综　述　　肿瘤免疫治疗：机制、靶向及治疗策略专题

NF-κB信号通路在胰腺癌耐药机制中的研究进展

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[摘要]　胰腺癌具有明显的耐药性，尽管治疗方案不断更新，患者5年生存率仍较低。核因子κB(NF-κB)信号通路在肿瘤中常发生突变，被认为是引发肿瘤耐药的关键因素。多项研究发现，靶向NF-κB信号转导的策略在胰腺癌治疗中显示出了令人鼓舞的结果。因此，探索NF-κB信号通路与胰腺癌耐药之间的关系已成为胰腺癌治疗相关的研究热点。本文总结了NF-κB信号通路与肿瘤耐药的关系及其在胰腺癌治疗中作用的研究进展，并从化疗和免疫治疗两个角度阐述了NF-κB信号通路介导胰腺癌耐药的具体机制，旨在为胰腺癌的治疗及未来的研究提供参考。

[关键词]　胰腺癌；核因子κB；耐药性；化学治疗；免疫治疗

Research progress on the role of NF-κB signaling pathway in drug resistance mechanisms of pancreatic cancer

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[**Abstract**]　Pancreatic cancer is characterized by significant drug resistance, and despite continuous advancements in treatment regimens, the 5-year survival rate of patients remains low. The nuclear factor-κB (NF-κB) signaling pathway, frequently mutated in tumors, has been identified as a critical factor in triggering drug resistance. Multiple studies have demonstrated that strategies targeting NF-κB signaling transduction exhibit promising outcomes in pancreatic cancer treatment. Therefore, exploring the relationship between the NF-κB signaling pathway and drug resistance in pancreatic cancer has become a research hotspot in pancreatic cancer treatment. This review summarizes recent advances in the relationship between NF-κB signaling pathway and tumor drug resistance, as well as its role in pancreatic cancer treatment. Specifically, the mechanisms by which the NF-κB signaling pathway mediates drug resistance in pancreatic cancer are elaborated from two perspectives: chemotherapy and immunotherapy, aiming to provide insights for pancreatic cancer treatment and future research.

[**Key words**]　pancreatic cancer; nuclear factor-κB; resistance; chemotherapy; immunotherapy

胰腺癌是致命的恶性肿瘤之一，其中90%为胰腺导管癌(pancreatic ductal adenocarcinoma，PDAC)，5年生存率低于11%[1]。手术切除是胰腺癌的根治性手段，但由于其临床表现隐匿且早期诊断手段不完善，发现时多已处于晚期，仅15%~20%的患者适合手术治疗[2]。目前，化疗与免疫治疗在胰腺癌患者中得到了广泛应用，但药物长期使用易导致耐药，缺乏持续有效的治疗反应和生存获益。因此，寻找

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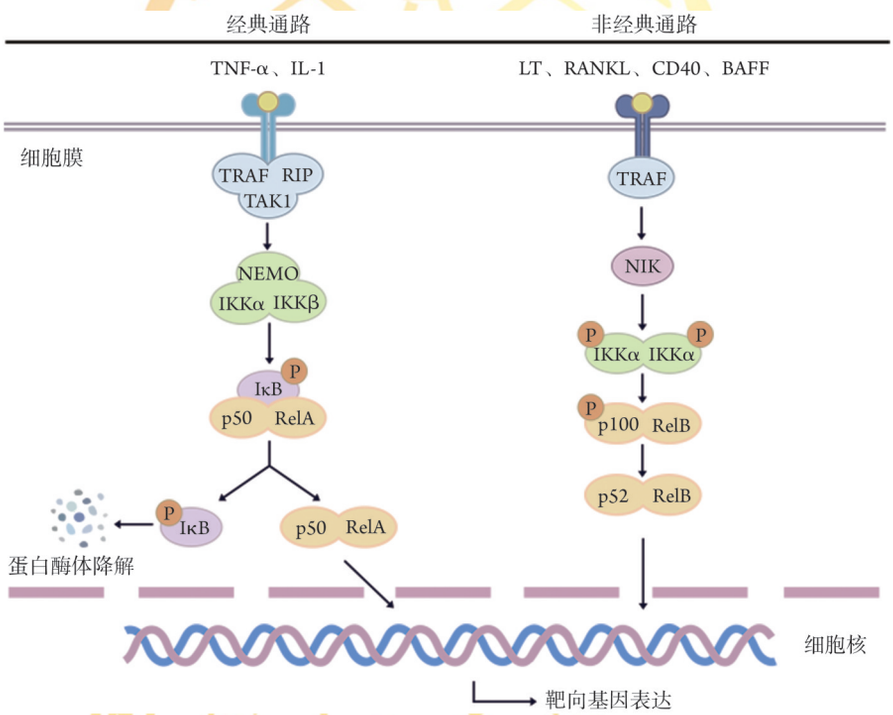
新的靶点以及更深入地了解其作用机制对提高疗效和改善患者预后具有重要意义[3]。

