into S phase by regulating the cyclin dependent kinases (CDK) and the cyclins (74). EGFR can also cause Ras activation, which involves large number of protein factors, including Raf, mitogen-activated protein kinase (MAPK), cytosolic kinases and nuclear transcription factors (75,76). Activation of Ras will in turn accelerate cell-cycle progression and contribute to poor prognosis of patients with cancers (12,77). Moreover, it is possible that transactivation of EGFR regulates cancer through PI3K/Akt pathway, as shown in breast cancer (78), head and neck cancer (79), and prostate cancer (80).

Finally, BDNF/TrkB is considered to be able to directly activate Ras and PLC-γ pathways, both of which play a vital role in a wide range of cancers (Fig. 2). In the central nervous system, it is well documented that BDNF/TrkB activates the Ras-Raf-MEK-ERK signaling and regulates the neuronal differentiation (81). BDNF/TrkB pathway is also demonstrated to regulate synaptic plasticity by promoting the PLCγ-mediated expression of protein kinase C (82). Recent studies showed Ras and PLC-γ mediated oncogenic role may be triggered by BDNF/TrkB. For example, BDNF/TrkB activates NF-κB expression through stimulation of PLCγ and therefore enhances ovarian cancer cell survival by suppressing anoikis (83). BDNF/TrkB is also demonstrated to promote epithelia-mesenchymal transition, as well as the migration and invasion of cervical cancer by activating Ras-Raf-MEK-ERK pathway (84).

5. Clinical trials of targeting Trk receptors for treatment of cancer

Scientists have developed two highly potent and selective TrkB inhibitors, cyclotraxin-B (85) and antinuclear antibodies (ANA)-12 (86), which can inhibit TrkB and its downstream processes. However, they are not applied to clinical trials since targeting all Trk receptors seems more promising to treat cancer. Like TrkB, TrkA and TrkC are up-regulated in many types of cancers and demonstrated to be oncogenic as well (13). For example, Light *et al* (87) reported TrkA up-regulation in neuroblastomas was associated with poor prognosis, while activated expression and signaling of TrkC corresponded to a more aggressive and invasive neuroblastoma. Besides, the kinase domain of the three receptors are remarkably conservative. TrkB and TrkC share 100% identical residues in the ATP binding sites, and there is only a 2-residue difference between TrkA and TrkB (88). Considering kinase domain determines their activity, it is reasonable and applicable to design inhibitors targeting the conservative kinase domain. Based on the fact that the three Trk receptors share similar kinase domain and all have oncogenic role, drugs targeting all of them were designed and applied to clinical trials.

Entrectinib is an ATP-competitive inhibitor of the Trk proteins, c-ros oncogene 1 (ROS1), and anaplastic lymphoma kinase (ALK). It is currently being investigated in multiple phase II studies, including breast cancer, renal cancer, ovarian cancer, non-small cell lung cancer (NSCLC), and sarcomas (89). Promising results have been reported, including increased objective response rate, median progression-free survival rate and overall survival rate. Interestingly, Entrectinib has also shown the efficacy to treat brain tumors, implying that it can penetrate blood-brain barrier (BBB) (90). Similar to Entrectinib, Larotrectinib is another pan-Trk inhibitor which is able to penetrate BBB and shows positive results in multiple phase II clinical trials, including glioblastoma, small cell lung cancer (SCLC), colorectal cancers, melanoma pancreatic and ovarian (91,92). A table was made to summarize all clinical trials for the two Trk inhibitors (Table I).

Cabozantinib is an orally bioavailable small molecule inhibitor of Trk receptors, c-Met, RET, ROS1, ALK, and vascular endothelial growth factor 2 (VEGFR2) with approved treatment for metastatic medullary thyroid cancer and prostate cancer (13). Recently, Cabozantinib was approved as an anti-angiogenic therapy for advanced renal cell carcinoma, by eliciting significant improvements in response rates, progression-free survival, and overall survival (93,94). Currently, more clinical trials are underway to evaluate its role in CNS tumors, like gliomas (95). Considering its capacity of penetrating BBB, promising results are expected.

