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PDZ连接激酶，又一新的原癌基因*

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摘要 PDZ连接激酶（PBK）是一种丝-苏氨酸激酶，属于丝裂原活化蛋白激酶激酶（MAPKK）家族成员. PBK能调控细胞周期进程，促进细胞增殖. 近年发现，其在乳腺癌、结肠癌、皮肤癌和前列腺癌等多种恶性肿瘤组织中均呈高表达，与多种癌症预后不良关联密切. PBK主要通过Wnt、PI3K/AKT/mTOR和MAPK等信号通路，调控肿瘤细胞有丝分裂，参与多种癌症的增殖、侵袭转移和耐药等，并受miR-216b-3p、miR-770-5p和miR-372-5p等多种microRNA调控. 提示PBK可能作为又一新的原癌基因，有望成为抑癌药物新的分子靶点.

关键词 PDZ连接激酶，原癌基因，增殖，侵袭转移，耐药，microRNA调控
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PDZ连接激酶（PDZ-binding-kinase，PBK），也称T-LAK细胞源蛋白激酶（T-LAK cell-originated protein kinase，TOPK），是一种丝/苏氨酸蛋白激酶（serine/threonine-protein kinase B-Raf，BRAF），属于丝裂原活化的细胞外信号调节激酶（mitogen-activated extracellular signal-regulated kinase，MEK）3/6相关的蛋白质家族，包含322个氨基酸，主要分布在细胞质与细胞核中[1-3]. 该蛋白质主要表达于具有高增殖潜力的组织，以及睾丸、胎盘、活化的T细胞和神经祖细胞等部位，而在分化程度高的组织和细胞中表达极低[4-6]. 近年发现[7-10]，PBK在乳腺癌、结肠癌、皮肤癌和前列腺癌等多种癌组织中表达显著升高，可通过Wnt、磷脂酰肌醇3激酶（phosphatidylinositol 3 kinase，PI3K）/蛋白激酶B（protein kinase B，PKB，即AKT）/哺乳动物雷帕霉素靶蛋白（mammalian target of rapamycin，mTOR）和有丝分裂原活化蛋白激酶（mitogen-activated protein kinase，MAPK）等信号通路，调控细胞周期素（cyclin）B1表达，加速癌细胞有丝分裂进程，促进癌细胞增殖，并且PBK也能上调叉头盒（forkhead box，FOX）M1、β联蛋白（β-catenin）、核因子κB（nuclear factor-κB，NF-κB）、基质金属蛋白酶（matrix metalloproteinase，MMP）2和9的表达，促使癌组织侵袭转移，而且PBK参与肿瘤耐药. 进一步的研究提示，上述作用可能与miR-216b-3p、miR-770-5p和miR-372-5p等多种microRNA调控关联. 因PBK的高表达往往预示多种癌症的预后不良[11-12]，有望成为一种新的原癌标志物，本文就近年PBK在促癌方面的作用和相关机制进行综述.

1 PBK在多种癌组织中表达显著增强

有报道[13-14]，作为早期预测原发性中枢神经系统淋巴瘤的预后因子，PBK不仅在儿童恶性淋巴瘤中异常高表达，而且在其他血液系统恶性肿瘤中的表达也显著升高，提示PBK与血液系统恶性肿瘤密切关联. 此外，PBK的这种过表达也存在于

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前列腺癌[15]. PBK能促进前列腺癌的侵袭转移[16]，并可影响该类患者对放疗的敏感性，关联放疗后复发，成为前列腺癌患者又一独立的预后因子. 另有文献显示[17]，结直肠癌患者中Kirsten鼠类肉瘤病毒癌基因（kirsten rat sarcoma viral oncogene，KRAS）和BRAF突变致使PBK高表达，也直接影响患者预后. 以此为基础，我们在线收集乳腺癌、结肠癌、胃癌、前列腺癌、食管鳞癌、肝癌、肺癌和膀胱癌的癌症基因组图谱（The Cancer Genome Atlas，TCGA）临床组织样本，筛选分析结果显示，相较于癌旁组织，PBK在上述癌组织的表达均显著增强（P<0.001，图1）. 提示PBK可能成为又一新的原癌基因，推进癌症进程.

