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Visions & Reflections

The neurotrophic receptor TrkB: a drug target in anti-cancer therapy?

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Abstract. Increasing evidence implies altered signaling through the neurotrophic receptor tyrosine kinase TrkB in promoting tumor formation and metastasis. TrkB, sometimes in conjunction with its primary ligand BDNF, is often overexpressed in a variety of human cancers, ranging from neuroblastomas to pancreatic ductal adenocarcinomas, in which it may allow tumor expansion and contribute to resistance to anti-tumor agents. *In vitro*, TrkB acts as a potent suppressor of anoikis (detachment-induced apoptosis), which is associated with the acquisition of an aggressive tumorigenic and metastatic phenotype *in vivo*. In view of its predicted contribution to tumorigenicity and metastasis in humans, TrkB corresponds to a potential drug target, and preclinical models have already been established. The encouraging results of pharmacological Trk inhibitors in tumor xenograft models suggest that TrkB inhibition may represent a promising novel anti-tumor therapeutic strategy. This hypothesis is currently being evaluated in clinical trials. Here, we will discuss the latest developments on TrkB in these contexts as well as highlight some critical questions that remain to be addressed for evaluating TrkB as a therapeutic target in cancer.

Keywords. TrkB, human tumors, metastasis, anoikis, Trk inhibitors, clinical trials, xenograft models.

TrkB signaling in cell proliferation, differentiation and survival

TrkB is a receptor tyrosine kinase belonging to the Trk family of neurotrophin receptors, which comprises two other members: TrkA and TrkC. TrkB is preferentially activated by brain-derived neurotrophic factor (BDNF) [1], neurotrophin (NT)-4/5 [2], and less efficiently by NT-3 [1]. Following ligand binding, TrkB forms homodimers resulting in auto-phosphorylation on tyrosine residues, which is required for its catalytic and signaling activities. Three of the phosphorylated tyrosines (Y670, Y674 and Y675) lie within the activation loop of the kinase domain and potentiate the tyrosine kinase activity of the receptor [3], while two other phosphorylated tyrosines (Y484 and Y785) serve as docking sites for proteins containing PTB or SH2 domains [3, 4]. Recruitment of adaptor proteins subsequently leads to the activation of multiple signaling pathways, including PI3 kinase (PI3K) [5, 6], phospholipase C-γ (PLC-γ) [7], Ras-mitogen-activated protein kinase (MAPK) [8, 9] and protein kinase C (PKC) cascades [7] (reviewed in [10] and [11]).

As all these signaling pathways play important roles in the context of cell proliferation, differentiation and survival, TrkB activation is likely to profoundly affect all of these cellular processes. For example, in cultured cerebellar granule neurons, TrkB-mediated activation of PLC-γ, PKC and PI3K enhances cell survival [5, 7], while TrkB-mediated activation of MAPK signaling promotes the differentiation of cortical progenitors into neurons [12]. In NIH 3T3 fibroblasts, TrkB-mediated PLC-γ and MAPK activation leads to enhanced proliferation and

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survival [13, 14]. Finally, activation of PI3K by TrkB contributes to resistance to anoikis of epithelial cells [15]. Therefore, by influencing a plethora of physiological cellular signals associated with proliferation and survival, it is conceivable that deregulation of TrkB has a significant impact on tumor and metastasis development.

TrkB signaling in cancer and metastasis: lessons from human tumors

Support for a role of TrkB in human tumors first came from studies on its expression pattern in neuroblastoma. Neuroblastoma is the most common solid tumor in childhood, likely arising from primitive cells of the sympathetic nervous system [16]. Most of the patients can be roughly divided into two main groups: a 'low-risk' group with good prognosis tumors that sometimes regress spontaneously, and a 'high-risk' group with poor prognosis tumors with aggressive behavior, which is associated with increased metastasis. TrkB is often overexpressed in neuroblastoma (~35% of the cases), frequently in association with amplification of the *MYCN* locus, one of the more reliable markers of poor disease outcome [17, 18]. Overexpression of TrkB is likely to play an unfavorable role in neuroblastoma, as supported by the following observations: (i) as some neuroblastomas with poor prognosis also overexpress BDNF [17, 19], autocrine loops may exist in which activation of TrkB signaling promotes tumor cell survival [20]; (ii) TrkB overexpression protects neuroblastoma cells from anti-tumor agent-induced apoptosis, at least in cell culture systems [21–23]; and (iii) TrkB overexpression may promote neuroblastoma cell dissemination and invasive potential, which might contribute to the metastatic phenotype of bad prognosis neuroblastomas [20, 24].

