

药物遗传学和药物基因组学在肿瘤治疗中的应用

王立峰, 钱晓萍, 刘宝瑞

■背景资料

近来医学科技的进步使得肿瘤治疗取得了一些进展, 尽管如此, 在全人类不同种族人群中、不同个体间仍有显著的化疗药物治疗有效率/毒性反应的异质性。随着赫赛汀(herceptin)、格列卫(gleevec)这些分子靶向药物的应用, 肿瘤学家们期望在未来5-10 a内, 分子病理学和分子诊断技术的临床应用将对药物的研究、发展带来彻底变革, 从药物的选择、剂量、给药方式及新药的应用等全方面实现真正意义上的个体化医疗。

王立峰, 钱晓萍, 刘宝瑞, 南京大学医学院附属南京市鼓楼医院肿瘤中心 江苏省南京市 210008
通讯作者: 刘宝瑞, 210008, 江苏省南京市, 南京大学医学院附属南京市鼓楼医院肿瘤中心, baoruiliu@medmail.com.cn
电话: 025-83304616-21002 传真: 025-83107095
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摘要

人类基因组计划的顺利完成及目前正在进行的蛋白质组学研究使当今的医疗领域产生了重大变化。肿瘤分子基础知识的不断扩展使人们认识到对于包括肿瘤、心血管等多种疾病而言, 基因表达谱及某些基因的单核苷酸多态性(single nucleotide polymorphism, SNPs)可用于指导治疗。药物遗传学/药物基因组学作为肿瘤新的治疗平台受到广泛关注并使得真正意义上的个体化治疗成为可能。我们着重论述了临床上与肿瘤治疗疗效/毒性反应相关的基因多态性与基因表达谱的变化, 初步探讨了药物遗传学/药物基因组学在恶性肿瘤中的广泛应用前景与目前现状之间的差距及相关原因。

关键词: 药物遗传学; 药物基因组学; 肿瘤治疗;

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0 引言

尽管目前肿瘤治疗取得了一些进展, 但在不同种族人群中、不同个体间仍有显著的化疗有效率/毒性反应的异质性。目前应用的抗肿瘤药物对至少70%的患者疗效有限, 20%-40%的患者甚至有可能接受了错误的药物治疗^[1-4]。肿瘤分子生物学领域的不断扩展使人们逐渐认识到, 分子生物学基因表达谱的显著差异是指导肿瘤个体化化疗的基础^[5,6]。药物遗传学/药物基因组学作为肿瘤新的治疗平台受到广泛关注, 肿瘤药物基因组学/遗传学的核心目的是通过对个体基因/遗传多态性的研究, 预测其对某种药物的反应性/毒性^[7-13]。我们将着重讨论一些具有重要临床意义的预测因子。

1 药物效应预测分子

1.1 5-Fu相关药物效应预测分子 5-FU进入体内后被活化为氟脲嘧啶脱氧核苷酸(5-FdUMP), 通过形成稳定的三联体复合物(胸苷酸合成酶、5, 10-甲酰四氢叶酸、5-FdUMP)抑制胸苷酸合成酶, 从而阻碍脱氧尿苷酸(dUMP)转变为脱氧胸苷酸(dTMP)。

1.1.1 胸苷酸合成酶mRNA (thymidylate synthase mRNA, TS mRNA) 的表达 TS的表达不仅与以5-Fu为基础的化疗抵抗相关, 而且与临床预后相关。Lenz *et al* ^[14]发现TS mRNA水平高的胃癌患者中位生存期6 mo, 而TS mRNA水平低者中位生存期43 mo。随后, TS mRNA水平的高低与化疗有效率、生存期之间的关系在肠癌^[15,16]、肺癌^[17]、乳腺癌^[18]中也得到进一步证实。综合分析若干肠癌患者5-Fu化疗有效率与TS水平相关性的文献发现^[19-24], 转移性的肠癌患者肿瘤组织内低表达TS者可从姑息性5-Fu化疗获益; 相反, 局部进展肠癌患者肿瘤组织内低表达TS者未见明显获益于辅助化疗。然而, 这些结果大多来源于以5-Fu为基础化疗的回顾性分析, 因此有必要在前瞻性研究中使用新的联合化疗方案重新进行评估。