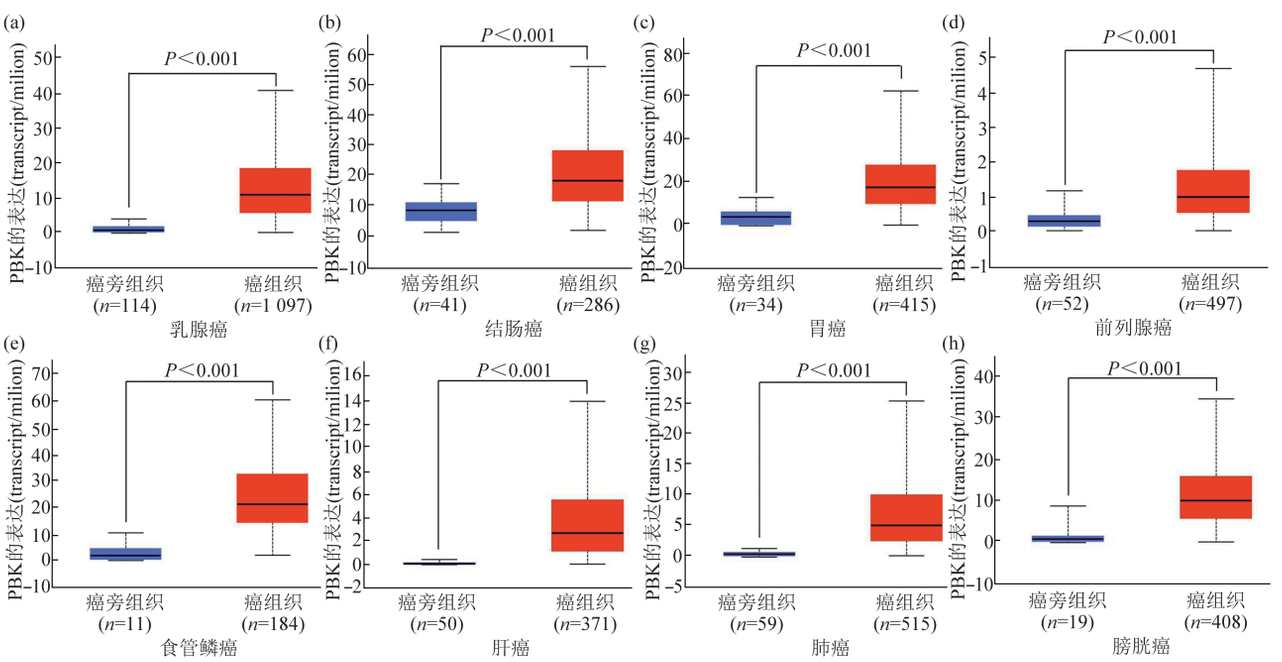

Fig. 1　Expression of PBK in different cancers from TCGA databases

图1　TCGA数据库中PBK在多种癌组织的表达

（a）PBK在乳腺癌的表达；（b）PBK在结肠癌的表达；（c）PBK在胃癌的表达；（d）PBK在前列腺癌的表达；（e）PBK在食管鳞癌的表达；（f）PBK在肝癌的表达；（g）PBK在肺癌的表达；（h）PBK在膀胱癌的表达.

2　PBK推进癌症进程

作为又一可能的原癌基因，PBK不仅在癌组织中表达显著升高，而且可通过促进癌细胞增殖、侵袭和转移，还能参与癌细胞耐药，从而多层次推进癌症进程.

2.1　PBK促进癌细胞增殖

PBK在正常的高分化组织中含量较低，主要在有丝分裂间期的胞质和胞核中有一定表达，能调控cyclinB1/细胞周期蛋白依赖性激酶1（cyclin-dependent kinase 1，CDK1）复合体[11, 18]，促进有丝分裂中的染色体分离，磷酸化锌指基序、亮氨酸-甘氨酸-天冬酰胺重复序列富集蛋白（Leu-Gly-Asn repeat-enriched protein，LGN）/G蛋白信号调节蛋白2（G-protein signaling modulator 2，GPSM2）和组蛋白3（histone 3，H3）等多种靶标，减少其对DNA的亲和力，均能调控细胞增殖[19].

研究发现[20-21]，脂多糖（lipopolysaccharide，LPS）和胰岛素样生长因子1（insulin-like growth factor，IGF-1）均可诱导多种癌细胞中PBK高表达，其他原癌基因如c-Myc通过细胞周期相关转录因子E2F1也可上调PBK的表达[22]，类似的细胞周期转录因子环磷腺苷效应元件结合蛋白1（cAMP response element binding protein 1，CREB1）则可直接绑定PBK启动子，刺激其转录[23]. PBK进而通过多条信号通路促进癌细胞增殖：PBK可通过上调p38 MAPK的活性促进乳腺癌细胞增殖[24]；

