

## 幽门螺杆菌与胃癌相关机制的研究进展

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### Relationship between *Helicobacter pylori* infection and gastric cancer

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### Abstract

Gastric cancer is one of the most common malignancies worldwide, and *Helicobacter pylori* (*H. pylori*) infection is the most important risk factor. More than 50% of the world population is infected by *H. pylori*, but less than 2% develop gastric cancer. Other risk factors like host and environmental factors also play a role in the occurrence of gastric cancer. The pathogenesis of gastric cancer is a

multi-factorial and multi-step process, and its outcome is influenced by a combination of host, bacterial, and environmental factors.

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Key Words: Gastric cancer; *Helicobacter pylori*; MicroRNA; Environment

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### 摘要

胃癌是最常见的恶性肿瘤之一, 幽门螺杆菌 (*Helicobacter pylori*, *H. pylori*) 感染是最重要的危险因素。全球超过50%的人口感染 *H. pylori*, 但只有不到2%最终患胃癌。宿主因素, 环境因素也起着非常重要的作用, 因此胃癌的发生是一个多因素、多步骤的过程, 是 *H. pylori*、宿主、环境因素共同作用的结果。

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关键词: 胃癌; 幽门螺杆菌; MicroRNA; 环境

核心提示: 胃癌的发生是一个长期的, 多阶段及多因素的过程, 幽门螺杆菌 (*Helicobacter pylori*, *H. pylori*) 感染是最重要的病因学因素。但只有很少一部分感染 *H. pylori* 的患者最终发展为胃癌。胃癌的肿瘤风险是 *H. pylori* 自然多态性, 宿主基因型, 环境暴露因素综合作用的结果。

李斌, 李玉民, 郭继武, 魏育才. 幽门螺杆菌与胃癌相关机制

### 背景资料

胃癌是全世界最常见的恶性肿瘤, 发病率位于第5位, 在肿瘤相关性死亡中排名第3位。每年大约有100万胃癌新发病例, 男女比例大约为2:1, 每年大约有70万人死于胃癌。幽门螺杆菌 (*Helicobacter pylori*, *H. pylori*) 是胃癌最重要的致病因子, 在每年新发的胃癌病例中, 至少75%与 *H. pylori* 有密切关系。

### 同行评议者

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# □ 研发前沿

*H. pylori*是胃癌最重要的致病因子,但感染*H. pylori*的患者只有很少一部分最终发展为胃癌。*H. pylori*自然多态性,以及*H. pylori*与宿主、环境因素的相互作用对胃癌发生的影响需进一步深入研究。

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## 0 引言

胃癌是全世界最常见的恶性肿瘤,发病率位于第5位,在肿瘤相关性死亡中排名第3位. 每年大约有100万胃癌新发病例,男女比例大约为2:1,每年大约有70万人死于胃癌. >70%的新发病例及胃癌相关的死亡发生在发展中国家,尤其是在东亚<sup>[1,2]</sup>. 在每年新发的胃癌病例中,至少75%与幽门螺杆菌(*Helicobacter pylori*, *H. pylori*)有密切关系<sup>[3]</sup>. 胃癌是一个多步骤过程,最开始*H. pylori*使正常胃黏膜变为慢性浅表性胃炎,慢性浅表性胃炎进展为慢性萎缩性胃炎,肠上皮化生,不典型增生,最终发展为胃癌<sup>[4]</sup>. 胃癌的发生是受宿主、细菌和环境因素综合影响的结果<sup>[5]</sup>. 现将从*H. pylori*毒力因子、microRNA(miRNA)及环境因素3个方面将近年来*H. pylori*与胃癌相关机制研究进展做一简要综述.

