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胰腺癌的吉西他滨耐药机制

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摘　要

胰腺癌作为致死率极高的恶性肿瘤，严重威胁着人类的健康。吉西他滨作为胰腺癌治疗的基石，其临床应用中普遍存在的耐药性极大限制了治疗效果。本文阐述了胰腺癌的治疗现状和吉西他滨的临床应用，回顾了关于吉西他滨的作用机制、代谢转运、化疗耐药的最新知识，重点从分子机制、肿瘤微环境、表观遗传学、干细胞等多方面介绍吉西他滨的耐药机制。在讨论各方面的耐药机制的同时，发现相关可干预的靶点，简单介绍了有前景的相关耐药规避策略。同时，讨论了新型治疗措施纳米颗粒，为治疗吉西他滨耐药的胰腺恶性肿瘤提供新思路。

关键词

吉西他滨，化疗耐药，胰腺癌，分子机制

Mechanisms of Gemcitabine Resistance in Pancreatic Cancer

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Abstract

Pancreatic cancer, as a malignant tumor with an extremely high mortality rate, poses a grave threat to human health. As a cornerstone of pancreatic cancer treatment, the widespread occurrence of resistance in the clinical application of gemcitabine significantly limits therapeutic efficacy. This paper outlines the current state of pancreatic cancer treatment and the clinical application of gemcitabine. It reviews the latest knowledge on gemcitabine's mechanism of action, metabolic transport, and chemotherapy resistance, focusing on the mechanisms of gemcitabine resistance from multiple perspectives,

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including molecular mechanisms, tumor microenvironment, epigenetics, and stem cells. Whilst discussing these diverse resistance mechanisms, the paper identifies relevant interventionable targets and briefly outlines promising strategies for circumventing resistance. Furthermore, it explores novel therapeutic approaches involving nanoparticles, offering fresh perspectives for treating gemcitabine-resistant pancreatic malignancies.

Keywords

Gemcitabine, Chemotherapy Resistance, Pancreatic Cancer, Molecular Mechanisms

1. 引言

1.1. 胰腺癌的流行病学与治疗现状

胰腺癌(Pancreatic Cancer, PC)是最致命的恶性肿瘤之一，其中胰导管腺癌(Pancreatic Ductal Adenocarcinoma, PDAC)约占 90%。因缺乏早期特异症状，绝大多数患者在确诊时已处于晚期，肿瘤往往已发生转移。因此，PC 患者的预后普遍较差，诊断后的中位生存期不足五个月，即使进入缓解期，五年生存率也低于 5% [1]。据全球癌症统计数据，2022 年全球新增 510,992 人罹患胰腺癌，死亡人数为 467,409 [2]，预计 2030 年胰腺癌将成为第二大癌症相关死亡原因[3]。

目前，PC 的主要治疗方法包括化疗和手术，然而，只有极少数患者在确诊时符合手术指征，且即使进行手术，3 年后复发率高达 60%。无论手术是否可行，大多数患者仍需接受全身化疗。目前 PC 临床一线治疗方案包括 5-氟尿嘧啶(5-FU)、白油氨酸、依立替康和草沙利铂的组合(FOLFIRINOX)，还有吉西他滨与白蛋白紫杉醇结合(nab-paclitaxel)的经典高效疗法[4] [5]。

1.2. GEM 的作用机制与临床应用

吉西他滨(Gemcitabine, GEM)是一种合成脱氧胞苷核苷类似物，是 PC 药物治疗的基石。GEM 在人类平衡核苷转运蛋白(hENTs)和人凝聚核苷转运蛋白(hCNT)的辅助下穿透细胞脂质膜，脱氧胞苷激酶(dCK)将其磷酸化为单磷酸(dFdCMP)，接着被核苷酸激酶转化为二氟脱氧胞苷三磷酸(dFdCTP)。在 DNA 合成过程中，dFdCTP 掺入新合成的 DNA 链中，导致 DNA 链的合成受到干扰[6]。此外，GEM 的单磷酸还可被脱氨生成 dFdUMP，作为胸苷酸合酶的抑制剂增强抗癌效果；GEM 代谢物还可抑制其他代谢酶从而增强细胞毒性。

近年来，GEM 在治疗多种恶性肿瘤方面取得显著进展，但胰腺癌患者对单剂 GEM 治疗并不敏感。这提示了存在内源性或获得性 GEM 耐药，严重限制患者的临床获益。因此，深入研究 PC 对 GEM 的耐药性机制至关重要。

