*REVIEW ARTICLE*

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# Brain-derived neurotrophic factor in gastroenterology oncology – short review of current literature

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## Abstract

Brain-derived neurotrophic factor (BDNF) is a member of the neurotrophins group which plays a crucial role in brain development and neurogenesis. In the hypothalamus it is described as playing a role in energy metabolism and feeding behaviour. The hippocampal concentration of BDNF is believed to play an important role in learning and memory, it has a protective role in neurodegeneration and stress responses. BDNF is also known to take part in many other processes, e.g. angiogenesis, proliferation, cell migration and apoptosis. With its receptor TrkB, neurotrophins are important agents that playa role in neural diseases, as well as in cardiovascular and metabolic disorders, such as diabetes mellitus or acute coronary syndrome. Over the last few years, BDNF interaction with TrkB has also been found to be involved in cancer development, including brain, breast, urinary and gastrointestinal cancer. TrkB expression itself has been described as an aggressive neural tumour. BDNF/TrkB signalling takes part in promoting tumour growth and metastasis. The presented review focuses on gastrointestinal cancer and presents the current literature concerning influence of BDNF and TrkB receptor in cancer progression. Special attention is also paid to data confirming the possible role of BDNF/TrkB interaction in chemotherapy resistance. This might present the opportunity to assess the BDNF and TrkB pathway as a possible novel target for anticancer therapies.

## Key words

cancer, gastrointestinal tract, BDNF, Neurotrophins, TrkB

## INTRODUCTION

Nowadays, cancer has become one of the greatest challenges for the diagnosis and treatment of cancer diseases. Many studies have searched for new targets and key-points for anticancer therapy, including growth factors with their receptors. The neurotrophins family applies to these investigations and seems to be a promising signalling pathway.

In the 1980s, for the first time, Ivens Brade isolated Brain Derived Neurotrophic Factor (BDNF) from a pig's brain, and was later confirmed to be present widely in human tissues. It is a member of the neurotrophin family of growth factors, along with nerve growth factor (NGF) and neurotrophin 3, 4, 5 (NT3, NT4, NT5). In 1991, it was identified as being a ligand for tropomyosin kinase receptor B (TrkB), a family of cell membrane receptors TrkA, TrkB, TrkC for NGF, BDNF and NT3, respectively. Binding BDNF to TrkB receptor initiates multiple signalling cascades, including mitogen-activated protein kinase (MAPK) pathway, phosphatidyl-inositide 3-kinase (PI3K) pathway and phospholipase C-gamma (PLC-γ) pathways. BDNF plays a crucial role in human brain development and neurogenesis, and influences proliferation and angiogenesis. It participates not only in the migration and differentiation of foetal neurons, adult neurogenesis and neural plasticity, but also mediates energy metabolism, feeding behaviour and takes part in learning and memory [1]. With its receptor, TrkB also claims to be an important factor outside the nervous system, both are present in several non-neuronal tissues, including muscle, adipose, thymus, liver, lung, heart, spleen and the gastrointestinal tract [2, 3]. BDNF is secreted by inflammatory cells including lymphocytes T, B, monocytes and macrophages, and their serum and tissue concentration is associated with many diseases and conditions.

According to its origin, BDNF is well-known and described as playing a role in psychiatric and neurologic disorders, such as depression [4], diseases of autoimmune pathogenesis, as well as multiple sclerosis [5] or neurodegenerative conditions, e.g. Alzheimer's disease [6]. Further investigation revealed the importance of BDNF in cardiovascular and metabolic diseases, like acute coronary syndrome, stroke [7] or type 2 diabetes [8, 9], obesity, and eating disorders [10]. Moreover, according to their role in neuroplasticity, neurotrophins appear to be crucial for the rehabilitation process; for example, in stroke patients [11].

BDNF/Tr interaction attracted attention because of its of its possible significance in oncogenesis; however, that role remains unclear. This signalling pathways, of which PI3K is of the highest relevance, seems to be very important in the progression of multiple cancers, and might prime

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cancer cells to resist substantial genotoxic stressors, most of which are first-line chemotherapies. On the other hand, high expression of BDNF in the hypothalamus is associated with the induction of immune cells that have activity against tumour cells, and might be associated with better outcomes [12, 13].

