Oncogenic role of the brain-derived neurotrophic factor-TrkB axis with a focus on gallbladder cancer (Review)

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Abstract. Brain-derived neurotrophic factor (BDNF) belongs to the neurotrophin family of growth factors that regulate the development of the central nervous system during fetal growth. Apart from its role in neurogenesis, BDNF, along with its high-affinity receptor tropomyosin-related receptor kinase B (TrkB), serves a key role in the pathogenesis of several tumors such as breast, cervical and colorectal cancer, and gliomas. The oncogenic effects of BDNF and TrkB upregulation, including effects on the aggressiveness, metastatic potential and resistance to standard chemotherapeutic agents, are mediated by the downstream activation of the PI3K/Akt pathway, EGFR activation and MAPK pathways. In view of the key role served by BDNF and TrkB in various steps of oncogenesis, there have been attempts to develop inhibitors of the TrkB receptor to block the effects of BDNF upregulation, and these have shown promising results. The role of the BDNF-TrkB pathway in the pathogenesis of gallbladder cancer (GBC), a biliary tract malignancy with high mortality, has still not been fully elucidated. Immunohistochemical expression of TrkB at the invasive front of GBC has been demonstrated along with the growth inhibitory effect of TrkB siRNA on GBC cell lines, suggesting the role of this pathway in the aggressiveness of GBC. The present review explores the mechanisms of action of the BDNF-TrkB axis, focusing on GBC, in an attempt to provide future research directions for delineating the role of this pathway in the pathogenesis of GBC and the potential therapeutic implications.

Contents

1. Introduction

Brain-derived neurotrophic factor (BDNF) is a member of the neurotrophin family that includes nerve growth factor, neurotrophin 3 and neurotrophin 4. BDNF contributes to neuronal development and regeneration through dendritic branching and maintaining dendritic spine morphology (1). Due to this role, BDNF has been implicated in a variety of neurodegenerative disorders such as Alzheimer's disease and Huntington's chorea, as well as other neurogenic diseases such as depression, schizophrenia and anxiety disorders (2). Apart from in neuronal tissues, BDNF expression has also been detected in immune cells, endocrine cells, macrophages, smooth muscle cells in

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blood vessels and striated muscles of the heart (2). BDNF exerts its physiological and pathological effects by binding with its high-affinity receptor, tropomyosin-related receptor kinase B (TrkB) (1). Activation of TrkB leads to the activation of multiple downstream pathways such as the PI3K/Akt, EGFR and RAS pathways (Fig. 1) (3,4). Activation of the PI3K/Akt pathway then leads to the activation of pro-migratory, anti-apoptotic and pro-survival proteins. BDNF-TrkB binding also leads to a constitutive activation of EGFR, even without the presence of its ligand, epidermal growth factor (5). EGFR activation in turn activates the phospholipase C γ (PLC-γ)-dependent pathways, including the protein kinase C pathway (5). The activation of the MAPK/RAS signaling pathway exerts anti-apoptotic and pro-survival effects (6). Thus, the binding of BDNF with its receptor TrkB leads to pro-oncogenic effects.

Gallbladder cancer (GBC) is a common malignancy of the biliary tract with a ~70% mortality rate due to delayed diagnosis in the majority of cases (7). A number of factors such as cholelithiasis, porcelain gallbladder, congenital biliary abnormalities and dietary exposures have been associated with the occurrence of GBC (8). The most commonly used serum markers for the diagnosis of GBC, carbohydrate antigen 19-9 and CEA, have low sensitivity and specificity (9). Hence, there is a need to identify more sensitive and specific biomarkers that could help in the early diagnosis of GBC and improve the prognosis of this malignancy. Over the past decades, research has focused on identifying novel biomarkers for the early diagnosis of GBC. Due to late diagnosis in the majority of cases of GBC, the 5-year survival rates are low (~10%) due to local or distant metastasis of the tumor at the time of diagnosis (7). Apart from diagnostic biomarkers, several molecules such as EGFR, HER2, VEGF and cyclooxygenase-2 have been shown to be dysregulated in GBC, with the potential to be developed as a therapeutic target for patients with GBC (10). A study by Xiong *et al* (7) demonstrated higher immunoreactivity for BDNF in GBC and in lesions with moderate to severe dysplasia, suggesting a role of the BDNF-TrkB axis in the early pathogenic steps in GBC. Despite the few more recent reports discussing this pathogenetic mechanism (10,11), reviews of GBC pathogenesis have not summarized the BDNF-TrkB axis in GBC. The present review summarizes the currently available literature on the role of BDNF in GBC in order to provide a direction for the development of biomarkers for early detection or therapeutic targets for improved management and survival of patients with GBC.

For the present review, databases such as PubMed (https://pubmed.ncbi.nlm.nih.gov/), Cochrane (https://www.cochranelibrary.com/) and Web of Science (https://access.clarivate.com/login) were searched from inception to September 2024 using the keywords 'cancer', 'gallbladder cancer', 'BDNF' and 'TrkB'. Studies providing data on the role of BDNF or TrkB in the pathogenesis of epithelial cancer, including GBC either as cell line studies or in *in vivo* models of GBC, published in English or having adequate data in an English abstract were included in the present review. Case reports or series, reviews and editorials were excluded.