也可与抑癌基因p53相互作用，调控细胞周期蛋白p21，促进直肠癌细胞增殖；结直肠癌患者中EWS-FLI1融合蛋白可直接与尤文氏肉瘤中PBK的第一个内含子结合，诱导PBK高表达[25]. 进一步通过实验证实[3, 6]，磷酸化结肠癌HCT116细胞中PBK重要的Thr-9位点，诱导PBK过表达，能促进结肠癌的发生发展. PBK也可直接磷酸化激活皮肤癌中p53相关蛋白激酶（p53-related protein kinase，PRPK）[26]；PBK还可在Thr89和Ser209位点磷酸化Y盒结合蛋白1（Y-box binding protein 1，YB1），进而激活AKT/mTOR/核糖体40 S小亚基S6蛋白激酶（p70S6K）信号通路促进食管鳞癌细胞增殖[27-28]. 由于PBK位于AKT/mTOR/p70s6K和ERK信号通路的交叉点，因此PBK表达异常时，可直接调控AKT/mTOR/p70s6K和ERK等多条信号通路，在癌症的发生发展中发挥关键作用[27]. PBK也能通过其他途径促进癌细胞增殖. 如在肝细胞癌中过表达FOXM1可调控PBK，再经FOXM1/PBK/β-catenin信号通路促进癌细胞增殖[29]. 另有文献指出[12]，敲低PBK后结肠癌HCT116细胞中p21表达上调，抑制结肠癌细胞增殖；下调PBK或p53表达时，可抑制非小细胞肺癌增殖[30]；阻断PBK或能促进肾癌细胞生长的母体胚胎亮氨酸拉链激酶（maternal embryo leucine zipper kinase，MELK）通路，均能下调FOXM1，抑制肾癌细胞增殖[31]. 而敲低或过表达FOXM1又能调控PBK和MELK mRNA的表达. 进一步研究提示[32-33]，Polo样激酶（polo-like kinase，PLK）1与PBK在肝癌SMMC-7721细胞有丝分裂的中后期和胞质分裂期共定位，PLK1能通过PBK调控cyclinB1的稳定性，参与癌细胞的有丝分裂，影响细胞增殖；PBK还能与PLK1直接作用，共同参与肝癌细胞有丝分裂进程. 在乳腺癌MDA-MB-231细胞中[34]，转录共激活因子Yes相关蛋白（Yes-associated protein，YAP）也可诱导PBK蛋白高表达，而YAP介导的信号转录还可激活PBK的功能，从而与癌增殖密切相关. 上述研究通过明确PBK促进癌细胞增殖涉及的多条信号通路，为抑制癌症发生发展提供了新的治疗思路.

2.2 PBK促使多种癌症侵袭转移

高表达PBK可经PI3K /磷酸酶与张力素同源物（phosphatase and tensin homolog，PTEN）/AKT途径促进肺癌侵袭转移[35]，PTEN与AKT呈负相关. PBK虽不能直接调控PTEN，但可通过刺激PTEN的蛋白酶体调控其蛋白质稳定性，下调PTEN表达，再经PI3K/AKT促进癌细胞迁移. 敲低PBK则通过活化p53以依赖TP53突变方式抑制胃癌细胞增殖，并以TP53突变非依赖性方式抑制PTEN诱导的侵袭转移[36-37]. 且FOXM1被证实可通过调控PBK启动子的活性控制其表达，在过表达PBK的癌细胞中，β-catenin靶向增强MMP7、cyclinD1和T细胞特异性转录因子1（transcription factor 1，TCF1）的活性，促进肝细胞癌侵袭转移. 不仅肝细胞癌患者组织中存在PBK与核β-catenin共定位，前列腺癌的结果也显示β-catenin的核定位与PBK高表达密切相关. PBK通过上调β-catenin/TCF/淋巴增强因子1（1ymphoid enhancer 1，LEF1），调控MMP2和MMP9的启动子活性，促进前列腺癌细胞的侵袭迁移[38]. 并且，在探讨雄激素受体（androgen receptor，AR）能否调节PBK表达的同时，发现在PBK的启动子区域中没有共有的AR应答元件，即使用二氢睾酮或AR信号传导的有效抑制剂恩杂鲁胺处理VCaP和22Rv1等前列腺癌细胞，仍对PBK表达没有影响. 之后其他研究组证实[39]，在正常前列腺上皮细胞中，AR活性受PBK水平控制，维持细胞分化、存活和生长功能，当过表达PBK时，AR活性明显增强，促进侵袭性前列腺癌（prostate cancer，PrCa）的发生发展，加速PrCa细胞迁移. 同时，过表达PBK还可导致AR稳定性增强和AR信号传导增加，进而产生更多的PBK，从而过度激活AR和PBK之间的前馈刺激环. PBK在PrCa中显著上调，体内外实验证实PBK为AR调节蛋白，其表达受雄激素直接调节，促进PrCa转移.

