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文献综述 REVIEW

幽门螺杆菌对左氧氟沙星耐药的研究进展

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Advances in research of *Helicobacter pylori* resistance to levofloxacin

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Abstract

Helicobacter pylori (*H. pylori*) has been identified as the most important risk factor for chronic active gastritis and peptic ulcer disease. Resistance to antibiotics is increasing in *H. pylori* and is the main reason for failure of *H. pylori* eradication therapy. It is now widely accepted that resistance to fluoroquinolones (levofloxacin) is related with mutations of *H. pylori gyrA* gene. Molecular mechanisms of and detection methods for *H. pylori* resistance to levofloxacin have become the focus of current research. Therefore, study on *H. pylori* resistance to antibiotics is of great significance for eradication therapy of *H. pylori* infection.

Key Words: *Helicobacter pylori*; Resistance; Levofloxacin; Genetic mutations

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摘要

幽门螺杆菌(*Helicobacter pylori*, *H. pylori*)是慢性胃炎、消化性溃疡的主要致病因子. 随着抗生素广泛使用, *H. pylori*对抗生素耐药日渐严重, 而耐药是导致其根治和清除失败的主要原因. 现已证实*H. pylori*耐氟喹诺酮类药物(左氧氟沙星)的机制与*gyrA*基因的点突变有关. 随着*H. pylori*耐药率的逐年升高, 有关*H. pylori*的耐药分子机制和检测技术成为研究热点. 因此, 开展*H. pylori*耐药的相关研究对*H. pylori*的治疗有重大意义.

关键词: 幽门螺杆菌; 耐药; 左氧氟沙星; 基因突变

核心提示: 高分辨率溶解曲线(high-resolution melting, HRM)分析幽门螺杆菌(*Helicobacter pylori*, *H. pylori*)耐药基因, 无需特殊仪器, 可快速、准确分析*H. pylori gyrA*基因突变, 有着较高的应用价值及推广前景.

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0 引言

幽门螺杆菌(*Helicobacter pylori*, *H. pylori*)是慢性胃炎、消化性溃疡的主要致病因子, 与胃癌、胃黏膜相关淋巴组织淋巴瘤(mucosa associated lymphoid tissue, MALT)及一些胃外疾病关系密切, 已被世界卫生组织列入Ⅰ类致癌原[1-6]. 近年来国内外学者推荐左氧氟沙星(levofloxacin)作为根除*H. pylori*的一线或序贯治疗药物[7-10], 然而随着左氧氟沙星广泛使用, *H. pylori*的耐药菌株也日益增加[11]. 因此, 研究*H. pylori*对左氧氟沙星耐药情况、耐药机制和检测方法对指导临

■背景资料
幽门螺杆菌(*Helicobacter pylori*, *H. pylori*)*gyrA*基因突变是*H. pylori*对左氧氟沙星耐药的重要机制. 基因突变可导致氨基酸替代造成gyrA蛋白空间构象改变, 使左氧氟沙星不能与*gyrA*基因结合, 进而不能抑制*H. pylori*基因组复制, 最终导致左氧氟沙星耐药.

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■研发前沿
细菌的耐药基因的检测已成为研究热点, 如何通过快速、准确的分子生物学技术检测耐药基因是研究关键.

床用药显得尤为重要. 本文就*H. pylori*对左氧氟沙星耐药情况作一综述.