2. Pathogenesis of GBC: Current concept

The tumorigenesis model of GBC has only been elucidated in recent decades. GBC has been reported in association with hereditary cancer syndromes, including Lynch syndrome, neurofibromatosis 1 and Gardner's syndrome (12-14). In the late 20th century, multiple studies provided evidence for a model of stepwise progression in the development of GBC (15,16). Roa *et al* (17) presented a description of the metaplasia-dysplasia-carcinoma sequence in gallbladder and indicated a time lapse of ~15 years for the transformation from dysplasia to carcinoma. This model postulates that chronic inflammation due to gall stones or anomalous pancreaticobiliary ductal junction may lead to metaplasia or hyperplasia. Genetic mutations such as loss of p16, gain of cyclin D1 or upregulation of cyclooxygenase 1 may be responsible for progression from metaplasia/hyperplasia to dysplasia and *in situ* carcinoma (17). This pathogenetic mechanism provides a window of about one decade for early detection of GBC if an appropriate biomarker is shown to be sensitive and specific for gallbladder dysplasia. A minor fraction of cases of GBC (5-10%) follow the adenoma-carcinoma sequence, similar to those observed in colon carcinoma (18). Regardless of the pathogenetic mechanism of development of GBC, tumor progression and metastasis through epithelial-mesenchymal transition (EMT) and anoikis resistance appear to be the common strategies utilized by tumor cells for invasion (19) and, thus, may be explored as markers for predicting GBC progression.

3. BDNF in GBC

The upregulation of BDNF expression in GBC was delineated for the first time in 2010 by Artico *et al* (10) as high immunoreactivity for BDNF in GBC tissues compared with chronic cholecystitis tissues. This was followed by a study by Xiong *et al* (7) in 2013 that reiterated the results of Artico *et al* (10). In addition, Xiong *et al* (7) reported that benign lesions such as adenoma, polyps or peritumoral tissues with upregulation of BDNF expression exhibited moderate to severe dysplasia in the gallbladder epithelium, suggesting a role of BDNF in an early stage of the pathogenesis of GBC (7). A cell line-based study of GBC has also demonstrated a positive impact of BDNF/TrkB signaling on the proliferative ability of GBC cells. Kawamoto *et al* (11) revealed that inhibition of TrkB using small interfering RNA (siRNA) resulted in reduced proliferation of GBC cell lines. This was also confirmed in *in vivo* experiments with TrkB siRNA-transfected mice that demonstrated reduced tumor volume and Ki-67 expression (11). In addition, BDNF/TrkB signaling has been revealed to impact the invasiveness of GBC cell lines. The addition of recombinant BDNF increased invasion, while the inhibitor K252a reduced invasion in the GBC cell lines. These experiments indicate that the BDNF-TrkB axis serves a key role in the pathogenesis and progression of GBC (11). These studies have been summarized in Table I.

4. BDNF-TrkB and EMT in tumors

EMT is a process whereby epithelial cells lose their cell-cell contact and acquire mesenchymal-like gene expression and a migratory phenotype (20). EMT is a well-accepted mechanism that contributes to fibrosis and tumor invasion and metastasis. Cancer-associated fibroblasts secrete growth factors and

