

## 2016 Colorectal Cancer: Global view

# Tropomyosin-related kinase B/brain derived-neurotrophic factor signaling pathway as a potential therapeutic target for colorectal cancer

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**Author contributions:** Akil H wrote and designed the paper; Jauberteau MO and Mathonnet M contributed equally to this work; and Akil H, Perraud A, Jauberteau MO and Mathonnet M contributed to conception, critical revision and final approval of the manuscript.

**Supported by** Conseil Régional du Limousin and the CORC Comité Orientation Recherche Cancer.

**Conflict-of-interest statement:** Authors declare no conflict of interests for this article.

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Received: April 25, 2015

Peer-review started: April 27, 2015

First decision: September 11, 2015

Revised: September 25, 2015

Accepted: October 12, 2015

Article in press: October 13, 2015

Published online: January 14, 2016

## Abstract

Colorectal cancer (CRC) is the second most common cause of cancer-related death in western countries. Approximately one-quarter of newly diagnosed patients for CRC have metastases, and a further 40%-50% experience disease recurrence or develop metastases after all standard therapies. Therefore, understanding the molecular mechanisms involved in the progression of CRC and subsequently developing novel therapeutic targets is crucial to improve management of CRC and patients' long-term survival. Several tyrosine kinase receptors have been implicated in CRC development, progression and metastasis, including epidermal growth factor receptor (EGFR) and vascular EGFR. Recently, tropomyosin-related kinase B (TrkB), a tyrosine kinase receptor, has been reported in CRC and found to clearly exert several biological and clinical features, such as tumor cell growth and survival *in vitro* and *in vivo*, metastasis formation and poor prognosis. Here we review the significance of TrkB and its ligand brain derived-neurotrophic factor in CRC. We focus on their expression in CRC tumor samples, and their functional roles in CRC cell lines and in *in vivo* models. Finally we discuss therapeutic approaches that can lead to the development of novel therapeutic agents for treating TrkB-expressing CRC tumors.

**Key words:** Colorectal cancer; Tyrosine kinase receptor B; Brain-derived neurotrophic factor; Therapeutic targets; Cell survival

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**Core tip:** Recently, the tropomyosin-related kinase B (TrkB)/brain derived-neurotrophic factor (BDNF) signaling pathway has emerged as a key player in the pathogenesis and prognosis of several non-neural cancers. Indeed, the TrkB tyrosine kinase receptor has been recently found to play an important role in the biological and clinical behavior of colorectal cancer (CRC). Here, we review the implications of TrkB and its ligand BDNF in CRC. Additionally, we discuss possible therapeutic strategies targeting this pathway.

Akil H, Perraud A, Jauberteau MO, Mathonnet M. Tropomyosin-related kinase B/brain derived-neurotrophic factor signaling pathway as a potential therapeutic target for colorectal cancer. *World J Gastroenterol* 2016; 22(2): 490-500 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v22/i2/490.htm> DOI: <http://dx.doi.org/10.3748/wjg.v22.i2.490>

## INTRODUCTION

Colorectal cancer (CRC) is the second most common cause of cancer-related death in the western world and the third most common malignancy diagnosed worldwide<sup>[1]</sup>. With present-day therapies, curative (R0) surgical resection is used in approximately 70%-80% of newly diagnosed patients with localized CRC<sup>[2]</sup>. However, the overall prognosis remains poor for CRC patients, with a median survival time of approximately 20-24 mo<sup>[3-5]</sup>. In fact, the remaining 20%-30% of newly diagnosed patients present advanced unresectable metastatic disease, and an additional 40%-50% of patients with initially localized CRC experience disease recurrence despite surgical resection and adjuvant therapy, or develop hepatic and/or lung metastases<sup>[5,6]</sup>.

