

原肌球蛋白相关激酶B在肿瘤中的研究进展

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摘要 原肌球蛋白相关激酶B(tropomyosin-related kinase B, TrkB)是一种神经营养性酪氨酸受体激酶, 通过介导丝裂原活化蛋白激酶(mitogen-activated protein kinases, MAPK)、磷脂酶C- γ (phospholipase C- γ , PLC- γ)、磷脂酰肌醇3-激酶(phosphatidylinositol 3-kinase, PI3K)、Janus激酶(Janus kinase, JAK)/信号转导子和转录激活因子3(signal transducer and activator of transcription 3, STAT3)、Wnt/ β -catenin等信号通路, 调节细胞分化、增殖、凋亡和迁移。现已证明, *TrkB*基因融合、蛋白质过表达或单核苷酸改变与多种癌症密切相关。因此, 该文针对TrkB的生物学特性、相关信号通路以及TrkB在肿瘤中的作用及机制进行了综述。

关键词 TrkB; 信号通路; 肿瘤; 调控

Research Progress on Tropomyosin-Related Kinase B in Tumors

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Abstract TrkB (tropomyosin-related kinase B), a neurotrophic tyrosine receptor kinase, regulates cell differentiation, proliferation, apoptosis and migration by MAPK (mitogen-activated protein kinases), PLC- γ (phospholipase C- γ), PI3K (phosphatidylinositol 3-kinase), JAK (Janus kinase)/STAT3 (signal transducer and activator of transcription 3) and Wnt/ β -catenin signaling pathways. The gene fusion, protein overexpression and single nucleotide changes of TrkB are strongly related to cancers. Here, the study reviewed the biological characteristics related signaling pathways and mechanism in tumors of TrkB.

Keywords tropomyosin-related kinase B; signal pathway; tumor; regulation

原肌球蛋白相关激酶B(tropomyosin-related kinase B, TrkB)是一种在脑、甲状腺、脂肪组织和胆囊等部位表达的膜结合酪氨酸受体激酶, 主要由脑源性神经营养因子(brain-derived neurotrophic factor, BDNF)和神经营养因子4(neurotrophin 4, NT4)激活。目前, 已有大量研究表明, TrkB与癌症的发生密切相关^[1-5], 因此本文综述了原肌球蛋白相关激酶(tropomyosin-related kinase, Trk)家族成员、TrkB的生物学特性、TrkB参与的信号通路, 并深入剖析TrkB在肿

瘤中的作用及机制。

1 Trk家族

原肌球蛋白相关激酶(tropomyosin-related kinase, Trk)家族成员包括原肌球蛋白相关激酶A(tropomyosin-related kinase A, TrkA)、原肌球蛋白相关激酶B(tropomyosin-related kinase B, TrkB)和原肌球蛋白相关激酶C(tropomyosin-related kinase C, TrkC), 其激酶结构域非常保守^[6]。与Trks受体相

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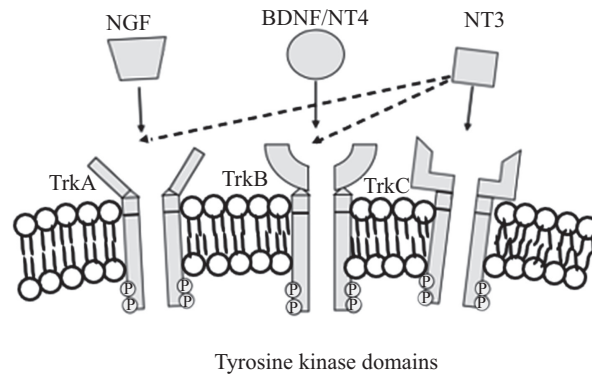
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虚线: 结合能力较弱。

Dotted line: weak binding ability.

