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文献综述 REVIEW

ERCC1在食管癌顺铂化疗中的作用

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Role of ERCC1 in cisplatin resistance in esophageal cancer

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Abstract

Cisplatin is one of several chemotherapeutic drugs commonly used to treat esophageal cancer. Nucleotide excision repair (NER) pathway plays an important role in repairing cisplatin-caused DNA damage. It has been demonstrated recently that the key enzyme of this pathway, excision repair crosscomplimenting 1 (ERCC1), is a factor determining cisplatin resistance and patient's response to cisplatin treatment. Further studies on the relationship between ERCC1 and cisplatin resistance will improve our understanding of cisplatin resistance in patients with esophageal cancer.

Key Words: Excision repair cross-complimenting 1; Cisplatin resistance; Esophageal cancer

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摘要

顺铂是治疗食管癌的常用化疗药物, 但其耐药性的产生是临床上的重大挑战. 核苷酸切除修复是细胞修复顺铂造成的DNA损伤的重要途径, 近年来的研究发现这条途径的关键酶切除修复交叉互补基因1在决定顺铂耐药和患者对顺铂治疗的反应中起很大作用, 深入研究此蛋白和顺铂耐药的关系对进一步理解食管癌的顺铂耐药有重要作用.

关键词: 切除修复交叉互补基因1; 顺铂耐药; 食管癌

核心提示: 准确预测肿瘤患者对治疗的反应是肿瘤治疗的一大挑战. 切除修复交叉互补基因1(excision repair crosscomplimenting 1)有望成为预测食管癌, 肺癌等多种肿瘤对顺铂治疗反应的标志物, 但仍需进一步大样本的研究并解决抗体特异性等问题.

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0 引言

食管癌是中国常见的肿瘤, 虽然有放化疗, 手术等多种治疗手段, 其死亡率依然很高[1-3]. 顺铂自上世纪60年代偶然发现具有抗肿瘤活性以来[4,5], 一直是临床常用的抗肿瘤药物, 是治疗睾丸癌[6]、卵巢癌[6]、头颈部鳞癌[6]、食管癌[7,8]等的一线用药, 但顺铂耐药的发生是治疗失败的重要原因[9,10]. 核苷酸切除修复(nucleotide excision repair, NER)是细胞修复顺铂造成的DNA损伤的重要途径[11], 同时增高的NER是顺铂耐药的原因之一[12]. 切除修复交叉互补基因1(excision repair

■背景资料
切除修复交叉互补基因1(excision repair crosscomplimenting 1, *ERCC1*)是肿瘤细胞修复顺铂导致的DNA损伤的关键蛋白, 食管癌患者肿瘤表达此蛋白的高低可能成为预测患者对顺铂治疗反应性的标志物.

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■相关报道
Huang等研究了46位接受紫杉醇+顺铂治疗的转移性食管癌的患者, 发现ERCC1低表达(利用免疫组织化学检测)的患者对治疗的反应更好, 中位生存期更长.

crosscomplimenting 1, *ERCC1*)是NER的关键酶, 在顺铂耐药和对顺铂治疗的反应中起重要作用. 本文就近年来在ERCC1与食管癌顺铂耐药方面取得的进展作一综述.

1 顺铂导致肿瘤细胞损伤的机制

顺铂进入细胞后, 其铂原子与DNA的嘌呤碱基的N7位置共价结合[9], 形成链内交联等单加成物[13], 引发细胞毒[14]. 这些DNA加合物的形成改变了DNA的结构, 阻碍DNA的复制和转录[11], 这些都能够被细胞蛋白识别, 引发DNA损伤反应[9], 导致细胞周期停滞[15]、加成物移除、DNA修复[16]、衰老[17-19]和细胞凋亡[20,21]. 细胞DNA修复有多种方法, 这些修复系统有损于我们希望看到的顺铂的细胞不良反应[22]. 其中核苷酸切除修复是切除顺铂-DNA加成物, 修复顺铂造成的DNA损伤的最主要方法[11].