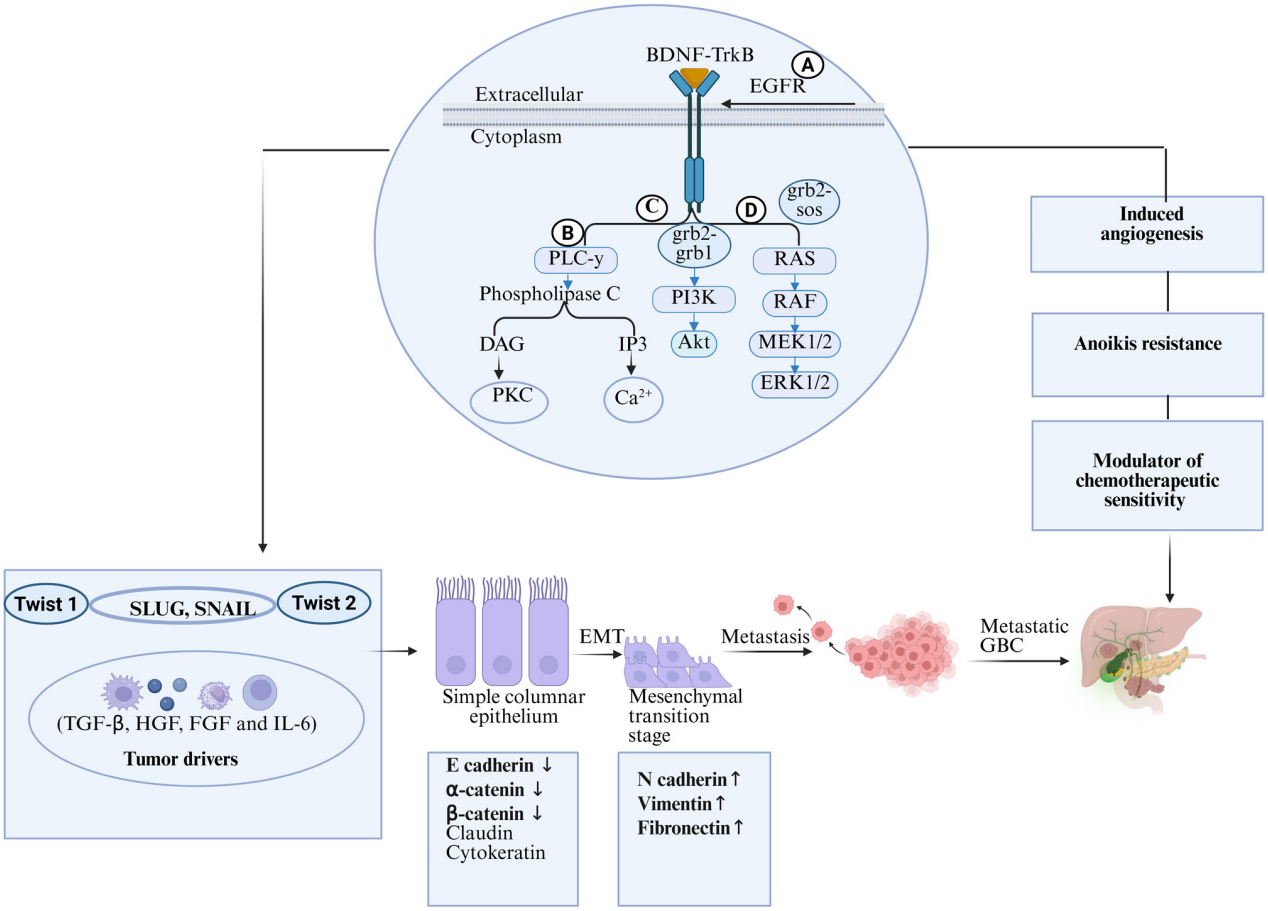

Figure 1. Schematic representation of the four downstream pathways which are activated when BDNF binds to its receptor TrkB: (A) EGFR transactivation, driving angiogenesis, anoikis resistance, and chemoresistance, contributing to tumor progression and metastasis; (B) PLCγ-PKC, triggering calcium signaling and migration through PLCγ-mediated hydrolysis of PIP2 into DAG and IP3, leading to PKC activation and Ca^{2+} release; (C) PI3K-Akt, enhancing cell growth and survival by PI3K-mediated Akt activation; and (D) RAS-MEK-ERK, which promotes cell proliferation and survival via RAS activation of RAF, MEK1/2 and ERK1/2. Akt, protein kinase B; BDNF, brain-derived neurotrophic factor; DAG, diacylglycerol; EMT, epithelial-mesenchymal transition; EGFR, epidermal growth factor receptor; ERK, extracellular signal-regulated kinase; FGF, fibroblast growth factor; GBC, gallbladder cancer; grb, growth factor receptor-bound protein; HGF, hepatocyte growth factor; IP3, inositol 1,4,5-triphosphate; PI3K, phosphatidyl inositol 3-kinase; PKC, protein kinase C; PLC-γ, phospholipase C γ; RAS, rat sarcoma virus; Raf, rapidly accelerated fibrosarcoma kinase; sos, son of sevenless; TrkB, tropomyosin-related receptor kinase B.

inflammatory mediators (TGF-β, hepatocyte growth factor, fibroblast growth factor and IL-6) that mediate EMT. EMT is characterized by the downregulation of epithelial adhesion proteins (E-cadherin, α-catenin and β-catenin) coupled with induction of mesenchymal proteins such as vimentin, N-cadherin and fibronectin (21,22). This change is usually mediated by transcription factors of the SNAIL and zinc finger E-box binding homeobox families along with Twist and E12/E47 (23). SNAIL proteins bind to E-box DNA sequences through their carboxy-terminal zinc-finger domains, thereby repressing epithelial genes (24). Basic helix-loop-helix transcription factors such as Twist1 and Twist2 serve a role in EMT. Twist1 suppresses E-cadherin expression and enhances N-cadherin expression, and this is independent of the SNAIL protein (25). Oncogenes, including RAS, MET, EGFR and TGF-β, induce EMT through various transcription factors (22). A study in mouse xenografts by Smit *et al* (26) demonstrated that TrkB induced transformation resembling EMT via the Twist-SNAIL signaling pathway, resulting in inhibition of E-cadherin expression and upregulation of N-cadherin protein expression (26). Bao *et al* (27) demonstrated the effect of TrkB on the 'cadherin switch' in endometrial cancer cell lines; TrkB-overexpressing cell lines exhibited morphological transition to spindle-shaped cells, while sh-TrkB-transfected cell lines had a more differentiated keratinocyte-like morphology. TrkB overexpression or BDNF-induced stimulation led to increased expression levels of Twist in the endometrial cancer cell lines (27). Similar changes have also been demonstrated in prostate cancer cell lines (28) and parotid gland cancer (29).

Apart from directly regulating the EMT transcription factors, the BDNF-TrkB axis utilizes downstream signaling cascades such as the PI3K/Akt, Ras/MAPK and PLC-γ pathways to induce EMT-like changes. The PI3K/Akt pathway induces EMT by increasing Snail expression levels, facilitating its nuclear localization and inhibiting GSK3β, which normally targets Snail for degradation (30). Ras/MAPK signaling upregulates Slug levels, while PLC-γ activates protein kinase C to increase the expression levels of vimentin and fibronectin (26). Furthermore, BDNF/TrkB can promote EMT indirectly by inducing the secretion of EMT-inducing factors such as TGF-β, epidermal growth factor and hepatocyte growth factor from tumor cells in an autocrine/paracrine manner. These soluble factors then activate their respective receptors and feed into the EMT transcriptional program (31).

Table I. Summary of the studies investigating the molecular mechanisms of the BDNF-TrkB axis in GBC.