图1 原肌球蛋白受体激酶(Trk)家族成员及其神经营养蛋白配体(根据参考文献[7-8]修改)

Fig1 Trk (members of the tropomyosin receptor kinase) family and their neurotrophic protein ligands (modified from references [7-8])

作用的神经营养蛋白配体包括神经生长因子(nerve growth factor, NGF)、脑源性神经营养因子(brain-derived neurotrophic factor, BDNF)、神经营养因子4(neurotrophin 4, NT4)、神经营养因子3(neurotrophin 3, NT3), 其中NGF优先与TrkA结合, BDNF和NT4优先与TrkB结合, 而NT3优先与TrkC结合, 此外, NT3还以较小的亲和力与TrkA和TrkB结合^[7], 如图1所示。

活化的TrkB可激活Ras-MAPK、蛋白激酶C(protein kinase C, PKC)、磷脂酶C- γ (phospholipase C- γ , PLC- γ)和PI3K等途径, 并在细胞存活、增殖和侵袭等生物学过程中发挥重要作用。例如, 活化的TrkB通过激活PLC γ 1增加NF- κ B活性并增强细胞存活信号, 进而抑制神经失调^[8]。敲低HeLa细胞和宫颈癌CaSki细胞中的TrkB会导致上皮-钙黏蛋白(epithelial cadherin, E-cadherin)显著增加, 神经-钙黏着蛋白(neural cadherin, N-cadherin)和波形蛋白表达减少, 并伴随着细胞增殖和侵袭能力下降^[2]。

2 TrkB的生物学特性

2.1 TrkB的类型与结构

人类编码TrkB的基因位于9号染色体, 由NTRK2编码。TrkB蛋白分为全长TrkB(full-length TrkB, TrkB-FL)和截短TrkB(truncated TrkB, TrkB-T)^[9], TrkB-FL亚型具有胞外配体结合结构域、单个跨膜结构域和典型的含酪氨酸激酶的胞内结构域, 可以调节与癌症相关的多种途径, 并引发BDNF和NT4诱导的信号转导, 研究表明, BDNF/TrkB信号通路参与细胞存活、迁移、轴突和树突的生长、突触形成、

突触传递和突触重塑等过程。TrkB-T包括TrkB-T1和TrkB-T2, 它们的胞外配体结合结构域和单个跨膜结构域与TrkB-FL相同, 但缺少“激酶”结构域^[10], 并与发育、损伤密切相关。

2.2 TrkB的表达调控

TrkB的表达受转化生长因子- β 1(transforming growth factor- β 1, TGF- β 1)调节, 在鳞癌(squamous carcinoma, SCC-25)细胞中, TGF- β 1诱导TrkB产生^[11]。外源性肝细胞生长因子在mRNA和蛋白水平上诱导TrkB表达^[3], 而miR-1-3p通过调节BDNF抑制TrkB磷酸化^[12]。

在脊髓损伤(spinal cord injury, SCI)的大鼠中, BDNF表达增加, 增加的BDNF通过TrkB/p38 MAPK信号传导减轻脊髓损伤模型中的炎症, 在体外模型中, BDNF过表达诱导TrkB表达、抑制磷酸化p38(p-p38)表达, 并伴随着白介素-1 β (interleukin-1 β , IL-1 β)、白介素-6(interleukin-6, IL-6)、白介素-18(interleukin-18, IL-18)和肿瘤坏死因子- α (tumor necrosis factor- α , TNF- α)等炎症因子水平的降低。相反, TrkB抑制剂ANA-12抑制TrkB蛋白表达、诱导p-p38的蛋白表达并促进炎症因子升高^[13]。溴氰菊酯(deltamethrin, DM)通过激活内源性BDNF/TrkB介导的MAPK和mTOR途径促进神经突生长^[14], 喹啉酸(quinolinic acid, QUIN)诱导JNK持续激活从而抑制大鼠纹状体中的BDNF/TrkB信号通路^[15]。

2.3 TrkB与癌症的关系

由于TrkB能够参与肿瘤细胞中自分泌和旁分泌信号的激活^[3], 因此, TrkB的异常表达还与乳腺癌、宫颈癌、结直肠癌等多种癌症密切相关。研究

表明, BDNF/TrkB途径的异常激活可以调节多种信号途径, 包括PI3K、JAK/STAT、核因子 κ B(nuclear factor κ B, NF- κ B)、Wnt/ β -catenin和血管内皮生长因子(vascular endothelial growth factor, VEGF)途径, 从而增强细胞生存、侵袭、转移、血管生成和耐药性, 使细胞获得肿瘤发生所需的多种特征。

