

doi: 10.3978/j.issn.2095-6959.2022.04.031

View this article at: <https://dx.doi.org/10.3978/j.issn.2095-6959.2022.04.031>

脑源性神经营养因子与肿瘤的相关性

巨春雷¹, 胡昌辰² 综述 陈胜利² 审校

(1. 山西医科大学, 太原 030000; 2. 山西医科大学附属人民医院神经外科, 太原 030000)

[摘要] 近年来, 由于肿瘤的发病率和病死率逐渐升高, 关于肿瘤病因学的研究也不断深入。脑源性神经营养因子(brain-derived neurotrophic factor, BDNF)作为神经营养因子超家族中的一员, 目前已被证明与多种疾病的发生、发展相关, BDNF与酪氨酸激酶受体B(tyrosine kinase B, TrkB)结合后可通过促进肿瘤血管、神经生成, 诱导肿瘤细胞上皮间质转换等途径, 在肿瘤的转移、侵袭及耐药性的产生中发挥重要作用。

[关键词] 脑源性神经营养因子; 肿瘤; 微RNA; 长链非编码RNA

Correlation between brain-derived neurotrophic factor and tumor

JU Chunlei¹, HU Changchen², CHEN Shengli²

(1. Shanxi Medical University, Taiyuan 030000; 2. Department of Neurosurgery, People's Hospital Affiliated to Shanxi Medical University, Taiyuan 030000, China)

Abstract In recent years, incidence rate and mortality rate of cancer have been increasing. As a member of the neurotrophic factor superfamily, brain-derived neurotrophic factor (BDNF) has been proved to be associated with the occurrence and development of many diseases, among them, the binding of BDNF with tyrosine kinase B (TrkB) plays a key role in tumor metastasis, invasion, and drug resistance by promoting tumor angiogenesis and neurogenesis, as well as epithelial mesenchymal transition of tumor cells.

Keywords brain-derived neurotrophic factor; tumor; microRNAs; long non-coding RNA

脑源性神经营养因子(brain-derived neurotrophic factor, BDNF)是一种具有神经营养作用的蛋白质, 广泛表达于神经系统, 在神经元的发育及功能维持中发挥重要作用。近些年, 随着肿瘤发病率和病死率的升高, 肿瘤研究的不断深

入。BDNF被发现在肿瘤组织中高表达。而且可通过与酪氨酸激酶受体B(tyrosine kinase B, TrkB)结合激活Ras/MAPK、PI3K/Akt和PLC- γ /PKC等信号通路促进肿瘤血管生成、细胞增殖、浸润、转移及耐药性产生^[1-3]。

收稿日期 (Date of reception): 2021-01-16

通信作者 (Corresponding author): 陈胜利, Email: shenglic@163.com

基金项目 (Foundation item): 国家自然科学基金 (30901774); 山西省重点研发计划项目 (国际合作) (201803D421055)。This work was supported by the National Natural Science Foundation (30901774) and Shanxi Provincial Key Research and Development Program (201803D421055), China.

1 BDNF 的表达及分布

BDNF是继神经营养因子(neurotrophic factor, NF)之后第2个被发现的神经营养素(neurotrophin, NT)家族成员,是一种由477个氨基酸组成的蛋白质,其基因位点位于11号染色体的短链,可通过与高亲和力受体酪氨酸激酶受体B和低亲和力受体p75神经生长因子相结合发挥生物学效应。BDNF除广泛分布于哺乳动物脑皮质、下丘脑、海马、杏仁核等组织外,还表达于骨骼肌细胞、血管平滑肌细胞及发育中的肠管、脾、心脏等组织器官。BDNF和TrkB在肺癌^[4]、卵巢癌^[5]、乳腺癌^[6]、星形胶质细胞瘤^[7]等肿瘤组织中也呈高表达。BDNF前体往往具有与成熟BDNF相反的功能^[8]。