现已证实PBK促使多种癌症侵袭转移还存在着其他相关信号通路，如：PBK在Ser250处磷酸化其潜在新底物PRPK，促进结直肠癌小鼠肝转移的发生[40]；而在乳腺癌MCF7细胞中[41]，LPS/TLR4信号传导通过增强PBK的表达和活性，诱导NF-κB活化，从而上调MMP9的表达，降解细胞外基质（extracellular matrix，ECM），激活Toll样受体4（Toll-like receptor 4，TLR4），从而增强MCF7乳腺癌细胞的侵袭性，促进乳腺癌侵袭转移. 沉默PBK则可抑制LPS诱导的乳腺癌细胞中MMP9蛋白表达和启动子活性，下调LPS/TLR4信号，降低癌细胞迁移能力. 因此，PBK成为LPS/TLR4信号

促进乳腺癌侵袭过程的关键. PBK多条信号通路的研究结果更加丰富了癌症侵袭转移的分子机制，为抑制癌症侵袭转移提供了更多治疗方法.

2.3　PBK参与癌细胞耐药

研究发现[42-44]，PBK在癌症放射和化学治疗中也出现异常表达，并可能与癌细胞耐药的发生密切关联. 一方面，抑制PBK的作用可恢复细胞对凋亡信号传导和复制控制机制的反应；有文献显示[42]，PBK过表达增强了癌细胞对肿瘤坏死因子相关凋亡诱导配体诱导的凋亡抵抗力. 与对照细胞相比，稳定沉降PBK的表达可显著增加相关凋亡诱导配体介导的NF-κB活性，促进人宫颈癌HeLa细胞的凋亡，降低HeLa细胞对化疗药的耐药出现. 最近研究发现[43]，过表达PBK通过在高度浆液型卵巢癌中靶向亲嗜性病毒整合位点1（ecotropic viral integration site-1，EVI-1）诱导自噬，增强卵巢癌细胞对顺铂耐药. 当PBK抑制剂OTS514作用后，在体内和体外均增强了对顺铂治疗的反应性. 肺癌和皮肤癌的放、化疗中[44]，高表达PBK磷酸化c-Jun促进皮肤癌对表皮生长因子受体酪氨酸激酶抑制剂（epidermal growth factor receptor tyrosine kinase inhibitors，EGFR-TKIs）呈现耐药. 另一方面，PBK通过使癌细胞对DNA损伤剂敏感而克服致癌化学抗性. 如过表达PBK影响表皮生长因子受体（epidermal growth factor receptor，EGFR）抑制剂吉非替尼治疗非小细胞肺癌引起的耐药，提示靶向PBK应与吉非替尼同时应用于非小细胞肺癌的治疗[45]. 存在KRAS或BRAF突变和对EGFR耐药的结肠癌患者，高表达PBK参与耐药，抑制PBK的靶向治疗可以使30%~40%的结肠癌患者获益[46]. 现有研究提示，在癌症患者放化疗时，PBK抑制剂和临床药品协同给药能降低患者对化疗药的耐药性，增强临床用药反应性，有利于癌症患者治疗.

3　PBK受多种microRNA调控

近年研究还发现[47-49]，PBK在上述癌症中增殖、侵袭转移等的作用受多种microRNA调控. 有研究表明[47]，PBK可能是miR-216b-3p的直接靶基因，可能由miR-216b-3p负调控. 当miR-216b-3p表达上调时能抑制PBK的表达减慢GLC-82细胞增殖；进一步研究发现，miR-216b-3p可能是通过抑制PBK信号通路，增强p53和p21的表达水平，并降低p-p38相关基因表达来产生抗肿瘤作用. 研究还发现[48]，PBK可以受miR-770-5p调控. 将miR-770-5p转染至MCF7细胞，明显降低了PBK mRNA和蛋白质表达. miR-770-5p转染的HCT116人结肠癌细胞中，PBK mRNA和蛋白质水平也明显降低. 进一步探究转染miR-770-5p细胞接种的异种移植瘤小鼠模型中PBK的表达，结果显示移植瘤组织中PBK表达明显减弱. miR-770-5p主要是通过调节PBK信号通路DDR、ATM和ATR等相关基因的表达使癌症对辐射敏感抑制癌症发展. 而且PBK的3'-UTR与miR-372之间存在理论互补序列，PBK是miR-372的潜在靶基因[49]. 在鼻咽癌NPC细胞中，miR-372过表达导致PBK和Bcl-2表达明显下调，显著抑制Akt磷酸化程度，进而促进p53、Caspase-3和Bax表达上调. 而miR-372抑制剂作用的NPC细胞组趋势则恰好相反. 证明miR-372通过激活PBK依赖的p53信号通路，抑制鼻咽癌侵袭转移. 因此，我们进一步使用公共数据库TargetScan（http://www.targetscan.org/vert_72/）筛选以PBK为靶标的microRNA，结果证实（图2），人miR-216b-3p、miR-770-5p和miR-372-5p的3'UTR均存在能与PBK匹配的结合序列，说明PBK可作为miR-216b-3p、miR-770-5p和miR-372-5p的候选靶标.