3 TrkB在不同信号通路中的作用

现有研究表明, 活化的TrkB会激活MAPK、PI3K、JAK/STAT3和PLC γ 途径, 调控细胞存活、增殖、凋亡、分化和迁移等生物学过程, 如图2所示^[16-17]。

3.1 TrkB与MAPK信号通路

丝裂原活化蛋白激酶(mitogen-activated protein kinases, MAPK)信号通路参与细胞分化、凋亡和运动等多种生物学过程, 并与肺癌、结肠癌、卵巢癌和乳腺癌等癌症的发生密切相关。该途径主要通过激活三种激酶: 丝裂原活化的蛋白激酶激酶激酶(mitogen-activated protein kinase kinase kinases, MAPKKK)、丝裂原活化的蛋白激酶激酶(mitogen-activated protein kinase kinase, MAPKK)和MAPK启动蛋白级联反应, 典型MAPK包括细胞外信号调

节激酶1/2(extracellular signal-regulated kinase 1/2, ERK1/2)、C-Jun N末端激酶1/2/3(Jun amino-terminal kinases, JNK1/2/3)、p38-有丝分裂原活化蛋白激酶(p38 mitogen-activated protein kinase, p38-MAPK)和细胞外信号调节激酶5(the extracellular-regulated protein kinase 5, ERK5)。

TrkB参与MAPK信号传导途径, 研究表明, TrkB的Y484、Y785^[18]或Y490发生磷酸化后可作为含PTB或SH2结构域蛋白的停泊位点, 鸟嘌呤核苷酸交换因子(son of sevenless, SOS)通过生长因子受体结合蛋白2(growth factor receptor bound protein 2, Grb2)的SH2结构域间接与受体结合, 进而活化Ras^[19], 活化的Ras蛋白激活Raf/MEK/ERK信号传导, 促进癌细胞的存活、增殖和迁移^[20]。

3.2 TrkB与PI3K信号通路

PI3K基因突变或过表达与卵巢癌、乳腺癌、胃癌、结直肠癌、成胶质细胞瘤等癌症的发生密切相关。PI3K/丝氨酸/苏氨酸激酶B(serine/threonine kinase B, PKB/Akt)/雷帕霉素的哺乳动物靶标(the mammalian target of rapamycin, mTOR)信号通路能够调节细胞存活, 并在细胞生长和增殖中起重要