核因子-κB(nuclear factor-κB，NF-κB)信号通路在胰腺癌细胞系、胰腺癌动物模型和人类胰腺癌标本中均处于持续激活的异常状态，参与胰腺癌的进展并与治疗耐药密切相关。NF-κB的激活不仅可通过阻碍药物的递送和摄取、抑制肿瘤细胞凋亡等途径加剧胰腺癌化疗耐药，还可促进程序性死亡配体-1(programmed death-ligand 1，PD-L1)的表达和免疫抑制性肿瘤微环境(tumor microenvironment，TME)的形成，导致胰腺癌免疫治疗效果不佳。本文总结NF-κB信号通路在肿瘤耐药和胰腺癌治疗中的作用，重点介绍NF-κB信号通路介导胰腺癌化疗耐药(主要是吉西他滨耐药)和免疫治疗耐药机制的研究进展，旨在为胰腺癌的治疗和未来的研究提供参考。

1 NF-κB信号通路与肿瘤耐药的关系

1.1 NF-κB信号通路的组成及调控 NF-κB蛋白家族包括5个成员：RelA(p65)、RelB、c-Rel、p50(p105前体)及p52(p100前体)[4]。NF-κB信号通路由配体、受体、受体近端信号接头蛋白、κB抑制因子激酶(inhibitor of kappa B kinase，IKK)复合物、NF-κB抑制蛋白(inhibitor of NF-κB，IκB)和NF-κB二聚体共同构成。生理状态下，NF-κB在细胞质中与IκB结合保持非活化状态。当细胞受到各种配体刺激时，IKK复合物被激活，导致IκB蛋白泛素化降解。随后，NF-κB二聚体得到释放并易位到细胞核，促进靶基因转录[5]。如图1所示。



TNF-α. 肿瘤坏死因子-α；IL-1. 白细胞介素-1；TRAF. 肿瘤坏死因子受体相关因子；TAK1. 转化生长因子-β激活激酶1；RIP. 受体相互作用蛋白；NEMO. NF-κB必须调节剂；IKK. κB抑制因子激酶；IκB. NF-κB抑制蛋白；LT. 淋巴毒素；RANKL. 破骨细胞分化因子；CD40. 簇分化抗原40；BAFF. B细胞激活因子；NIK. NF-κB诱导激酶；P. 磷酸化