## OBJECTIVE

The aim of the study was to review existing literature on the role of BDNF and TrkB in gastrointestinal cancers, focusing on possible values as prognostic or monitoring factors, and a potential target for new anticancer strategies.

**BDNF/TrkB mechanisms of interaction.** To date it is known that the BDNF/TrkB pathway plays an important role in tumour growth, invasion and metastasis. The pathway was also shown to be responsible for some resistance to standard chemotherapy drugs [14, 15, 16].

TrkB was confirmed to cross-talk with the epidermal growth factor receptor (EGFR) signalling pathway, which is commonly up-regulated in many cancers. Administration of BDNF results in changes of EGF serum concentration which facilitates the migration of lung and ovarian cancer cells. It has also been reported that synergistic inhibition of EGFR and TrkB suppresses colon cancer cell proliferation. TrkB/EGFR inhibition was also shown to reduce the pro-migratory effects of BDNF/EGF administration in lung cancer. BDNF/TrkB signalling also might play role in resistance to an anti-tumour peptide that blocks gastrin-releasing peptide receptor (GRPR) through a mechanism dependent on EGFR. TrkB blockage may potentiate anti-tumour effects of anti-EGFR therapy [17, 18].

The BDNF/TrkB pathway was also shown to mediate resistance to anoikis of several cancers. Anoikis is a type of apoptosis suggested to act as barrier to metastasis. Its braking may support tumour cells migration and the appearance of distant metastases. Metastatic tumour cells revealed higher expression of BDNF/TrkB proteins, compared to non-metastatic tissues, and were resistant to cell death. This may explain the pro-survival role of BDNF [19, 20].

The invasion of tumour cells is related to degradation of the extracellular matrix. The proteolytic pathway is regulated by the balance of activators, including matrix metalloproteinases (MMPs), serine proteases, and inhibitors of MMPs called tissue inhibitors of metalloproteinases (TIMPs). It was confirmed that enhanced TrkB expression in neuroblastoma is associated with a significant increase in a subset of MMPs, especially MMP-1, MMP-2 and MMP-9, which potentiates BDNF/TrkB impact on the invasiveness of tumour cells [21].

BDNF may modulate the sensitivity of cancer cells to standard drugs as n universal attenuator of chemotherapeutic efficacy. The known pathway of this action goes through different mechanisms which probably depend on the type of cancer cell. BDNF administration in head and neck squamous cell carcinoma is related to the upregulation of multi-drug resistance pump 1 (MDR1). In neuroblastoma, PI3K inhibition abrogated the ability of BDNF to protect cancer cells against therapy. The protection is also mediated by the down-regulation of Bim, a pro-apoptotic protein that facilitates mitochondrial-mediated or intrinsic apoptosis. Decreases of Bim protected neuroblastoma cells from paclitaxel cell death [15]. Potentially, BDNF might have importance in resistance to apoptosis by up-regulation of proteins associated with delay of activation of transmembrane death receptors. In breast cancer cells, production of apoptotic molecule 2 (FAIM2) is directly correlated to PI3K activity which is downstream of TrkB and FAIM2 countermine apoptosis induced by cisplatin [16].

BDNF takes part in oncogenic transformation and tumour relapse after successful treatment of cancer in animal models. TrkB positive cancer stem cells were shown to play a role in tumour relapse in mice breast cancer models. Cancer stem cells are tumour-initiating cells which slowly express stem cells markers and divides, which may demonstrate the mechanism of resistance to standard chemotherapy targeted on rapidly dividing tumour cells. Thus, treatment with TrkB inhibitors, even after standard chemotherapy, may prolong the disease-free survival time [17].