In recent decades, the development of early detection methods for CRC, together with the evolution of systemic chemotherapy for patients with CRC, has led to a decrease in CRC incidence and mortality worldwide<sup>[1]</sup>. 5-Fluorouracil (5-FU), discovered in 1957 by Heidelberger *et al*<sup>[7]</sup>, was for many years, in combination with leucovorin the only treatment for patients with metastatic CRC (mCRC)<sup>[8-11]</sup>. In the early 2000s, the use of the topoisomerase I inhibitor irinotecan, and subsequently the platinum-containing agent oxaliplatin, were key developments in CRC treatment<sup>[5]</sup>. These agents were found to significantly prolong the median overall survival (OS) of patients with mCRC from 12.6 mo (5-FU/leucovorin alone as first-line therapy) to 14.8 mo (bolus 5-FU/leucovorin

with irinotecan)<sup>[12]</sup>, then from 15 mo (5-FU/leucovorin with irinotecan) to 19.5 mo (FOLFOX; 5-FU/leucovorin with oxaliplatin)<sup>[13]</sup>. In 2004, Hurwitz *et al*<sup>[14]</sup> reported that treatment of CRC patients with bevacizumab (humanized monoclonal antibody against vascular endothelial growth factor) led to a significant increase in OS. Next, in several key trials, monoclonal antibodies to the anti-epidermal growth factor receptor (EGFR), namely cetuximab and panitumumab, were proposed as a novel agents for mCRC treatment. These anti-tyrosine kinase receptor antibodies were the first therapeutic targeted agents in patients with the *KRAS* wild-type metastatic CRC (mCRC)<sup>[5,15,16]</sup>. Recently, Regorafenib, the first small-molecule tyrosine kinase inhibitor, was approved as a potential new line of therapy for patients who have progressed after all standard therapies<sup>[17]</sup>.

Expression of the tyrosine kinase receptor TrkB is increasingly reported in CRC, and there is a growing body of evidence that the TrkB/BDNF pathway is an important player in CRC tumor growth and progression. Although mainly recognized for its role in the nervous system, the TrkB/BDNF pathway has been implicated in the pathogenesis and prognosis of several tumors outside of the brain, such as pancreatic<sup>[18-20]</sup>, prostatic<sup>[21,22]</sup>, pulmonary<sup>[23,24]</sup>, ovarian<sup>[25]</sup>, bladder<sup>[26]</sup> and head and neck cancers<sup>[27,28]</sup>, in addition to choriocarcinoma<sup>[29]</sup>, myeloma<sup>[30]</sup> and B-lymphocytic leukemia<sup>[31,32]</sup>. This review will focus on the role of TrkB and its ligand BDNF in promoting CRC progression and survival. In addition, we outline potential therapeutic approaches targeting the TrkB/BDNF pathway.

## BRAIN-DERIVED NEUROTROPHIC FACTOR

BDNF is a member of the neurotrophin (NT) family, which is a group of closely related growth factors originally known for their involvement in the differentiation, proliferation, and survival of neural cells in both the central and peripheral nervous systems<sup>[33]</sup>.

The NT family includes NGF (nerve growth factor), BDNF (brain-derived neurotrophic factor), NT-3 (neurotrophin 3) and NT-4/5 (neurotrophin 4/5). In 1982, Barde *et al*<sup>[34]</sup> first isolated BDNF from pig brain as a survival factor for cultured embryonic chick sensory neurons. NTs are synthesized *via* the same process of maturation. Indeed, NTs are generated from single protein precursors of approximately 27 kDa called pre-pro-NTs. The latter is composed of a pre-pro-domain, a pro-domain and a mature domain that are sequentially cleaved to obtain mature NTs of approximately 13 kDa. Immature NTs (pre-pro-NTs) are cleaved in the endoplasmic reticulum to generate pro-NTs<sup>[35,36]</sup>. Pro-NTs are then proteolytically cleaved to mature NTs. Cleavage can occur either intracellularly, by the action of furin or proconvertase, or extracellularly, by the action of plasmin and matrix

metalloproteinases (MMPs) such as MMP-3, MMP-7 or MMP-9<sup>[36,37]</sup>. Accordingly, pro-NTs can be released as soluble forms or processed as mature NTs, each with specific receptor binding properties and physiological consequences. Generally, immature NTs or pro-NTs bind to p75<sup>NTR</sup> and sortilin (a member of the VPS10p-domain receptor family) to induce apoptosis *via* the JNK kinase pathway<sup>[38]</sup>. In their mature forms, NTs mediate their effects through binding to two structurally unrelated cell membrane receptors, the Trk tyrosine kinase receptors and the common NT receptor p75<sup>NTR</sup><sup>[39,40]</sup>. BDNF effectively signals through the low affinity receptor (p75<sup>NTR</sup>) that belongs to the tumor necrosis factor (TNF) receptor superfamily and through the high-affinity TrkB tyrosine kinase receptor.