First author/s, year	Type of samples	Molecular mechanisms studied	Main findings	(Refs.)
Artico *et al*, 2010	Clinical samples	Immunohistochemistry of BDNF and TrkB in GBC and normal gallbladder samples	BDNF expression was upregulated in epithelial glands and stroma in GBC, while TrkB was expressed in the stroma in GBC.	(10)
Xiong *et al*, 2013	Clinical samples	Immunohistochemistry of BDNF in GBC and chronic cholecystitis samples	BDNF expression was upregulated in GBC compared with chronic cholecystitis. Benign lesions with upregulated BDNF expression exhibited moderate to severe epithelial dysplasia. Patients with GBC with upregulation of BDNF expression had a lower disease-specific survival.	(7)
Kawamoto *et al*, 2017	*In vitro* (cell culture)	Proliferation of GBC cell lines	TrkB inhibitor K252a reduced cell proliferation. TrkB siRNA transfection inhibited proliferation. Recombinant BDNF or BDNF siRNA did not induce marked differences in cell proliferation.	(11)
		Invasiveness of GBC cell lines	Recombinant BDNF enhanced, while TrkB inhibitor reduced, Matrigel invasion of GBC cell lines.	
		EMT	Recombinant BDNF enhanced expression of vimentin and EMT transcription factors (Slug, Snail and Twist), while reducing E-cadherin expression.	
		Angiogenesis	TrkB and HIF-1α were both expressed at the invasive front of human GBC tissues. TrkB siRNA transfection reduced the expression levels of HIF-1α, VEGF-A, VEGF-C and VEGF-D.	
	In vivo (xenograft model)	Tumorigenicity and tumor growth	TrkB siRNA-transfected cell lines exhibited decreased tumorigenicity when subcutaneously injected into athymic nude mice. Tumors from mice injected with TrkB siRNA-transfected cells were smaller.	
	Clinical samples	Patient survival	Immunohistochemical expression of TrkB at the invasive front of surgically resected GBC tissues was associated with increased tumor stage and reduced survival.	
Kawamoto *et al*, 2018	*In vitro* (cell culture)	Proliferation of GBC cell lines	Trk inhibitor ONO-7579 inhibited BDNF/TrkB induced migration and invasiveness of GBC cell lines as well as the BDNF/TrkB-induced VEGF expression	(57)

GBC, gallbladder cancer; BDNF, brain-derived neurotrophic factor; TrkB, tropomyosin-related receptor kinase B; siRNA, small interfering RNA; HIF-1α, hypoxia inducible factor 1α; EMT, epithelial-mesenchymal transition.

BDNF-TrkB and EMT in GBC. At present, the mechanisms of BDNF-induced oncogenesis in GBC have not been fully elucidated. In their *in vitro* experiments, Kawamoto *et al* (11) demonstrated the enhanced expression of Slug, Snail and Twist in GBC cell lines as a response to recombinant human BDNF (rhBDNF), while this was counteracted by the administration of the TrkB inhibitor K252a. Exposure to rhBDNF enhanced the expression of vimentin, while reducing the expression of E-cadherin in GBC cell lines. GBC cells transfected with TrkB-siRNA exhibited more epithelial morphology (11). Therefore, the authors concluded that BDNF-TrkB upregulates transcription factors associated with EMT in GBC.

5. BDNF/TrkB and anoikis resistance

Anoikis refers to 'anchorage-independent cell death', implying cell death once cells lose contact with the neighboring cells or the supporting extracellular matrix (32). In physiological conditions, anoikis maintains tissue homeostasis and, in cancer, this mechanism prevents metastasis to other sites since the detached cells are not able to survive in circulation (32). Therefore, malignant tumors require resistance to anoikis to acquire their metastatic potential. Anoikis resistance is associated with EMT, since a reduction in E-cadherin expression and increased N-cadherin expression promote anoikis resistance in tumor cells (32). Upregulation of growth factors, including EGFR, insulin-like growth factor receptor, VEGF receptor and neurotrophin receptor, along with the activation of downstream pathways such as the PI3K/Akt and Ras/MAPK pathways, imparts anoikis resistance to tumor cells, thereby allowing them to survive (33). BDNF-TrkB has been shown to be associated with anoikis resistance in cervical cancer (34). A study of endometrial carcinoma also demonstrated that cell lines with overexpression of TrkB exhibit reduced anoikis (27). The molecular mechanism of anoikis resistance includes upregulation of Twist (35).

Anoikis resistance in GBC. Although the molecular pathogenesis and significance of anoikis resistance in GBC have yet to be elucidated, the enhanced expression levels of Snail and Twist in GBC cell lines demonstrated by Kawamoto *et al* (11) may be implicated in the anoikis resistance that imparts a survival advantage to GBC cells during metastasis (11). Further elucidation of the significance and mechanisms of anoikis resistance in GBC could potentially provide therapeutic targets for this cancer.

6. Angiogenesis mediated by BDNF/TrkB

BDNF has been shown to serve a role in physiological vascular development, especially in the heart and skeletal muscle and in the vascular response to injury by promoting vessel stabilization (36,37). The pro-angiogenic effect of BDNF is mediated via the PI3K/Akt pathway in TrkB-expressing endothelial cells (38). In tumors, BDNF/TrkB interaction leads to activation of both the PI3K and mTOR pathways. Both of these pathways increase the expression levels of hypoxia inducible factor-1α (HIF-1α) (37). HIF-1α induction stimulates transcription of VEGF mRNA, thereby leading to an increase in VEGF levels, as seen in neuroblastoma cells (39). In addition, BDNF/TrkB activation enhances the recruitment of endothelial precursor cells from the bone marrow (38). This angiogenic role of BDNF has been demonstrated in neuroblastoma, ovarian cancer, multiple myeloma, chondrosarcoma and other solid tumors (39-42). Hypoxia-induced activation of HIF-1α has been demonstrated to promote transcription of the neurotrophic receptor tyrosine kinase 2 gene, leading to upregulation of TrkB expression under hypoxic conditions (43). This creates an autocrine/paracrine loop of BDNF-TrkB-induced pro-angiogenic switching in tumors. Solid tumors usually have hypoxic areas within them where the autocrine/paracrine loop leads to increased angiogenesis, thereby imparting increased invasiveness and metastatic potential (43).

BDNF-TrkB-induced angiogenesis in GBC. Kawamoto *et al* (11) also demonstrated a correlative expression of TrkB and HIF-1α at the invasive front of the GBC cell lines. The expression of these molecules during hypoxic conditions was increased compared with that in the normoxic state (11). The pro-angiogenic effect of the BDNF-TrkB axis in GBC also offers a potential therapeutic target.