2. GEM 耐药分子机制

2.1. 转运代谢相关耐药

人平衡核苷转运蛋白-1 (hENT1)促进核苷及其衍生药物的跨膜运输，在癌症化疗中发挥重要作用[7]。GEM 是核苷类似物，主要通过 hENT1 转运体的介导进入细胞。有研究指出，hENT1 高表达与 PC 患者

更长的生存期显著相关，hENT1 可作为该类患者的重要预后指标[8]。有争议的是，另一些研究者认为，hENT1 的表达与 PC 患者的预后无关[9] [10]。但不可否认的是，hENT1 表达降低可能是 GEM 的耐药机制之一。胸苷酸合酶(TS)抑制剂的预处理可提升 hENT1 表达，增强 GEM 治疗效果[11]；而胸苷酸合酶抑制剂 5-氟尿嘧啶(5-FU)的类似发现也可通过增加 hENT1 表达增强 GEM 治疗敏感性[12]。另外，跨膜糖蛋白粘青素 4 (MUC4)可通过 NF-κB 途径抑制 hCNT1 表达，沉默致癌受体(MUC4 的膜伴侣)通过上调 hCNT1 和 hCNT3 表达，进而提高 GEM 敏感性[13] [14]。

脱氧胞苷激酶(DCK)是一种通过磷酸化激活 GEM、促进胞内药物积累的关键酶。研究者发现，DCK 失活在获得 GEM 耐药性中起着关键作用，且并不影响癌细胞增殖[15] [16]。治疗前的 dCK 蛋白水平与 GEM 治疗后的总体生存率相关也证实这一点[17]。

核糖核苷酸还原酶(RR)是新生核苷酸合成途径中的关键酶，RR 活性增加会扩增 dNTP 池，通过直接分子竞争减少 GEM 掺入 DNA。研究表明，GEM 耐药 PC 细胞系中 RR 亚基 M1 (RRM1)过度表达，且与 GEM 的疗效存在显著关联，验证了 RR 是 GEM 耐药性的关键酶之一[18]。干预限速酶疗法面临挑战，这与靶点生物学复杂性、精准调控难度及耐药网络冗余性相关。

2.2. DNA 损伤修复途径激活

GEM 干扰 DNA 链合成并引起损伤，癌细胞中 DNA 损伤修复能力增强是耐药性的关键，同源重组(HR)是修复 DNA 双链断裂(DSBs)和保持基因组完整性的重要机制。临床上，超过 15%的 PC 患者携带 DNA 损伤响应基因(如 BRCA)突变，导致同源重组(HR)缺乏表型，而 GEM 的联合治疗在该类患者中取得良好疗效[19] [20]。近年，Calheiros 等人首创同源重组 DNA 修复抑制剂 BBIT20，不仅上调 hENT1 转运蛋白增强 GEM 的摄取，还下调 miR-20a 水平及参与嘧啶代谢的关键酶，如 RRM1 等[21] [22]，均与 GEM 耐药性相关。

氧化性 DNA 碱基损伤的积累会严重破坏基因组的完整性，且与癌症发展密切相关[23]。碱基切除修复(BER)具有诱变性或基因毒性的 DNA 碱基损伤，BER 基因的缺乏将影响肿瘤抑制因子和致癌基因对内源性氧化应激或环境致癌物的响应能力[24]。肿瘤细胞常常通过增强 BER 来抵御氧化应激，修复药物毒性或细胞静态碱基损伤，因此靶向 BER 被认为是通过 DNA 损伤压倒癌细胞并提升放疗和化疗疗效的有效策略[25]，但相关药物并未纳入研究。作为 BER 通路中的关键蛋白，APE1 已被证明能促进细胞存活和对多种化疗药物的耐药性[26]-[28]，而 APE1 的下调能使 PC 细胞对包括 GEM 在内的多种临床常见化疗药物的敏感性显著提高[29]。