### TrkB TYROSINE KINASE RECEPTOR

TrkB belongs to the Trk family of tyrosine kinase receptors, which consists of an extracellular ligand-binding domain, a transmembrane domain and a cytoplasmic tyrosine kinase domain<sup>[41,42]</sup>. The extracellular domain of these receptors consists of a leucine-rich domain surrounded by two cysteine rich regions that are thought to be essential for NTs high affinity binding. Near those regions and close to the cell membrane there are two immunoglobulin-like (IG-like) domains that are followed by the transmembrane domain. The IG-like domain directs ligand-binding specificity. The cytoplasmic domain consists of a Shc binding site, a tyrosine kinase domain and a tail region that includes a phospholipase C-gamma binding site (PLC- $\gamma$ )<sup>[43]</sup>. Trk was first described in 1986 by Martin-Zanca *et al.*<sup>[44]</sup> as an oncogene in colonic carcinoma. The Trk family includes three members, TrkA, TrkB and TrkC, each of which is activated by one or more of the four NTs. NGF preferentially binds to TrkA and BDNF and NT-4/5 preferentially bind to TrkB. NT-3 preferentially binds to TrkC but also to TrkA and TrkB to a lesser extent and only in certain cellular contexts<sup>[45-48]</sup>. The TrkB gene (*NTRK2* about 590 kb) is located on chromosome 9q22 and contains 24 exons<sup>[43,49]</sup>. The TrkB gene can create more than 100 RNA transcripts (due to alternative splicing) and at least 36 of these transcripts are translated, among which there are three major protein isoforms<sup>[43,50]</sup>. In addition to the full-length TrkB (TrkB-FL, 145 kDa), there are two alternatively spliced TrkB isoforms (95 kDa) that lack the tyrosine kinase domain, TrkB-T1 and TrkB-Shc, which are slightly longer and include the Shc binding site<sup>[50]</sup>. BDNF binding to the TrkB-FL (full-length) receptor results in its dimerization and subsequent autophosphorylation of tyrosine (Y) Y484 and Y785. Generally, TrkB-FL induces survival and differentiation through the three principle growth factor signaling pathways: Ras/MAPK, PI3Kinase (PI3K)/Akt and PLC- $\gamma$ /PKC pathways<sup>[42,50]</sup> (Figure 1). For an expanded review on Trk signaling, see<sup>[45,46]</sup>.

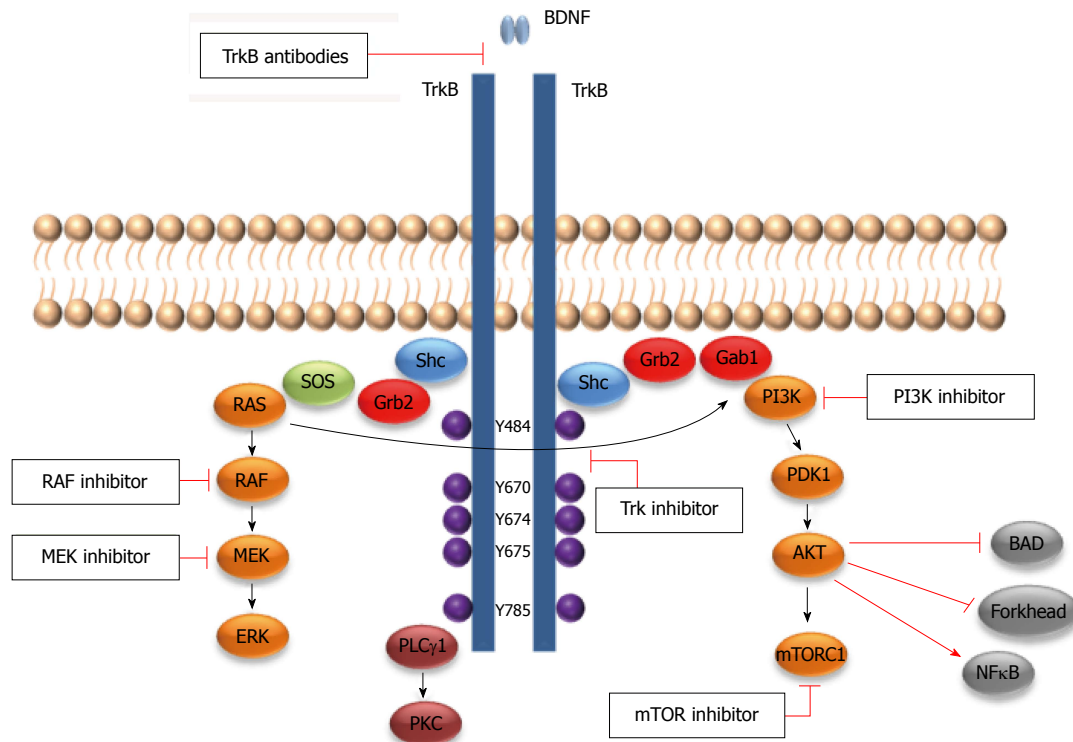
TrkB-T1 is abundantly expressed in adult neural

