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·文献综述·

ERCC1 基因表达对胰腺癌铂类药物化疗效果影响的研究进展

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摘 要 胰腺癌起病隐匿，进展迅速，绝大部分患者就诊时已处于进展期，即使根治性切除，半数以上的患者仍在术后早期复发，其 5 年生存率极低。系统化疗虽可提高胰腺癌患者的总生存率，但较其他腺癌患者，其疗效仍然欠佳。铂类是胰腺癌化疗方案的主要药物，但高表达 ERCC1 的肿瘤细胞可能对其产生耐受，使肿瘤对化疗出现原发耐药。能否通过检测胰腺癌细胞 ERCC1 的表达预测其对铂类化疗药的敏感性，以及能否对其调控来提高化疗敏感性，有可能成为提高胰腺癌化疗效果的突破点。目前此类研究仍处在较早阶段，笔者对相关研究进展进行简要综述，以期对后续研究提供线索。

关键词 胰腺肿瘤；化放疗；核苷酸切除修复交叉互补基因 1；综述文献
中图分类号： R735.9

Research progress of influence of ERCC1 gene expression on the efficacy of platinum-based chemotherapy for pancreatic cancer

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Abstract Pancreatic cancer has an insidious onset but rapid progress. Most patients are in advanced stage at the time of admission to the hospital. More than half of the patients still relapse early even after a radical resection, with an extremely low 5-year survival rate. Although systemic chemotherapy can improve the overall survival rate of pancreatic cancer patients, its efficacy is still worse than inpatients with other adenocarcinomas. Platinum compounds are the main agents for chemotherapy of pancreatic cancer, to which, resistance may arise in tumor cells with high expression of ERCC1, causing primary drug resistance of the tumor to the chemotherapy. Whether the sensitivity of the pancreatic cancer cells to platinum-based chemotherapy regimen can be predicted by determining the their ERCC1 expression levels, and whether their response to chemotherapy can be improved by regulating the ERCC1 expression may be the breakthrough for increasing the chemotherapy efficacy of pancreatic cancer. At present, the researches in this field are still in their infancy. Here, the authors briefly review the relevant research progress, so as to provide assistance for future studies.

Key words Pancreatic Neoplasms; Chemoradiotherapy; Nucleotide Excision Repair Cross-Complementing Gene 1; Review
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胰腺癌约90%为起源于胰腺外分泌系统的导管腺癌，是全球第四大癌症死亡原因。目前其主要治疗方法包括手术切除和系统性全身化疗，但其总体5年生存率仍低于7.2%[1-2]。患者出现临床表现而就诊时部分已处于病程中晚期，失去了手术切除的机会[3]。即使行手术切除，患者术后1、2、5年复发或转移率分别为56.7%、77.6%、84.1%[4]。因此全身化疗在胰腺癌的综合治疗中仍占据重要的位置。吉西他滨联合铂类（顺铂或奥沙利铂）的化疗方案已在晚期患者的随机对照试验中证实能够显著提高患者总生存期，且与单独的吉西他滨化疗相比，联合方案还能降低化疗毒副反应，提高患者对化疗的依从性[5-8]。而且，铂类药物的添加与无进展生存期的改善正相关[5-7, 9]。因此，《NCCN胰腺癌治疗指南》直至2018版仍将“FOLFIRINOX”化疗方案（氟尿嘧啶+奥沙利铂+伊立替康+亚叶酸钙）作为胰腺癌主要一线化疗方案，吉西他滨联合铂类药物的化疗方案也同时被列入新辅助化疗（交界性可切除患者）和晚期患者的一线化疗方案（适用于已知抑癌基因BRCA1/2突变的患者）[10]。铂类化疗药以DNA为靶作用部位，导致链内或链间交联，从而破坏DNA分子的结构，导致螺旋的空间变化，破坏肿瘤细胞DNA的复制、转录，从而诱导细胞的凋亡。核苷酸切除修复交叉互补基因1（excision repair cross-complementation gene 1，ERCC1）是核苷酸外切修复酶家族中的重要成员之一，是细胞存活必需的DNA修复基因，具有对损伤基因片段的识别和切除修复功能，其表达的高低能反映整个DNA核酸切除修复（nucleotide excision repair，NER）活性的水平[11]。已有研究证实，检测肿瘤标本中ERCC1的表达可以较好地预测非小细胞肺癌[12]，卵巢癌[13]，睾丸癌[14]，结直肠癌[15]和宫颈癌[16]对铂类化疗药物的原发性耐药。赵海波等[17]分析了60例上皮性卵巢癌术后ERCC1与铂类药物化疗敏感性的关系，结果显示，ERCC1低表达组中62.5%的患者对铂类药物敏感，ERCC1高表达组中16.7%的患者对铂类药物敏感，两组差异有统计学意义（P<0.05），从而认为ERCC1阳性可预测上皮性卵巢癌对铂类药物化疗的敏感性。徐向勇等[18]分析了69例晚期非小细胞肺癌RECC1与铂类药物化疗敏感性的关系，结果显示，ERCC1低表达组中铂类药物化疗客观缓解率为48.8%，ERCC1高表达组中铂类药物化疗客观缓解率为29.1%，两组差异有统计学意义（P<0.05），从而认为ERCC1阳性可预测晚期非小细胞肺癌对铂类药物化疗的敏感性。但ERCC1的表达在预测胰腺癌对铂化疗有效性方面的研究甚少，现对胰腺癌 ERCC1的表达影响铂类化疗药疗效的研究进展进行简要综述。