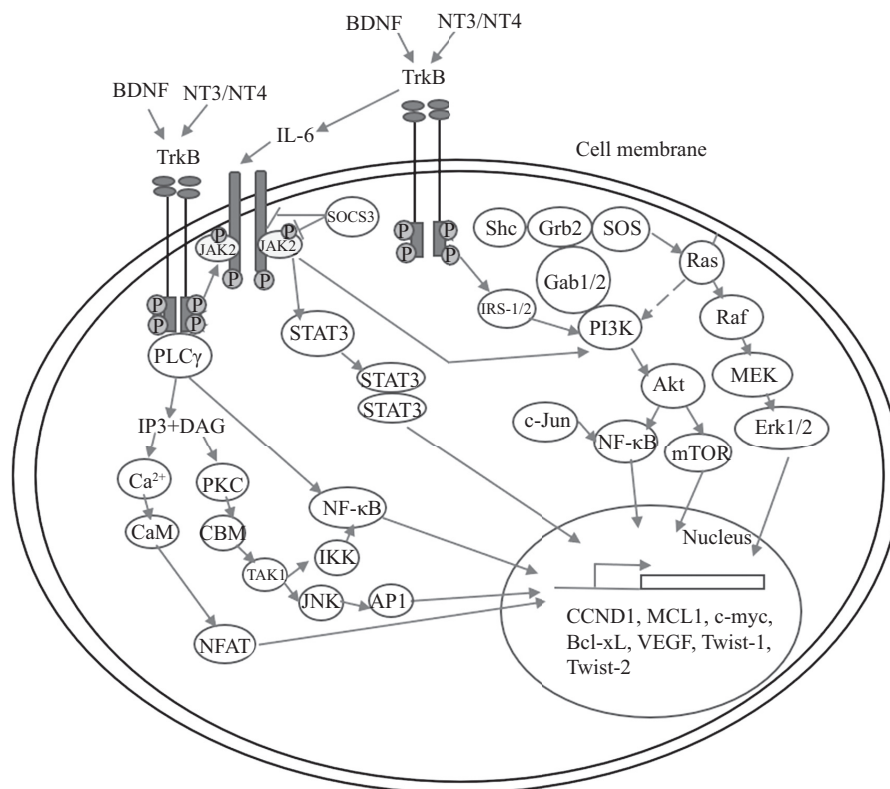


图2 与活化的TrkB受体相关的信号通路(根据参考文献[16-17]修改)

Fig.2 Signaling pathways associated with activated TrkB receptors (modified from references [16-17])

作用。PI3K通过受体的调节亚基或衔接子,例如胰岛素底物受体(insulin substrate receptor, IRS),与受体相结合,活化的PI3K利用磷脂酰肌醇-4,5-二磷酸(phosphatidylinositol-4,5-bisphosphate, PIP2)的催化结构域将PIP2转化成磷脂酰肌醇3,4,5-三磷酸酯(phosphatidylinositol 3,4,5-triphosphate, PIP3)。Akt与位于质膜上的PIP3结合后,丝氨酸/苏氨酸激酶3-磷酸肌醇依赖性蛋白激酶-1(serine/threonine kinase 3-phosphoinositide-dependent protein kinase-1, PDK1)磷酸化Akt蛋白上的T308,导致部分Akt激活^[21]。mTOR或DNA依赖性蛋白激酶(DNA-dependent protein kinase, DNA-PK)磷酸化Akt羧基末端疏水基序中的S473刺激Akt完全活化^[22-23],完全活化的Akt介导转录、蛋白质合成、细胞增殖和凋亡。

TrkB参与Ras依赖性PI3K激活,衔接子IRS-1或IRS-2被TrkB磷酸化后,诱导PI3K激活^[24]。此外,研究表明,Akt在TrkB抑制细胞凋亡中起核心作用,药理抑制PI3K会阻断Akt依赖性信号传导,并显著干扰TrkB介导的细胞存活。

3.3 TrkB与JAK/STAT3信号通路

STAT3参与癌细胞的增殖、分化、侵袭、炎症和免疫功能。失调的Janus激酶(Janus kinase, JAK)/信号转导子和转录激活因子3(signal transducer and activator of transcription 3, STAT3)信号传导会引发以慢性炎症和纤维化为特征的疾病。

JAKs家族成员包括四种非受体酪氨酸激酶:JAK1、JAK2、JAK3和酪氨酸激酶2(tyrosine kinase 2, Tyk2),JAKs通过受体二聚化而活化。活化的JAKs催化受体酪氨酸磷酸化,并提供与信号转导子和转录激活子(signal transducers and activators of transcriptions, STATs)的SH2结构域相结合的停靠位点。STATs与受体相结合并被磷酸化后,活化的STAT以二聚体的形式入核,并与相应的靶基因启动子结合,启动细胞周期蛋白D1(cyclin D1, *CCND1*)、MCL1凋亡调节剂(MCL1 apoptosis regulator, *Mcl1*)、MYC原癌基因(MYC proto-oncogene, *c-myc*)、超大型B细胞淋巴瘤(the B-cell lymphoma-extra large, *Bcl-xL*)和血管内皮生长因子(vascular endothelial growth factor, *VEGF*)等靶基因的转录和表达^[25]。

研究表明,TrkB活化JAK2/STAT3通路的同时会导致转录因子扭转家族bHLH转录因子-1(twist family bHLH transcription factor-1, Twist-1)和扭转