7. BDNF as a modulator of chemotherapeutic sensitivity

Over the last 2 decades, BDNF has been shown to modulate cancer cell sensitivity to chemotherapeutic agents. For instance, BDNF expression has been revealed to be cytoprotective in neuroblastoma cells against cisplatin, etoposide and vinblastine (44). In squamous cell carcinoma of the head and neck, BDNF expression upregulates multi-drug resistance pump levels, leading to resistance to chemotherapy (45). The mechanism of cytoprotection of BDNF in tumor cells may depend on the cell type. For instance, chemoresistance of neuroblastoma cells to etoposide is dependent on PI3K (44), while upregulation of multi-drug resistance pumps accounts for the drug resistance in squamous cell carcinoma (45). The PI3K/Akt pathway upregulates anti-apoptotic proteins such as Bcl-2 and Bcl-xL, conferring resistance to chemotherapy-induced apoptosis in neuroblastoma (46). Another mechanism of BDNF-mediated chemotherapeutic resistance in neuroblastoma cells is the downregulation of the pro-apoptotic protein Bim (47). EMT induced by BDNF-TrkB signaling is associated with enhancement of cancer stem cell properties and intrinsic resistance to chemo-drugs (48). Experimental inhibition of BDNF by antibodies against BDNF or the TrkB inhibitor K252a enhances the sensitivity of the tumor to vincristine, etoposide and doxorubicin in Ewing's sarcoma and lung cancer (49,50). Combining BDNF/TrkB inhibitors with chemotherapeutic agents has been shown to synergistically enhance apoptosis and overcome acquired drug resistance in various cancer models (44). Overall, the BDNF-TrkB axis represents a potential therapeutic target to circumvent treatment resistance and improve chemotherapy outcomes across multiple cancer types.

BDNF and chemoresistance in GBC. Currently employed regimes for chemotherapy in GBC are based on gemcitabine or cisplatin, although drug resistance is a considerable challenge (51). Various mechanisms, including autophagy, cancer stemness, the PI3K/Akt pathway, EMT and signaling pathways, such as Akt/mTOR, have been implicated in the

drug resistance of GBC cells (51). However, to the best of our knowledge, the role of the BDNF-TrkB axis in imparting chemoresistance in GBC has not been studied yet.

8. Serum BDNF levels as a biomarker in different types of cancer

BDNF has been explored as a serum-based biomarker in colorectal cancer (CRC) with conflicting results. Brierley *et al* (52) demonstrated that serum BDNF levels were lower in patients with CRC compared with controls, and the levels did not differ between Dukes' stages (52). By contrast, Wang *et al* (53) reported a marked increase in serum BDNF levels in CRC compared with healthy controls. The serum BDNF levels were revealed to be associated with tumor size, tumor, node and metastasis staging, and tumor differentiation (53). Receiver operating characteristic curve analysis in the study by Wang *et al* (53) showed that the combination of serum BDNF and CEA levels had a sensitivity of 85.2% and a specificity of 67.7% for the diagnosis of CRC (53). Another study by Guzel *et al* (54) demonstrated that serum BDNF levels were considerably reduced after surgical resections of pancreatic cancer and CRC (54). In pancreatic cancer, a reduction in serum BDNF levels was observed only in patients who underwent resection, indicating that BDNF might be indicative of completeness of curative resection in pancreatic cancer (54). Similarly, serum BDNF concentrations have been shown to be markedly reduced 24 h after surgery in patients with breast cancer (55). Serum BDNF levels have been demonstrated to be increased in children with recurrent neuroblastoma and are reduced in patients in remission (56). These findings suggest that serum BDNF levels have potential for exploration as an early diagnostic biomarker, and predictor of recurrence and completeness of resection in various solid tumors.

Serum BDNF levels in GBC. Although the immunohistochemical expression of BDNF has been explored in GBC (7,10), to the best of our knowledge, no study has been published at present on the serum levels of BDNF in patients with GBC compared with patients with non-tumorous gallbladder resections. Studies are required to explore the potential role of serum BDNF or TrkB levels as an early diagnostic biomarker or predictor of residual/recurrent tumor.

9. Future direction for research on the BDNF-TrkB axis in GBC

Currently, there is experimental evidence of reduction in tumor progression, invasiveness and aggressiveness by TrkB inhibitor K252a. Apart from this molecule, research has also revealed the potential therapeutic efficacy of pan-Trk inhibitor ONO-7579 in GBC cell lines (57). Although the evidence of the benefit of TrkB inhibitor in cancer therapy is still at an experimental stage, the effect on cancer cell lines suggests that there is future potential for a specific TrkB-inhibitor therapy for solid tumors, including GBC. Research is needed to demonstrate the *in vivo* effect of the TrkB inhibitor on the control of GBC progression and invasiveness.

Since the study by Xiong *et al* (7) demonstrated the expression of BDNF in gallbladder tissues with epithelial dysplasia, it may be hypothesized that the BDNF/TrkB axis is involved in the early phase of carcinogenesis in GBC. At present, to the best of our knowledge, there has been no study comparing the tissue RNA or protein expression of molecules of the BDNF-TrkB axis in GBC or the serum levels of BDNF in patients with gallbladder epithelial dysplasia and GBC. Such a study would help to delineate the role of BDNF-TrkB in the early detection of GBC. Serum BDNF may have the potential to be developed as an early biomarker of GBC.

