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文献综述 REVIEW

白介素-1B基因多态性与胃癌易感性关系的研究进展

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Progress in understanding the association between interleukin-1B gene polymorphisms and susceptibility to gastric cancer

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Abstract

Gastric cancer is one of severe diseases threatening human health and has a close association with *Helicobacter pylori* infection. Interleukin-1B (*IL-1B*) gene polymorphisms have been suggested to be associated with susceptibility to gastric cancer; however, there is still controversy over this point of view. In this paper we will summarize recent progress in understanding the association between *IL-1B* gene polymorphisms and susceptibility to gastric cancer in population in different areas or of different races.

Key Words: Interleukin-1B; Gene polymorphism; Gastric cancer

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摘要

胃癌(gastric cancer, GC)是严重危害人类健康的恶性肿瘤之一, 除与幽门螺杆菌(*Helicobacter pylori*, *H. pylori*)感染有密切关系外, 部分研究认为白介素-1B(interleukin-1B, *IL-1B*)基因多态性与GC易感性存在关联, 从而增加GC的发生风险. 然而, 此观点尚存在争议. 综述*IL-1B*基因多态性在不同地区、不同种族间与GC易感性之间关系的研究和进展, 为进一步探讨二者关系提供参考.

关键词: 白介素-1B; 基因多态性; 胃癌

核心提示: 本文列举了近些年来有影响力的国内外研究, 通过研究事实说明胃癌的发生与白介素-1B(interleukin-1B, *IL-1B*)基因的关系存在争论. 而本文的精华部分是对研究结果不一致的可能因素或者原因进行的探讨和分析, 为进一步明确二者关系进行梳理.

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0 引言

胃癌(gastric cancer, GC)是世界上第5大最常见的肿瘤, 也是世界范围内第2大最普遍的肿瘤相关性死亡原因[1]. GC的发生被认为是多重危险因素的组合: 幽门螺杆菌(*Helicobacter pylori*, *H. pylori*)菌株毒力, 环境因素及长期积累, 特定的基因学改变, 及长期合并萎缩性胃炎的年长者等[2]. 由*H. pylori*感染诱导的慢性炎症反应被认为是重要的致癌机制[3]; 但*H. pylori*感染被认为是必需但不充分的诱发胃腺癌的原因, 因为只有不足1%感染*H. pylori*的个体最终发展成为胃

■背景资料
随着世界范围内人均寿命的逐步提高及生活水平的不断改善, 人们越来越重视生活质量的高低. 而恶性肿瘤由于致残、致死率高及其带来的疾病负担, 已成为威胁人类健康最大的杀手之一. 其中, 胃癌的高发是人类面临的最棘手问题之一; 因此积极探索其发病成因及机制从而制定一系统防治措施成为全人类的课题. 而胃癌的发生与基因究竟是否存在关系是其中的一个研究热点.

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■研发前沿
*IL-1B*基因多态性在不同种族、不同地区间的分布频率不同, 与胃癌易感性的关系长期存在争论. 是何原因导致的分布频率不同及其与胃癌究竟是否相关仍是一个难点.

腺癌[4]. 因此, GC代表了炎症诱导恶性肿瘤的典型例子, 并且突出了宿主因素在疾病发展过程中的重要性[5]. 在一系列针对GC易感性的研究中, 白介素-1B(interleukin-1B, *IL-1B*)基因多态性已成为一个研究热点. 然而, 目前众多涉及二者间是否存在相关性的研究尚未得到一致结论.

1 白介素-1β的生物学效应及白介素-1B基因多态性

IL-1是一种典型的前炎性细胞因子及炎症反应中的关键因子, 全身多种细胞如单核-巨噬细胞细胞、嗜中性粒细胞、自然杀伤细胞、淋巴细胞、表皮细胞等都可以产生. 他具有激活炎性细胞游走和增强其功能、诱导血管内皮细胞表达黏附分子等功能, 从而参与炎症反应、肿瘤性疾病、自身免疫性疾病、动脉粥样硬化症以及移植排斥反应等病理过程. 其亚型IL-1β参与到宿主感染*H. pylori*以及感染后的病理过程中, 被认为是*H. pylori*感染后诱发胃癌的协同因子.