家族bHLH转录因子-2(twist family bHLH transcription factor-2, Twist-2)表达上调^[26]。缺乏c-Src的TrkB直接与JAK2结合并抑制细胞因子信号传导抑制剂3(suppressor of cytokine signaling3, SOCS3)介导的JAK2降解,导致JAK2/STAT3激活和Twist-1上调。TrkB还可通过诱导IL-6分泌,激活JAK2/STAT3途径,导致上皮-间质转化(epithelial-mesenchymal transition, EMT)程序激活^[21]。此外,BDNF是肺癌细胞中STAT3的主要调节因子,阻断TrkB活性可降低STAT3磷酸化。

3.4 TrkB与PLC- γ 信号通路

哺乳动物磷脂酰肌醇特异性磷脂酶C(phospholipase C, PLC)包括 β 、 γ 和 δ 三种亚型,其中磷脂酶C γ (phospholipase C- γ , PLC γ)分为PLC γ 1和PLC γ 2两种亚型。

PLC- γ 1包含SH2、SH3以及PH结构域,PLC- γ 1的SH2结构域允许该酶与磷酸化的酪氨酸相互作用,例如Trks羧基端的酪氨酸^[27],TrkB的Y816位点发生磷酸化后会活化PLC γ 1,进而激活下游信号通路^[28],例如,BDNF通过TrkB/原癌基因酪氨酸蛋白激酶Src/PLC- γ 1信号通路刺激了皮质神经元的谷氨酸释放^[29]。

活化的磷脂酶C磷酸化PIP2并生成二酰基甘油(diacylglycerol, DAG)和肌醇1,4,5-三磷酸(inositol 1,4,5-trisphosphate, IP3),从而控制或调节细胞分化、凋亡和运动^[22]。一方面,二酰基甘油(diacyl glycerol, DAG)激活PKC后会通过CBM(CARMA1/Bcl10/MALT1)三元复合物活化TGF β 激活激酶1(TGF β -activated kinase 1, TAK1),进而激活I κ B激酶(I κ B kinase, IKK)和JNK,IKK能够活化NF- κ B,JNK则进一步活化激活蛋白1(activator protein 1, AP1)。另一方面,IP3会诱导细胞内Ca²⁺浓度增加,导致钙调蛋白(calmodulin, CaM)激酶活性增加,并使活化T细胞核因子(nuclear factor of activated T cells, NFAT)蛋白上的多个磷酸丝氨酸去磷酸化,导致NFAT核转运和激活^[30]。

4 TrkB与癌症

如图3所示,TrkB的异常表达与乳腺癌、肺癌、神经母细胞瘤、卵巢癌和结直肠癌的发生密切相关,该过程涉及JAK/STAT3、PI3K、PLC- γ 和MAPK等信号通路。