2 BDNF 影响肿瘤的进展及耐药性

BDNF/TrkB及调控的下游信号通路的激活可通过促进肿瘤血管的生成、提高肿瘤对化疗药物的耐药性、抑制肿瘤细胞的凋亡、增强肿瘤细胞的转移侵袭能力,进而促进肿瘤的侵袭和进展^[9-10]。

2.1 BDNF 促进肿瘤的进展、转移

肿瘤血管的生成对肿瘤组织的生长具有重要意义, BDNF/TrkB信号通路不仅可直接促进肝癌小鼠模型肿瘤血管的生成及生长^[9], 而且还可通过与血管内皮生长因子(vascular endothelial growth factor, VEGF)信号通路交叉串扰促进肿瘤的生成^[10]。此外, BDNF/TrkB信号通路与内皮细胞生长因子受体(endothelial growth factor receptor, EGFR)之间的信号串扰, 可使得EGFR在不依赖内皮细胞生长因子(endothelial growth factor, EGF)的情况下发生磷酸化, 一方面促进胚胎皮层神经元的迁移, 另一方面促进肺癌及卵巢癌细胞的迁移和侵袭^[11-13]。BDNF/TrkB信号通路可通过抑制肿瘤细胞的失巢凋亡, 在肿瘤细胞的转移过程中发挥重要作用^[14]。BDNF/TrkB可通过激活其下游的PI3K/Akt和NF- κ B信号通路, 诱导 β 5整合素的表达从而促进软骨肉瘤的转移^[1]; 激活AKT/mTOR信号途径, 诱导GTP酶Rac1和肌动蛋白重组引起肿瘤转移^[15]; 激活PLC γ 信号通路, 最终通过抑制卵巢癌肿瘤细胞的凋亡, 引起癌细胞的浸润、进展^[5]。BDNF高表达还与乳腺癌淋巴结转移、肿瘤复发、生存期短及预后差具有相关性^[6]。

嗜神经侵袭是胰腺癌侵袭和转移的主要途

径^[16], 也是胃癌^[17]、结直肠癌^[18]、前列腺癌^[19]等肿瘤的侵袭和转移途径之一。在正常胰腺组织的腺泡细胞及导管细胞中BDNF不表达, 而在嗜神经侵袭(perineural invasion, PNI)的胰腺导管腺癌组织中可见BDNF的表达^[20]。BDNF引起嗜神经侵袭的可能机制: 1)通过促进轴突生长来引起神经侵袭; 2)诱导癌细胞主动侵犯神经纤维, 或者通过诱导神经定向生长接触病变位置, 最终使得肿瘤细胞扩散^[21]。

2.2 BDNF 诱导肿瘤耐药性的产生

目前, 肿瘤的治疗手段主要有手术、放疗、化疗、免疫治疗。但是耐药性的产生严重影响了肿瘤患者的无进展生存期和总生存期。BDNF/TrkB及其调控的下游信号通路在肿瘤耐药性的产生中也发挥着重要的作用。BDNF/TrkB一方面可通过诱导Akt的磷酸化使得神经母细胞瘤对长春新碱、顺铂、多柔比星、依托泊苷等化疗药物产生耐药, 另一方面可通过抑制长春碱解聚微管蛋白, 对长春碱产生耐药性^[22]。外源性BDNF、TrkB可通过上调MDR1和抗凋亡蛋白XiAP使得头颈部肿瘤对化疗药物顺铂产生耐药性^[23]。此外, BDNF亦可通过下调促凋亡蛋白Bim, 进而抑制线粒体介导的细胞凋亡及内源性凋亡, 最终使得肿瘤细胞对化疗药物产生耐药性^[24]。使用Akt抑制剂LY29400或哌立福辛抑制P13K/Akt通路后可增加神经母细胞瘤细胞对药物的敏感性, 抑制肿瘤细胞的生长、侵袭、转移, 可作为治疗靶点^[3]。