TrkB is overexpressed in several other types of human cancers as well. For example, in prostate adenocarcinomas, TrkB overexpression was observed in 22 out of 32 cases of primary tumors and 6 out of 10 bone metastases derived from such tumors [25]. The limited number of metastases analyzed in this study does not allow concluding whether TrkB overexpression is associated with metastasis in this type of cancer. In Wilms's tumor, however, TrkB overexpression is associated with increased mortality risk [26]. Furthermore, in two independent studies on pancreatic ductal adenocarcinomas, elevated TrkB expression was seen in tumor cells compared with surrounding normal tissue in 63% of 47 and 50% of 54 cases examined, respectively [27, 28]. Importantly, undetectable levels of TrkB are significantly associated with absence of liver metastases, while liver metastasis occurs earlier in patients with TrkB-positive tumors compared with patients with TrkB-negative tumors [28]. Finally, the increased metastatic potential of a pancreatic cancer cell line following multiple *in vivo* selection cycles has been reported to be associated with increased expression of TrkB [28].

Altered TrkB signaling may not be associated with solid malignancies only. Indeed, elevated expression of TrkB and/or its primary ligand BDNF has been reported to also occur frequently in multiple myeloma (24 and 12 out of 25 cases studied, respectively), promoting myeloma cell survival [29].

Despite overwhelming evidence that high levels of TrkB generally correlate with aggressive tumor behavior, TrkB overexpression may not always be associated with poor cancer outcome. To our knowledge, for full-length TrkB only one exception has been reported. During the progression of medullary thyroid carcinoma, overexpressed TrkB in hyperplastic C cells has been suggested to inhibit neoangiogenesis, correlating with reduced tumor growth [30]. In addition, overexpression of alternatively spliced, truncated TrkB isoforms lacking the kinase domain has been correlated with good prognosis in Wilms's tumor [26], and with a more differentiated phenotype in neuroblastic tumors [17]. Importantly, as it has been proposed that truncated TrkB isoforms act as dominant-negative inhibitors of full-length TrkB signaling, thereby compromising tumor expansion [31, 32], these observations are consistent with a pro-oncogenic role of full-length TrkB. Interestingly, there is accumulating evidence that truncated TrkB retains the capacity to engage in functional complexes with intracellular signaling molecules, thereby eliciting specific biological responses [33–35]. Together, these observations justify a thorough analysis of the regulation, relative expression and biological relevance of TrkB splice variants in human tumors.

As illustrated by the examples discussed above, the primary mechanism leading to increased TrkB activity in cancer seems to occur through overexpression of the full-length receptor. Unlike TrkA and TrkC [11], TrkB has not been reported to be activated in cancer by fusing to multimerizing proteins or by abnormal alternative splicing (leading to an activated protein). On the other hand, mutation of the TrkB gene has been reported to occur, in colorectal cancer [36], but further studies are required to determine the frequency of such mutations. The two identified point mutations in this study were both located within the region encoding TrkB's kinase domain. However, their impact on TrkB activity remains elusive. Nevertheless, this study suggests that large-scale screening for mutations of TrkB in cancer might allow identification of new tumor-associated TrkB mutants. Hopefully, this will also identify much needed tumor cell lines for thorough functional analysis of cancer-associated TrkB mutants.

As discussed above, TrkB overexpression is often associated with increased metastatic potential, for example in neuroblastomas and pancreatic ductal adenocarcinomas,

which has been suggested to be causally related to their aggressive behavior [20, 24, 28, 37]. Interestingly, BDNF, too, might contribute to a poor prognosis phenotype. By promoting the recruitment of pro-angiogenic hematopoietic cells expressing TrkB, BDNF is a potent inducer of neo-angiogenesis [38]. The TrkB-BDNF axis might therefore play a role in tumor and metastasis neo-vascularization, but this remains to be demonstrated in mouse models.

In further support of a role of TrkB in metastasis, TrkB acts as a potent mediator of anoikis resistance in epithelial cells [15, 39], which is believed to contribute to efficient metastasis [40, 41]. In order to disseminate from primary tumors and metastasize to distant organs, epithelium-derived tumor cells first need to survive in the blood or lymphatics, in which they are deprived of physiologic adhesion signals. In suspension, or within any 'foreign' milieu for that matter, the lack of appropriate stimuli provided by the extracellular matrix or cell-cell contacts normally induces anoikis of epithelial cells [42, 43]. Indeed, TrkB-mediated anoikis resistance is associated with the formation of rapidly growing and highly metastatic tumors in mice [15]. Those results, therefore, provide the first evidence that aberrant TrkB signaling is sufficient to induce tumorigenesis as well as metastasis. Interestingly, it has recently been proposed that some of the genes whose expression is altered early on during tumorigenesis, promoting cell transformation and primary tumor growth, may also be responsible for giving tumor cells a proclivity to metastasize [44]. Such genes could thus be considered as early indicators of the metastatic potential of primary tumors. The observation that TrkB activation in epithelial cells induces both tumorigenesis and metastasis formation raises the possibility that TrkB activation represents such an early event in tumorigenesis, endowing primary cells with a wide spectrum of capacities contributing to cancer.