图1 NF-κB信号通路的激活

Fig.1 Activation of the NF-κB signaling pathway

1.2 NF-κB信号激活在肿瘤耐药中的作用 肿瘤耐药性限制了多种治疗方法的疗效，是肿瘤学领域的重要挑战。越来越多的研究表明，NF-κB信号通路激活可促进多种肿瘤对治疗耐药。在焦亡巨噬细胞和肿瘤细胞共培养模型中，焦亡巨噬细胞可分泌白细胞介素-18(interleukin-18，IL-18)上调Toll样受体4(Toll-like receptor 4，TLR4)的表达，激活NF-κB及下游的抗凋亡信号，导致T细胞淋巴瘤恶性增殖及化疗耐药[6]。在三阴性乳腺癌中，脑选择性蛋白激酶2可介导磷脂酰肌醇结合网格蛋白组装蛋白相互作用有丝分裂调节因子(phosphatidylinositol binding clathrin assembly protein interacting mitotic regulator，PIMREG)在S16位点的磷酸化，促进NF-κB信号激活，造成顺铂的治疗效率降低[7]。脂肪酸合酶可通过磷酸化IKKα和IκBα激活NF-κB/信号转导及转录激活因子3(signal transducer and activator of transcription 3，STAT3)信号转导，促进肿瘤细胞中谷胱甘肽过氧化物酶4的表达，从而抑制铁死亡，致使弥漫性B细胞

淋巴瘤对阿霉素耐药[8]。肿瘤坏死因子(tumor necrosis factor，TNF)超家族受体调节基因*RIPK1*可通过NF-κB通路介导TNF信号转导，促进肿瘤细胞免疫抑制性化学趋化因子的产生，这不仅能提高肿瘤细胞的存活率，还可减少T细胞和自然杀伤细胞的浸润，导致免疫治疗耐药[9]。

2 NF-κB信号通路在胰腺癌治疗中的作用

2.1 NF-κB信号通路与胰腺癌治疗的相关性 多项研究指出，NF-κB信号的激活可促进胰腺癌的进展。在PDAC标本中过表达的白细胞介素-1受体相关激酶2(interleukin-1 receptor-associated kinase 2，IRAK2)可通过增强NF-κB的磷酸化驱动PDAC细胞中的糖酵解，为PDAC细胞存活和增殖提供生物能量，加速PDAC的生长[10]。此外，NF-κB的其他靶基因，如血管内皮生长因子(vascular endothelial growth factor，VEGF)、成纤维细胞生长因子和血小板衍生生长因子可与IL-8共同介导血管基底膜降解及细胞外基质(extracellular matrix，ECM)重塑，促进血管生成[11]。胰腺癌细胞中过表达的癌基因*AHNAK2*可通过激活NF-κB促进基质金属蛋白酶-9的表达，进而增强胰腺癌细胞的侵袭能力[12]。巨噬细胞可通过CC基序趋化因子配体5上调胰腺癌细胞中TNF受体相关因子6的表达而激活NF-κB，增强胰腺癌细胞对TNF样细胞凋亡弱诱导剂的非自主激活，进而促进去神经支配诱导的肌肉萎缩，导致胰腺癌患者恶病质的形成[13]。

2.2 NF-κB信号通路作为胰腺癌治疗靶点的潜力 现有研究显示，抑制NF-κB信号转导可有效抑制胰腺癌的进展。一种新的喹喔啉尿素类似物84可在低浓度条件下降低胰腺癌细胞中IKKβ的磷酸化水平，诱导肿瘤细胞凋亡，抑制肿瘤细胞的生长、集落形成及迁移[14]；新型抗癌剂GP-2250可直接干扰p65与DNA的结合，阻止NF-κB激活，抑制细胞周期蛋白D1和B细胞淋巴瘤-2基因(B-cell lymphoma-2，Bcl-2)的表达，进而抑制胰腺癌细胞的增殖并促进其凋亡[15]。此外，天然产物具备出色的化学多样性，在癌症治疗中引起广泛关注。例如，姜黄素可在低氧条件下抑制胰腺癌星状细胞分泌IL-6的能力，降低NF-κB的磷酸化水平，抑制胰腺癌转移[16]；啤酒花中的黄腐酚可通过阻断NF-κB的活化来抑制VEGF和IL-8的表达，从而抑制胰腺癌血管生成[17]；摄入富含花青素果汁志愿者的血浆提取物与胰腺癌细胞共孵育后，可阻断胰腺癌细胞中p65和黏附斑激酶的磷酸化，从而抑制细胞黏附分子的表达，降低胰腺癌细胞的迁移能力[18]。