## 1 *H. pylori*毒力因子

**1.1 细胞毒素相关基因A蛋白(cytotoxin-associated gene A, CagA)** CagA是目前研究最广泛的*H. pylori*毒力因子,大约有60%-70%的西方*H. pylori*菌株和几乎100%的东亚菌株表达CagA<sup>[6-8]</sup>. CagA干扰多种宿主信号通路. 一方面,被CagA异常上调的信号被整合直接致癌;而另一方面因为他们所造成遗传的不稳定性. 尽管在胃癌的发展过程起决定性作用, CagA不需要在癌细胞中维持一个肿瘤表型. 因此, CagA在诱导胃癌发生过程中通过一种“打了就跑”的机制,在CagA<sup>+</sup> *H. pylori*长期的感染过程中,通过遗传或表观遗传改变编译肿瘤易感细胞使之癌变<sup>[9]</sup>. Chaturvedi等<sup>[10]</sup>证实CagA<sup>+</sup>菌株能导致精胺氧化酶(spermine oxidase, SMO)、细胞凋亡、胃上皮细胞DNA损伤的水平增加;而敲除或抑制SMO可以阻碍细胞凋亡和DNA损伤. 在*H. pylori* CagA<sup>+</sup>菌株感染的人类胃组织中观察到同样的情况. CagA能通过诱导SMO生成导致细胞的氧化性DNA损伤,使这些细胞亚群抗细胞凋亡,发生胃恶性肿瘤风险增高. 在CagA<sup>+</sup> *H. pylori*感染的人胃癌组织中磷脂酶D1的表达异常上调,其可能通过上调磷脂酶D1的表达诱导核因子-κB

(nuclear factor-κB, NF-κB)激活,导致胃癌的发生<sup>[11]</sup>. CagA能促进细胞外调节蛋白激酶(extracellular regulated protein kinases, ERK)通路下游信号级联细胞功能异常,导致胃癌的发生, CagA与细胞的相互作用激活ERK信号通路可能是胃癌发展一个起点<sup>[12]</sup>. 烯醇酶-1(enolase-1, ENO1)是一种新近发现的癌蛋白,在许多肿瘤呈高表达. CagA通过激活Src家族激酶和MEK/ERK信号通路上调ENO1的表达,是*H. pylori*介导胃疾病发生的一种新的机制<sup>[13]</sup>. 一旦进入细胞, CagA将位于细胞膜,通过Src家族激酶和非受体酪氨酸激酶(cellular-abelson gene, C-Abl)进行酪氨酸磷酸化<sup>[14]</sup>, CagA的酪氨酸磷酸化具有特异的5个氨基酸序列,称为EPIYA基序,位于CagA C-端可变区域<sup>[15]</sup>. 迄今为止已经描述出4种不同的EPIYA基序(A, B, C和D)<sup>[16]</sup>. Batista等<sup>[17]</sup>的研究结果表明, *H. pylori*菌株携带一个以上的CagA EPIYA C基序与胃癌的发生明显相关,有较多EPIYA C片段也与胃癌癌前病变密切相关. *H. pylori*菌株含有越多的CagA EPIYA C基序,发生胃萎缩和胃癌的风险明显增大,而那些不含有EPIYA C基序的*H. pylori* CagA<sup>+</sup>菌株同CagA<sup>-</sup>菌株相比并没有显著增加胃癌风险<sup>[18]</sup>.

**1.2 空泡毒素A(vacuolating cytotoxin A, VacA)** VacA是*H. pylori*另一个重要的毒力因子,能被几乎所有的菌株产生和分泌. VacA通过V型自转运蛋白通路到细胞外,并且一部分黏附到细胞表面<sup>[19]</sup>. 分泌的VacA蛋白在细胞平面脂双层形成阴离子选择性膜通路<sup>[20]</sup>. 因此VacA被认为是一种成孔毒素,目前已经有3个VacA多态性区域被确认,分别为s、i和m区域. 每一个多态性区域进一步分为1型和2型(s1, s2; i1, i2; m1, m2)<sup>[21,22]</sup>. s区域编码N端信号序列, s区域的多态性影响阴离子通路形成毒素的效力<sup>[23]</sup>. m区域的多态性影响毒素的细胞趋向性<sup>[24]</sup>. Rahimian等<sup>[25]</sup>认为感染*H. pylori* VacA s1和s1 m1基因型的菌株能诱导转化生长因子-β(transforming growth factor-β, TGF-β) mRNA表达水平显著提高,从而抑制T细胞的增殖和免疫反应,有助于*H. pylori*长期感染. VacA通过引起胃黏膜细胞程序化坏死,并且以释放促炎症蛋白高迁移率族蛋白1(high-mobility group box 1 protein, HMGB1)的方式促进*H. pylori*诱导的人胃黏膜炎症. 可能是胃癌和消化性溃疡的发病机制之一<sup>[26]</sup>. VacA能