6. Potential side effects of targeting BDNF/TrkB pathway to treat cancer

Though the clinical trials received promising results, we should not ignore the potential side effects of targeting BDNF/TrkB for cancer treatment. As a neurotrophin factor in the nervous system, BDNF regulates multiple processes including neuron differentiation, survival, dendritic pruning, patterning of innervation, synaptic function and plasticity (1,2). Our lab has demonstrated BDNF plays a vital role in the central and peripheral nervous system by regulating the developmental and mature taste system (19-21), and maintaining adult hippocampal neurogenesis (22,23). A recent clinical trial even showed elevation of BDNF levels by using CX1846 can correct age-related issues (96). Therefore, we should be extremely careful when targeting BDNF/TrkB to treat cancer. Doses of BDNF/TrkB inhibitors and side effects of nervous system should be closely monitored. Dysfunction of central nervous system may be expected, like memory loss, ataxia, anhedonia, lethargy and depression (97). As a result, it is necessary to specifically target tumors with administration of BDNF/TrkB inhibitors. Gene delivery using viral vectors may be a good option since it can specifically target tumor cells with appropriate promoters.

Besides, recent studies suggest that BDNF overexpression in the hypothalamus may have an oncolytic effect. It is found that mice with enriched environmental (EE) housing had high expression of BDNF in the hypothalamus and also got augmented T-cell cytotoxicity. This increased anti-tumor immune response was abrogated by hypothalamic knockdown of BDNF, implying BDNF mediates the oncolytic effects of EE housing (98). Besides, tumors of EE mice had reduced expression of several pro-survival proteins like VEGF, IGF-1 and p-ERK, which normally confer resistance to chemotherapeutic agents. These results were derived from mice transplanted with breast cancer cells (99), melanoma cancer cells (100), and even glioma cells (101). It is suggested that up-regulation of BDNF in the central nervous system may have an effect of oncolysis rather than oncogenesis, even if the tumor is within the central nervous system. The underlying mechanism may be due to that BDNF supports survival and

Table I. Ongoing clinical trials for Entrectinib and Larotrectinib in different types of cancers.

NCT identifier	Drug	Phase	Cancer type	Status
NCT02568267	Entrectinib	II	Breast cancer, cholangiocarcinoma, colorectal cancer, head and neck neoplasms, lymphoma, large-cell, anaplastic, melanoma, neuroendocrine tumors, non-small cell lung cancer, ovarian cancer, pancreatic cancer, papillary thyroid cancer, primary brain tumors, renal cell carcinoma, sarcomas, salivary gland cancers, and adult solid tumor	Recruiting
NCT03330990	Entrectinib	I	Advanced solid tumor	Completed
NCT02650401	Entrectinib	I	Solid tumors, CNS tumors, and neuroblastoma	Recruiting
NCT02097810	Entrectinib	I	Locally advanced solid tumors, metastatic solid tumors	Active, not recruiting
NCT02587650	Entrectinib	II	ALK fusion protein expression, BRAF wt Allele, invasive skin melanoma, MET fusion gene positive, NRAS wt Allele, NTRK1 fusion positive, NTRK2 fusion positive, NTRK3 fusion positive, RET fusion positive, ROS1 fusion positive, stage III cutaneous melanoma AJCC v7, stage IIIA cutaneous melanoma AJCC v7, stage IIIB cutaneous melanoma AJCC v7, stage IIIC cutaneous melanoma AJCC v7, and stage IV cutaneous melanoma AJCC v6 and v7	Recruiting
NCT02576431	Larotrectinib	II	Non-small-cell lung carcinoma, thyroid neoplasms, sarcoma, colorectal neoplasms, salivary gland neoplasms, biliary tract neoplasms, brain neoplasm, primary, carcinoma, ductal, breast, melanoma, solid tumors, glioblastoma, bile duct neoplasms, astrocytoma, head and neck squamous cell carcinoma, pontine glioma, pancreatic neoplasms, ovarian neoplasms, renal cell carcinoma, cholangiocarcinoma, bronchogenic carcinoma, bronchial neoplasms, lung neoplasms, respiratory tract neoplasms, thoracic neoplasms, neoplasms, nerve tissue, nevi and melanomas	Recruiting
NCT02637687	Larotrectinib	I and II	Neoplasms, central nervous system neoplasms	Recruiting
NCT03213704	Larotrectinib	II	Advanced malignant solid neoplasm, malignant glioma, ann arbor stage III childhood non-hodgkin lymphoma, ann arbor stage IV childhood non-hodgkin lymphoma, malignant glioma, NTRK1 fusion positive, NTRK2 fusion positive, NTRK3 fusion positive, recurrent central nervous system neoplasm, recurrent childhood ependymoma, recurrent childhood malignant germ cell tumor, recurrent childhood medulloblastoma, recurrent childhood non-hodgkin lymphoma, recurrent childhood rhabdomyosarcoma, recurrent childhood soft tissue sarcoma, recurrent ewing sarcoma, recurrent glioma, recurrent hepatoblastoma, recurrent langerhans cell histiocytosis, recurrent malignant solid neoplasm, recurrent neuroblastoma, recurrent osteosarcoma, recurrent peripheral primitive neuroectodermal tumor, refractory central nervous system neoplasm, refractory childhood malignant germ cell tumor, refractory langerhans cell histiocytosis, refractory malignant solid neoplasm, refractory neuroblastoma, refractory non-hodgkin lymphoma, rhabdoid tumor, stage III osteosarcoma AJCC v7, stage III soft tissue sarcoma AJCC v7, stage IV osteosarcoma AJCC v7, stage IV soft tissue sarcoma AJCC v7, stage IVA osteosarcoma AJCC v7, stage IVB osteosarcoma AJCC v7, and wilms tumor	Recruiting
NCT02122913	Larotrectinib	I	Unspecified adult solid tumor, protocol specific	Recruiting