cells but also in non-neural cells, yet its biological role in BDNF-mediated signaling remains poorly understood<sup>[51]</sup>. For many years, both truncated TrkB receptor isoforms were thought to act as dominant-negative inhibitors of TrkB-FL and did not signal directly<sup>[52-54]</sup>. For example, TrkB-T1 or TrkB-Shc can bind to and internalize BDNF or dimerize with TrkB-FL to prevent its autophosphorylation and subsequently inhibit intracellular signaling pathways<sup>[50,55]</sup>. However, recent studies have demonstrated that TrkB-T1 sequesters and translocate BDNF<sup>[56]</sup>, induces filopodia and neurite outgrowth<sup>[57-59]</sup>, regulates Rho GTPase signaling<sup>[60]</sup> and intracellular signaling cascades<sup>[30,61,62]</sup>, and mediates cell proliferation<sup>[63,64]</sup>. Rose *et al.*<sup>[65]</sup> have demonstrated that astrocytes predominantly express TrkB-T1 and that BDNF-mediated activation of the truncated TrkB-T1 controls calcium release from intracellular stores through an inositol-1,45-phosphate (IP3)-dependent pathway. In addition, Li *et al.*<sup>[63]</sup> have shown that TrkB-T1 enhanced cell proliferation, promoted formation of colonies in soft agar, stimulated tumor cell invasion and induced liver metastasis in an orthotopic xenograft mouse model of pancreatic cancer. For a recent and extensive review on truncated TrkB, refer to Fenner<sup>[55]</sup>.

### TrkB/BDNF EXPRESSION AND FUNCTION IN CANCERS

Overexpression of the TrkB receptor was first described in human neuroblastoma, which is a childhood malignant tumor derived from primitive cells of the developing sympathetic nervous system<sup>[66]</sup>. TrkB and BDNF are highly expressed in biologically unfavorable, *MYCN*-amplified, aggressive neuroblastomas<sup>[67]</sup>. Indeed, patients with neuroblastoma, whose tumors express elevated levels of TrkB and BDNF, have a poor prognosis<sup>[67,68]</sup>. It has also been shown that in neuroblastoma tumor cells the TrkB/BDNF pathway is involved in epithelial-mesenchymal-transition-like transformation (EMT), metastasis<sup>[69,70]</sup>, anoikis<sup>[71]</sup>, chemotherapeutic resistance<sup>[72,73]</sup>, and hypoxia *via* activation of angiogenesis<sup>[74]</sup>. Thus, BDNF/TrkB signaling in neuroblastoma contributes to tumor growth and an unfavorable outcome in an autocrine/paracrine manner<sup>[75]</sup>.

Activity of the BDNF/TrkB pathway is mainly recognized in the field of neurobiology. However there is now increasing recognition that the TrkB/BDNF pathway regulates important processes and may contribute to the pathogenesis of numerous non-neural carcinomas whose cells express the TrkB receptor, including pancreas<sup>[18,19]</sup>, prostate<sup>[21,22]</sup>, ovarian<sup>[76,77]</sup>, Wilms' tumors, head and neck<sup>[27,28]</sup>, lung<sup>[23,78]</sup>, breast<sup>[79,80]</sup>, gastric<sup>[81,82]</sup>, and hepatocellular carcinomas<sup>[83,84]</sup>, as well as myelomas<sup>[30,85,86]</sup> and lymphoid cancers<sup>[31,32,87]</sup>. Indeed, overexpression of TrkB was found in the highly metastatic pancreatic