1 ERCC1 介导的癌细胞抗铂机制

NER机制是一种高度保守，通用且强大的DNA修复途径，可处理多种DNA损伤，改变DNA分子的螺旋结构并干扰DNA复制和转录。该途径中的重要步骤包括识别DNA损伤和受影响的特定区域的分界，然后形成复合物以解开受损部分并将其切除。最后，将切除的区域重新合成并连接以维护DNA分子[19]，这其中涉及包括ERCC1等多种修复基因的表达。ERCC1基因于1984年由Westerveld等[20]首先报道，其发现是从海拉细胞中分离出被切割成平均片段大小为50~60 kb的碱基对，将其连接到线性化质粒pSV3gptH，并转染到中华仓鼠卵巢（Chinese hamster ovary，CHO）突变细胞系43-3B，使用Ecogp探针从二级转化体的粘粒文库中分离出独特的1.0-kbp B3-B4基因修复片段，在DNA介导的基因转移的帮助下，克隆了该基因片段，根据在第17次人类基因绘图中提出的命名法，将该基因片段命名为ERCC1。后续研究证实，该片段位于染色体19q13.2并且有10个外显子分布在15 kb的基因组中，编码含有297个氨基酸的蛋白质，表观分子量约为32.5 kDa[21]。ERCC1的活性表达是与着色性干皮病基因（xeroderma pigmentosum group F，XPF）形成ERCC1-XPF的异二聚体，此二聚体是一种存在于许多哺乳动物细胞内具有独特构造的核酸内切酶。在ERCC1-XPF中，ERCC1的核心区域具有核酸内切酶催化活性，但缺乏解旋酶样活性，而XPF同时具备核酸内切酶和解旋酶样的作用[22]。ERCC1和XPF通过高度保护性区域HhH2的互相反应、链接成ERCC1-XPF异二聚体[23-25]。该二聚体在NER途径中参与多种方式的DNA损伤修复，如DNA双链断裂的修复和DNA链间交联，ERCC1活性的高低可反映整个NER修复活性的水平。当铂类药物进入癌细胞时，铂与DNA配位形成铂-DNA加合物[26]。