1 *H. pylori*对左氧氟沙星耐药的流行病学调查

左氧氟沙星是一种新型的氟喹诺酮类抗生素, 其抗菌谱广、疗效高、不良反应少[9]. 有研究结果[12]显示标准三联方案[质子泵抑制剂(proton pump inhibitor, PPI)+克拉霉素+阿莫西林/甲硝唑]对*H. pylori*的根除率接近80%, 而含有左氧氟沙星的新三联疗法(PPI+左氧氟沙星+克拉霉素)对*H. pylori*根除率高达90.6%, 且新三联疗法具有不良发生率低、费用相对便宜等优势[13-16]. *H. pylori*对左氧氟沙星的耐药率在不同的国家和地区不尽一致. 在欧美地区, 法国学者Cattoir等[17]报道2004-2005年巴黎128株*H. pylori*菌株对左氧氟沙星的耐药率为17.2%. Bogaerts等[18]2006年调查了比利时地区*H. pylori*对氟喹诺酮药物的耐药率, 488株分离菌株对左氧氟沙星的耐药率为16.8%. 爱尔兰学者O'Connor等[19]采用E-test分析了2008-2009年85例*H. pylori*分离株对左氧氟沙星的耐药率, 其结果显示45岁以下年龄组的左氧氟沙星耐药率为2.6%, 而45岁以上年龄组则为19.1%. 意大利Marzio等[20]2006年研究结果显示83株*H. pylori*菌株中, 对左氧氟沙星的原发性耐药率为9.7%, 而继发性耐药率为12.2%. 2012年, 意大利另一学者[21]报道左氧氟沙星为22.1%, 女性成为耐药的高风险群体. 美国学者Carothers等[22]研究结果显示125例*H. pylori*感染者中对左氧氟沙星的耐药率为8.8%, 左氧氟沙星耐药和患者在过去的10年超量使用氟喹诺酮药物有关. 在亚洲地区, Binh等[23]在2008年对越南Vietnam地区103株*H. pylori*菌株对左氧氟沙星耐药情况进行了分析, 左氧氟沙星的耐药率为18.4%, 菌株耐药和*H. pylori*感染者的性别、年龄并无关联. 伊朗学者[24]报道伊朗2009-2010年*H. pylori*对左氧氟沙星的耐药率为5.3%. 然而, 在马来西亚, 有文献[25]报道*H. pylori*菌株对左氧氟沙星的耐药率为0. 香港学者[26]报道香港地区2004-2005年*H. pylori*对左氧氟沙星的耐药率为11.5%. Hung等[27]分析了台湾南部地区1998-2007年*H. pylori*对左氧氟沙星的耐药率及耐药趋势, 结果显示耐药率从2.8%(1998年-2003年)上升至11.8%(2004年-2007年). Su等[28]对中国东部沿海两省八个地区的7731例*H. pylori*分离株进行抗生素敏感性试验, 结果表明左氧氟沙星的耐药率为20.6%. 施莉等[29]报道浙江金华地区*H. pylori*对左氧氟沙星的耐药率高达31.58%. Gao等[30]分析了2000-2009年北京地区374株*H. pylori*菌株对左氧氟沙星的耐药趋势, 发现*H. pylori*分离株平均耐药率高达50.3%, 其耐药呈逐年上升趋势(27.1%-63.5%), 继发性耐药率明显高于原发性.

总之, (1)各国家或地区的*H. pylori*菌株对左氧氟沙星耐药率差别较大, 耐药率为0%-50.3%, 存在明显的地域差异, 中国属于耐药率较高的国家, 且耐药呈上升势态; (2)尽管有报道高年龄组、女性耐药率显著高于低年龄组及男性, 但年龄、性别和耐药的关联还有待进一步确证; (3)左氧氟沙星继发耐药率明显高于原发耐药率, 氟喹诺酮的用药史与*H. pylori*继发性耐药率的上升有一定的相关性.

2 *H. pylori*对左氧氟沙星的耐药分子机制

氟喹诺酮类药物的抗菌机制是通过抑制细菌DNA旋转酶和拓扑异构酶, 从而干扰细菌DNA复制. 就普通细菌而言, 氟喹诺酮类药物的耐药主要是由其DNA旋转酶上的*gyrA*基因或拓扑异构酶Ⅳ上的*parC*基因的喹诺酮类药物耐药决定区(quinolone resistance determining region, *QRDR*)发生突变所致, 然而, *H. pylori*缺乏拓扑异构酶Ⅳ, 所以*H. pylori*对左氧氟沙星的耐药主要是由DNA旋转酶上*gyrA*基因的QRDR发生点突变引起[31-33]. *gyrA*基因位于细菌染色体第38分位, 编码DNA解旋酶A亚基, 该基因核苷酸存在一定的保守区, 尤其是编码122位氨基酸周围的区域. *gyrA*基因耐药突变区域主要集中在67-106位氨基酸, 该区域的核苷酸变化在细菌对氟喹诺酮类药物方面具有十分重要的作用. Wang等[34]研究显示: 在45株*H. pylori*菌株中, 27株耐药菌株发生*gyrA*基因突变, 其中16株发生Asn-87突变, 11株发生Asp-91突变. Miyachi等[35]也报道在原发性耐药菌株中, *gyrA*基因Asn-87突变几率高于Asp-91突变, 且Asp-91突变菌株呈低浓度耐药趋势, 仅有4.4%的耐药菌株发生*gyrB*基因突变. 香港学者[26]则报道耐药菌株*gyrA*基因在87、91及130发生氨基酸改变, 而突变频率最高的为91, 日本学者Murakami等[36]也发现在105株*H. pylori*菌株中, 44株发生*gyrA*基因突变, 其中14株Asn-87突变, 25株Asp-91突变, 剩余5株在其他基因区突变. 施莉等[29]研究结果显示: 在10例耐药菌株中, 2例C261A突变, 1例C261G突变, 2例G271A突变, 2例A272G突变, C261A与G271A、

A272G双突变2例, G271A与A272G双突变1例而在26株敏感菌株中未发现突变. Fujimura等[37]对左氧氟沙星耐药菌株的*gyrA*基因进行序列分析发现了G271A、G271T和A272G突变, 证实了DNA旋转酶上A亚基Asn-91密码子发生了突变. Rimbara等[38]则报道高浓度左氧氟沙星耐药菌株*gyrA*出现Asn-87突变, 并发现gyrB氨基酸361位置突变可视为一个和氟喹诺酮类药物耐药相关的新位点.