**Figure 1** TrkB-mediated signaling pathways and possible therapeutic targets in cancer. Schematic representation of TrkB receptor, its main downstream signaling pathways, and possible therapeutic targets. Shc: Src homology 2 domain containing transforming protein; Grb2: Growth factor receptor-bound protein 2; Gab1: Grb2 associated binding protein 1; PI3K: Phosphatidylinositol 3-kinase; PDK1: Phosphoinositide-dependent protein kinase 1; mTOR: Mammalian target of rapamycin; mTORC1: mTOR complex 1; SOS: Son of sevenless; MEK: Mitogen-activated protein kinase (MAPK)/ERK kinase; ERK: Extracellular signal-regulated kinase; PLC: Phospholipase C; PKC: Protein kinase C.

cancer cells. Moreover, TrkB expression was correlated with perineural invasion, positive retroperitoneal margin, and earlier liver metastasis development in patient samples<sup>[19]</sup>. In prostate cancer, TrkB and BDNF may be considered as possible diagnostic markers<sup>[21]</sup>. Furthermore, TrkB therapeutic effects were shown in an *in vivo* xenograft model using Trk-specific inhibitors, such as CEP-751 or CEP-701. In these studies, results have shown that targeting of the TrkB receptor induces cell death in a cell cycle-independent manner and inhibits tumor growth and metastasis development in prostate cancer<sup>[88,89]</sup>. In Wilms' tumors, TrkB overexpression correlated with a higher risk of mortality<sup>[90]</sup>. The role of the TrkB/BDNF pathway in head and neck squamous cell carcinoma (HNSCC) was also investigated by Kupferman *et al.*<sup>[27]</sup> who demonstrated that these proteins are expressed in greater than 50% of human HNSCC tumors, but not in the normal upper aerodigestive tract. *In vitro* and *in vivo* studies have revealed that TrkB is directly implicated in EMT, tumor growth and invasive behavior of HNSCC. Furthermore, BDNF stimulation of HNSCC cells enhances cell migration and invasion, drug-resistance and anti-apoptotic protein expression<sup>[27,28]</sup>. BDNF was also described as an autocrine factor in human multiple myeloma cells contributing in tumor progression and survival by activating signaling in the mitogen-activated protein kinase (MAPK) pathway

and the phosphatidylinositol 3-kinase-Akt (PI3K/Akt) pathway. In addition, BDNF was able to protect human multiple myeloma (MM) cell lines from apoptosis induced by dexamethasone or bortezomib<sup>[30]</sup>. Finally, TrkB and BDNF were also reported to be associated with a significant increase in the survival and proliferation of non-Hodgkin lymphoma cells<sup>[91]</sup> and malignant B cell lines<sup>[31,32]</sup>. For example, Fauchais *et al.*<sup>[31]</sup> have shown that endogenous BDNF released under stress culture conditions exerts antiapoptotic effects in human B cell lines. Such autocrine production was linked to the presence of sortilin, an endogenous protein that is able to transport and release BDNF in culture media. In diffuse large B cell lymphoma, *in vitro* studies have shown that the Trk-inhibitor K252a enhances apoptosis and exhibits additive apoptotic effects with rituximab, a chimeric anti-CD20 monoclonal antibody<sup>[32]</sup>.

## TrkB/BDNF PATHWAY IN CRC

### *TrkB and BDNF expression: Correlation with clinicopathological parameters in CRC*

There is now accumulating evidence that the TrkB/BDNF pathway is involved in CRC tumor growth, progression and metastasis. The first investigation on the effect of TrkB in CRC was published in 2010 by Yu *et al.*<sup>[92]</sup> who demonstrated that TrkB was up-regulated