4.1 乳腺癌

乳腺癌是造成女性癌症患者死亡的主要原因,

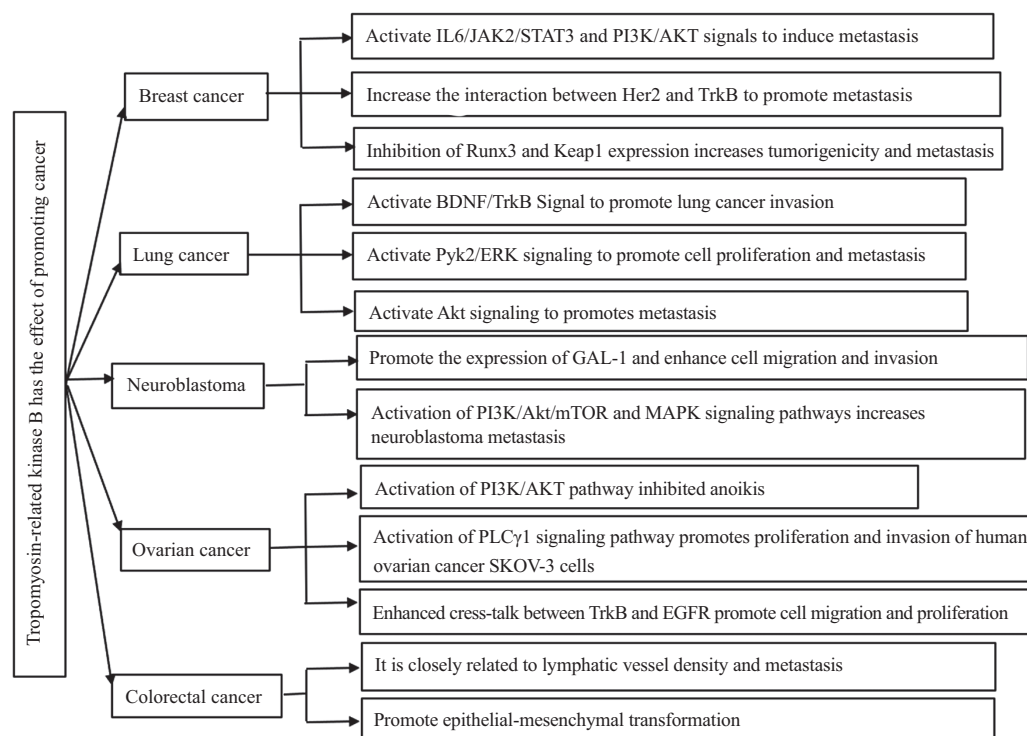


图3 TrkB在不同肿瘤中的分子机制及作用

Fig.3 Molecular mechanism and role of TrkB in different tumors

据估计, 2018年乳腺癌发病率高达11.6%, 发病人数约为210万, 死亡率为6.6%^[31], 因此, 深入研究乳腺癌的发生机制对改善乳腺癌的临床结局具有重大意义。

已有证据表明, TrkB对乳腺癌具有促进作用并且TrkB的过表达与乳腺癌患者的不良生存结果显著相关^[4,26,32]。对17个乳腺癌患者肿瘤组织中的TrkB进行检测, 发现14个组织中的*TrkB* mRNA水平显著升高, TrkB激活显著促进乳腺癌细胞的存活和迁移^[4]。此外, 神经营养蛋白受体TrkB也在乳腺癌细胞系中过表达, 并通过激活IL6/JAK2/STAT3和PI3K/AKT信号诱导转移潜能^[26]。由于人类表皮生长因子受体2(human epidermal growth factor receptor 2, Her2)与TrkB受体发生异源二聚化从而为乳腺癌细胞在大脑中提供了生存优势, 而敲低乳腺癌细胞中的TrkB会抑制细胞生长并减少其向大脑转移的频率, 因此, TrkB和Her2受体的双重抑制可能具有治疗潜力^[33]。

此外, TrkB对肿瘤抑制因子Runt相关转录因子3(Runt-related transcription factor 3, Runx3)和Kech样ECH相关蛋白1(Kelch-like ECH-associated protein 1, Keap1)的抑制作用也是乳腺癌发病机制中涉及的原因之一, 敲低TrkB或用TrkB抑制剂处理乳腺癌细胞,

Runx3和Keap1的表达会显著增加, 即TrkB通过抑制Runx3或Keap1在乳腺癌细胞的致瘤性和转移中起关键作用^[32]。

4.2 肺癌

肺癌是导致全世界癌症发生与死亡的主要原因, 据估计2018年约有180万人死于肺癌, 其死亡率高达18.4%^[31]。肺癌主要可分为非小细胞肺癌(non-small cell lung cancer, NSCLC)和小细胞肺癌(small cell lung cancer, SCLC), 肺癌因其转移能力强而臭名昭著, 因此, 研究肺癌的发生机制对其治疗具有重要意义。

BDNF/TrkB信号与肺癌的侵袭性和致瘤性密切相关, BDNF或TrkB的活化会促进肺癌的侵袭。利用免疫组织化学方法对58例SCLC患者和20例NSCLC患者肿瘤标本中的BDNF和TrkB蛋白进行检测, 发现BDNF和TrkB显著升高并与SCLC患者的预后不良有关, TrkB的激活是由分泌因子BDNF诱导的, BDNF会促进TrkB过表达的SCLC细胞发生迁移^[5]。进一步研究发现, 在肺癌细胞中BDNF通过激活STAT3增加BDNF的自分泌活性, 分泌的BDNF进而激活TrkB信号传导, TrkB和STAT3的激活有助于下游信号传导, 并促进人类非小细胞肺癌的增殖^[34]。此外, 研究