1.1.2 胸苷酸合成酶启动子增强区域 (thymidylate synthase promoter enhancer region, TSER) TS的调节控制机制相当复杂, TSER的基因多态性在一定程度上控制着TS的表达。TSER由不同拷贝数的28 bp (base pair)三联子重复序列构成, 提高28 bp三联子重复序列数目将导致TS基因表达增加, TS酶活性提高^[25]。研究接受新辅助放疗的肠癌患者TSER遗传表型发现, 与3R纯合子相比, 携带有2R等位基因的患者病理分期程度相对较高^[26]。另一组221例肠癌患者接受辅助5-Fu+CF方案化疗的研究中更加确定了TSER多态性的临床价值: 2R纯合子和2R/3R杂合子(163/221)有显著临床生存期的提高, 而3R纯合子(58/221)无生存获益^[27]。Sarries *et al* ^[28]分析400例(100例对照, 300例肠癌、肺癌、乳腺癌)标本发现TSER多态性与TS mRNA表达相关, 3R纯合子有较高的TS mRNA表达活性。而来自日本

的报道TS遗传型与TS mRNA表达无明显关系, 同时发现TS多态性分布与欧美研究结果不同^[29]. 这表明种族的不同在很大程度上影响着TS遗传表型.

1.2 卡培他滨(xeloda)相关药物效应预测分子 由于卡培他滨具有在高表达胸苷酸磷酸化酶(thymidine phosphorilase, TP)的肿瘤细胞内释放5-Fu这一特点, 使其成为一个很有前景的肿瘤特异性药物. TP是血小板源性的内皮细胞生长因子, 也是肿瘤相关血管生成因子, 主要与肿瘤细胞的高增殖率、转移侵袭力以及肿瘤性血管生成有关, 同时有抗凋亡作用^[30,31]. 有资料表明高表达TP的肿瘤组织能更有效地激活5氟脱氧尿苷为5-Fu^[32,33]. 因此对于准备接受卡培他滨治疗患者的遗传特性分析有必要包括TP、TS、二氢嘧啶脱氢酶(dihydropyrimidine dehydrogenase, DPD)三方面以评估治疗失败的风险并判断预后^[16]. 实际上, 在转移性肠癌患者中, 低表达TS、DPD、TP基因者生存率最高^[16,21]; 同时TP/DPD基因表达的比值在化疗敏感与抵抗肿瘤中显著不同^[34].

1.3 铂类药物相关药物效应预测分子 铂类药物通过形成链内/链间DNA加合物抑制细胞复制. 对铂类药物的抵抗可通过以下机制发生: 减少药物积聚、通过共轭结合解除药物毒性, 提高对铂类药物诱导产生的DNA加合物的耐受性, 或者提高DNA修复能力^[35,36]. 核苷酸减切修复(nucleotide excision repair, NER)途径与铂类抵抗有很强的相关性, 核苷酸切除修复交叉互补组1(excision repair cross-complmenting group 1, ERCC1)、XPD(xeroderma pigmentosum complementation group D)、XPG(xeroderma pigmentosum complementation group G)等均是NER途径中的关键因子.

1.3.1 ERCC1 56例接受GP方案化疗的非小细胞肺癌(NSCLC)患者, ERCC1高表达者中位生存期仅5 mo, 而低表达者中位生存期达15 mo. 这一有显著统计学意义的结果表明ERCC1水平可作为铂类治疗一独立的预后变量, 是评价DDP抵抗的一个关键基因^[28].

