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Short Communication Open Access

Resistance to Anti-EGFR Therapy and Strategies to Overcome it: Possible Role of BDNF/TrkB

de Farias CB[1,2*], Schwartsmann G[1,3] and Roesler R[1,4]

[1]*Cancer and Neurobiology Laboratory, Clinical Hospital, Federal University of Rio Grande do Sul, RS, Brazil*
[2]*Children's Cancer Institute, Porto Alegre, RS, Brazil*
[3]*Department of Internal Medicine, Federal University of Rio Grande do Sul, Porto Alegre, RS, Brazil*
[4]*Department of Pharmacology, Federal University of Rio Grande do Sul, Porto Alegre, RS, Brazil*

Abstract

Acquired resistance to anti-epidermal growth factor receptor (EGFR) monoclonal antibodies such as cetuximab and panitumumab represents an important limitation to the treatment of colorectal cancer (CRC), and research efforts have increasingly been directed towards understanding molecular mechanisms of resistance. We propose that neurotrophin signaling mediated by brain-derived neurotrophic factor (BDNF) and its receptor, tropomyosin-related kinase B (TrkB), might be a compensatory mechanism contributing to decreased response to anti-EGFR therapy in CRC. The combined targeting of EGFR and TrkB is a novel strategy worth of further investigation.

Keywords: Brain-derived neurotrophic factor; TrkB; Neurotrophin; Epidermal growth factor receptor; Cetuximab; Colorectal cancer

Short Communication

The emergence of secondary resistance to monoclonal antibodies that selectively target the epidermal growth factor receptor (EGFR), cetuximab and panitumumab, constitutes a current challenge in the treatment of patients with colorectal cancer (CRC). Although most research has focused particularly on genetic alterations that activate downstream signaling effectors, such as mutations in *KRAS, BRAF*, and *PIK3CA* [1], the contribution to resistance of compensation by parallel tyrosine kinase receptor pathways has also been recently highlighted [2].

In this context, we propose that an emerging target is the tropomyosin-related kinase B (TrkB, also called tropomyosin receptor kinase B or receptor tyrosine kinase B), encoded by *NTRK2* and activated by the neurotrophin brain-derived neurotrophic factor (BDNF). TrkB shares several downstream effectors with EGFR, including the mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase (*PI3K*) pathways, and activation of EGFR plays a role in upregulating BDNF mRNA and protein levels in the brain [3]. In neurons, BDNF/TrkB signaling plays an important role for normal development, survival and plasticity [4], but it has also been proposed to play a role in cancer progression, metastasis, and resistance to chemotherapy [5].

We and others have reported that BDNF and TrkB levels are increased in CRC tumors [6,7]. Treating human CRC cells with an experimental anticancer peptide increases the mRNA expression, protein content, and secretion of BDNF, through a mechanism that depends on EGFR activity. The increase in BDNF results in a compensatory response that rescues CRC cell proliferation and survival [6]. Importantly, BDNF protects against the anti-proliferative effect of cetuximab in a human CRC cell line, whereas a TrkB inhibitor can sensitize the cells to a low dose of cetuximab [8].

This evidence raises the possibility that BDNF/TrkB upregulation might contribute to resistance against anti-EGFR therapy in CRC. Whether tumors from patients with intrinsic resistance to anti-EGFR therapy present increased BDNF and TrkB expression and activity remains to be determined. It is possible that the combined inhibition of EGFR and TrkB could increase tumor responses to treatment [8,9]. This may be a novel opportunity to overcome resistance to anti-EGFR therapy, and it warrants further experimental exploration.

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***Corresponding author:** de Farias CB, Cancer and Neurobiology Laboratory, Experimental Research Center, Clinical Hospital, Federal University of Rio Grande do Sul. Rua Ramiro Barcelos, 2350, CPE, 2° Andar, 90035-003 Porto Alegre, RS, Brazil, Tel: +555151 33597616; Fax: +5551 33598012; E-mail: labpesquisa@ici-rs.org.br

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