表明, BDNF/TrkB信号也可促进肺鳞状细胞癌(squamous cell carcinoma, SCC)的增殖、迁移和侵袭^[35]。

进一步研究表明, 活化的TrkB通过富含脯氨酸的酪氨酸激酶2(proline-rich tyrosine kinase 2, Pyk2)/细胞外信号调节激酶(extracellular signal-regulated kinase, ERK)途径促进腺癌人类肺泡基底上皮细胞增殖和转移, 并与非小细胞肺癌的发生有关^[36]。在胶质瘤相关癌基因同源物1(glioma-associated oncogene homolog 1, GLI1) siRNA转染的SBC-5细胞中, TrkB的表达显著升高, 单独敲低GLI1并不影响人类小细胞肺癌(SBC-5)细胞的侵袭性, 但TrkB和GLI1两者一起被敲除时, 会显著降低细胞侵袭性^[37]。此外, 活化的TrkB能够激活转移性肺癌细胞中的Akt信号传导, 敲低人肺癌细胞系中的TrkB显著降低了其在体内和体外的迁移和转移能力^[38]。

4.3 神经母细胞瘤

神经母细胞瘤是儿童中最致命的实体颅外肿瘤之一, 占有儿童期恶性肿瘤的8%~10%, 其5年生存率低于75%^[39]。研究表明, TrkB及其配体BDNF在50%至60%高风险神经母细胞瘤(neuroblastoma, NB)中表达^[40], TrkB的过表达或突变与神经母细胞瘤的高风险和不良预后相关。此外, 通过qRT-PCR和Western印迹分析发现, TrkB在神经母细胞瘤癌症干细胞中的表达升高^[41]。

TrkB激活导致NB细胞的致癌潜力增强。在表达TrkB的人类神经母细胞瘤中, BDNF以自分泌或旁分泌方式促进生存并诱导神经突生长, 全长TrkB转染细胞会导致细胞分化。更深入的研究发现, 在侵袭性神经母细胞瘤(neuroblastoma, NB)的临床前模型中, 半乳糖凝集素-1(galectin-1, Gal-1)会上调, Gal-1有助于增强细胞迁移和侵袭特性, 而Gal-1的表达与TrkB激活有关^[42]。此外, BDNF/TrkB通过PI3K/Akt/mTOR和MAPK信号途径增加神经母细胞瘤转移, 用PI3K、MAPK、Akt或mTOR的抑制剂进行预处理均可阻断BDNF/TrkB诱导的四环素调节表达TrkB的神经母细胞瘤细胞(tetracycline-regulated TrkB-expressing NB cell, TB3)的细胞迁移和侵袭, 并阻断BDNF/TrkB诱导的p-Akt、p-Erk和p-mTOR表达^[43]。另外, 研究表明, 新型pan-Trk抑制剂GNF-4256以剂量依赖性方式抑制TrkB磷酸化并抑制表达TrkB的NBs的体外生长, 即GNF-4256抑制TrkB可以增强NB化学疗法的疗效^[40]。另有研究表明, 新型结

构性TrkB抑制剂GZD2202会抑制BDNF介导的神经母细胞瘤模型中的增殖、转移和侵袭^[44]。

4.4 卵巢癌

卵巢癌是最致命的妇科恶性肿瘤, 其预后不良主要是由于癌细胞在疾病晚期出现转移所致。目前, 大量研究表明, BDNF/TrkB通路对卵巢癌发生至关重要, TrkB可作为卵巢癌的潜在治疗靶标^[2,45-48]。TrkB和BDNF在上皮性卵巢癌中过表达, 且与其预后不良有关^[45], TrkB可能通过激活卵巢癌细胞中的PI3K/AKT途径抑制失巢凋亡, 当TrkB被小干扰RNA沉默时PI3K/AKT途径会被抑制。进一步研究发现, BDNF通过激活TrkB/PLC γ 1信号通路促进人类卵巢癌SKOV-3细胞的增殖和侵袭^[46], 飞燕草素(delphinidin)会通过降低Akt活化从而抑制BDNF诱导的SKOV3卵巢癌细胞迁移和侵袭^[49]。

