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脑源性神经营养因子与肿瘤的相关性

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[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、发展具有相关性，其中，BDNF与酪氨酸激酶受体B(tyrosine kinase B，TrkB)的结合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；机制；microRNAs；lncRNA

Correlation between brain-derived neurotrophic factor and tumor

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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; mechanism; microRNAs; lncRNA

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逐渐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)的结合激活Ras/MAPK、PI3K/Akt和PLC-γ/PKC等信号促进肿瘤血管生成、细胞增殖、浸润、转移及耐药性产生[1-3]。

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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、脾脏、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有相反的功能[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-KB信号通路，诱导β5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PLCγ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)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，对于肿瘤治疗手段主要有手术、放疗、化疗、免疫治疗。但是由于耐药性的产生，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]。对于头颈部鳞癌，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，降低肿瘤细胞生长并抑制其侵袭和转，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、碱基对小的、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BDNF蛋白的表达，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-1β、VEGF的分泌，进一步抑制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-3β启动子相结合，抑制GSK-3β的表达，具有抑制肿瘤的作用[39]。在视网膜母细胞瘤中，BDNF可通过下调BDNF，抑制细胞周期转换，诱导细胞周期阻滞于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。

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