Taken together, the data obtained from analyses of human tumors strongly suggest that altered TrkB signaling drives important aspects of tumor formation and metastasis (Fig. 1), consistent with recent *in vitro* and *in vivo* studies on the effect of TrkB in non-malignant cells.

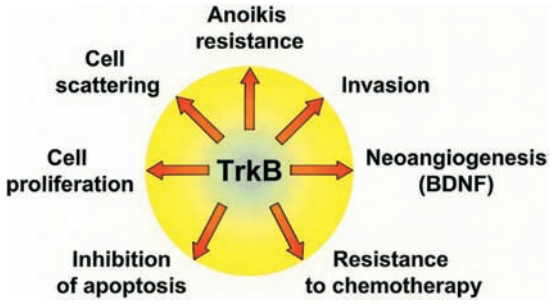

Figure 1. Overview of the cellular effects through which TrkB is likely to promote tumor and metastasis development.

TrkB as a therapeutic anti-tumor target?

The prevalence of its overexpression among various types of human tumors suggests that TrkB represents a valuable therapeutic anti-tumor target [45]. In order to assess the impact of Trk inhibition on tumor growth, recently developed pan-Trk inhibitors – which fail to discriminate between TrkA, TrkB and TrkC [46] – have been used in tumor xenograft and transplantation models. These studies showed that pan-Trk inhibitors can reduce, albeit to various extents, the expansion of transplanted or xenografted neuroblastoma [47, 48], medulloblastoma [47], prostatic [25, 49, 50] and pancreatic [51] cancer cell lines. However, the interpretation of these observations is not always straightforward, for multiple reasons. First, most of these studies were performed on transplanted cell lines rather than on mouse models developing spontaneous tumors. Second, the expression profile of Trk receptors was often poorly characterized, which precludes correlating the observed anti-tumor effects with Trk inhibition, or discriminating between the relative contribution of each individual Trk family member to tumor growth. Finally, the currently available pan-Trk inhibitors display relatively poor specificity and also inhibit other targets such as FLT3 [52, 53].

Although the results from these preclinical studies are encouraging, the precise contribution of TrkB to the tumorigenic and metastatic phenotype has as yet remained largely unclear. Evaluating its potential use as an anti-tumor therapeutic target will require addressing a number of issues thoroughly. First and foremost, is inhibition of TrkB activity, or downregulation of TrkB overexpression, sufficient to inhibit the proliferation or induce apoptosis of TrkB-overexpressing tumor cells? This question is highly relevant in the context of the feasibility of TrkB as a valuable drug target. Second, is altered TrkB signaling sufficient to induce oncogenic cell transformation and/or promote metastasis of spontaneous tumors *in vivo*? One study on transgenic mice overexpressing TrkB post-natally in Thy1-positive neurons argues with this simple view, as these mice do not appear to suffer from an obvious tumor-prone phenotype [54]. This suggests a more complex picture, like a cell type- or genetic context-dependency. Interestingly, evidence is accumulating that such a dependency on genetic context represents a more common phenomenon [B. D. Rowland and D. S. Peeper (2006) KLF, p21 and context-dependent opposing forces in cancer. Nat. Rev. Cancer **6:** 11–23]. For example, the Notch1 receptor has been associated with both oncogenic and tumor-suppressive properties [55]. This also highlights the need for mouse models of TrkB overexpression that recapitulate the role, in the appropriate tissues, of TrkB in human cancer.

Trk inhibitors have already been used in phase I clinical trials [56, 57]. They appear to be tolerated well, but fail to elicit a tumor response in patients suffering from mostly solid tumors. However, these trials have been performed on a limited number of tumor-affected patients, and it was not determined whether their tumors expressed any Trk receptor. Phase II clinical trials are currently under way, which may bring additional data on the suitability of Trks as anti-cancer therapeutic targets.

Taken together, the vast majority of the available evidence points to an important contribution of TrkB to the aggressive behavior of a substantial percentage of human tumors. We have begun to define the contribution of TrkB to tumor and metastasis biology. Clearly, further investigations are needed in order to provide a more solid experimental as well as molecular basis for anti-cancer therapies targeting TrkB. The development of rationale therapies will benefit from a more accurate characterization of the roles of the Trk receptor family in tumor biology. Therefore, the generation of mouse models as well as the identification of TrkB target genes will undoubtedly allow a better understanding of the mechanisms by which TrkB mediates its diverse actions, as well as to identify potential additional targets for cancer therapy.

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