2.3. 常见细胞信号通路与耐药

刺猬(Hedgehog)信号传导促进肿瘤发生及纤维化病变形成，改变肿瘤微环境，对异常增殖和肿瘤发生至关重要[30] [31]。基因分析显示，Hh 是 PC 中最常改变的通路之一[32]。该通路异常活化不仅促进肿瘤发生和上皮－间质转化，还通过影响凋亡相关蛋白的表达，被证明与化疗耐药密切相关。多项研究表明，抑制 Hh 信号途径与 GEM 在 PC 细胞系和小鼠异种移植中具有协同效应[33]-[35]。维莫德吉(Vismodegib)是靶点为 SMO 蛋白的 Hh 抑制剂，在联合 GEM 治疗 PDAC 的 II 期临床试验并未显著提高 PC 患者生存期，考虑可能与 Hh 通路的旁分泌及复杂的肿瘤微环境相关。

转录因子核因子 κB (NF-κB)通路是重要的促生存和炎症通路，其激活上调多种抗凋亡蛋白，促进炎症因子分泌，参与塑造免疫抑制微环境，与 GEM 耐药性相关。最初，人们在 GEM 耐药性 PC 细胞中发现 NF-κB 水平偏高[36]，而后续有研究表明，抑制 NF-κB 仅对 GEM 敏感的 PC 细胞系而言可提升治疗效果，耐药性 PC 细胞并不依赖 NF-κB 作为主要生存通路[37]。NF-κB 通路的异常激活是 PC 产生 GEM 耐

药性的关键因素之一，因 NF-κB 广泛参与正常机体生理过程，目前直接靶向 NF-κB 疗法尚未成功。

KRAS 是最常被激活的致癌基因之一，超过 90% PC 存在 KRAS 基因突变。致癌性 KRAS 突变通常会提高活性 GTP 结合形式的蛋白质稳态水平，推动通过下游效应通路驱动原肿瘤信号传导，如有丝分裂原激活蛋白激酶(MAPK)和磷脂酰肌醇 3-激酶(PI3K)通路[38]。多项实验表明，在体外和体内实验中，KRAS 抑制都能提高 PC 对 GEM 治疗的敏感性[39] [40]。目前，KRAS 抑制剂如针对 G12D 突变的 HRS-4642、针对泛 G12 突变的 RMC-6236 等已获得突破性研究进展，前者的单药疗法已在晚期经治 PC 患者中显示出初步疗效。

丝氨酸/苏氨酸激酶(Akt)参与调控细胞增殖与存活、血管生成和葡萄糖代谢等[41]。磷脂酰肌醇 3-激酶(PI3K)是 Akt 的上游激活因子，在 PC 中，PI3K/Akt 信号通路的失调与 GEM 化学耐药性相关[42]。Akt 一方面通过调控 IKK、MDM2 和 CREB 介导的信号，进一步调控细胞凋亡的转录；另一方面可直接调控凋亡蛋白表达。现已有多种 Akt 的靶向抑制剂被开发，并陆续进入临床实验[43]。其单药疗效有限，联合治疗是明确趋势。

Ras/Raf/MAPK(MEK)/ERK 通路是有丝分裂蛋白激酶(MAPK)信号通路中最重要的信号级联反应，参与调控细胞增殖、存活、代谢、凋亡等[44] [45]，该通路障碍是几乎所有癌症中最常见的致癌诱因[46] [47]。ERK 级联反应的持续激活驱使癌细胞生长，抑制 RAS-MAPK 级联中下游靶点是一种有前景的治疗策略。先前研究报告称，抑制 ERK 信号通路可使癌细胞对化疗的敏感性增加[48]，然而，另有研究表明该通路激活在化疗药物诱导的凋亡中可起促进作用[49] [50]。值得注意的是，尽管 ERK 通路的本质性激活可能是化疗耐药的标志，但该通路对 PC 细胞化疗耐药的影响依赖药物[51]。相关抑制剂研究进展值得期待，例如 Akt-ERK 双通路抑制剂 ONC201，能同时阻断两条关键通路并诱导凋亡，在前期研究中与 GEM 前药联用协同抑制 PDAC [52]，目前该药正处于向临床转化阶段。

3. 肿瘤微环境介导的耐药

PC 细胞对 GEM 化疗药物的耐药性研究，不仅要针对癌细胞本身，还要针对肿瘤微环境(TME)。复杂的 TME 在癌症发展中发挥着关键作用，也对 GEM 的耐药作出不可忽视的贡献[53]-[56]。