2.3 BDNF 的抗肿瘤作用

丰富环境(enriched environment, EE)可诱导小鼠下丘脑表达BDNF, 靶向作用于外周白色脂肪组织, 最终使得瘦脂素血浆浓度降低, 脂联素水平升高, 进而增强免疫细胞的免疫力, 对肿瘤有抑制作用^[25-26]。

3 MicroRNAs、lncRNA 可通过调控 BDNF 的表达影响肿瘤的结局

3.1 MicroRNAs 对 BDNF 表达的影响

MicroRNAs是一类内源性、碱基对少的非编码RNA, 可通过与靶向信使RNA3'端的结合来调节转录后翻译。研究^[27]表明: microRNA对BDNF/TrkB信号通路亦具有调节作用, 当肿瘤发生时, miR-1、miR-10b、miR-191的低表达可过度激活BDNF/TrkB信号通路, 促进肿瘤组织BDNF高表

达。MiR-200C可靶向作用于TrkB, 增加肿瘤细胞失巢凋亡的敏感性, 另外还可增强乳腺癌、卵巢癌对化疗药物的敏感性^[15]。在肝癌细胞中, miR933可通过靶向作用于BDNF抑制肝癌的侵袭和迁移^[28]。MiR-10-5p可抑制BDNF mRNA及蛋白质的表达, 进而抑制宫颈癌的增殖和分化^[29]。在非小细胞肺癌中, BDNF可通过PI3K/Akt信号通路引起跨膜AMPA受体的增加, 继而引起BDNF mRNA的表达增加, 正反馈促进BDNF的表达。而miR-496可通过抑制BDNF介导的PI3K/Akt信号通路, 发挥抑制肿瘤的作用^[30]。MiR-497可通过抑制BDNF, 进而通过PI3K/AKT通路来抑制甲状腺癌细胞的增殖和侵袭^[31]。在多发性骨髓瘤中, miR-129-5p能直接靶向负调控抑制BDNF的表达, 进而抑制细胞增殖, 在诱导细胞凋亡的同时, 抑制IL-5、TNF- α 、IL-1 β 、VEGF的分泌, 进一步阻止多发性骨髓瘤的进展^[32]。

3.2 lncRNA对BDNF表达的影响

长链非编码RNA(long non-coding RNA, lncRNA)是一类长度超过200个核苷酸的小分子非编码RNA, 可在转录、转录后和表观遗传等多个方面调控基因的表达, 与神经系统疾病、自身免疫性疾病、肿瘤等多种疾病的发生、发展密切相关^[33-34]。SNHG7(lncRNA small nucleolar RNA host gene 7)可通过促进BDNF的表达, 促进甲状腺癌细胞的增殖和抑制甲状腺癌细胞的凋亡, 最终促进肿瘤的进展^[35]。linc-ITGB1可促进BDNF的表达, 最终引起结直肠癌转移^[36]。

lncRNA BDNF-AS作为BDNF的反义转录物, 可通过抑制BDNF的表达来抑制宫颈癌的进展^[37]。在骨肉瘤中, BDNF-AS可通过调控cleaved caspase-3的表达来诱导骨肉瘤细胞凋亡, 抑制骨肉瘤细胞的增殖, 最终抑制骨肉瘤的进展^[38]。在结直肠癌中, BDNF-AS通过与EZH2介导的GSK-3 β 启动子相结合, 抑制GSK-3 β 的表达, 具有抑制肿瘤的作用^[39]。在视网膜母细胞瘤中, BDNF-AS可通过下调BDNF, 抑制细胞周期转换, 使细胞周期阻滞于G₀/G₁期, 抑制肿瘤的进展^[40]。

4 结语

BDNF几乎高表达于所有肿瘤组织中。MicroRNAs、lncRNA可通过调控BDNF的表达影响肿瘤的进展, BDNF可通过调控下游的Ras/MAPK、PI3K/Akt和PLC- γ /PKC信号通路促进肿