Moving forward, a multi-pronged approach leveraging the BDNF/TrkB pathway is required to improve clinical outcomes in GBC. On one front, validating the BDNF/TrkB pathway and related biomarkers in large prospective cohorts is key for developing robust early detection strategies. In parallel, advancing selective TrkB inhibitors through preclinical testing and early-phase clinical trials will be vital to establish their safety and efficacy as novel targeted therapies. Combination regimens with chemotherapy, radiation or other genomically-guided therapies could potentially enhance their antitumor effects.

Limitations of the present review. The limitations of the present review include the relatively small number of studies that have explored the BDNF-TrkB axis in GBC. Although the pathogenetic role of BDNF in other solid types of cancer have been studied in numerous reports, this has not been conducted for GBC. Another limitation is that the aforementioned studies have been mainly conducted in Japan with little input from other countries that have a high incidence of GBC. The therapeutic effect of TrkB inhibitors has been evaluated in cell cultures and xenograft mouse models. Therefore, clinical evaluation of these drugs is yet to be undertaken.

Unraveling resistance mechanisms that restore BDNF/TrkB signaling despite inhibition will be key to overcoming treatment failure. Exploring the interplay between BDNF/TrkB and cancer stem cells, epithelial plasticity programs such as EMT, as well as cross-talk with other oncogenic pathways could reveal rational combinatorial approaches. Leveraging biomarker-driven patient selection strategies and adaptive trial designs will be the key to enrich targeted therapies for benefiting populations. Furthermore, integrating findings from epidemiological, molecular pathology and health economics analyses could quantify the translational impact and cost-effectiveness of a BDNF/TrkB-centric paradigm shift in gallbladder cancer management. Such a concerted, multi-disciplinary research focus holds the potential to shift the therapeutic paradigm and improve overall outcomes for this lethal malignancy.

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Availability of data and materials