NCT, National Clinical Trials.

maturation of peripheral T-cell (102). As a result, when we target BDNF/TrkB for cancer treatment, a close monitoring of T-cell activity is necessary so that the antitumor immune response won't be attenuated.

7. Conclusion and discussion

BDNF plays an important role in a wide range of cancers by binding its receptor TrkB (6-12). Up-regulation of BDNF/TrkB results in a series of downstream signalings, including PI3K/Akt, Ras-Raf-MEK-ERK, PLCγ pathway, and transactivation of EGFR, etc (Fig. 2). Stimulation of these signalings exerts oncogenic effects by mediating cancer cell's growth, proliferation, survival, migration, epithelial to mesenchymal trasition, anoikis, relapse and chemotherapeutic sensitivity (6-12). Although BDNF/TrkB regulates several downstream signalings and these pathways may correspond to each other, not all these signalings will be stimulated in response to BDNF/TrkB. For example, it was reported that BDNF can rescue neuroblastoma cells from etoposide. Inhibition of PI3K but not MAPK can abrogate this ability, indicating MAPK pathway may not be involved in this oncogenic role (103).

Entrectinib (90), Larotrectinib (91), and Cabozaninib (93) are three drugs targeting Trk receptors for treatment of cancer and the clinical trial results are promising. In some cancers, patients have increased objective response rate, median progression-free survival rate and overall survival rate. Considering the three drugs can all penetrate BBB, we should pay close attention to their side effects on central nervous system. Larotrectinib has shown toxicity profile with fatigue, dizziness and memory loss (92). Besides, BDNF in central nervous system, especially hypothalamus, have an oncolytic role by increasing T-cell toxicity (98,100,101). When targeting Trk receptors for treatment of cancer, these drugs will also decrease activity of BDNF/TrkB in the central nervous system and thus may attenuate BDNF-mediated anti-cancer immune response. A close monitoring of T-cell activity is therefore necessary.

Since BDNF plays a crucial role in oncogenesis, is it still safe to activate BDNF/TrkB for treatment of some neurodegenerative diseases? Like human hormones, too much or too little of BDNF may be harmful. It is not suggested that healthy people should take BDNF as a supplement due to the potential risk of oncogenesis. Nevertheless, administration of BDNF may be beneficial in some aging and neurodegenerative diseases, such as amyotrophic lateral sclerosis (ALS), peripheral neuropathy, Parkinson's disease and Alzheimer's disease (104-106). Under these unhealthy conditions, BNDF/TrkB is down-regulated and there is no evidence that administration of BDNF can cause cancer. For clinical application, BDNF is not directly administrated since it is a moderately-sized and charged protein, and can't easily cross BBB. Therefore, scientists have spent decades trying to establish small drugs that could penetrate BBB and safely augment BDNF levels in the brain. Recently, Ampakines, a modulator of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor, have been found to significantly elevate BDNF levels in some brain regions and also successfully correct age-related memory issues without severe side effects (96,107).

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LM, BL and RJ wrote the manuscript. XJ and XY critically revised the manuscript for important intellectual content. YX reviewed and edited the manuscript.

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Patient consent for publication

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Competing interests

The authors declare that they have no competing interests.

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