PC 细胞周围有胰腺星状细胞、免疫细胞、内皮细胞和神经细胞等细胞成分，其中胰腺星状细胞产生胶原蛋白间质。胰腺星状细胞(PSCs)能通过 Notch 信号通路诱导对 GEM 的化疗耐药[54]。PSCs 通过旁分泌 SDF-1α/CXCR4 信号引发 PC 细胞的 IL-6 自分泌环[53]，还通过分泌肿瘤干细胞(CSC)特异性配体肝细胞生长因子并结合其受体，这些都可促进 GEM 治疗耐药性[57]。与此同时，TME 中浸润的免疫细胞可促进侵袭性肿瘤中的化疗耐药和转移性扩散，而靶向肿瘤浸润巨噬细胞可有效克服耐药性[58]。早期有药物 PEGPH20 通过降解透明质酸靶向肿瘤基质，但在 III 期临床试验中未能显著延长生存期，这提示单纯消除基质抗肿瘤效果有限，可能与 TME 高度复杂及肿瘤异质性相关。现有新药物 PXS-5505 旨在重塑基质而非消除，减少肿瘤纤维化和基质硬化，在临床前研究中能较好地促进 GEM 疗效，现正积极推进转化临床试验。

低氧环境与多种癌症耐药性有关[59]。在 PC 中，缺氧主要通过 PI3K/Akt/NF-κB 通路，部分通过 MAPK (Erk)通路诱导 PC 细胞对 GEM 产生耐药性[60]。癌症相关成纤维细胞(CAFs)是位于 TME 中的纺锤形非肿瘤细胞，一方面产生致密胶原网络阻止化疗药物递送，另一方面，密集的间质和血管发育不良会导致严重缺氧[61]。之前的研究表明，缺氧可促进氧诱导因子(HIF)的产生，这些因子促进上皮间质转化，且在耐药 PC 中过度表达[62]。缺氧诱导因子 1α (HIF1α)可介导葡萄糖摄取增加，增强了肿瘤细胞的抗凋亡能力，而抑制 HIF-1α 被证实可提升 GEM 的敏感性[63] [64]。HIF-1α 还能通过抑制 hENT1 和 hENT2 的转录，降低核苷转运蛋白的表达，减少 GEM 的细胞吸收[65] [66]。

TME 中肿瘤坏死因子 α (TNFα)、转化生长因子 β (TGF-β)、HIF1α 及信号通路如 Notch 促使癌细胞发生上皮－间充质转变(EMT) [67]，这对 PC 的早期传播、肿瘤侵袭和晚期转移至关重要。研究表明，EMT 调节因子维持 PC 的药物耐药性，而靶向沉默可提升药物敏感性[68]。直接抑制 EMT 也会提高核苷转运蛋白表达水平、增强 GEM 治疗的敏感性并提高实验动物生存率[69]。除此之外，EMT 还与 CSC 相互联系、共同调控耐药性[70]。最新研究显示，谷胱甘肽过氧化物酶 4 (GPX4)抑制剂 ML210 通过诱导膜脂质过氧化，从而抑制 EMT、增强 GEM 抗癌效果，这提供了一个新的潜在联合治疗策略[71]。

4. 表观遗传学调控与耐药

GEM 耐药同样涉及表观遗传修饰，指基因表达的可遗传变化，不涉及 DNA 序列的改变。微小 RNA (miRNA)在转录后水平调控基因，在正常细胞癌变和肿瘤发展中起关键作用。多种 miRNA 与 GEM 耐药性相关。例如，microRNA-210 过表达可诱导 caspase-3 介导的凋亡，并抑制集落形成，且能增强 GEM 敏感性[72]。miRNA 可调控 PDAC 中的 K-Ras、PI3K-AKT、NF-kB、P53 和 Hedgehog 通路，且靶向 miRNA 已被证明能在多种环境中诱导 PDAC 细胞的化学或放射敏感性变化[73]。miRNA 靶向疗法通过抑制或恢复特定 miRNA 表达增强疗效，是目前 PC 治疗研究的前沿领域，但因投递、脱靶、毒性等因素仍面临巨大挑战。

长非编码 RNA (lncRNA)是一种内源性细胞 RNA。越来越多的证据表明，lncRNA 在包括 PC 在内的多种癌症中调控其恶性特征。转移相关肺腺癌转录本 1 (MALAT-1)，一种高度进化保守且广泛表达的 lncRNA，在 PC 中过度表达，增加胰腺 CSC 的比例，降低 GEM 化学敏感性并加速体外肿瘤血管生成[74]。MALAT-1 的高表达与 GEM 耐药及低生存率相关，因而可作为 GEM 疗效预测标志物。HOTAIR 是一种长期间隔的非编码 RNA，在 PC 中表达更高，其促致癌活性已被证明，可作为胰腺癌负性预后因子[75]。Wang 等人首次证明，胰腺 CSC 中由 GEM 诱导的 lncRNA HOTAIR，促进了增殖和迁移，减弱凋亡并增加化疗耐药，可作为潜在干预调控因子和新颖治疗靶点[76]。