In turn, there are some data concerning a positive role of BDNF over-expression in anti-cancer therapy. In an animal study, mice living in enriched environmental housing and receiving melanoma xenografts, showed suppressed tumour growth when compared to mice living in a standard environmental. In this group, over-expression was confirmed of BDNF in the hypothalamus, reduced expression of several pro-survival proteins, and a significantly augmented natural killer and T-cell cytotoxicity. Reduced hypothalamic BDNF expression abrogated mice tumour resistance [12]. These findings indicated that environmental or genetic activation of hypothalamic BDNF might support T-cell cytotoxicity. The immunoaugmenting capacity of BDNF may be explained by the fact that BDNF is required for the proper T-cell maturation needed for anticancer action [17].

**BDNF in malignancies.** The first reported malignancy focused on the importance of increased BDNF/TrkB expression – neuroblastoma. High levels of TrkA and TrkC expression were associated with a better outcome, whereas high levels of TrkB and BDNF were related to aggressive features and poor prognosis. In addition, over-expression of BDNF/TrkB promoted resistance to standard chemotherapy. To-date, there have been many studies concerning BDNF/TrkB expression in several cancers, including cancer of the gastrointestinal tract. The studies cited here have described these proteins as a useful prognostic tool and possibly a new anchorage target for anticancer therapies.

**Gastric cancer.** The basic study published by Okugawa et al. showed BDNF over-expression in tumour tissues compared to normal mucosa, especially in invasive front malignancy (compared to tumour core) [22]. Clinically over-expression was associated with the younger age of patients, vessel involvement, lymph node metastases and peritoneal dissemination. BDNF/TrkB co-expression correlated with intestinal type of cancer and worse prognosis for the post-operation survival period. Invasive tumour was characterised by epithelial mesenchymal transition which enabled cancer invasion and metastatic spread.

The role of the BDNF/TrkB axis was also investigated by Choi et al. who confirmed its biological significance in the progression of human gastric cancer. In the current study, BDNF via TrkB receptor increased the level of long pentraxin-related protein 3 (PTX3), known as TNF-inducible gene 14

protein (TSG-14). PTX3 is produced and released by several types of cells in response to primary inflammatory signals. It acts rather as a tumour promoter by enhancing inflammation than onco-suppressor that restrain complement-dependent tumour promoting inflammation, as suggested by other authors [23]. Choi et al. confirmed that PTX3 activation was related to bone metastatic status of gastric cancer by enhancing cancer-osteoblastic niche interactions [24]. It was also reported that BDNF stimulates Receptor Activator of Nuclear Factor Kappa B Ligand (RANKL) production from osteoblasts. RANKL activates maturation of osteoclasts and is known to induce osteoclastogenesis thereby contributing to the formation of osteolytic bone lesions from multiple myeloma [25, 26, 27].

BDNF also serves as a target for micro-RNA (miRNA), including miRNA-744, miRNA-613 and miRNA-107 which expression was low in gastric cancer. miRNAs underexpression correlated with lymph node metastases, invasive depth and TNM staging and was inversely related to BDNF expression, which provided as a functional mediator of miRNAs in gastric cancer patients [28, 29, 30].

A recent study by Esfandi et al. admittedly revealed overexpression of BDNF in tumours with lymphatic and vascular invasion [31]. Authors investigated BDNF gene and BDNF-antisense (noncoding RNA) expression and noted that transcript level correlated with the site of primary tumours – it was lower in fundus and higher in body, antrum of stomach compared to normal tissues. Researchers noted higher tumour BDNF transcript levels in older patients. These results are contrarily to the previous study by Okugawa. Inconsistency between studies might be explained by heterogeneity of patients (younger age) and different site of gene assessment (in whole tumour bulk, not in tumour invasive front), but the main discrepancy in BDNF expression in cancer and non-cancer tissues requires further investigation.