3 NF-κB信号通路介导胰腺癌耐药的机制

3.1 NF-κB激活与吉西他滨耐药

3.1.1 阻碍吉西他滨的递送和摄取 NF-κB信号的激活可调节与吉西他滨递送和摄取相关蛋白的表达，从而限制吉西他滨的生物学效应。吉西他滨被细胞膜上表达的人平衡核苷转运蛋白(human equilibrative nucleoside transporter，hENT)和人浓缩核苷转运蛋白(human concentrative nucleoside transporter，hCNT)摄取后渗透到细胞质而发挥细胞毒作用[19]。研究显示，黏蛋白4可通过激活NF-κB而抑制hCNT1的表达，从而减少胰腺癌细胞对吉西他滨的摄取，减弱其细胞毒性[20]。此外，多药耐药(multidrug resistance，MDR)是肿瘤化疗面临的重要挑战，其主要机制之一是介导化疗药物外排的转运蛋白过表达。P-糖蛋白(P-glycoprotein，P-gp)是一种重要的外排转运蛋白，可将化疗药物泵出细胞外，降低化疗药物在细胞内的浓度，进而导致MDR[21]。研究发现，在吉西他滨耐药的PDAC细胞中，TLR3通过髓样分化因子88(myeloid differentiation primary response 88，MYD88)依赖和非依赖性的途径激活NF-κB，进而促进P-gp的表达，将进入细胞的吉西他滨泵出细胞外，降低吉西他滨对PDAC的治疗效果[22]。

3.1.2 抑制肿瘤细胞凋亡 诱导细胞凋亡是吉西他滨发挥抗癌作用的机制之一。其中，凋亡途径中某些核心调控因子的表达失衡是驱动化疗耐药的关键分子机制[23]。NF-κB信号的激活与凋亡相关调控因子的表达密切相关。研究发现，NF-κB的激活可促进胰腺癌细胞中Bcl-2的表达，抑制Bcl-2相关X蛋白(Bcl-2 associated X protein，BAX)向线粒体的渗透，从而抑制线粒体外膜的通透性和细胞色素C的释放，阻断胱天蛋白酶-3/9(cysteinyl aspartate specific proteinase-3/9，caspase-3/9)的激活[24]。因caspase的级联激活在细胞凋亡中发挥着关键作用[25]，故抑制caspase激活可促使肿瘤细胞逃避吉西他滨诱导的凋亡作用，引发化疗耐药。另一项研究发现，吉西他滨治疗后NF-κB的激活可导致细胞凋亡抑制蛋白如生存素和X连锁凋亡蛋白抑制剂(X-linked inhibitor of apoptosis protein，XIAP)的表达增加，直接抑制caspase-3/9的活性，阻止胰腺癌细胞凋亡[26]。

3.1.3 诱导癌症干细胞(cancer stem cell，CSC)表型 CSCs具有强大的自我更新能力，被视为胰腺癌治疗抵抗的重要因素[27]。NF-κB信号激活可诱导CSC表型，促进化疗耐药[28]。研究发现，吉西他滨可通过NADPH氧化酶介导胰腺癌细胞产生活性氧(reactive oxygen species，ROS)，激活NF-κB/STAT3信号的级联反应，增加$CD24^+$、$CD133^+$细胞的比例和*Bmi1*、