DNA 甲基化修饰通常导致转录抑制，因为 CpG 岛的甲基化抑制了转录因子与基因启动子区域的结合[77]。Schlafen-11 (SLFN11)是一种 DNA 损伤应答蛋白，影响 GEM 在内的多种化疗药物的敏感性。近年来，SLFN11 与细胞对化疗药物敏感性之间的高度相关性引发越来越多的关注[78]，启动子甲基化可能是 SLFN11 表达水平下降的主要原因[79]。有研究表明，热休克蛋白 β-1 (HSPB1)在 PC 中发挥促进肿瘤作用，通过减少启动子甲基化可增强 PC 中的 GEM 抗性[80]，这为解决 GEM 耐药性 PC 提供了新的视角。

组蛋白修饰为基因表达的快速调控提供保障，也与核苷类药物治疗癌症过程中出现的化疗耐药性息息相关。例如，促自噬基因 CSNK2A1 的转录调控由 PDAC 中的 H3K27 乙酰化介导，增强的自噬驱动 GEM 耐药性[81]。在长期使用 GEM 治疗胰腺癌时，胞苷脱氨酶 CDA 的组蛋白乙酰化迅速增加，导致溶酶体中 GEM 的降解，转化为细胞外非活性代谢物[82]。尽管临床前数据可观，但临床转化仍面临难题。组蛋白去乙酰化酶抑制剂恩替诺特(Entinostat)的 II 期试验结果显示，单一的靶向组蛋白去乙酰化酶不足以为 PC 患者带来可观的生存获益，这推动了后续研究从单靶点抑制向多通路联合的转向。

5. 肿瘤干细胞与耐药

部分具有无限自我更新潜力的肿瘤细胞称为肿瘤干细胞(CSCs)，与其他肿瘤细胞相比，CSCs 对 GEM 的化疗耐药性也更显著。Yin 等人的研究表明，CSC 富集显著提高 PC 肿瘤迁移能力和 GEM 耐药性，而靶向抑制 CSC 代表了一种克服胰腺癌化疗耐药性和转移的新治疗策略[83]。CSCs 主要通过提升 ATP 结合盒转运蛋白的表达、规避细胞死亡、高表达解毒酶如醛脱氢酶(ALDH)、调控 EMT 以及逃避免疫监测

来调控药物耐药性[84]。因 CSCs 高耐药性，相关药物旨在靶向表面标志物或关键信号通路调节代谢。先前药物研究主要靶向如 Notch、Hedgehog 等单一通路，大多因 CSCs 信号网络冗余性宣告失败。针对 CD47 抗体药物如 Magrolimab 仍处于 II 期研究，后续可持续关注。

6. 结论与挑战

胰腺癌号称“癌中之王”，其化疗药物 GEM 作为具有潜力的临床化疗药物，耐药性是除其本身复杂性之外的公认治疗难点，为临床治疗带来挑战。尽管许多标志物在研究中展示出了预测价值，但仍缺乏相关标准化检测方法及大规模前瞻性临床试验验证。目前，纳米技术投递药物在体外和体内均展现出较大前景，其特点在于延长药物释放，将药物送达目标位点，增强细胞内部吸收，是克服耐药性的新型策略[85] [86]。尽管如此，纳米技术仍面临诸多挑战，例如对机体免疫网络的影响尚不可知，潜在免疫原性限制疗效，存在促进肿瘤转移潜在风险等[87]，需进一步优化和深入研究。

近年来，多种 GEM 化学耐药性和敏感性相关分子机制和通路已被报道，但通路网络复杂冗余，抑制单一通路易引发旁路代偿性激活，一些网络机制尚不完全明了。通过研究 GEM 耐药机制，发现新的治疗方向与新靶点，为治疗顽固的 GEM 耐药性胰腺癌提供新思路；而如何通过合理组合化疗、靶向治疗、免疫治疗及微环境调节等改善 GEM 耐药性，仍需系统探索。

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