1.3.2 XPD与XPG 分析73例接受5-Fu+草酸铂治疗的转移性肠癌患者的XPD基因多态性, 发现1个SNP导致XPD蛋白第751密码子上赖氨酸(Lys)转变为谷氨酰胺(Glu), 这一多态性与疗效显著相关: Lys/Lys基因型患者中位生存期17.4 mo, 而Lys/Glu杂合子12.8 mo, Glu/Glu纯合子3.3

mo; 而且, Lys/Lys基因型患者客观有效率更高($P = 0.015$)^[37]. 尽管目前对这一SNP突变导致铂类疗效异同的具体机制尚不清楚, 但并不影响这一SNP作为铂类药物效应预测因子的进一步应用. 此外, Lys突变导致DNA修复能力的变化尚在进一步研究中. 对33例接受草酸铂治疗肠癌患者, Vila *et al*^[38]分析了与DNA修复相关的多种基因SNPs. 发现XPD第751位密码子C—A碱基的突变与草酸铂治疗毒性/有效率相关, 与XPD A/A型相比, 携带XPD C/C型等位基因患者更易发生血液学毒性(44% vs 9%); 同时发现, XPG第3位密码子C—T碱基变异与草酸铂药物有效率相关, 携带XPG C/C型等位基因的患者客观缓解率显著高于XPG C/T、T/T基因型患者(70% vs 8%, $P = 0.002$). 所以认为, XPD C/C与血液学毒性相关, 而XPG C/C可作为缓解率、TTP及生存期的预测指标.

1.3.3 XRCC1(X线修复交叉互补组1, X-ray repair cross-complementing group 1) Stoehlmacher *et al*^[39]研究61例接受5-Fu+草酸铂治疗的进展期肠癌, 发现XRCC1基因中第399位密码子的一个SNP影响其氨基酸产物为精氨酸(Arg)或谷氨酰胺(Glu). 由于Glu可导致DNA修复能力增加, 使得铂类化疗抵抗^[40]. 故这一SNPs与治疗效果有明显关系: 73%的缓解者具有Arg/Arg遗传型, 66%无反应者具有Glu/Glu或Arg/Glu遗传型^[39].

1.3.4 谷胱甘肽-S-转移酶P1(Glutathione-S-transferas P1, GSTP1) 谷胱甘肽-S-转移酶催化谷胱甘肽与多种毒性复合物(包括铂类制剂)结合, 形成低毒高水溶性物质排出细胞外^[41]. GST家族包括5个亚型: GSTA1、GSTP1、GSTM1、GSTT1、GSTZ1. Stoehlmacher *et al*^[42]发现GSTP1的一个SNPs与107例接受5-Fu+草酸铂化疗的转移性肠癌患者总体生存率相关. 这一SNPs导致在GSTP1蛋白密码子105位异亮氨酸(Iso)转变为缬氨酸(Val), 酶活性降低^[43], 从而产生了疗效的差异: 中位生存期Val纯合子24.9 mo, Val杂合子13.3 mo, Iso纯合子7.9 mo($P < 0.001$).

1.4 紫杉类相关药物效应预测分子 目前认为紫杉类抵抗的重要机制是微管蛋白的过度表达. 有研究表明 β 微管蛋白III表达水平与卵巢癌、前列腺癌及非小细胞肺癌细胞系中的紫杉类药物抵抗有关^[44]. Montgomery *et al*^[45]报道在NIH3T3细胞系中, EGFR超家族成员HER2的过表达导致 β 微管蛋白IV表达水平增加3倍, 从而导致转化细胞对紫杉类药物抵抗. 因此, 对微管

■ 研究前沿

在肿瘤分子生物学领域知识的不断扩展使得人们逐渐认识到, 对各种实体肿瘤和血液学肿瘤, 分子生物学基因表达谱的显著不同是指导个体化疗的基础. 药物遗传学/药物基因组学作为肿瘤新的治疗平台受到广泛关注.