microRNA (targeting PBK)	Binding site	Binding sequence to miRNA (target prediction)
miR-216b-3p	16–22	5′ …UGAUCAUCUCAGCUG - - AAGUGUGG… 3′ AUCUUAGAGAUGCCCAUUCACACA
miR-770-5p	185–191	5′ …UAAGCACUUGGAAUUGUACUGGG… 3′ ACCGGGACUGUGCACCAUGACCU
miR-372-5p	99–105	5′ …CUCUAAAAUUGGCAUAUUUGAGG… 3′ UCUUAUCACGAGGUGUAAACUCC

Fig. 2　Targetscan predicts targeted microRNA binding PBK

图2　Targetscan预测靶向结合PBK的microRNA

4　结论与展望

综上，PBK/TOPK通过复杂的信号通路参与癌症的增殖、侵袭转移和耐药等过程，并受多种microRNA调控（图3）. 但是对PBK的研究，尚有待进一步证实. 过表达多种癌症中PBK能促进肿瘤细胞持续生长、调控细胞凋亡、增加侵袭能力和转移性生长的多种通路的激活，且PBK在一些癌症类型中参与的信号通路已有雏形. 然而，PBK的具体促癌机制和在各类癌症中信号通路的具体分子机制并不明确. 目前尚不清楚参与这些细胞通路是PBK生理作用的一部分，还是通过有丝分裂使抑癌蛋白失活以促进癌症进展，或在各种癌症类型和细胞系中更高水平表达，混杂磷酸化等非生理学靶标. PBK过度表达的原因不明，在不同的癌症组织中的作用差异性则有待深入研究，但能肯定的是PBK能通过一系列分子靶标来促成肿瘤不同方面的表型. 尤其是靶向治疗概念的提出，PBK抑制剂的发现和开发，让其具备成为肿瘤特异性治疗新型靶标的巨大潜力.

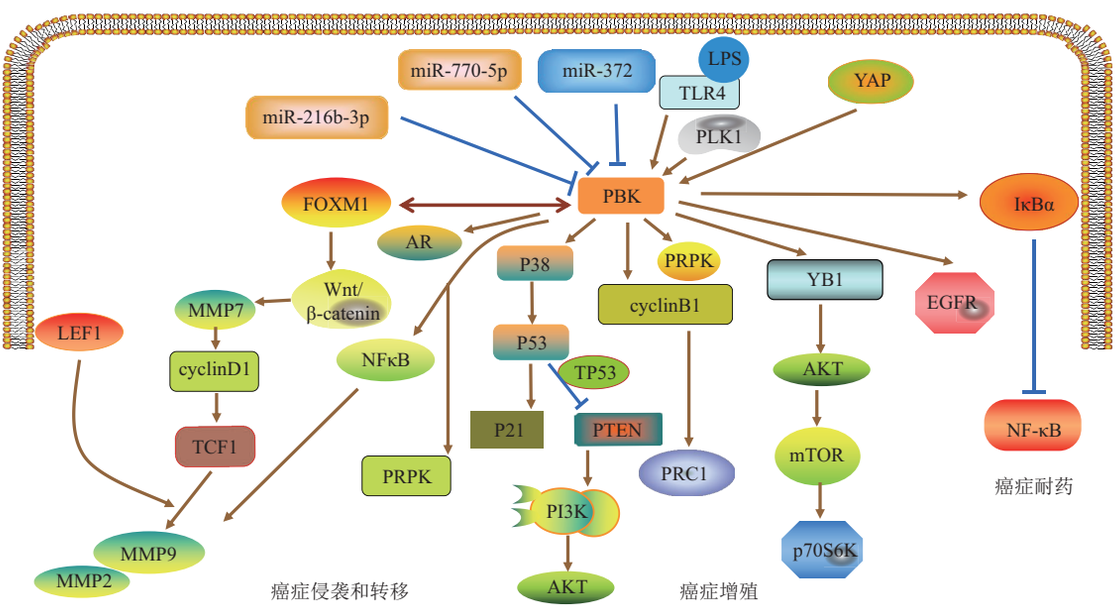

Fig. 3　Role and mechanism of PBK involved in different cancers

图3　PBK参与癌症的作用及其机制

参　考　文　献

[1] Abe Y, Matsumoto S, Kito K, *et al*. Cloning and expression of a novel MAPKK-like protein kinase, lymphokine-activated killer T-cell-originated protein kinase, specifically expressed in the testis and activated lymphoid cells. J Biol Chem, 2000, **275**(28): 21525-21531