这类铂诱导性DNA加合物可表现为链内或链间交联，从而破坏DNA分子的结构，导致螺旋的空间变化，这些交联可破坏细胞DNA的复制，使受损的细胞分裂周期阻滞在G_2/M期，同时破坏细胞膜结构，从而达到抗肿瘤效果[27-29]。而ERCC1-XPF分别切除损伤DNA片段的5′和3′端，将铂-DNA加合物从基因组中解离下来，从而修复其引起的DNA损伤，导致癌细胞对铂类药物化疗的耐药[22]。

2　ERCC1 预测胰腺癌铂类化疗效果的相关研究

Strippoli等[30]收集了71例胰腺癌伴发转移后接受“FOLFIRINOX”化疗方案治疗的患者，使用逆转录-聚合酶链反应（RT-PCR）检测各自病理标本中ERCC1-mRNA的表达量，结果ERCC1水平正常的患者与ERCC1高表达患者比较，中位无进展生存期（PFS）分别为11个月和4个月（*HR*=0.26，95% *CI*=0.14~0.50，*P*<0.000 1），中位总生存期（OS）分别为16个月和8个月（*HR*=0.23，95% *CI*=0.12~0.46，*P*<0.000 1），疾病控制率（DCR）分别为93%和50%（*P*=0.000 06）。因而认为，ERCC1的表达可能是胰腺癌转移后能否对FOLFIRINOX化疗方案敏感的有效负性预测因子。Mancuso等[31]检测57例胰腺癌患者标本中ERCC1基因表达水平，使用铂化疗的ERCC1阴性患者OS明显长于ERCC1阳性患者[11.9（95% *CI*=8.65~17.69）个月*vs.* 9.9（95% *CI*=6.13~12.77）个月，*P*<0.05]，而在未用铂化疗的患者中，ERCC1表达高与低的患者间未观察到OS的差异。从而认为，ERCC1的表达量可预测胰腺癌患者采用铂类化疗的有效性。然而，Postlewait等[32]用免疫组化方法（IHC法）检测22例胰腺癌患者病理标本ERCC1蛋白水平，然后全部患者均接受吉西他滨（1 000 mg/m^2）+顺铂（50 mg/m^2）方案化疗，随访结果ERCC1低表达者与高表达者的中位PFS分别为16.7、12.4个月（*P*=0.68），OS分别为（未达到中位数*vs.* 21.6个月，*P*=0.22）。此研究结论为，ERCC1的状态与胰腺癌患者接受吉西他滨+顺铂方案化疗治疗的PFS或OS无关。究其原因，可能由于部分患者在4 号外显子中ERCC1密码子118处发生沉默突变，从“胞嘧啶“突变为“胸腺嘧啶”，即从野生型（AAC）向突变型（AAT）转变，两者都编码天冬酰胺，与野生型细胞相比，突变型细胞对Pt-NDA加合物的识别度低。Kamikozuru等[33]使用PCR-RFLP分析67例胰腺癌患者ERCC1密码子118多态性，39例患者（58.2%）为AAC密码子纯合子，7例（10.4%）为AAT密码子纯合子，21例（31.3%）为杂合子。在用顺铂治疗的患者中，具有AAT纯合子和杂合子患者的PFS和OS显着长于AAC等位基因纯合子的患者（PFS：338 d *vs.* 106 d，*P*=0.006；OS：763 d *vs.* 415 d，*P*=0.030）。因此，提出ERCC1多态性可能影响采用铂类化疗的胰腺癌患者预后。

3　ERCC1 的表达调节及临床应用

ERCC1启动子位于ERCC1基因转录起始位点上游±170个碱基对的区域，Yu等[34]研究发现，Ras基因的表达可激活一系列参与DNA修复的基因，其中包括c-fos和c-jun基因，其表达产物为AP-1，AP-1可通过与其结合位点的调节元件相互作用来调节ERCC1基因的表达。Altaha等[35]研究亦证实AP-1与ERCC1表达的调控密切相关。目前调节 ERCC1 基因表达的方法主要有反义基因调节及RNA干扰（RNAi）。反义基因调节，即用ERCC1-mRNA的反义RNA或反义寡核苷酸转染铂耐药细胞株，而后ERCC1-mRNA的反义RNA或反义寡核苷酸以分子形式存在并与ERCC1基因转录的RNA（包括mRNA）分子形成复合体，此复合物可影响RNA的剪接、加工以及与核糖体的结合，使ERCC1-mRNA不能正常的翻译和表达，导致ERCC1基因被特异度抑制或产生下向调节来增加细胞对铂的化疗敏感性。RNAi即将与ERCC1-mRNA对应的正义链、反义链组成的双链RNA（dsRNA）导入细胞，从而使ERCC1-mRNA产生特异度的降解，导致ERCC1基因沉默。