in tumor tissues compared with the non-tumorous counterparts, and this overexpression correlates with lymphatic vessel density and metastasis. Next, the expression of TrkB was confirmed in samples from CRC patients at both the mRNA and protein levels, with a higher expression in tumor tissues compared to adjacent non-cancerous tissues<sup>[93-96]</sup>. Thereafter, TrkB expression has been correlated with clinicopathological parameters in CRC<sup>[95-99]</sup>. These studies have shown that TrkB mRNA expression levels are positively correlated with lymph node metastasis, distant metastasis and CRC tumor stage progression<sup>[97]</sup>. Moreover, high TrkB mRNA expression was correlated with poor prognosis<sup>[97,98]</sup>. However, TrkB mRNA expression was not correlated with histological grade of CRC<sup>[97]</sup>. Interestingly, immunohistochemistry studies have also shown that TrkB was overexpressed in CRC tissues compared with adjacent non-cancerous tissues<sup>[95,96]</sup>. Additionally, TrkB expression was correlated with local progression, clinical stage, nodal metastasis, distant metastasis, and poor prognosis<sup>[95,96,99]</sup>. Interestingly, Dawson *et al.*<sup>[99]</sup> further showed that TrkB is overexpressed in tumor budding cells, and this overexpression was positively correlated with *KRAS*-mutated tumors. More importantly, they found that among patients with membranous/cytoplasmic TrkB-positive buds, high tumor membranous/cytoplasmic TrkB expression is a significant independent adverse prognostic factor in CRC. These data clearly suggest that the TrkB receptor may indeed be a useful diagnostic and prognostic factor for CRC.

BDNF has also been studied in CRC patient tissues. Like its receptor TrkB, BDNF mRNA expression levels are significantly higher in CRC patient samples compared with control samples<sup>[93-95,100]</sup>. Further, this overexpression is positively correlated with differentiated CRC tumors, T-staging and poor prognosis<sup>[100]</sup>. In line with this finding, a recent report showed significant association between BDNF mRNA expression level and poor overall survival, liver metastasis and peritoneal metastasis. Nonetheless, no significant associations were found between BDNF mRNA and any other clinicopathological parameters in CRC tissues<sup>[98]</sup>. On the other hand, serum levels of BDNF were significantly decreased in CRC patients compared with control patients, and there were no significant associations between serum BDNF levels and Dukes' stages<sup>[101]</sup>.

### **TrkB/BDNF pathway: Fine-tuning the role in CRC**

*In vitro* studies have shown that TrkB and its ligand, BDNF, are expressed in several CRC cell lines (corresponding to different CRC tumor stages) at both mRNA and protein levels<sup>[92-98]</sup>. In addition, under stress culture conditions these cells were able to produce and secrete the BDNF<sup>[93,94]</sup>, together with a relocation of its receptor TrkB to the cell membrane<sup>[94]</sup>. Thus, the expression of both BDNF and TrkB within the same cell lines has raised the question of an autocrine

effect in CRC. Indeed, it was found that exogenous BDNF enhanced cell survival, proliferation, migration, invasion, and inhibited anoikis through the TrkB receptor in CRC cell lines<sup>[93,94,98,102]</sup>. BDNF was also found to trigger Akt phosphorylation in CRC cell lines through the TrkB receptor, as assessed by K252a, a Trk tyrosine kinase inhibitor that competes with Trks' ATP binding site. K252a suppressed both BDNF-induced TrkB and Akt activation, in addition to cell survival, proliferation, migration, invasion and anoikis resistance<sup>[93,94,98]</sup>. Furthermore, gene knockdown of TrkB decreased the expression of PI3K (PIK3CA) and AKT1, their downstream effector mTOR, and the MAPK p38<sup>[95]</sup>. Recent studies have shown that cell survival, anoikis and chemotherapeutic agent resistance in tumor cells are mediated in part by TrkB receptor through activation of the PI3K/Akt pathway<sup>[30,71,83,103]</sup>. Thus, it is possible that BDNF/TrkB-induced CRC cell survival and anoikis resistance may be mediated through the PI3K/Akt pathway. TrkB silencing by siRNA also enhanced apoptosis and anoikis, while proliferation, migration and invasion were inhibited in TrkB siRNA-transfected cells<sup>[92,95-97]</sup>. Conversely, Fan *et al.*<sup>[96]</sup> have shown by using regulated-TrkB expression models that TrkB overexpression protects CRC cell lines from anoikis. They also showed that Akt signaling pathway was functionally linked to TrkB-induced anoikis resistance in CRC cells. Furthermore, Akt phosphorylation levels were related with the expression pattern of TrkB in CRC cell lines<sup>[96]</sup>.