[2] Stefka A T, Johnson D, Rosebeck S. Potent anti-myeloma activity of the TOPK inhibitor OTS514 in pre-clinical models. Cancer Med, 2020, **9**(1): 324-334

[3] Matsumoto S, Abe Y, Fujibuchi T, *et al*. Characterization of a MAPKK-like protein kinase TOPK. Biochem Biophys Res Commun, 2004, **325**(3): 997-1004

[4] Chen D D, Cox J, Annam J, *et al*. LIN28B promotes neuroblastoma metastasis and regulates PDZ binding kinase. Neoplasia, 2020, **22**(6): 231-241

[5] Dougherty J D, Garcia A D R, Nakano I, *et al*. PBK/TOPK, a proliferating neural progenitor-specific mitogen-activated protein kinase kinase. J Neurosci, 2005, **25**(46): 10773-10785

[6] Fujibuchi T, Abe Y, Takeuchi T, *et al*. Expression and phosphorylation of TOPK during spermatogenesis. Dev Growth Differ, 2005, **47**(9): 637-644

[7] Zhao R, Choi B Y, Wei L X, *et al*. Acetylshikonin suppressed growth of colorectal tumour tissue and cells by inhibiting the intracellular kinase, T-lymphokine-activated killer cell-originated protein kinase. Br J Pharmacol, 2020, **177**(10): 2303-2319

[8] Ohashi T, Komatsu S, Ichikawa D, *et al*. Overexpression of PBK/TOPK contributes to tumor development and poor outcome of esophageal squamous cell carcinoma. Anticancer Res, 2016, **36**(12): 6457-6466

[9] Zhang Y, Yang X J, Wang R, *et al*. Prognostic value of PDZ-binding kinase/T-LAK cell-originated protein kinase (PBK/TOPK) in patients with cancer. J Cancer, 2019, **10**(1): 131-137

[10] Ohashi T, Komatsu S, Ichikawa D, *et al*. Overexpression of PBK/TOPK relates to tumour malignant potential and poor outcome of gastric carcinoma. Br J Cancer, 2017, **116**(2): 218-226

[11] Mao P, Bao G, Wang Y C, *et al*. PDZ-binding kinase-dependent transcriptional regulation of CCNB2 promotes tumorigenesis and radio-resistance in glioblastoma. Transl Oncol, 2020, **13**(2): 287-294

[12] Gao T T, Hu Q F, Hu X, *et al*. Novel selective TOPK inhibitor SKLB-C05 inhibits colorectal carcinoma growth and metastasis. Cancer Lett, 2019, **445**: 11-23

[13] Simons-Evelyn M, Bailey-Dell K, Toretsky J A, *et al*. PBK/TOPK is a novel mitotic kinase which is upregulated in burkitt's lymphoma and other highly proliferative malignant cells. Blood Cells Mol Dis, 2001, **27**(5): 825-829

[14] Ishikawa C, Senba M, Mori N. Mitotic kinase PBK/TOPK as a therapeutic target for adult T-cell leukemia/lymphoma. Int J Oncol, 2018, **53**(2): 801-814

[15] Chen J H, Liang Y X, He H C, *et al*. Overexpression of PDZ-binding kinase confers malignant phenotype in prostate cancer *via* the regulation of E2F1. Int J Biol Macromol, 2015, **81**: 615-623

[16] Sun H M, Zhang L, Shi C H , *et al*. TOPK is highly expressed in circulating tumor cells, enabling metastasis of prostate cancer. Oncotarget, 2015, **6**(14): 12392-12404

[17] Su T C, Chen C Y, Tsai W C, *et al*. Cytoplasmic, nuclear, and total PBK/TOPK expression is associated with prognosis in colorectal cancer patients: a retrospective analysis based on immunohistochemistry stain of tissue microarrays. Plos One, 2018, **13**(10): e0204866

[18] Rizkallah R, Alexander K E, Hurt M M. Global mitotic phosphorylation of C2H2 zinc finger protein linker peptides. Cell Cycle, 2011, **10**(19): 3327-3336