■创新盘点

本文较为全面地概述了药物遗传学/基因组学在化疗中对药物疗效及毒性的预测作用,着重探讨了一些相对比较成熟的分子,并客观分析了该领域所面临的相关问题,对开展相关研究具有一定帮助。

蛋白各亚型基因突变和基因表达水平的分析在评估肿瘤细胞是否对紫杉类药物敏感中可能具有一定作用。最近研究指出乳腺癌易感基因家族 (breast cancer susceptibility gene, BRCA) 的功能失活在散发性乳腺癌、卵巢癌中也有发现, BRCA功能失活与DNA双链断裂的修复功能受损有关, 相关患者对DNA交联剂、诱导DNA双链断裂药物敏感, 而对作用于有丝分裂纺锤体的药物如紫杉类抵抗^[46]。

1.5 健择相关药物效应预测分子 核糖核苷酸还原酶M1(ribonucleotide reductase M1, RRM1): 核糖核苷酸还原酶是DNA合成途径的限速酶, 在DNA合成修复途径中发挥重要作用。它主要催化二磷酸核糖核苷酸转化为二磷酸脱氧核糖核苷酸, 包括M1、M2两种亚型。多篇文献报道 RRM1过表达者健择化疗不敏感^[28,37,47]。Rosell *et al*^[47]研究了100例NSCLC, 发现RRM1与DNA合成、修复及GEM代谢有关; ERCC1与DDP活性有关, 二者的表达水平高度相关。RRM1 mRNA低表达或RRM1、ERCC1 mRNA均低表达者GP方案显著获益, 中位生存期明显延长 (13.7 mo vs 3.6 mo)。

1.6 表皮生长因子受体(epidermal growth factor receptor, EGFR)抑制剂 EGFR是一跨膜糖蛋白, 与配体交联发生二聚化作用, 从而刺激细胞增殖^[48,49]。大量研究表明EGFR信号通路涉及各种实体瘤的生成及预后。EGFR酪氨酸激酶(TK)的活化已被确认为起始细胞内信号传递的关键事件, 能调节细胞增殖、分化及细胞生存^[50,51]。肿瘤中EGFR信号途径中EGFR基因的过表达是一普遍现象, 其基因的转录起始于富含GC启动子区的多个起始位点。EGFR基因的第一个内含子能调节基因转录, 它位于转录增强子附近, 包含一具有高度遗传多态性的CA二核苷酸重复序列^[52]。Gebhardt *et al*^[53]报道CA重复序列的数目与EGFR基因转录活性呈负相关。近来一些新的药物通过胞内/胞外途径阻断EGFR功能或阻断其胞内信号通路发挥抗肿瘤作用^[54]。Lynch *et al*^[55]研究发现9例对gefitinib治疗有效患者中8例在EGFR基因酪氨酸激酶区域存在体细胞突变; 在25例未接受过gefitinib治疗的NSCLC患者中2例也存在类似突变。体外实验进一步证实EGFR突变株对EGF反应性高且对gefitinib治疗更为敏感。其他研究者也有类似报道^[56]。虽然上述研究结果有待于大样本临床试验证实, 但提示检测EGFR基因可能是一有效的筛选合适患者接受gefitinib

治疗的途径。

2 药物毒性预测分子

2.1 5-FU相关毒性预测因子 二氢嘧啶脱氢酶(dihydropyrimidine dehydrogenase, DPD)是5-FU代谢的限速酶, 在5-FU代谢中有着重要作用。体内5-FU剂量的85%都是通过DPD代谢失活。DPD活性丧失时由于代谢清除途径受损大量活性代谢产物5-FdUMP生成, 导致发生严重的5-FU相关毒性反应。迄今为止已确定DPD有39种不同的基因突变和多态性^[57], 其中最常见的是DPD基因第1986位发生A到G的转化(等位基因DPYD*2A)导致外显子14缺失, 形成无活性的酶。在发生严重5-FU毒副作用的患者中, 24%-28%可检测到这种突变^[58]。当然, DPYD*2A并不是发生严重5-FU毒性的唯一机制^[58]。由于体内存在复杂的分子机制调控DPD活性, 因而使得将DPD基因型的检测用于预测严重5-FU毒性的发生仍需不断深入。