表皮生长因子受体(epidermal growth factor receptor, EGFR)和TrkB之间相互串扰增强了卵巢癌细胞的迁移和增殖, EGFR和TrkB激酶抑制剂会抑制EGF和BDNF诱导的TrkB和EGFR活化、Akt磷酸化、增殖和迁移^[47]。另外, miRNA的下调与肿瘤进展和化学抗性有关, miRNA-200c在卵巢癌细胞系和III期卵巢肿瘤中被下调, 低miR-200c与不良预后相关, 进一步研究发现, miR-200c可靶向TrkB, 恢复人类卵巢癌异种移植模型中的miR-200c水平会减少肿瘤形成和肿瘤负担^[48]。另外, 有研究发现BRCA1-IRIS能够激活BDNF/TrkB的自分泌信号传导环, 在正常的卵巢上皮细胞过表达BRCA1-IRIS后, 该细胞会在小鼠体内形成转移^[50]。

4.5 结直肠癌

据估计, 在全世界范围内, 2018年将有88万人死于结直肠癌, 其发病率高达6.1%, 死亡率在所有癌症中排名第二^[31], 因此, 结直肠癌的发病机制亟待研究人员去探索。

TrkB的过表达会促进结肠癌的发生。通过蛋白质印迹法检测了30例结肠癌和匹配的非肿瘤患者组织中TrkB的表达, 发现与非肿瘤对应物相比, TrkB在结肠肿瘤中上调, 并且TrkB的过表达与淋巴管密度和转移密切相关^[51]。且siRNA对TrkB的抑制作用会提高细胞的凋亡率, 同时减少增殖和侵袭细胞的数量^[51]。

厄洛替尼(erlotinib)减轻了C-X-C基序趋化配体8(C-X-C motif chemokine ligand 8, CXCL8)诱导的结

肠癌细胞转移, 并且抑制上皮-间质转化(epithelial-mesenchymal transition, EMT)的发生, 但TrkB的过表达会消除这些作用^[52], 西妥昔单抗在降低HT-29人结肠癌细胞增殖的同时会降低*BDNF*和*TrkB*的mRNA表达, 并且Trk抑制剂K252a会增强西妥昔单抗对细胞增殖的抑制作用^[53]。

5 问题与展望

TrkB的过表达与乳腺癌、肺癌、神经母细胞瘤、卵巢癌和结直肠癌的预后不良有关, 因此, TrkB参与恶性肿瘤的发生机制已成为当今的研究热点。

目前, 针对Trk家族的靶向药物层出不穷, 部分药物已被运用于临床试验中, 由于Trk家族在蛋白结构上具有显著的保守性, 所以部分研究人员认为, 开发pan-Trk抑制剂可能比产生具有特异性的抑制剂更加容易且高效。目前已知的运用于临床试验治疗中的Trk蛋白酪氨酸激酶抑制剂包括拉罗替尼(larotrectinib, LOXO-101)、恩替替尼(entrectinib)、梅瑞替尼(merestinib)、卡波替尼(cabozantinib), 这些化合物在多种癌症的临床试验中反应良好, 到目前为止, 上述四种化合物均已参与非小细胞肺癌的II期临床治疗试验, 此外, 拉罗替尼还被用于结直肠癌、卵巢癌的II期临床试验, 而恩替替尼则涉及神经母细胞瘤、乳腺癌、大肠癌、卵巢癌等多种癌症的II期临床试验^[54]。

但是由于癌症发生的机理非常复杂, 在一些癌症中, Trk家族成员的表达情况截然不同, 例如在神经母细胞瘤中, TrkA的表达标志着良好的预后^[55], 而高水平的TrkB则可导致肿瘤细胞的生长和侵袭, 所以更加精准的治疗能够更有效减轻药物对病人身体的潜在危害。因此, 在未来设计开发特异性更强的新型TrkB靶向药对提高特定癌症治疗效果并减少药物使用的副作用具有重要意义。

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