[19] Fukukawa C, Ueda K, Nishidate T, *et al*. Critical roles of LGN/GPSM2 phosphorylation by PBK/TOPK in cell division of breast cancer cells. Genes Chromosomes Cancer, 2010, **49**(10): 861-872

[20] Seol M A, Park J H, Jeong J H, *et al*. Role of TOPK in lipopolysaccharide-induced breast cancer cell migration and invasion. Oncotarget, 2017, **8**(25): 40190-40203

[21] Nandi A, Tidwell M, Karp J, *et al*. Protein expression of PDZ-binding kinase is up-regulated in hematologic malignancies and strongly down-regulated during terminal differentiation of HL-60 leukemic cells. Blood Cells Mol Dis, 2004, **32**(1): 240-245

[22] Hu F, Gartenhaus R B, Zhao X F, *et al*. c-Myc and E2F1 drive PBK/TOPK expression in high-grade malignant lymphomas. Leuk Res, 2013, **37**(4): 447-454

[23] Nandi A K, Rapoport A P. Expression of PDZ-binding kinase (PBK) is regulated by cell cycle-specific transcription factors E2F and CREB/ATF. Leuk Res, 2006, **30**(4): 437-447

[24] Aksamitiene E, Kholodenko B N, Kolch W, *et al*. PI3K/Akt-sensitive MEK-independent compensatory circuit of ERK activation in ER-positive PI3K-mutant T47D breast cancer cells. Cell Signal, 2010, **22**(9): 1369-1378

[25] Herrero-Martin D, Osuna D, Ordóñez J L, *et al*. Stable interference of EWS-FLI1 in an Ewing sarcoma cell line impairs IGF-1/IGF-1R signalling and reveals TOPK as a new target. Br J Cancer, 2009, **101**(1): 80-90

[26] Lei B, Liu S G, Qi W J, *et al*. PBK/TOPK expression in non-small-cell lung cancer: its correlation and prognostic significance with Ki67 and p53 expression. Histopathology, 2013, **63**(5): 696-703

[27] Yang L, Liu Y Q, Wang M, *et al*. Celastrus orbiculatus extract triggers apoptosis and autophagy *via* PI3K/Akt/mTOR inhibition in human colorectal cancer cells. Oncol Lett, 2016, **12**(5): 3771-3778

[28] Hao Y J, Huang J W, Ma Y, *et al*. Asiatic acid inhibits proliferation, migration and induces apoptosis by regulating Pdcd4 *via* the PI3K/Akt/mTOR/p70S6K signaling pathway in human colon carcinoma cells. Oncol Lett, 2018, **15**(6): 8223-8230

[29] Yang Y F, Pan Y H, Cao Y, *et al*. PDZ binding kinase, regulated by FoxM1, enhances malignant phenotype *via* activation of β-catenin signaling in hepatocellular carcinoma. Oncotarget, 2017, **8**(29): 47195-47205

[30] Roh E, Lee M H, Zykova T A, *et al*. Targeting PRPK and TOPK for skin cancer prevention and therapy. Oncogene, 2018, **37**(42): 5633-5647

[31] Kato T, Inoue H, Imoto S, *et al*. Oncogenic roles of TOPK and MELK, and effective growth suppression by small molecular inhibitors in kidney cancer cells. Oncotarget, 2016, **7**(14): 17652-17664

[32] Agarwal R, Narayan J, Bhattacharyya A, *et al*. Gene expression profiling, pathway analysis and subtype classification reveal molecular heterogeneity in hepatocellular carcinoma and suggest subtype specific therapeutic targets. Cancer Genet, 2017: 37-51

[33] Chen F, Li R W, Wang C J, *et al*. T-LAK cell-originated protein kinase is essential for the proliferation of hepatocellular carcinoma SMMC-7721 cells. Cell Biochem Funct, 2013, **31**(8): 736-742

[34] Dou X Y, Wei J, Sun A Q, *et al*. PBK/TOPK mediates geranylgeranylation signaling for breast cancer cell proliferation. Cancer Cell Int, 2015, **15**: 27

[35] Shih M C, Chen J Y, Wu Y C, *et al*. TOPK/PBK promotes cell migration *via* modulation of the PI3K/PTEN/AKT pathway and is associated with poor prognosis in lung cancer. Oncogene, 2012, **31**(19): 2389-2400

[36] Lei B, Qi W J, Zhao Y F, *et al*. PBK/TOPK expression correlates with mutant p53 and affects patients' prognosis and cell proliferation and viability in lung adenocarcinoma. Hum Pathol, 2015, **46**(2): 217-224