2.2 CPT-11相关毒性预测因子 CPT-11是一无活性的前药, 需经羧酸酯酶的活化转变为其活性代谢产物SN-38而发挥效用^[59]。活性SN-38的主要清除途径是通过肝脏UGT1A1的糖基化作用转变为无活性的SN-38G, 后者通过尿液、胆汁排出。作为CPT-11主要的剂量限制性毒性作用, 腹泻、中性粒细胞减少均与SN-38水平增高有关^[60]。目前关于CPT-11的药物遗传学方面的研究主要集中于由UGT1A1多态性引起的SN38G变化。研究发现UGT1A1的表达是高度可变的, 由此引起不同患者间SN-38糖化反应的速率相差最高达50倍^[60-62]。UGT1A1基因启动子区具有一定多态性, 其不典型TATA盒区域中包含了5-8个TA重复序列。其中以含6个TA重复序列的基因型最为常见, 并观察到随着TA重复序列数目的增加, UGT1A1表达下降^[60,63]。UGT1A1的变异型——UGT1A1*28启动子不典型TATA盒区域包含7个TA重复序列, 该变异型与UGT1A1表达下降有关, 并导致SN-38G水平降低^[60-62,64]。在CPT-11治疗中, UGT1A1*28等位基因的存在导致活性代谢产物SN-38的显著增加, 从而发生腹泻/中性粒细胞减少的几率显著增加^[64,65]。提示UGT1A1基因型的检测可能用于临床预测与CPT-11相关的严重毒副作用的发生。

3 问题与展望

尽管药物遗传学/基因组学领域的相关研究备受瞩目且其实验证据水平高^[66,67], 但该领域在临床

中的应用却处于早期阶段. 究其原因有多种, 首先, 实验室结论的临床推广涉及实用性、可操作性、社会及伦理等多方面的因素; 其次, 早期的一些相关临床实验在实验设计时未能充分考虑到临床环境因素等多种客观因素的影响, 由此产生一些有争议的结果, 可能对药物遗传学/基因组学的临床应用产生了一些负面影响; 再次, 药物基因组学的广泛应用面临的另一个重要问题是检测的标准化问题. 当前在基因芯片技术领域存在多种微阵列技术平台, 使用不同系列的基因及不同的杂交信号、检测方法等, 为同一目的而进行的研究常常得到不同的结果. 但随着基因芯片技术及数据分析系统的不断完善, 相信这些问题在不久的将来可被解决. 毫无疑问, 在下一阶段药物遗传学/基因组学的研究中将致力于在科学证据与临床应用间建立桥梁, 这需要来自学术界、技术领域 (如计算机生物信息技术)、临床上、伦理方面、社会、法律、政府调节机构及财政上多方面的支持^[68]. 随着分子生物技术日新月异的进展, 药物遗传学/基因组学研究在近年来取得迅猛发展, 为医疗领域带来革命性变革. 在艾滋病治疗领域, 药物基因组学已用于临床以指导对艾滋病患者进行适当的抗病毒治疗, 使真正意义上的个体化治疗成为可能^[69,70]. 这一点对于艰难的肿瘤治疗尤为重要. 该领域研究的最终目标是通过个体肿瘤患者遗传状态分析, 选择最佳治疗方案, 不仅仅提高药物治疗的有效率而且避免相关严重毒性反应的发生, 从而开辟个体化化疗的新纪元.

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■应用要点

有助于深入开展药物遗传学和药物基因组学相关的实验研究, 有助于临床开展基因指导下的个体化化疗, 以提高疗效、降低毒副反应.

■名词解释

药物遗传学
(pharmacogenetics) 是研究与药物反应性/毒性相关的个体间DNA序列/基因多态性的差异的一门学科, 药物作用靶点、相关致病基因或药物代谢酶等多个环节的遗传变异都可被当作预测药物效应或毒性的指标。

药物基因组学
(pharmacogenomics) 是将全基因组技术(即基因和蛋白表达数据)用于预测一个患病个体对一个/一组药物的敏感性或抵抗性的学科。

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■同行评价

药物遗传学/药物基因组学在肿瘤治疗中的作用日益受到重视, 本文综述了药物遗传学/药物基因组学在化疗中对药物疗效及毒性的预测作用。文章引用文献较全面, 基本概括了最新在这一方面研究的进展, 条理性强, 具有一定的学术水平, 对开展研究有帮助。

电编 张勇 编辑 管鑫妍 审读 张海宁