*In vivo*, TrkB inhibition has been suggested to sensitize CRC cells to anoikis, which consequently protects against metastases formation in xenograft mouse models<sup>[96,98]</sup>. In these studies, TrkB blockade using the Trk pharmacological inhibitor K252a<sup>[98]</sup> or short hairpin (sh) RNA<sup>[96]</sup> significantly reduces the size and number of peritoneal and lung metastatic nodules in treated mice. Furthermore, a lower risk of metastasis-induced death has been found in mice injected with CRC-shTrkB cells compared with control<sup>[96]</sup>.

Though TrkB-T1 has been found in CRC cells, *in vitro* and *in vivo* data suggest that the effects of the autocrine TrkB/BDNF loop are likely mediated by TrkB-FL, as assessed by K252a-induced inhibition of TrkB activation. Moreover, it is important to note that PCR primers used in some of the aforementioned studies were not able to clearly distinguish between TrkB-FL and TrkB-T1 in patient samples or in CRC cell lines. Further assessment will be necessary to clarify the functional role of TrkB-T1 in CRC.

EMT is now thought to play a fundamental role in tumor progression and metastasis formation. In fact, EMT enhances tumor dissemination by inducing individual cell delamination from its primary tumor site, which allows tumor cells to migrate through stroma and further invade adjacent tissues<sup>[104]</sup>. Additionally, the loss of E-cadherin expression is considered as a

fundamental step in EMT<sup>[104]</sup>. In colorectal cancer, EMT takes place at the invasive front, allowing tumor cells that lost E-cadherin expression to migrate and gain the ability to disseminate to the metastatic sites<sup>[105]</sup>. This phenomenon was also found in other solid tumors such as papillary thyroid carcinoma, breast carcinoma and cervical carcinoma, whose cells show increased vimentin expression and loss of E-cadherin<sup>[104]</sup>. The relationship between TrkB and EMT has been clearly described in neuroblastoma tumors, yet there are now recent reports indicating that TrkB may induce EMT in cells derived from endometrial carcinoma<sup>[106]</sup>, lung<sup>[107]</sup> and oral cancer cells<sup>[108]</sup>, and head and neck<sup>[27]</sup> and CRC tumor cells<sup>[97,99]</sup>. Indeed, Fujikawa *et al.*<sup>[97]</sup> have shown that TrkB was inversely correlated with E-cadherin at both the mRNA and protein levels in CRC patient tissues. *In vitro*, TrkB silencing enhances E-cadherin and reduces vimentin expressions in CRC cell lines. In line with these findings, Dawson *et al.*<sup>[99]</sup> found that membranous/cytoplasmic TrkB expression was inversely correlated with both Ki-67 and caspase-3 in CRC tumor buds, and cytoplasmic TrkB overexpression was correlated with tumors presenting high-grade tumor budding at the invasive front, in agreement with the EMT-inducing function of TrkB. Thus, these results strongly suggest that TrkB receptor may be a promoter of EMT, anoikis resistance, and consequently metastasis formation in CRC.

#### **TrkB/BDNF pathway as a potential therapeutic target in CRC**

Because the TrkB/BDNF pathway plays an important role in the biological and clinical behavior of CRC, the TrkB tyrosine kinase receptor as a potential therapeutic target is beginning to draw increasing attention. Thus, inhibiting the tyrosine kinase activity of TrkB may be an important addition to CRC therapy. Indeed, Lestaurtinib (CEP-701) a Trk-selective tyrosine kinase inhibitor derived from the prototypical K252a that blocks NT-induced Trk activation, has shown efficacy in treating solid cancers whose cells overexpress TrkB receptor in preclinical xenograft models, including models of neuroblastoma<sup>[109,110]</sup>, prostate<sup>[88]</sup>, pancreatic<sup>[111,112]</sup>, and breast cancer<sup>[113]</sup>. The use of Lestaurtinib was also found to be feasible, as this agent does not show toxicity against normal tissue. Furthermore, Lestaurtinib (CEP-701) and the prodrug CEP-2563 and CEP-751 are currently in phase I and phase II clinical trials for treatment of neuroblastoma and other non-neural solid and blood-derived cancers<sup>[114-116]</sup>. Likewise, other selective Trk kinase inhibitor compounds have been recently developed and tested for cancer treatment, such as the pan-Trk inhibitor ZD6918 and AZ-23 (TrkA/TrkB selective kinase inhibitor; orally bioavailable)<sup>[117]</sup>. Based on these preclinical and clinical data, investigating the therapeutic potential of the TrkB receptor would be of great importance in CRC treatment. Thus, inhibiting