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Authors' contributions

SB, STH and RG contributed to conceptualization. SB, STH, SSe and RG contributed to methodology of the literature review, and formal literature analysis. SB and RG wrote the original draft. STH, SSe, PSa, AA, SSi, RC, SG, PSi and MA reviewed and edited the manuscript. RG acquired funding, provided resources and supervised the study. Data authentication is not applicable. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Numakawa T, Odaka H and Adachi N: Actions of brain-derived neurotrophin factor in the neurogenesis and neuronal function, and its involvement in the pathophysiology of brain diseases. Int J Mol Sci 19: 3650, 2018.
2. Colucci-D'Amato L, Speranza L and Volpicelli F: Neurotrophic factor BDNF, physiological functions and therapeutic potential in depression, neurodegeneration and brain cancer. Int J Mol Sci 21: 7777, 2020.
3. Kasemeier-Kulesa JC, Spengler JA, Muolo CE, Morrison JA, Woolley TE, Schnell S and Kulesa PM: The embryonic trunk neural crest microenvironment regulates the plasticity and invasion of human neuroblastoma via TrkB signaling. Dev Biol 480: 78-90, 2021.
4. Jia S, Wang W, Hu Z, Shan C, Wang L, Wu B, Yang Z, Yang X and Lei D: BDNF mediated TrkB activation contributes to the EMT progression and the poor prognosis in human salivary adenoid cystic carcinoma. Oral Oncol 51: 64-70, 2015.
5. Reichardt LF: Neurotrophin-regulated signalling pathways. Philos Trans R Soc Lond B Biol Sci 361: 1545-1564, 2006.
6. Sinkevicius KW, Kriegel C, Bellaria KJ, Lee J, Lau AN, Leeman KT, Zhou P, Beede AM, Fillmore CM, Caswell D, *et al*: Neurotrophin receptor TrkB promotes lung adenocarcinoma metastasis. Proc Natl Acad Sci USA 111: 10299-10304, 2014.
7. Xiong L, Deng X, Wen Y, Yang Z and Miao X: Association of BDNF and BMPR1A with clinicopathologic parameters in benign and malignant gallbladder lesions. World J Surg Oncol 11: 80, 2013.
8. Carrasco C, Tittarelli A, Paillaleve N, Pozo MD, Rojas-Sepúlveda D, Barría O, Fluxá P, Hott M, Martin C, Quezada C and Salazar-Onfray F: The evaluation of 17 gastrointestinal tumor markers reveals prognosis value for MUC6, CK17, and CD10 in gallbladder-cancer patients. Diagnostics (Basel) 11: 153, 2021.
9. Srivastava K, Srivastava A, Sharma KL and Mittal B: Candidate gene studies in gallbladder cancer: A systematic review and meta-analysis. Mutat Res 728: 67-79, 2011.
10. Artico M, Bronzetti E, Alicino V, Ionta B, Bosco S, Grande C, Bruno M, Leali FM, Ionta G and Fumagalli L: Human gallbladder carcinoma: Role of neurotrophins, MIB-1, CD34 and CA15-3. Eur J Histochem 54: e10, 2010.
11. Kawamoto M, Onishi H, Ozono K, Yamasaki A, Imaizumi A, Kamakura S, Nakano K, Oda Y, Sumimoto H and Nakamura M: Tropomyosin-related kinase B mediated signaling contributes to the induction of malignant phenotype of gallbladder cancer. Oncotarget 8: 36211-36224, 2017.
12. Watson P, Vasen HFA, Mecklin JP, Bernstein I, Aarnio M, Järvinen HJ, Myrhøj T, Sunde L, Wijnen JT and Lynch HT: The risk of extra-colonic, extra-endometrial cancer in the Lynch syndrome. Int J Cancer 123: 444-449, 2008.
13. Kim ET, Namgung H, Shin HD, Lee SI, Kwon JE, Chang MC and Park DG: Oncologic manifestations of neurofibromatosis type 1 in Korea. J Korean Surg Soc 82: 205-210, 2012.
14. Lowenfels AB, Maisonneuve P, Boyle P and Zatonski WA: Epidemiology of gallbladder cancer. Hepatogastroenterology 46: 1529-1532, 1999.
15. Laitio M: Histogenesis of epithelial neoplasms of human gallbladder I. Dysplasia. Pathol Res Pract 178: 51-56, 1983.
16. Albores-Saavedra J, Alcántra-Vazquez A, Cruz-Ortiz H and Herrera-Goepfert R: The precursor lesions of invasive gallbladder carcinoma. Hyperplasia, atypical hyperplasia and carcinoma in situ. Cancer 45: 919-927, 1980.
17. Roa I, de Aretxabala X, Araya JC and Roa J: Preneoplastic lesions in gallbladder cancer. J Surg Oncol 93: 615-623, 2006.
18. Watanabe H, Date K, Itoi T, Matsubayashi H, Yokoyama N, Yamano M, Ajioka Y and Nishikura K: Histological and genetic changes in malignant transformation of gallbladder adenoma. Ann Oncol 10 (Suppl 4): S136-S139, 1999.
19. Barreto SG, Dutt A and Chaudhary A: A genetic model for gallbladder carcinogenesis and its dissemination. Ann Oncol 25: 1086-1097, 2014.
20. de Moraes JK, Wagner VP, Fonseca FP, Vargas PA, de Farias CB, Roesler R and Martins MD: Uncovering the role of brain-derived neurotrophic factor/tyrosine kinase receptor B signaling in head and neck malignancies. J Oral Pathol Med 47: 221-227, 2018.
21. Gao F, Chen X, Li X, Deng C and Luo P: The pro-migratory and pro-invasive roles of cancer-associated fibroblasts secreted IL-17A in prostate cancer. J Biochem Mol Toxicol 39: e70047, 2025.
22. Cai Q, Shi L, Zhang M and Chen P: Multi-scale transcriptomics reveals that specific tumor cells promote lung adenocarcinoma metastasis through crosstalk with the microenvironment. Discov Oncol 15: 520, 2024.
23. Huber MA, Kraut N and Beug H: Molecular requirements for epithelial-mesenchymal transition during tumor progression. Curr Opin Cell Biol 17: 548-558, 2005.
24. Ibi H, Takahashi K, Harada H, Watabe T and Podyma-Inoue KA: Transforming growth factor-β signals promote progression of squamous cell carcinoma by inducing epithelial-mesenchymal transition and angiogenesis. Biochem Biophys Res Commun 714: 149965, 2024.
25. Yang F, Sun L, Li Q, Han X, Lei L, Zhang H and Shang Y: SET8 promotes epithelial-mesenchymal transition and confers TWIST dual transcriptional activities. EMBO J 31: 110-123, 2012.
26. Smit MA, Geiger TR, Song JY, Gitelman I and Peeper DS: A twist-snail axis critical for TrkB-induced epithelial-mesenchymal transition-like transformation, anoikis resistance, and metastasis. Mol Cell Biol 29: 3722-3737, 2009.
27. Bao W, Qiu H, Yang T, Luo X, Zhang H and Wan X: Upregulation of TrkB promotes epithelial-mesenchymal transition and anoikis resistance in endometrial carcinoma. PLoS One 8: e70616, 2013.
28. Li T, Yu Y, Song Y, Li X, Lan D, Zhang P, Xiao Y and Xing Y: Activation of BDNF/TrkB pathway promotes prostate cancer progression via induction of epithelial-mesenchymal transition and anoikis resistance. FASEB J 34: 9087-9101, 2020.
29. Moriwaki K, Wada M, Kuwabara H, Ayani Y, Terada T, Higashino M, Kawata R and Asahi M: BDNF/TRKB axis provokes EMT progression to induce cell aggressiveness via crosstalk with cancer-associated fibroblasts in human parotid gland cancer. Sci Rep 12: 17553, 2022.
30. Zhang WJ, Luo C, Huang C, Pu FQ, Zhu JF and Zhu ZM: PI3K/Akt/GSK-3β signal pathway is involved in P2X7 receptor-induced proliferation and EMT of colorectal cancer cells. Eur J Pharmacol 899: 174041, 2021.
31. Andreska T, Lüningschrör P and Sendtner M: Regulation of TrkB cell surface expression-a mechanism for modulation of neuronal responsiveness to brain-derived neurotrophic factor. Cell Tissue Res 382: 5-14, 2020.
32. Kim YN, Koo KH, Sung JY, Yun UJ and Kim H: Anoikis resistance: An essential prerequisite for tumor metastasis. Int J Cell Biol 2012: 306879, 2012.
33. Liu JY, Wang SZ, Yuan HQ, Li JL and Xing PY: Patients with non-small cell lung cancer with the exon 21 L858R mutation: From distinct mechanisms to epidermal growth factor receptor tyrosine kinase inhibitor treatments (Review). Oncol Lett 29: 109, 2024.