侵入胃内的*H. pylori*主要驻留在胃黏膜表面的黏液凝胶层, 很少入侵腺体[5]. 他可通过脲酶介导的肌球蛋白II的激活破坏胃黏膜屏障功能[6], 并诱导黏膜上皮细胞异常的CpG岛甲基化从而促进抑癌基因失活[7]. 同时, 他还可影响线粒体的功能及DNA修复, 进而直接调节胃黏膜细胞的遗传不稳定性[8]. 此外, *H. pylori*在胃内的局部感染上调了胃黏膜IL-1β水平[9], 后者启动和增强了针对*H. pylori*感染的炎症反应. 作为目前已知的最强大抑酸剂[1], IL-1β的过度产生导致胃酸分泌过少, 进一步促进细菌定植[10]; 并在胃内通过IL-1RI/核因子κB(nuclear factor-κB, NF-κB)通路激活骨髓来源的抑制性细胞(myeloid-derived suppressor cells, MDSCs), 使MDSCs显著增加; 他还降低了E-钙黏蛋白的表达[11], 并诱导胃泌素及自由基的过多产生, 从而促使上皮细胞向间质细胞转变、促进异型增生, 最终导致黏膜的肿瘤性转化[2,12,13]. 不仅如此, 持久的炎症反应还可导致遗传的不稳定性, 通过一代又一代的致突变化学物质, 如活性氧[14], 可直接损害宿主细胞核和线粒体DNA, 降低胃黏膜的抗氧化能力[15]. 在形成肿瘤以后, IL-1β还可调整GC细胞中ATP-结合盒转运蛋白亚族G2(ATP-binding cassette sub-family G member 2, ABCG2)在转录和转录后水平的表达, 增强了ABCG2在GC细胞中的功能[16], 从而增加GC化疗过程中的多药耐药几率; 并通过上调黏附分子的表达影响GC细胞黏附[17]. 基础研究已证实, 在转基因的小鼠中, 人类IL-1β在胃中特定的表达可诱导胃炎和GC的发生[18-20]. 虽然IL-1β的产生依赖多种因素, 有越来越多的证据表明个体遗传背景扮演了主要角色. IL-1的编码基因位于人类2号染色体q13-q14, 编码区全长430 bp; 其内含有3个相关联的基因, 即*IL-1A*、*IL-1B*和IL-1受体拮抗剂(IL-1 receptor antagonist, *IL-1RN*), 分别编码IL-1α、IL-1β和IL-1ra. 其中*IL-1B*基因在转录起始区-511、-31位点存在多态性, 即-511C/T和-31T/C的转换; 并且他们是连锁不平衡的[2]. 这种基因多态性可能会导致编码的IL-1β高表达, 进而影响胃酸的分泌量及炎症反应, 直接加重*H. pylori*感染后胃黏膜炎症反应及萎缩程度, 从而增加GC发生的风险. Chen等[21]通过基因测序全面研究了*IL-1B*的基因多态性, 并在12 kb的基因上确定了20个人单核苷酸多态性(single nucleotide polymorphism, SNP); 其中在-3737、-1464、-511、-31四个位点的频率>4%, 并且他们在功能和流行病学方面各具特色. 不仅如此, Chiurillo等[22]认为在慢性胃炎患者中特定*H. pylori*感染与此种基因多态性存在关联.