总之, *H. pylori*的*gyrA*基因发生点突变是耐左氧氟沙星的主要机制, 点突变主要以Asn87、Asp91为主, 突变形式存在地区差异, *gyrB*基因突变及一些新的点突变需进一步研究证实.

3 *H. pylori*对左氧氟沙星耐药生物学的检测方法

*H. pylori*耐药的传统生物学检测方法是取胃黏膜或组织, 细菌增殖培养后, 进行E-test、琼脂稀释法、纸片扩散法等体外药敏试验. E-test操作简便, 但试纸价格昂贵; 琼脂稀释法技术要求较高; 纸片扩散法简便易行, 但结果受诸多因素的影响, 不够准确[39]. 随着分子生物学技术的发展, 越来越多基于PCR技术的分子诊断技术被应用于检测*H. pylori*的耐药性, 这些技术都是建立在检测和*H. pylori*耐药相关的基因突变的基础上. Hung等[27]、Wang等[34]、Fujimura等[37]、Garcia[40]采用PCR技术扩增出*gyrA*和*gyrB*基因的特定片段, 随后对扩增产物进行测序, 该法能准确检测*gyrA*和*gyrB*基因QRDR发生的突变. Nishizawa等[41]建立了等位基因特异性PCR快速准确检测*H. pylori*左氧氟沙星耐药基因, 该法将突变碱基设计于突变引物的3'端, 利用Taq酶缺乏3'→5'外切酶活性, 延伸反应因磷酸酯键形成困难而受阻, 扩增反应后, 根据电泳谱即可确定样品的基因型. Rajper等[42]应用PCR结合反向线性探针杂交技术快速、准确检测耐左氧氟沙星*H. pylori*菌株*gyrA*基因发生的突变. 施莉等[31]根据*H. pylori gyrA*出现的和左氧氟沙星耐药相关的点突变, 设计特异性探针构建了荧光基因芯片, 该芯片检测体系可以对临床分离的*H. pylori*菌株进行准确耐药性分型.

总之, 大多数学者采用PCR结合DNA测序分析*H. pylori*的耐药基因, 但DNA测序一般实验室不能开展. 基因芯片技术以其快速、准确、高通量等优点广泛应用与分子检测领域[43-48], 但其需要特殊设备如: 芯片点样仪、荧光扫描仪等, 其普及条件尚不成熟. 高分辨率溶解曲线分析技术是近几年来在国外兴起的一种用于突变和基因分型的最新遗传学分析方法. 他不受突变碱基位点与类型局限, 无需序列特异性探针, 在PCR结束后直接运行高分辨熔解, 实现了真正的闭管操作, 可完成对样品突变、单核苷酸多态性-SNP、甲基化、配型等的分析. 因操作简便快速, 使用成本低、结果准确, 而受到学者普遍关注[49-53].

■相关报道

目前, 已有许多基于PCR技术的分子检测手段应用于检测*H. pylori-gyrA*基因突变. 施莉等在《芯片检测幽门螺杆菌左氧氟沙星耐药*gyrA*基因突变的应用》报道了荧光基因芯片可以快速检测*gyrA*基因突变, 具有高灵敏度及高特异性.

4 结论

随着喹诺酮类抗生素广泛使用, *H. pylori*对左氧氟沙星的耐药率有逐年上升的趋势. 因此, 建立一种快速、准确、方便及实用的检测手段对分析左氧氟沙星的耐药率, 以及指导临床规范用药都有着重要的临床意义. 高分辨率溶解曲线是近年来发展起来的一种突变和基因分型的最新遗传学分型方法, 操作简便、成本低廉、结果准确, 有着较高的应用价值及推广前景.

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■创新盘点

本文分析了近年来国内外*H. pylori*对左氧氟沙星的耐药率、耐药机制及分子检测手段, 可供科研及临床工作者参考.

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■同行评价
本文较全面地综述了喹诺酮类药物对*H. pylori*的耐药机制, 有一定参考价值.

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• 消息 •

《世界华人消化杂志》性质、刊登内容及目标

本刊讯 《世界华人消化杂志》[国际标准刊号ISSN 1009-3079 (print), ISSN 2219-2859 (online), DOI: 10.11569, Shijie Huaren Xiaohua Zazhi/*World Chinese Journal of Digestology*], 是一本由来自国内30个省、市、自治区、特别行政区的483位胃肠病学和肝病学专家支持的开放存取的同行评议的旬刊杂志, 旨在推广国内各地的胃肠病学和肝病学领域临床实践和基础研究相结合的最具有临床意义的原创性及各类评论性的文章, 使其成为一种公众资源, 同时科学家、医生、患者和学生可以通过这样一个不受限制的平台来免费获取全文, 了解其领域的所有的关键的进展, 更重要的是这些进展会为本领域的医务工作者和研究者服务, 为他们的患者及基础研究提供进一步的帮助.

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