目前已有多个相应的药物研究，如环胞菌素A和除莠霉素A，发现其可分别抑制c-fos和c-jun基因的表达，进而阻断顺铂诱导的ERCC1-mRNA水平的升高，使顺铂增效。乳胞素是一种由链霉菌合成的天然产物，亦可通过抑制ERCC1基因的转录来影响其表达量[36]。临床研究方面，Zhong等[37]发现选择性血管内皮生长因子抑制剂SU5416通过抑制NER相关蛋白的活性，从而抑制ERCC1及c-jun mRNA的表达从而增强顺铂的细胞毒作

用。而抑制NER的化疗药物，如吉西他滨、紫杉醇等，能通过下调ERCC1的表达，抑制靶细胞的DNA修复过程，故而与铂类药物有化疗协同增效作用[38]。

4 结论及展望

ERCC1-mRNA及其蛋白的表达水平与铂化疗效果呈负相关，ERCC1的多态性可能与癌细胞对铂类药物原发耐药相关，对其表达的检测有望作为指导胰腺癌个体化精确化疗的依据。但由于在胰腺癌ERCC1表达与铂类化疗药疗效方面缺乏大样本的RCT研究，ERCC1对于预测胰腺癌患者铂类化疗疗效及化疗后生存时间的预测价值仍然有限。单独1种基因去评价肿瘤的化疗反应，其敏感度及特异度往往比较局限，可联合BRCA1、BRCA2等基因提高准确性[39-40]。而且目前最能反映胰腺癌患者对铂类敏感的ERCC1基因的多态性、mRNA转录水平以及其蛋白表达量的截断值尚未有明确一致的定义，因此寻找能更为简便、精确地评估ERCC1表达水平的方法仍是需要解决问题之一。阻止ERCC1-XPF异源二聚体的形成是否能对抗ERCC1高表达导致的铂类耐药，可能是研究对其表达调节的切入点。拜周兰等[41]研究宫颈癌中ERCC1甲基化与顺铂化疗敏感性关系，多因素分析显示ERCC1甲基化是影响宫颈鳞癌以顺铂为基础化疗的敏感因素（P=0.002），然而尚未发现ERCC1甲基化是否影响胰腺癌铂化疗敏感性的相关研究。若在化疗方案拟定时对于ERCC1阳性表达患者可去除包含铂类制剂的化疗方案，以避免此类患者存在“陪打”现象，在治疗过程中亦可检测由铂类化疗诱导的ERCC1表达升高患者，联合药物抑制ERCC1的表达或更换化疗方案，以上这些均可能有益于为患者制定个体化的精准治疗。近些年胰腺癌EGFR、IGF和VEGF等信号转导通路相关分子靶向药物及免疫治疗的研究飞速发展，但尚处于早期研究阶段，尚难以证实有效性[42-43]，化疗仍然是目前治疗晚期胰腺癌的主要选择。而且随着对胰腺癌的临床研究和生物学行为的深入了解[44]，如今胰腺癌的治疗理念正在向多学科诊疗模式转变[45]。在多学科诊疗模式下，针对可能切除的胰腺癌提出了术前予以新辅助化疗为手术切除创造条件的理念[46]。研究ERCC1的表达预测胰腺癌对铂化疗的敏感性或调节ERCC1的表达来提高胰腺癌患者对铂类药物化疗的疗效，对提高患者生存期仍具有一定研究价值及前景。

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