2 *IL-1B*基因多态性与GC易感性关系的相关研究

*IL-1B*基因多态性与GC是否存在相关性的争论由来已久. 在对合并*H. pylori*感染的秘鲁人进行的一项涉及到334例伴有萎缩性胃炎或GC的住院患者及158例无萎缩胃炎对照组的病例对照分析后, Gehmert等[23]认为*IL-1B-511C*等位基因增加了个体罹患胃炎(OR = 5.60)和肠型GC(OR = 2.36)的风险; 而*IL-1B-511CC*纯合子基因型更显著增加胃炎和肠型GC风险(OR分别为11.22、4.15). 与该研究结果相似, Ikehara等[24]也认为C等位基因与GC进展存在关联.

一项针对我国广东省1010例GC患者及1500例健康人进行的病例对照研究在平均随访了14 mo后, 得到的结果认为与CC基因型相比, *IL-1B-511TT*基因型增加了个体罹患GC的风险(OR = 1.97, 95%CI: 1.29-3.01, *P* = 0.0016), 且该基因型与肠型GC显著相关(OR = 3.16, 95%CI: 1.74-5.71, *P* = 0.0001); 同时*IL-1B-511T*等位基因杂合子及纯合子基因型频率在GC患者中显著增加[25]. 2011年, 在哥伦比亚首都波哥大及通哈两地对46例GC及99例非萎缩性胃炎进行的病例对照研究也得出类似结果: IL-1B-511TT携带者增加了罹患GC的风险(OR = 11.31, 95%CI:

1.20-106.54)[26]. 同年, 南京医科大学第一附属医院在对392例GC患者及508例健康者进行研究后, 认为IL-1B-31CC/CT及IL-1B-511CC/TT基因型增加了中国人罹患胃癌的风险, 这种风险在感染*H. pylori*时进一步增加[27]. 上述3项研究结果与Yoo等[9]的观点一致: Yoo等在对*H. pylori*感染相关的111例慢性胃炎患者及78例胃癌患者研究后证实IL-1B-511T/T基因型显著增加了多个CpG岛甲基化水平, 如此便可能增加了*H. pylori*感染及IL-1B-511T/T基因型个体罹患GC的风险. 此外, Hnatyszyn等[28]最新的研究认为IL-1B+3954C>T基因型提高了胃黏膜在*H. pylori*感染过程中对炎症的敏感性.

2012年, 日本研究人员根据组织学上胃黏膜萎缩的严重程度, 将123例不伴有GC的研究对象分为非萎缩组、轻度萎缩组和严重萎缩组进行研究; 研究结果认为IL-1B-31C、-511T不同的等位基因加之相关的辅助因素(年龄、性别、*H. pylori*感染等), 可能加速胃黏膜炎症反应和萎缩程度[29]. 一个共涉及18项关于IL-1B-511、21项关于IL-1B-31、10项关于IL-1B+3954、20项关于 IL-1RN-511T多态性研究的荟萃分析, 认为IL-1B-511T等位基因与胃腺癌风险显著相关, 与非贲门GC或肠型GC更显著相关; 但是以上相关只在白种人中存在, 在亚洲人或拉美裔人并不存在[30]. 新近的一项系统综述及荟萃分析认为IL-1B+3954C/T基因多态性显著增加了总体罹患胃癌的风险(OR = 1.15, 95%CI: 1.01-1.30)[31]. 但是, 有关二者间不存在相关性的研究也诸见报道. Wex等[32]在对116例GC患者、142例“高风险胃炎”患者及94例健康对照者研究后, 认为*IL-1B*基因多态性与德国白种人发生GC的风险没有关联. 相同的是, Kupcinskas等[33]对212例来自立陶宛、拉脱维亚及66例来自台湾的萎缩性胃炎及胃肠上皮化生患者研究后, 认为在波罗的海地区和台湾地区*IL-1B*基因多态性与GC及癌前病变的风险没有相关性. 在世界其他区域, 如葡萄牙和莫桑比克, IL-1B-511基因型与个体罹患GC、癌前病变的风险也不存在关系[10].