2 核苷酸切除修复

NER是存在最普遍的进化保守的DNA修复方式[23,24], 能够清除多种DNA损伤, 包括紫外线导致的光损伤, 环氧二醇苯并芘和顺铂导致的DNA加成物等. NER修复过程可分为5步[25]: (1)DNA损伤的识别; (2)在损伤部位的两端引入切割酶; (3)切下损伤的核苷酸片段; (4)以互补链为模板合成新的核苷酸填补缺口; (5)DNA连接酶连接缺口完成修复. 根据NER是如何起始的, NER分为2条亚通路, 转录偶联的NER(transcription-coupled NER, TC-NER), 由转录过程中的RNA聚合酶Ⅱ复合物遇到阻碍(如顺铂-DNA加成物)停滞而起始的, 能够快速的修复活跃转录的基因的转录链的损伤. 停滞的RNA聚合酶Ⅱ复合物招募CSB和CSA, 二者进一步招募其他多种蛋白, 其中包括TFIIS[26]; 全基因组NER(global genome-NER, GG-NER), 不依赖转录, 能够修复全部的DNA损伤, 由UV-DDB和XPC-RAD23B-centrin 2蛋白复合物识别并结合到DNA损伤处始动[26]. DNA损伤识别步骤完成后, 2个亚通路汇合, 即剩余的切割、移除、合成新DNA片段和连接的步骤相同. DNA损伤识别蛋白随后结合TFIIS, 这是一个有多个蛋白组成的复合物, 包括XPB、p62、p52、p44、p34、p8、XPD和XPG[27]. TFIIS可以依赖XPB的ATP酶活性将DNA解链, 形成一个有27个核苷酸组成的气泡状的包含损伤DNA的结构, 而RPA、XPA、XPB、XPD等蛋白有稳定这个气泡状结构的功能. 然后结构特异性核算内切酶XPG和ERCC1-XPF被激活, 分别切断3'和5'端, 形成一段24-32个核苷酸组成的包含损伤DNA的片段, 并将其脱离DNA. 而由此形成的单链DNA缺口由DNA合成酶合成的新的DNA片段填补. 最后, 新合成的DNA片段与原DNA之间的断口有DNA连接酶Ⅲ-ERCC1和DNA连接酶Ⅰ缝接上从而完成修复的整个过程[26].

3 ERCC1与食管癌对顺铂治疗的敏感性

ERCC1的表达与多种肿瘤对化疗药物的敏感性相关, 如肺癌、胃癌、也包括食管癌[28-33]. 在食管癌治疗中, 顺铂为常用药物[7,8], 但并非所有患者都会从顺铂治疗或包含顺铂的放化疗中受益[9,10]. 因此许多研究都关注肿瘤ERCC1的表达与顺铂敏感性的关系, 特别是研究此蛋白能否作为患者从以顺铂为基础的放化疗中受益的指标. Lee等[34]利用免疫组织化学研究了72例转移食管鳞癌患者的ERCC1的表达, 发现高ERCC1表达是无进展生存期和总体生存期的不良预后指标. 不仅仅是蛋白质, ERCC1 mRNA的高表达也与食管癌患者的不良的总体生存期相关, ERCC1 mRNA高表达也与患者的肿瘤复发相关, ERCC1>3.0的患者的复发率是其他患者的2倍[35]. Tanaka等[36]研究了16例食管鳞癌患者的ERCC1的表达, 发现相对于正常组织, ERCC1蛋白在肿瘤组织中高表达, 对顺铂为基础的放化疗产生部分反应的患者的ERCC1表达量明显低于对此治疗方案无反应的患者的表达量. Kim等[37]研究所包含的食管癌患者首先接收了顺铂+5-氟尿嘧啶(5-fluorouracil, 5-Fu)+放疗或顺铂+卡培他滨+放疗的化疗治疗, 其后是化疗前肿瘤内镜活检组织ERCC1低表达的患者更可能产生组织学显著反应, 这些患者也表现出更长的无病生存期和整体生存期的趋势. 另一组的研究[38]得到了相似的结论, 36例局部进展期食管癌患者接受了顺铂+5-Fu+放疗的治疗方案, 然后手术. 结果显示只有ERCC1低表达的患者才会产生组织学显著反应, 才会从这个治疗方案受益. 中国协和医科大学Huang等[39]研究了复发或转移食管癌患者, 这些患者接受紫杉醇+顺铂治疗方案, 然后每8 wk进行影像学检测以确定患者对治疗的反应. 他们发现ERCC1免疫组织化学阴性的患者治疗反应性更高. 樊青霞等[40]和李笑秋等[41]分别利用RT-PCR和免疫组织化学检测了食管癌患者的肿瘤组织的ERCC1表达, 发现