*Nanog*等干性基因的表达，使胰腺癌细胞表现出更显著的增殖、自我更新、转移及耐药能力[29]。癌症相关成纤维细胞(cancer-associated fibroblast，CAF)中NF-κB的持续激活可促使其分泌ELR$^+$ CXC类趋化因子，这些因子可与CXC趋化因子受体2(CXC motif chemokine receptor 2，CXCR2)结合，促使胰腺癌细胞向CSC表型转变，增强胰腺癌细胞的侵袭能力[30]。研究发现，胰腺癌细胞中核心1β1-3半乳糖基转移酶1的缺失可导致CD44上O-糖基化截短，从而激活细胞外调节蛋白激酶(extracellular regulated protein kinases，ERK)/NF-κB信号通路，增加胰腺癌干细胞标志物Nanog的表达，促进CSC特征样改变[31]。

3.1.4 促进上皮-间质转化(epithelial-mesenchymal transition，EMT) EMT是上皮样细胞向间质细胞转变，促进肿瘤侵袭、转移的生物学过程[32]。EMT已被证实可诱导胰腺癌患者对吉西他滨耐药[33]。EMT受多种转录因子调节，如赖氨酰氧化物样2(lysyl oxidase-like 2，LOXL2)可与弹性蛋白和胶原蛋白共价交联，促进EMT[34]；E盒结合锌指蛋白1/2(zinc finger E-box binding homeobox 1/2，ZEB1/2)可负向调节E-钙黏蛋白的表达，破坏细胞黏附，促使EMT的发生[35-36]。多项研究表明，NF-κB的激活与EMT的发展密切相关，如PDAC细胞中NF-κB信号的激活可介导S期激酶相关蛋白2高表达，促进ZEB1转录，进而诱导EMT[37]。低氧条件可导致吉西他滨耐药的胰腺癌细胞中糖酵解的激活，从而引发NF-κB信号的活化，活化的NF-κB可上调LOXL2和ZEB1的转录，通过促进EMT维持耐药性[38]。在胰腺癌中过表达的细胞外基质蛋白多糖SPOCK1(sparc/osteonectin，cwcv，and kazal-like domains proteoglycan 1)可促进IκBα的磷酸化，激活NF-κB信号通路，上调ZEB2等转录因子的表达，促进EMT；使用NF-κB抑制剂BAY11-7082后，SPOCK1诱导的EMT被逆转[39]。

上述研究表明，NF-κB的激活可通过限制吉西他滨的递送和摄取、抑制肿瘤细胞凋亡、诱导CSC表型等途径促进胰腺癌化疗耐药。因此，将靶向NF-κB信号通路的药物与吉西他滨联合使用可能是治疗胰腺癌更好的选择。

3.2 NF-κB激活与免疫治疗耐药

3.2.1 促进PD-L1的表达 免疫检查点的主要功能是防止免疫系统对机体的无序攻击，但肿瘤细胞可借此机制逃避免疫系统的攻击，如肿瘤细胞的PD-L1可与活化T细胞上的程序性死亡受体-1(programmed death 1，PD-1)结合，抑制T细胞的抗肿瘤反应[40]，导致免疫治疗失败。