34. Yuan Y, Ye HQ and Ren QC: Proliferative role of BDNF/TrkB signaling is associated with anoikis resistance in cervical cancer. Oncol Rep 40: 621-634, 2018.
35. Frisch SM, Schaller M and Cieply B: Mechanisms that link the oncogenic epithelial-mesenchymal transition to suppression of anoikis. J Cell Sci 126: 21-29, 2013.
36. Anastasia A, Deinhardt K, Wang S, Martin L, Nichol D, Irmady K, Trinh J, Parada L, Rafii S, Hempstead BL and Kermani P: Trkb signaling in pericytes is required for cardiac microvessel stabilization. PLoS One 9: e87406, 2014.
37. Lin CY, Hung SY, Chen HT, Tsou HK, Fong YC, Wang SW and Tang CH: Brain-derived neurotrophic factor increases vascular endothelial growth factor expression and enhances angiogenesis in human chondrosarcoma cells. Biochem Pharmacol 91: 522-533, 2014.
38. Tsai YF, Tseng LM, Hsu CY, Yang MH, Chiu JH and Shyr YM: Brain-derived neurotrophic factor (BDNF)-TrKB signaling modulates cancer-endothelial cells interaction and affects the outcomes of triple negative breast cancer. PLoS One 12: e0178173, 2017.
39. Aygun N: Biological and genetic features of neuroblastoma and their clinical importance. Curr Pediatr Rev 14: 73-90, 2018.
40. Garrido MP, Torres I, Vega M and Romero C: Angiogenesis in gynecological cancers: Role of neurotrophins. Front Oncol 9: 913, 2019.
41. Łuczkowska K, Kulig P, Baumert B and Machaliński B: Brain-derived neurotrophic factor: Focus on the pathogenesis of multiple myeloma and the development of treatment-induced peripheral neuropathy. Leuk Lymphoma 63: 3044-3051, 2022.
42. Lin CY, Hung SY, Chen HT, Tsou HK, Fong YC, Wang SW and Tang CH: Brain-derived neurotrophic factor increases vascular endothelial growth factor expression and enhances angiogenesis in human chondrosarcoma cells. Biochem Pharmacol 91: 522-533, 2014.
43. Wu YF, Jin KY, Wang DP, Lin Q, Sun J, Su SH and Hai J: VEGF loaded nanofiber membranes inhibit chronic cerebral hypoperfusion-induced cognitive dysfunction by promoting HIF-1a/VEGF mediated angiogenesis. Nanomedicine 48: 102639, 2023.
44. Polacchini A, Albani C, Baj G, Colliva A, Carpinelli P and Tongiorgi E: Combined cisplatin and aurora inhibitor treatment increase neuroblastoma cell death but surviving cells overproduce BDNF. Biol Open 5: 899-907, 2016.
45. Lee J, Jiffar T and Kupferman ME: A novel role for BDNF-TrkB in the regulation of chemotherapy resistance in head and neck squamous cell carcinoma. PLoS One 7: e30246, 2012.
46. Hua Z, Gu X, Dong Y, Tan F, Liu Z, Thiele CJ and Li Z: PI3K and MAPK pathways mediate the BDNF/TrkB-increased metastasis in neuroblastoma. Tumour Biol 37: 16227-16236, 2016.
47. Li Z, Zhang J, Liu Z, Woo CW and Thiele CJ: Downregulation of Bim by brain-derived neurotrophic factor activation of TrkB protects neuroblastoma cells from paclitaxel but not etoposide or cisplatin-induced cell death. Cell Death Differ 14: 318-326, 2007.
48. Jaboin J, Kim CJ, Kaplan DR and Thiele CJ: Brain-derived neurotrophic factor activation of TrkB protects neuroblastoma cells from chemotherapy-induced apoptosis via phosphatidylinositol 3'-kinase pathway. Cancer Res 62: 6756-6763, 2002.
49. Heinen TE, Dos Santos RP, da Rocha A, Dos Santos MP, Lopez PL, Silva Filho MA, Souza BK, Rivero LF, Becker RG, Gregianin LJ, *et al*: Trk inhibition reduces cell proliferation and potentiates the effects of chemotherapeutic agents in Ewing sarcoma. Oncotarget 7: 34860-34880, 2016.
50. Okamura K, Harada T, Wang S, Ijichi K, Furuyama K, Koga T, Okamoto T, Takayama K, Yano T and Nakanishi Y: Expression of TrkB and BDNF is associated with poor prognosis in non-small cell lung cancer. Lung Cancer 78: 100-106, 2012.
51. Lai J, Yang S, Lin Z, Huang W, Li X, Li R, Tan J and Wang W: Update on chemoresistance mechanisms to first-line chemotherapy for gallbladder cancer and potential reversal strategies. Am J Clin Oncol 46: 131-141, 2023.
52. Brierley GV, Priebe IK, Purins L, Fung KY, Tabor B, Lockett T, Nice E, Gibbs P, Tie J, McMurrick P, *et al*: Serum concentrations of brain-derived neurotrophic factor (BDNF) are decreased in colorectal cancer patients. Cancer Biomark 13: 67-73, 2013.
53. Wang Z, Wang S, Liu Y, Gao S, Yu Y and Hu Z: Serum levels of BDNF in patients with adenoma and colorectal cancer. Dis Markers 2021: 8867368, 2021.
54. Guzel T, Mech K, Iwanowska M, Wroński M and Słodkowski M: Brain derived neurotrophic factor declines after complete curative resection in gastrointestinal cancer. PeerJ 9: e11718, 2021.
55. Zoladz JA, Nowak LR, Majerczak J, Kulpa J, Pilc A and Duda K: Breast cancer surgery decreases serum brain-derived neurotrophic factor concentrations in middle aged women: Relationship to the serum C-reactive protein concentration. J Physiol Pharmacol 70: doi: 10.26402/jpp.2019.4.01, 2019.
56. Xiong X, Zeng M, Peng X, Feng C, Li C, Weng W and Li Y: Serum brain-derived neurotrophic factor (BDNF) as predictors of childhood neuroblastoma relapse. BMC Cancer 23: 670, 2023.
57. Kawamoto M, Ozono K, Oyama Y, Yamasaki A, Oda Y and Onishi H: The novel selective pan-TRK inhibitor ONO-7579 exhibits antitumor efficacy against human gallbladder cancer in vitro. Anticancer Res 38: 1979-1986, 2018.