激活启动相关蛋白1(dynamin-related protein 1, drp1)介导线粒体分裂导致其形态动力学改变, 从而使胃黏膜细胞发生凋亡<sup>[27]</sup>. Winter等<sup>[28]</sup>证实小鼠的胃中VacA s1/i1菌株相比s2/i2菌株产生更高活性的毒素, 诱导更严重的化生和炎症. 同样在人胃黏膜内镜标本中VacA i1等位基因同肠上皮化生明显相关, 而感染VacA i2型菌株几乎完全没有发生肠上皮化生, 甚至在VacA s1和CagA<sup>+</sup>的背景下. González等<sup>[29]</sup>随访研究了西班牙一个胃癌高发省份的312例患者, 认为*H. pylori* CagA<sup>+</sup>菌株以及VacA s1和m1基因型的菌株与胃癌癌前病变的关系更为密切. Memon等<sup>[30]</sup>研究发现在比利时人中VacA s1和i1基因型是更好的胃癌相关标记, 认为VacA s和i区域是其活性决定区域. Ferreira等<sup>[31]</sup>认为葡萄牙人感染VacA i1菌株发生萎缩性胃炎和胃癌的风险会增加.

**1.3 其他毒力因子** 外膜炎性蛋白A(outer inflammatory protein, OipA)是一种*H. pylori*的外膜蛋白(outer membrane protein, OMP), 与*H. pylori*黏附和定植胃黏膜细胞有关, 并且与CagA关系密切, 有助于CagA<sup>+</sup>菌株在体内的适应性<sup>[32]</sup>. OipA和血型抗原结合黏附素(blood group antigen-binding adhesin, BabA)能导致更严重的*H. pylori*感染并增加白介素-6(interleukin-6, IL-6)和IL-11的表达水平, 导致更严重的炎症和细胞浸润, 增加*H. pylori*引起胃肠道疾病的危险<sup>[33]</sup>. BabA也是*H. pylori*外膜蛋白, 其在胃上皮细胞的表面结合岩藻糖基聚糖, 如路易斯乙血型抗原(Leb), 影响宿主黏膜的糖基化方式, 使*H. pylori*适应并长久定植于宿主<sup>[34]</sup>. BabA-Leb相互作用不仅对*H. pylori*黏附于宿主细胞表面非常重要, 而且有助于在细胞表面锚定细菌分泌系统, 使细菌毒力因子有效的注入细胞中. 因此, *H. pylori*能通过BabA-Leb结合触发IV型分泌系统依赖的宿主细胞信号诱导基因转录, 增加炎症, 肠化生的发展以及癌前病变的转化<sup>[35]</sup>. 十二指肠溃疡促进因子(duodenal ulcer promoting gene, dupA)位于*H. pylori*的“可塑性区域”, dupA作为一个标记能增加十二指肠溃疡的危险, 并减少胃黏膜萎缩和胃癌的风险<sup>[36]</sup>. *H. pylori* dupA<sup>+</sup>菌株有更好的胃酸耐受性, 更容易定植于胃酸更强部位, 比如胃窦部. 从而与十二指肠溃疡的发生呈正相关, 同胃溃疡和胃癌的发生呈负相关<sup>[37]</sup>.

毒力因子似乎在*H. pylori*感染的结果中的起着决定性的作用, 不同的毒力因子在疾病进程中发挥不同的作用, 其基因多态性有助于适应宿主环境并长期定植感染. 感染*H. pylori* CagA<sup>+</sup>菌株, 特别是含有高数量的EPIYA C基序, 发生胃癌的风险明显增高, 而相对于VacA s2, i2, m2基因型, s1, i1, m1基因型与*H. pylori*诱导的胃十二指肠疾病关系更为密切.