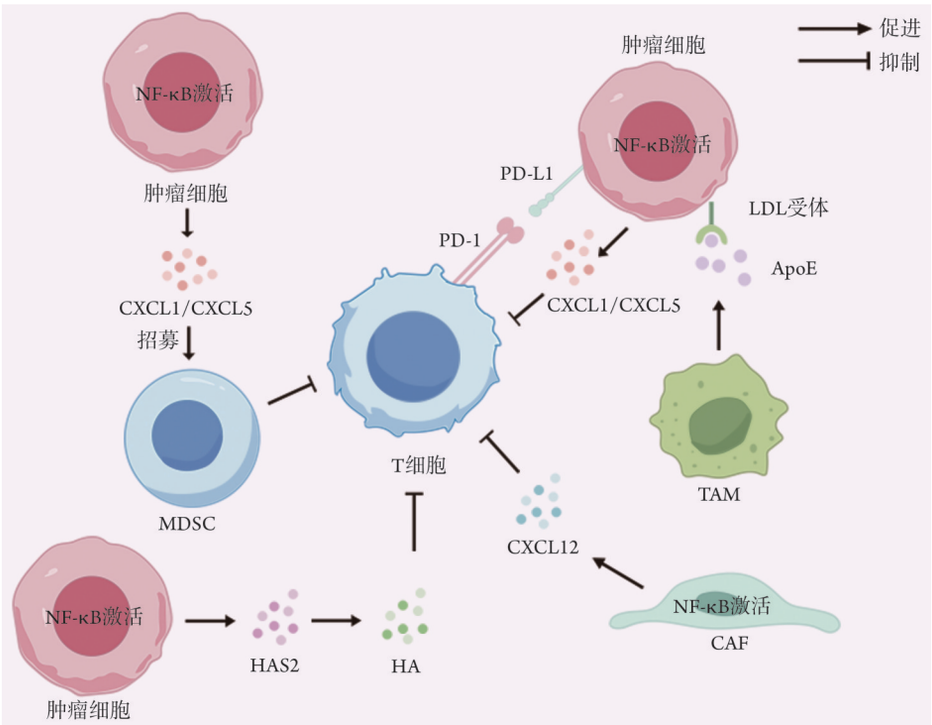
基于CRISPR/Cas9的筛选显示，NF-κB是肿瘤细胞免疫逃逸的关键介质[41]。后续研究发现，NF-κB和PD-L1在胰腺癌中的表达水平明显升高，而抑制NF-κB可降低PD-L1的糖基化并促进其降解，提示PD-L1可能通过NF-κB依赖的途径发挥免疫逃逸作用[42]。进一步的研究显示，PDAC细胞中升高的鸟嘌呤核苷酸结合蛋白亚基γ-12可通过激活NF-κB信号通路，促进PD-L1的高表达[43]。抑制Polo样激酶1可通过视网膜母细胞瘤蛋白依赖的机制激活NF-κB，上调PDAC细胞中PD-L1的表达[44]。肠道来源的脂多糖可结合TLR4招募MYD88，激活TLR4相关的级联信号通路，进一步激活NF-κB，促进PDAC细胞中PD-L1的转录[45]。因此，NF-κB信号的激活可导致PD-L1过表达，促进胰腺癌对免疫治疗耐药。

3.2.2 调控免疫抑制性TME 胰腺癌免疫抑制性TME由免疫抑制细胞、基质细胞和ECM等多种成分组成，它们共同促进机体的免疫抑制，进而对免疫治疗产生抵抗。

髓源性抑制细胞(myeloid-derived suppressor cells，MDSCs)是免疫抑制性TME的主要参与者，可增加PD-L1、精氨酸酶-1、一氧化氮合酶及ROS等免疫抑制分子的表达，抑制T细胞的激活[46-48]。研究发现，PDAC细胞的半胱氨酸肠道蛋白1可与p65蛋白形成复合物，并以输入蛋白依赖的方式促进其核易位，激活CXC趋化因子配体1(C-X-C motif chemokine ligand 1，CXCL1)和CXCL5的转录，增加MDSCs的招募，最终抑制T细胞的活化；而阻断该通路可减少MDSCs的聚集，提高PDAC对免疫治疗的敏感性[49]。肿瘤相关巨噬细胞(tumor-associated macrophage，TAM)是TME中另一个重要的免疫抑制因素。研究发现，TAM来源的载脂蛋白E(apolipoprotein E，ApoE)与肿瘤细胞的低密度脂蛋白(low-density lipoprotein，LDL)受体结合后可激活NF-κB，进而诱导肿瘤细胞产生趋化因子CXCL1和CXCL5，而这些因子可阻碍PDAC中T细胞的浸润，加剧免疫抑制性TME[50]。