[37] Zykova T, Zhu F, Wang L, *et al*. Targeting PRPK function blocks colon cancer metastasis. Mol Cancer Ther, 2018, **17**(5): 1101-1113

[38] Brown-Clay J D, Shenoy D N, Timofeeva O, *et al*. PBK/TOPK enhances aggressive phenotype in prostate cancer *via* β-catenin-TCF/LEF-mediated matrix metalloproteinases production and invasion. Oncotarget, 2015, **6**(17): 15594-15609

[39] Warren A Y, Massie C E, Watt K, *et al*. A reciprocal feedback between the PDZ binding kinase and androgen receptor drives prostate cancer. Oncogene, 2019, **38**(7): 1136-1150

[40] Zykova T A, Zhu F, Wang L, *et al*. The T-LAK cell-originated protein kinase signal pathway promotes colorectal cancer metastasis. EBioMedicine, 2017, **18**: 73-82

[41] Park J H, Jeong Y J, Won H K, *et al*. Activation of TOPK by lipopolysaccharide promotes induction of inducible nitric oxide synthase through NF-kappa B activity in leukemia cells. Cell Signal, 2014, **26**(5): 849-856

[42] Kwon H R, Lee K W, Dong Z G, *et al*. Requirement of T-lymphokine-activated killer cell-originated protein kinase for TRAIL resistance of human HeLa cervical cancer cells. Biochem Biophys Res Commun, 2010, **391**(1): 830-834

[43] Ma H L, Li Y W, Wang X X, *et al*. PBK, targeted by EVI1, promotes metastasis and confers cisplatin resistance through inducing autophagy in high-grade serous ovarian carcinoma. Cell Death Dis, 2019, **10**(3): 166

[44] Oh S M, Zhu F, Cho Y Y, *et al*. T-lymphokine-activated killer cell-originated protein kinase functions as a positive regulator of c-Jun-NH2-kinase 1 signaling and H-Ras-induced cell transformation. Cancer Research, 2007, **67**(11): 5186-5194

[45] Li Y, Yang Z W, Li W J, *et al*. TOPK promotes lung cancer resistance to EGFR tyrosine kinase inhibitors by phosphorylating and activating c-Jun. Oncotarget, 2016, **7**(6): 6748-6764

[46] Zlobec I, Molinari F, Kovac M, *et al*. Prognostic and predictive value of TOPK stratified by KRAS and BRAF gene alterations in sporadic, hereditary and metastatic colorectal cancer patients. Br J Cancer, 2010, **102**(1): 151-161

[47] Chai Y Q, Xue H J, Wu Y M, *et al*. MicroRNA-216b-3p inhibits lung adenocarcinoma cell growth *via* regulating PDZ binding kinase/T-LAK-cell-originated protein kinase. Exp Ther Med, 2018, **15**(6): 4822-4828

[48] Lee H C, Her N G, Kang D, *et al*. Radiation-inducible miR-770-5p sensitizes tumors to radiation through direct targeting of PDZ-binding kinase. Cell Death Dis, 2017, **8**(3): e2693

[49] Wang Z, Mao J W, Liu G Y, *et al*. MicroRNA-372 enhances radiosensitivity while inhibiting cell invasion and metastasis in nasopharyngeal carcinoma through activating the PBK-dependent p53 signaling pathway. Cancer Med, 2019, **8**(2): 712-728

PDZ-binding Kinase，a New Proto-oncogene*

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Abstract　PDZ-binding kinase (PBK), a member of the mitogen-activated protein kinase kinase (MAPKK) family, is a silk-threonine kinase containing 322 amino acids. Its protein is mainly expressed in the tissues with high proliferation potential, testis, placenta, activated T cells and neural progenitor cells while extremely low in the tissues and cells with a high degree of differentiation. In recent years, PBK expression has been found significantly enhanced in a variety of malignant tumor such as breast, colon, liver, lung, prostate, esophageal cancer, and so on, closely related to poor prognosis of the cancers mentioned above. Further studies have pointed out that PBK can also promote the proliferation, invasion and metastasis of many cancer cells through a series of complex signaling pathways including Wnt, PI3K/AKT/mTOR, MAPK, FOXM1, nuclear factor-κB and matrix metalloproteinase (MMP), and participate in drug resistance. Moreover, the role of PBK has been confirmed controlled by different microRNA like miR-216b-3p, miR-770-5p and miR-372-5p in the cancers. All above suggest that PBK might be a new proto-oncogene, which is expected to become a new molecular target for tumor suppressor drugs.

Key words　PDZ-binding kinase (PBK), proto-oncogene, proliferation, invasion and metastasis, drug resistance, controlled by microRNA
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