## 2 miRNA

miRNA是很小的非编码RNA, 通过翻译抑制和信使RNA降解调节目标基因的表达<sup>[38]</sup>. miRNA参与很多重要的生物学过程, 包括细胞生长, 凋亡, 分化以及组织器官生长等<sup>[39]</sup>. 在人胃黏膜中*H. pylori*感染可以通过免疫和炎症反应影响miRNA的表达模式<sup>[40]</sup>. *H. pylori* CagA能上调miRNA-584和miRNA-1290表达, 而过表达的miRNA-584和miRNA-1290诱导小鼠胃上皮细胞发生肠上皮化生. 并且证实CagA能通过上调miRNA-584和miRNA-1290表达促进上皮细胞间质转化和干扰干细胞分化. 认为miRNA是CagA导致胃癌新的致病机制<sup>[41]</sup>. *H. pylori*在胃上皮细胞及胃黏膜组织中上调miRNA-146a表达, 而miRNA-146a下调目的基因白介素1受体相关激酶1(interleukin 1 receptor-associated kinase 1, IRAK1)和肿瘤坏死因子受体相关因子6(tumor necrosis factor receptor-associated factor 6, TRAF6)表达. 此外, miRNA-146a通过减少NF-κB活性负调控*H. pylori*引起的IL-8, 生长相关癌基因1(growth-regulated oncogene 1, GRO1), 巨噬细胞炎性蛋白-3α(macrophage inflammatory protein, MIP)表达. 总之, *H. pylori*诱导的miRNA-146a表达通过目的基因IRAK1和TRAF6调节炎症反应, 起着一个负反馈回路的作用<sup>[42]</sup>. Wu等<sup>[43]</sup>发现通过转染使miRNA-146a过表达可以显著上调胃癌的细胞凋亡, 而这是通过抑制环氧化酶2(cyclooxygenase 2, COX-2)的表达引起的. 他们发现miRNA-146a的密度同*H. pylori*感染阳性的胃癌组织的凋亡率呈正相关, 位于肿瘤内的miRNA-146a的密度与*H. pylori*感染阳性的胃癌患者淋巴结转移呈负相关. Kiga等<sup>[44]</sup>证实*H. pylori*感染可引miRNA-210表观遗传沉默并促进胃上皮细胞增殖, 认为在*H. pylori*感染过程中炎症诱导miRNA-210沉默是慢性胃疾病包括肿瘤发展的风险因素. Li等<sup>[45]</sup>发现在*H. pylori*感染的

**□ 相关报道**  
近年来有研究表明, 高盐饮食对于*H. pylori*增殖、黏附以及毒力因子表达均有影响, 对*H. pylori*感染患者患胃癌有促进作用; 多个前瞻性病例对照研究证实吸烟能增加*H. pylori*感染者患胃癌的风险.



# 创新亮点

该文从*H. pylori*毒力因子, *H. pylori*与宿主miRNA以及*H. pylori*与环境因素3个方面较系统的总结了*H. pylori*与胃癌发生的相关机制。

胃癌黏膜中miRNA-222表达上调, 并且认为*RECK*基因是miRNA-222的目标基因, RNA干扰技术沉默*RECK*基因可以模仿miRNA-222的致癌作用. 从而证实*H. pylori*可以作为启动因子使miR-222表达上调, 进一步通过促进细胞增殖和抑制*RECK*基因表达参与肿瘤进程。

miRNA在细胞分化, 生物发育及肿瘤发生发展过程中发挥重要作用, 这些miRNA所起的作用类似于抑癌基因或致癌基因, 多重调控肿瘤发展过程. *H. pylori*相关性胃炎和胃癌中miRNA常常表达异常, 这或许说明干扰miRNA途径是*H. pylori*导致胃癌发生的致病机制之一。

## 3 环境因素

**3.1 高盐** Gaddy等<sup>[46]</sup>将蒙古沙鼠分别感染*H. pylori*野生型CagA<sup>+</sup>菌株和同基因CagA突变菌株, 持续给沙鼠喂养高盐饮食或正常饮食. 4 mo后高盐饮食喂养的野生型CagA<sup>+</sup>菌株感染沙鼠100%发生胃腺癌, 正常饮食喂养的野生型CagA<sup>+</sup>菌株感染沙鼠58%发生胃腺癌, 而同基因CagA突变菌株感染沙鼠没有发生胃腺癌. 那些高盐饮食喂养的沙鼠同正常喂食的相比发生更严重的胃炎, 更高的胃酸pH值, 失去更多的壁细胞, IL-1 $\beta$ 表达更高, H<sup>+</sup>-K<sup>+</sup> ATP酶表达更低. 证实高盐饮食可以增加*H. pylori* CagA<sup>+</sup>菌株致癌的能力. Gamboa-Dominguez等<sup>[47]</sup>研究指出*H. pylori*感染的长爪沙鼠喂食高盐饮食相比普通饮食能引起更严重的胃窦炎和更高水平的胃黏膜上皮细胞增殖. Sun等<sup>[48]</sup>报道在*H. pylori*感染的长爪沙鼠喂食高盐饮食相比普通饮食3种促炎细胞因子IL-1、IL-6和肿瘤坏死因子(tumor necrosis factor, TNF)的表达水平更高. 而Lee等<sup>[49]</sup>分别给感染*H. pylori* SS1菌株的C57BL/6小鼠喂养普通饮食及高盐饮食, 他们发现4 wk后高盐饮食组小鼠的胃黏膜细菌密度明显增加, 但两组小鼠的胃黏膜炎症程度没有明显差异, 高盐饮食组小鼠的胃黏膜髓过氧化物酶(myeloperoxidase, MPO)及TNF- $\alpha$ 水平并没有增加. Peleteiro等<sup>[50]</sup>在葡萄牙问卷调查了422例胃癌患者及649名社区对照人群, 认为盐摄入是胃癌重要的饮食危险因素, 但和*H. pylori*感染及其毒力因子, 吸烟, 肿瘤位置及组织分型无关。