**Small intestine and colon cancer.** Small intestine cancer is an extremely rare disease and to the best of our knowledge, there are no any reports concerning BDNF and TrkB expression in jejunal cancers. In turn, there are many papers applying to colorectal cancers (CRCs) and BDNF/TrkB status [32,33,34,35]. In 2010 the first investigation on the effect of TrkB in CRC was published. The authors confirmed TrkB and BDNF up-regulation in CRC tissues what correlated with lymph node and distant metastases, local progression, clinical stage and poor prognosis [36]. Dawson et al. showed that overexpression of TrkB in tumour cells is positively correlated with KRAS-mutated tumours and that it is a significant independent negative prognostic factor in colorectal cancer patients [35].

A study performed by Tanaka et al. revealed that high BDNF mRNA level in CRC tissues was significantly associated with liver and peritoneal metastases [34]. In turn high mRNA TrkB level correlated with lymph node metastases and co-expression of both BDNF and TrkB resulted the same as high levels of BDNF mRNA only. High level of mRNA accompanied higher expression of both proteins in CRC tissues. The authors performed also in vitro study and suggested that endogenous BDNF in TrkB-expressing CRC cells enhances tumour cell viability, motility, invasion and anoikis resistance. That might give possibility to treat CRC patients with TrkB receptor blockade. Using a TrkB inhibitor – K252a suggested that this pathway may inhibit either anoikis resistance, adhesion onto peritoneal surface and colonisation of the peritoneal cavity.

In experimental study Fan et al. confirmed that TrkB gene silencing and TrkB protein down regulation resulted in slight induction of apoptosis [35]. In animal mice model, it was shown that TrkB overexpression attenuated apoptotic trends of cancer cells. Overexpression of TrkB was associated with lymph node metastases and distant metastases. Survival curve analysis revealed also poorer prognosis when compared to models with weak or absent expression.

In a study conducted by Brierley et al. in 2013, BDNF serum concentration was investigated as a potential new biomarker in CRC [37]. Protein concentration did not differ significantly according to the Dukes stage, but significantly lower serum concentration in patients group compared to healthy control with 95% specificity and 18–25% sensitivity.

**Pancreatic cancer.** Almost 20 years ago Ketterer et al. conducted a study disclosing the potential actions of neurotrophins (nerve growth factor NGF, NT-3, NT-4/5, BDNF, TrkA, TrkB, TrkC, P75) in pancreatic cancer [38]. The authors confirmed high mRNA levels of all NTs and Trks (except TrkC) in pancreatic cancer cells lines. It also showed a significantly higher mRNA levels in cancer tissues compared to normal pancreas for BDNF, but not for TrkB receptor. The study remains in opposition to others that showed increased expression of TrkB (and other NTs) in cancer cells with the absence of BDNF expression [39, 40, 41]. All NTs and their receptors were expressed at higher levels in the nerve bundles than in cancer cells, which is in accordance with previous studies [41]. Thus, NTs might enhance cancer cell growth and promote their proclivity to infiltrate the nerve tracts in pancreatic cancer [38].

Recent studies by Gasparini et al. showed that perineural invasion (PI) present in pancreatic ductal adenocarcinoma with high prevalence might be associated with neurotrophins, chemokines and inflammatory cells pathways [42]. PI was detected even in the early stages of pancreatic cancer, and was associated with pain, increased tumour recurrence, and diminished overall survival. Both BDNF and TrkB were over-expressed in metastatic pancreatic cancer, but higher BDNF levels did not correlate with increased PI. Although *in vitro* studies, similarly to other gastrointestinal (GI) cancers, showed that over-expression of BDNF was linked to the proliferation and invasion of cancer cells, *in vivo* analysis did not confirm this dependency [42, 39].

In 2018, Renz et al. demonstrated the importance of adrenergic signalling in neurotrophin secretion in pancreatic cancer patients [43]. The authors hypothesized that catecholamines mediated nerve-tumour interactions by inducing neurotrophins which might promote pancreatic cancer cells development through tumour associated neurogenesis. Investigation on human pancreatic cancer tissues revealed BDNF expression in 52% of epithelial samples, whereas NGF in only 2%. After noradrenalin stimulation, both BDNF and NGF mRNA was upregulated but BDNF was over-expressed more than NGF. In conclusion, the authors underlined that NGF-BDNF/TrkB pathways were central to pancreatic cancer biology, and targeting these adrenergic and neurotrophins pathways may prove useful in the treatment of pancreatic cancer.