ERCC1表达与患者对顺铂+5-Fu或奈达铂+5-Fu的治疗反应密切相关, 但与患者年龄、性别、肿瘤分期、分级等无关. 另外有意思的是, 食管癌患者血液中肿瘤细胞ERCC1 mRNA的表达相对较高者容易对包含顺铂的放化疗产生轻微治疗反应[42], 若这个结论被进一步证实, 将为通过更方便的检测ERCC1预测患者治疗反应奠定基础. 综上所述, 在治疗前肿瘤组织中ERCC1的表达可能成为顺铂为基础的放化疗治疗方案的选择的良好指标, 可以预测哪些患者可能从这个治疗方案中受益, 而哪些患者不会对治疗产生反应.

*ERCC1*基因的多态性, 因为能够影响其mRNA、蛋白表达和蛋白活性, 也可以影响肿瘤对顺铂治疗的反应性. Metzger等[43]研究表明rs11615的多态性与食管腺癌对顺铂+5-Fu+放疗的治疗方案的反应性相关. 在顺铂治疗的患者中, ERCC1 8092 A/A, A/C的患者, 相比于C/C的患者更可能存活更长时间[44-46], 并显示出对顺铂治疗更好的治疗反应. 但在非顺铂治疗患者中, 此关系并不存在[37]. 同时研究发现另一个位于第4外显子的多态位点ERCC1 C118T也与食管癌患者对顺铂+5-Fu+放疗的反应相关, 70%的C/T基因型患者对此治疗方案有反应, 而T/T基因型患者中只有20%对此方案有反应[47].

此外, *ERCC1*基因启动子甲基化同样可影响ERCC1的表达, 如在胶质瘤中, ERCC1启动子的超甲基化与其mRNA, 蛋白质表达水平成反比, 与胶质瘤细胞对顺铂的抵抗相关[48], 但在食管癌中还未见类似研究.

4 存在问题

当前绝大多数对于ERCC1与食管癌对顺铂治疗反应性的研究都是回顾性的, 且包含的病例数较少, 为解答两者间的确切关系, 需要大样本前瞻性研究. 另外在病例选择时, 因为有研究显示患者接受顺铂为基础的放化疗治疗后ERCC1表达改变[36,49,50], 所以选择初次治疗前的病理组织进行研究可能是最恰当的. 另外需要特别注意的是, 有文章指出ERCC1最常用的抗体(8F1克隆)在免疫组织化学中存在与PCYT1A蛋白交叉反应的问题[51], 最近的文章[52]又进一步发现在ERCC1的16种抗体中, 没有一种能够区分ERCC1的4种蛋白亚型, 而在这4种亚型中只有一种能产生完全的核苷酸切除修复能力和顺铂抵抗能力. 作者同时指出ERCC1抗体(8F1克隆)的功能可能在2006年以后发生了改变. 这些抗体的交叉反应和低特异性问题使我们更难解释ERCC1与肿瘤顺铂抵抗的真正关系.

5 结论

选择出对患者有明显反应的治疗方案, 对提高疗效, 减少不必要治疗, 降低患者负担有重要意义. ERCC1作为肿瘤修复顺铂导致的细胞损伤的重要蛋白, 对预测患者对顺铂为基础的放化疗治疗方案的反应性显示出较好的前景.

■创新盘点

本文总结了ERCC1的表达、多态性等与食管癌患者对顺铂治疗反应性的关系, 并概括了当前研究中存在的问题, 内容新颖, 资料详实.

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■同行评价

本文综合描述了ERCC1在决定食管癌患者顺铂耐药和患者对顺铂治疗反应中起的作用, 该综述立意较好, 有一定的临床参考价值.

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