**3.2 吸烟** 吸烟可增加*H. pylori*相关胃癌的风险. Kim等<sup>[51]</sup>认为在韩国感染*H. pylori*的吸烟者携

带IL-10-1082G或IL-10-592C等位基因相对于未感染*H. pylori*的非吸烟者携带纯合子IL-10-1082A和IL-10-592A能明显增加肠型胃癌的患病风险. 日本以人群为基础的前瞻性研究<sup>[52]</sup>认为, 男性吸烟和*H. pylori*是胃癌的风险因素, 两者的结合进一步增加了患胃癌的风险. 在中国西安的一个病例对照研究<sup>[53]</sup>表明吸烟和*H. pylori* CagA<sup>+</sup>菌株感染被认为是非贲门胃癌重要的危险因素. 当这两个风险因素存在时, 非贲门胃癌的风险协同增高, 表明吸烟可能以某种方式影响*H. pylori* CagA<sup>+</sup>菌株的致癌过程, 从而增加了胃癌的风险. 在德国一个病例对照研究<sup>[54]</sup>发现, 吸烟增加感染*H. pylori* CagA<sup>+</sup>菌株者患胃癌的风险. 然而在日本一项病例对照研究<sup>[55]</sup>报道,*H. pylori*和吸烟与胃癌相关联是个别现象,*H. pylori*及吸烟之间的没有显著相关性。

高盐饮食以及吸烟是胃癌常见的两种环境风险因素. 对于患胃癌的风险,*H. pylori*感染与高盐饮食以及吸烟之间似乎是呈正相关, 并且可能是所有的环境因素的综合作用。

## 4 结论

胃癌仍然是目前世界上发生率和死亡率最高的恶性肿瘤之一. 而*H. pylori*作为其中最重要的致癌因子已经被广泛研究几十年, *H. pylori*感染十分普遍, 但只有很少一部分人最终发展为胃癌. 感染*H. pylori* CagA<sup>+</sup>菌株, 特别是有高数量的EPIYA C基序; 以及VacA的s1, m1和i1菌株, 被认为增加患胃癌的风险. 这些因素可以用于识别高风险患者, 进行紧密的随访, 并及时行根除*H. pylori*治疗, 以期能降低胃癌的发病率. 另外, 宿主因素和环境因素同样在*H. pylori*相关的胃癌发生中起到重要作用. *H. pylori*感染阳性的胃癌患者中miRNA可能表达异常, 这或许说明干扰miRNA途径是*H. pylori*导致胃癌发生的致病机制之一. 肿瘤风险应该是*H. pylori*自然多态性, 宿主基因型, 环境暴露因素的综合. 在*H. pylori*诱导胃癌的发病机制方面能有更多深入研究, 不仅能提供更有效的治疗措施, 而且能在预防胃癌方面给予更多的帮助。

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#### 应用要点

*H. pylori*感染十分普遍,但只有很少一部分人最终发展为胃癌。感染*H. pylori* CagA<sup>+</sup>菌株,特别是有高数量的EPIYA C基序;以及VacA的s1, m1和i1菌株,被认为增加患胃癌的风险。这些因素可以用于识别高风险患者,进行紧密的随访,并及时行根除*H. pylori*治疗,以期能降低胃癌的发病率。另外,宿主因素和环境因素同样在*H. pylori*相关的胃癌发生中起到重要作用。

# ■ 名词解释

MicroRNAs(miRNAs): 是在真核生物中发现的一类内源性的具有调控功能的非编码RNA, 其大小长约20-25个核苷酸。成熟的miRNAs是由较长的初级转录物经过一系列核酸酶的剪切加工而产生的, 随后组装进RNA诱导的沉默复合体, 通过碱基互补配对的方式识别靶mRNA, 并根据互补程度的不同指导沉默复合体降解靶mRNA或者阻遏靶mRNA的翻译。

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#### 同行评价

本文从*H. pylori*、miRNA、环境因素较系统阐述了*H. pylori*与胃癌的相关机制, 信息量较大, 结构较清晰, 具有一定的科学意义。

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