the TrkB receptor may become an important adjunct target to improve clinical outcome in patients with CRC. It is worth mentioning that both TrkA and TrkC, two other members of the Trk family, were not found in CRC cell lines, as described in our previous work<sup>[94]</sup>. In line with this finding, the TrkC receptor is highly downregulated in CRC tumor samples in comparison with adjacent normal tissues. Furthermore, reestablishment of TrkC expression in CRC cell lines induces apoptosis and inhibits tumor growth *in vitro* and *in vivo*, supporting the idea that TrkC is a CRC tumor suppressor<sup>[118]</sup>. However, the TrkC receptor was recently found in CRC cell lines and tumor samples, and its expression was positively correlated with liver metastasis<sup>[95]</sup>. Presumably, targeting TrkB receptor will likely render CRC tumor cells more sensitive to chemotherapy-induced apoptosis, as shown in neuroblastoma and other solid cancers<sup>[119]</sup>.

It has also been shown that TrkB has an anti-apoptotic effect in CRC. Therefore, combining Trk-targeted therapy with recombinant TRAIL (TNF related apoptosis induced ligand) or Fas ligand may also be useful in treatment of CRC. Indeed, normal colonic cells are resistant to TRAIL-induced apoptosis, whereas colonic tumor cells are sensitive to the TRAIL recombinant. Additionally, both 5-FU and oxaliplatin, two of the main chemotherapeutic agents used in the treatment of CRC, act by inducing apoptosis through the Fas (CD95) receptor<sup>[120]</sup>. Accordingly, inhibition of the TrkB receptor in CRC may potentiate the anti-tumor effects of apoptogenic agents used in treatment of advanced CRC.

Crosstalk between TrkB and the EGFR has been described in numerous solid tumors, such as ovarian cancer<sup>[25]</sup>. Indeed, BDNF-induced activation of TrkB was found to activate EGFR in ovarian cancer, and subsequently induce cell proliferation and migration through the PI3K/Akt pathway. Additionally, EGFR and TrkB kinase inhibitors blocked EGF- and BDNF-induced TrkB and EGFR activation, respectively, and blocked Akt phosphorylation. In line with this finding, De farias *et al.*<sup>[102]</sup> showed in an HT-29 CRC cell line that the TrkB/BDNF pathway protects CRC cells from the inhibitory effects of cetuximab (anti-EGFR monoclonal antibody). Furthermore, TrkB blockade was found to potentiate the inhibitory effects of cetuximab on CRC cell proliferation and survival<sup>[102]</sup>. Such results suggest a potential therapeutic benefit from the crosstalk between the TrkB/BDNF pathway and EGFR in CRC cells. It is possible that EGFR inhibition could be more effective in combination with TrkB inhibition in the treatment of advanced CRC. In addition to the crosstalk with EGFR, TrkB has also been found to activate angiogenesis in neuroblastoma and ovarian cancer. Although functional evidence supporting this possibility is lacking at present in CRC, Sasahira *et al.*<sup>[95]</sup>, showed that the TrkB receptor positively regulates VEGF-A and VEGF-C gene expression.

Targeting the TrkB/BDNF pathway, points toward a promising addition to the strategies for CRC therapy.

## CONCLUSION

Currently, among conventional therapies, advanced CRC remains a major therapeutic challenge with poor overall survival. Therefore, identifying novel molecular mechanisms involved in driving CRC development and progression is crucial for improving clinical management of CRC and patient outcome. TrkB has been shown to associate with CRC local progression, clinical stage, nodal metastasis, distant metastasis, and poor prognosis. Additionally, emerging data suggest that the TrkB/BDNF pathway enhances several biological processes in CRC, including proliferation, invasion, migration, EMT, apoptosis resistance and anoikis resistance. Hence, inhibition of the TrkB/BDNF pathway alone or in combination with other conventional and targeted agents in CRC may hold promise as an important approach to improve patients' long-term survival.

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ISSN 1007-9327