In turn, Johnson et al. investigated TrkB significance in patients who underwent surgery alone, compared with those who received neoadjuvant radiotherapy [44]. Authors

showed that although high expression of TrkB was present in pancreatic ductal adenocarcinoma tissues, it did not show any significant relationship to overall survival and incidence of distant metastases.

**Liver cancer.** In 2006, Yang et al. published a study concerning BDNF serum concentration and cell expression in hepatocellular carcinoma (HCC) tissues [45]. They confirmed neurotrophin expression in tumour tissues, and also to some extent in non-tumour tissues (33.3%), with strong evidence ofa significantly higher expression in cancer cells. There was also a significant decrease of BDNF serum level and BDNF/platelet ratio after hepatectomy due to HCC. A positive correlation between BDNF serum and tissue levels and similar serum level and platelet count was noted in these patients. Regarding the fact that the difference between serum and plasma BDNF concentration was about 200-fold, the authors indicated the important function of platelet BDNF as the source or repositorysite. A low platelet count in patients with cirrhosis resulted in lower BDNF serum levels. A higher BDNF/platelet ratio was associated with shorter disease-free survival, which provided further evidence that the platelets in HCC might store more BDNF than in the normal population and cirrhotic patients. Protein serum level correlated with tumour size of >5cm, poorly differentiated HCC and presence of microsatellite tumour nodules. However, only tumour differentiation was confirmed as an independent factor that affected the serum levels of BDNF [45, 46].

Other authors confirmed that liver cancer tissues manifested higher expression of BDNF and TrkB proteins. Guo et al suggested that BDNF/TrkB supported the survival of HCC cells and played a crucial role in tumour progression and intrahepatic dissemination [47]. Lam et al. noted that in human HCC tissues, BDNF expression was elevated in 46% and TrkB was upregulated in 33.3% in comparison to non-tumorous liver tissues and normal liver control. [48] This finding is in accordance with results of animal studies. The same group observed that BDNF over-expression promotes cell proliferation, tumour growth and induces resistance to apoptosis in mice.

Long et al. noted a role of micro-RNA (miRNA-15a-5p) in HCC carcinoma [49]. The miRNA-15a-5p acted as a tumour suppressor and its overexpression reduced proliferation, induced cell cycle arrest *in vitro* and inhibited tumour explants *in vivo*. The study found that BDNF was a target gene of miRNA in regulating HCC. The authors showed that although over-expression of BDNF was related to apoptosis inhibition and HCC cells invasion, it may also counteract oncogenic development via the miRNA pathway. Neurotrophins expression was not inversely related to miRNA as confirmed in gastric cancer, but ameliorated the inhibitory effect of miRNA-15a-5p on HCC proliferation and cell division.

## CONCLUSIONS

The role of BDNF in gastrointestinal cancers remains unclear. Studies confirmed the role of BDNF/TrkB and other neurotrophins pathway in neural, metabolic and oncologic diseases, but without any final conclusion. The more precise the investigations performed, the more ambiguous were the results obtained.

Although it has been proved that there is close correlation between BDNF and oncologic disorders, specific association in different types of cancer still needs confirmation. Studies suggest that the BDNF/TrkB pathway is a promising possible target for new drugs which are expected to diminish cancer cells potentiality; however, there is lack of data on the influence of different kinds of chemotherapeutics on blood BDNF There is also insufficient information about neurotrophin as a prognostic factor or as a marker oa disease-free survival period. It is believed that if any specific relationship is confirmed, it potentially become a useful tool during qualification to neoadjuvat/adjuvant chemotherapy. Further studies are required, although simplicity of investigation, sensitivity and sensibility of the applied methods remains a challenge. The authors believe that current and future studies will finally enable determination of the role of BDNF in oncogenesis, and evaluate the usefulness of neurotrophins as a target/marker helpful in new anti-cancer therapies.

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