2011年, 上海一项对74942例年龄在40-70岁间女性进行了平均随访4年的研究, 结论认为个体血浆中IL-1β水平与GC的发生风险没有相关性[34]. 更令人诧异的是, 在对130例日本GC患者研究分析后, Tahara等[35]认为GC患者中携带IL-1B-31CC、IL-1B-511TT基因型至少一种者, 个体会有更好的预后; 因为在该研究中IL-1B-3-CC(OR = 0.39, 95%CI: 0.15-0.96, *P* = 0.04)及IL-1B-511TT基因型(OR = 0.23, 95%CI: 0.08-0.67, *P* = 0.007)显著降低淋巴浸润的风险, 并与降低血管侵犯的风险微弱相关. 此外, 一项涉及14项研究的荟萃分析认为IL-1B-511C/T基因多态性与发生十二指肠溃疡的风险没有相关性[36].

■相关报道
本文列举了最近3年内的相关研究, 内容比较新, 同时知识面涉及不同地区、不同国家的研究, 为进一步充分阐明二者关系提供了论据.

3 结论

GC的发生涉及*H. pylori*菌株的毒力、宿主遗传特征、饮食模式的变化等多个伴随因素[37]. 近年来, *IL-1B*基因多态性对GC及癌前病变易感性的影响已成为研究的热点; 此外, 也有研究认为*COX2*基因多态性与肠型胃癌存在关联[38]. 之所以众多研究的结果未达成共识, 究其原因可能有以下几点: (1)研究的设计是否存在某些缺陷. 比如使用了不恰当的对照组或研究人群; (2)开展研究时被研究人群的GC患病率是否被考虑. 因为相较于GC高发区, *IL-1B*基因多态性与GC间的阳性关联似乎更容易在GC低发区被证实; (3)是否存在潜在的协同作用, 因为两个或两个以上基因标记可能会影响表型结果. 如: IL-1B-31等位基因仅仅在GTF2A1GG基因型的个体中被证实与GC存在相关性[5,39]; (4)是否考虑了环境因素的长期积累. 已知环境诱因的影响可以在基因水平发现[2], 饮食间的相互作用对基因稳定性的影响已被公认[40], 某些物质如绿茶可以影响基因的甲基化状态[41]. 还有研究指出, 食盐的摄入量与GC及癌前病变的风险显著相关[42]; 并且这种风险在特定的遗传易感性个体中是增加的[43]. 在感染了*H. pylori*个体中, 辣椒素摄入增多增加了IL-1B-31C等位基因携带者罹患GC的风险[1]; (5)是否考虑到不同种族间存在的遗传差异. 比如, 同是位于我国青海省的藏族、汉族及回族人群间*IL-1B*基因型发布就存在差异[44]. 此外, 不断增加的肥胖可能可以用来解释西方国家在食管癌、贲门腺癌发病率的上升, 因为食管癌、贲门腺癌的风险会随着越来越大的BMI而增加[45]; 动物实验也表明食物诱发的肥胖可促进胃癌的生长[46]. 而长期使用药物抑制胃酸, 是食管癌和贲门腺癌风险增加的另一个原因[47]. 当然, 有研究认为缺血性贫血也是胃癌的一个发生风险[48].

总之, GC的发生是多因素、多步骤的病理过程. 个体间的基因决定了细胞因子产生的差异, 从而影响*H. pylori*感染和GC结局[49,50].

■创新盘点
本文不是对相关研究进行简单的罗列，而是通过研究结果的不一致找到问题所在，重点分析、讨论研究结果不一致的因素；为以后可能进行的研究提供一些思路、改进一些方法.

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■应用要点
通过对近些年比较新、有影响力的研究报道及分析, 为进一步阐明IL-1B与胃癌关系进行梳理, 可能会对以后的研究有借鉴之处, 乃至对胃癌的基因靶向治疗提供思考.

■同行评价
本文从病因学角度阐述胃癌的发生，论述层次清晰，具有一定的创新性.

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• 消息 •

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