瘤的进展, 故BDNF有望成为多种肿瘤治疗新靶点。此外, BDNF启动子甲基化、BDNF Val66Met单核苷酸多态性、海马区及前额脑皮质BDNF的表达明显减少与患者抑郁、自杀倾向具有一定的相关^[41], 因此, 检测血清中BDNF可用于术后抑郁、自杀倾向的评估, 以便尽早针对性做出干预。然而, 关于下丘脑BDNF高表达的抑癌确切机制仍需进一步研究。

参考文献

1. Lin CY, Chen HJ, Li TM, et al. β 5 integrin up-regulation in brain-derived neurotrophic factor promotes cell motility in human chondrosarcoma[J]. PLoS One, 2013, 8(7): e67990.
2. Zhang S, Guo D, Luo W, et al. TrkB is highly expressed in NSCLC and mediates BDNF-induced the activation of Pyk2 signaling and the invasion of A549 cells[J]. BMC Cancer, 2010, 10: 43.
3. Li Z, Oh DY, Nakamura K, et al. Perifosine-induced inhibition of Akt attenuates brain-derived neurotrophic factor/TrkB-induced chemoresistance in neuroblastoma in vivo[J]. Cancer, 2011, 117(23): 5412-5422.
4. Zhang SY, Hui LP, Li CY, et al. More expression of BDNF associates with lung squamous cell carcinoma and is critical to the proliferation and invasion of lung cancer cells[J]. BMC Cancer, 2016, 16: 171.
5. Xu Y, Jiang WG, Wang HC, et al. BDNF activates TrkB/PLC γ 1 signaling pathway to promote proliferation and invasion of ovarian cancer cells through inhibition of apoptosis[J]. Eur Rev Med Pharmacol Sci, 2019, 23(12): 5093-5100.
6. Ma D, Chen C, Wu J, et al. Up-regulated lncRNA AFAP1-AS1 indicates a poor prognosis and promotes carcinogenesis of breast cancer[J]. Breast Cancer, 2019, 26(1): 74-83.
7. Liu TT, Wang H, Wang FJ, et al. Expression of nerve growth factor and brain-derived neurotrophic factor in astrocytomas[J]. Oncol Lett, 2018, 15(1): 533-537.
8. Lin PY. Regulation of proteolytic cleavage of brain-derived neurotrophic factor precursor by antidepressants in human neuroblastoma cells[J]. Neuropsychiatr Dis Treat, 2015, 11: 2529-2532.
9. Lam CT, Yang ZF, Lau CK, et al. Brain-derived neurotrophic factor promotes tumorigenesis via induction of neovascularization: implication in hepatocellular carcinoma[J]. Clin Cancer Res, 2011, 17(10): 3123-3133.
10. Au CW, Siu MK, Liao X, et al. Tyrosine kinase B receptor and BDNF expression in ovarian cancers - Effect on cell migration, angiogenesis and clinical outcome[J]. Cancer Lett, 2009, 281(2): 151-161.
11. Puehringer D, Orel N, Lüningschrör P, et al. EGF transactivation of Trk