CAF增加和ECM沉积是胰腺癌纤维化基质的主要特征[51]。CAF是PDAC中典型的促纤维化成分[52-53]。研究发现，CAF中NF-κB的激活可促进其分泌CXCL12，CXCL12与CXCR4相互作用阻止T细胞向肿瘤的浸润；而NF-κB p50亚基的耗竭则可促进CD8$^+$ T细胞的浸润，且伴随着CD8$^+$ T细胞活化标志物γ干扰素的高表达[54]。另一方面，透明质酸(hualuronic acid，HA)是ECM的重要组成部分[55]。PDAC中HA含量增高可增加间质压力并破坏化疗药物递送所必需的脉管系统。遗憾的是，在临床研究中，添加透明质酸酶并未提高化疗患者的生存率[56]。因此，针对HA的免疫治疗策略正在研发中[57]。透明质酸合酶2(hyaluronan synthase 2，HAS2)是HA合

成的关键酶[58]。研究发现，PDAC细胞中过表达的HAS2与T细胞耗竭有关[59]。从机制上看，白细胞介素-1受体相关激酶4(interleukin-1 receptor-associated kinase 4，IRAK4)可通过激活NF-κB信号上调PDAC中HAS2的表达，促进基质HA的合成，从而促使T细胞功能障碍；而抑制IRAK4可抑制NF-κB信号转导，促进T细胞的浸润，增强抗肿瘤免疫反应[59]。如图2所示。



CXCL1/CXCL5. CXC趋化因子配体1/5；MDSC. 髓源性抑制细胞；PD-1/PD-L1. 程序性死亡受体-1/配体-1；LDL. 低密度脂蛋白；ApoE. 载脂蛋白E；TAM. 肿瘤相关巨噬细胞；HAS2. 透明质酸合酶2；HA. 透明质酸；CXCL12. CXC趋化因子配体12；CAF. 癌症相关成纤维细胞

图2 NF-κB介导免疫治疗耐药的机制

Fig.2 Mechanisms of NF-κB-mediated immunotherapy drug resistance

由上可知，NF-κB信号激活可通过促进PD-L1的表达及免疫抑制性TME的形成，助长肿瘤的免疫逃逸，抑制该通路可能重塑胰腺癌TME，使其从“冷”肿瘤转变为“热”肿瘤，提升免疫治疗效果。

4 总结与展望

胰腺癌对常规治疗的耐药对患者的生命构成了严重威胁。目前大量研究显示，NF-κB的激活可加速胰腺癌的进展并从多个方面介导化疗和免疫治疗耐药。因此，NF-κB信号通路是胰腺癌治疗的潜在靶点，可通过调节IKK上游因素和下游效应以及IκB的稳定性来进行药理学抑制[60]。已经报道的NF-κB抑制剂包括生物小分子、天然化合物和合成化合物等[61]，近年来的研究主要集中在天然化合物联合吉西他滨来逆转胰腺癌耐药方面，并在耐药细胞、小鼠肿瘤移植模型和临床试验中显示了积极的效果。研究发现，在免疫治疗领域，对肿瘤浸润的T细胞实施IL-2重编程，并辅以应用NF-κB抑制剂，可显著提高脑癌的免疫治疗效果[62]。但NF-κB抑制剂与免疫治疗联合应用于胰腺癌的研究十分有限。此外，大多数报道缺乏对NF-κB上下游基因调控网络的研究，因此NF-κB如何被激活以及激活后调控胰腺癌耐药的具体机制尚不明确。未来需要增加实验的完整性，深入探讨联合治疗的有效性，并开展更多的前瞻性临床试验加以验证，以优化NF-κB靶向策略的临床应用。

此外，抑制NF-κB信号转导可能导致的问题也值得关注：(1)NF-κB通路成分众多，可影响多种生理反应，理想的抑制剂应具备特异靶向性，以免干扰其他功能；(2)长期使用此类抑制剂可能导致免疫缺陷，需进行系统研究，优化给药方案。总之，以阻断NF-κB信号转导为核心的治疗策略具有巨大的发展潜力和探索价值。随着新药物的开发和癌症研究的进展，期待发现更多对抗胰腺癌的方法。

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