- receptors regulates the migration of newborn cortical neurons[J]. *Nat Neurosci*, 2013, 16(4): 407-415.
12. Götz R, Sendtner M. Cooperation of tyrosine kinase receptor TrkB and epidermal growth factor receptor signaling enhances migration and dispersal of lung tumor cells[J]. *PLoS One*, 2014, 9(6): e100944.
 13. Qiu L, Zhou C, Sun Y, et al. Crosstalk between EGFR and TrkB enhances ovarian cancer cell migration and proliferation[J]. *Int J Oncol*, 2006, 29(4): 1003-1011.
 14. Geiger TR, Peeper DS. The neurotrophic receptor TrkB in anoikis resistance and metastasis: a perspective[J]. *Cancer Res*, 2005, 65(16): 7033-7036.
 15. 李林霞, 李双弟, 杨懿霞, 等. miRNA-200c在上皮性卵巢癌细胞株及肿瘤组织中的表达变化及意义[J]. *第二军医大学学报*, 2011, 31(6): 612-616.
LI Linxia, LI Shuangdi, YANG Yixia, et al. Changes of miRNA-200c expression in ovarian cancer and its clinical significance[J]. *Academic Journal of Second Military Medical University*, 2011, 31(6): 612-616.
 16. Ma J, Jiang Y, Jiang Y, et al. Expression of nerve growth factor and tyrosine kinase receptor A and correlation with perineural invasion in pancreatic cancer[J]. *J Gastroenterol Hepatol*, 2008, 23(12): 1852-1859.
 17. Deng J, You Q, Gao Y, et al. Prognostic value of perineural invasion in gastric cancer: a systematic review and meta-analysis[J]. *PLoS One*, 2014, 9(2): e88907.
 18. Yang Y, Huang X, Sun J, et al. Prognostic value of perineural invasion in colorectal cancer: a meta-analysis[J]. *J Gastrointest Surg*, 2015, 19(6): 1113-1122.
 19. Tollefson MK, Karnes RJ, Kwon ED, et al. Prostate cancer Ki-67 (MIB-1) expression, perineural invasion, and Gleason score as biopsy-based predictors of prostate cancer mortality: the Mayo model[J]. *Mayo Clin Proc*, 2014, 89(3): 308-318.
 20. 周杭城. BDNF、NT-4、GDNF与胰腺导管腺癌神经侵袭的相关性研究[D]. 合肥: 安徽医科大学, 2013.
ZHOU Hangcheng. Study on the correlation between BDNF, NT-4, GDNF and nerve invasion of pancreatic ductal adenocarcinoma[D]. Hefei: Anhui Medical University, 2013.
 21. 徐光辉, 丰帆, 赵国宏, 等. 食管癌对神经生长及导向作用的研究[J]. *中华胃肠外科杂志*, 2013, 16(5): 474-478.
XU Guanghui, FENG Fan, ZHAO Guohong, et al. Effects of esophageal cancer on the nerve fiber growth and guidance[J]. *Chinese Journal of Gastrointestinal Surgery*, 2013, 16(5): 474-478.
 22. Scala S, Wosikowski K, Giannakakou P, et al. Brain-derived neurotrophic factor protects neuroblastoma cells from vinblastine toxicity[J]. *Cancer Res*, 1996, 56(16): 3737-3742.
 23. Lee J, Jiffar T, Kupferman ME. A novel role for BDNF-TrkB in the regulation of chemotherapy resistance in head and neck squamous cell carcinoma[J]. *PLoS One*, 2012, 7(1): e30246.
 24. Li Z, Zhang J, Liu Z, et al. Downregulation of Bim by brain-derived neurotrophic factor activation of TrkB protects neuroblastoma cells from paclitaxel but not etoposide or cisplatin-induced cell death[J]. *Cell Death Differ*, 2007, 14(2): 318-326.
 25. Cao L, Liu X, Lin EJ, et al. Environmental and genetic activation of a brain-adipocyte BDNF/leptin axis causes cancer remission and inhibition[J]. *Cell*, 2010, 142(1): 52-64.
 26. Nachat-Kappes R, Pinel A, Combe K, et al. Effects of enriched environment on COX-2, leptin and eicosanoids in a mouse model of breast cancer[J]. *PLoS One*, 2012, 7(12): e51525.
 27. Tsai YF, Tseng LM, Hsu CY, et al. Brain-derived neurotrophic factor (BDNF)-TrkB signaling modulates cancer-endothelial cells interaction and affects the outcomes of triple negative breast cancer[J]. *PLoS One*, 2017, 12(6): e0178173.
 28. 朱建奎, 胡加运, 郑笑笑, 等. 微小RNA-933靶向调控BDNF表达及对肝癌细胞迁移侵袭的影响[J]. *临床肿瘤学杂志*, 2018, 23(7): 587-592.
ZHU Jiankui, HU Jiayun, ZHENG Xiaoxiao, et al. Targeted-regulation of microRNA-933 on BDNF expression and its effect on migration and invasion of hepatoma cells[J]. *Chinese Clinical Oncology*, 2018, 23(7): 587-592.
 29. Zhai L, Li Y, Lan X, et al. MicroRNA-10a-5p suppresses cancer proliferation and division in human cervical cancer by targeting BDNF[J]. *Exp Ther Med*, 2017, 14(6): 6147-6151.
 30. Ma R, Zhu P, Liu S, et al. miR-496 suppress tumorigenesis via targeting BDNF-mediated PI3K/Akt signaling pathway in non-small cell lung cancer[J]. *Biochem Biophys Res Commun*, 2019, 518(2): 273-277.
 31. Wang P, Meng X, Huang Y, et al. MicroRNA-497 inhibits thyroid cancer tumor growth and invasion by suppressing BDNF[J]. *Oncotarget*, 2017, 8(2): 2825-2834.
 32. Wang Y, Lin Q, Song C, et al. Depletion of circ_0007841 inhibits multiple myeloma development and BTZ resistance via miR-129-5p/JAG1 axis[J]. *Cell Cycle*, 2020, 19(23): 3289-3302.
 33. Chen Q, Huang X, Li R. lncRNA MALAT1/miR-205-5p axis regulates MPP(+)-induced cell apoptosis in MN9D cells by directly targeting LRRK2[J]. *Am J Transl Res*, 2018, 10(2): 563-572.
 34. Lucafò M, Di Silvestre A, Romano M, et al. Role of the long non-coding RNA growth arrest-specific 5 in glucocorticoid response in children with inflammatory bowel disease[J]. *Basic Clin Pharmacol Toxicol*, 2018, 122(1): 87-93.
 35. Wang YH, Huo BL, Li C, et al. Knockdown of long noncoding RNA SNHG7 inhibits the proliferation and promotes apoptosis of thyroid cancer cells by downregulating BDNF[J]. *Eur Rev Med Pharmacol Sci*, 2019, 23(11): 4815-4821.
 36. Wan WB, Kong QL. Knockdown of long noncoding RNA linc-ITGB1

- inhibits tumor metastasis in colorectal cancer through suppressing BDNF[J]. *Eur Rev Med Pharmacol Sci*, 2020, 24(14): 7551.
37. Zhang H, Liu C, Yan T, et al. Long noncoding RNA BDNF-AS is downregulated in cervical cancer and has anti-cancer functions by negatively associating with BDNF[J]. *Arch Biochem Biophys*, 2018, 646: 113-119.
38. Huang Q, Yang J, He X, et al. LncRNA BDNF-AS is associated with the malignant status and regulates cell proliferation and apoptosis in osteosarcoma[J]. *Biosci Rep*, 2018, 38(6): BSR20181498.
39. Zhi H, Lian J. LncRNA BDNF-AS suppresses colorectal cancer cell proliferation and migration by epigenetically repressing GSK-3 β expression[J]. *Cell Biochem Funct*, 2019, 37(5): 340-347.
40. Shang W, Yang Y, Zhang J, et al. Long noncoding RNA BDNF-AS is a potential biomarker and regulates cancer development in human retinoblastoma[J]. *Biochem Biophys Res Commun*, 2018, 497(4): 1142-1148.
41. Kim JM, Jang JE, Stewart R, et al. Determinants of suicidal ideation in patients with breast cancer[J]. *Psychooncology*, 2013, 22(12): 2848-2856.
39. Zhi H, Lian J. LncRNA BDNF-AS suppresses colorectal cancer cell

本文引用: 巨春雷, 胡昌辰, 陈胜利. 脑源性神经营养因子与肿瘤的相关性[J]. *临床与病理杂志*, 2022, 42(4): 969-973. doi: 10.3978/j.issn.2095-6959.2022.04.031

Cite this article as: JU Chunlei, HU Changchen, CHEN Shengli. Correlation between brain-derived neurotrophic factor and tumor[J]. *Journal of Clinical and Pathological Research*, 2022, 42(4): 969-973. doi: 10.3978/j.issn.2095-6959.2022.04.031