P.O.Box 2345 Beijing 100023, China
Fax: +86-10-85381893
Email: wcjd@wjgnet.com www.wjgnet.com

World Chin J Digestol 2005 November;13(21):2586-2590
世界华人消化杂志 ISSN 1009-3079 CN 14-1260/R

幽门螺杆菌与胃黏膜保护研究进展

林 辉, 任建林

林辉, 任建林, 厦门大学附属中山医院消化内科 厦门市消化病研究所 福建省厦门市 361004
通讯作者: 林辉, 361004, 福建省厦门市湖滨南路201号, 厦门大学附属中山医院消化内科, 厦门市消化病研究所. niliuhfz@yahoo.com.cn
电话: 0592-2292016 传真: 0592-2292017
收稿日期: 2005-09-20 接受日期: 2005-10-10

摘要

幽门螺杆菌(*H pylori*)是一种革兰阴性, S形或弧形弯曲的细菌, 基因序列呈环形, 大小为1 667 867 bp(*H pylori* 26 695), 有1 590个开放阅读框(ORFs), 定居于胃上皮细胞表面, 与慢性胃炎、消化性溃疡、胃腺癌等上消化道疾病关系密切. *H pylori*产生的毒素(如空泡细胞毒素与细胞毒素相关蛋白)和酶能破坏胃黏膜屏障, 使机体产生炎症和免疫反应, 影响胃酸、胃肠激素的分泌, 引起胃上皮细胞的凋亡.

关键词: 幽门螺杆菌; 胃黏膜保护

林辉, 任建林. 幽门螺杆菌与胃黏膜保护研究进展. 世界华人消化杂志 2005;13(21):2586-2590
http://www.wjgnet.com/1009-3079/13/2586.asp

0 引言

1983年澳大利亚皇家佩思医院的病理科医师Warren和实习医师Marshall[1]首次成功分离出幽门螺杆菌(*H pylori*), 揭开了人类研究*H pylori*与胃肠疾病关系的序幕, 彻底改变了很多胃肠道疾病的理论. 现已明确, *H pylori*与慢性胃炎、消化性溃疡、胃腺癌和黏膜相关性淋巴样组织(MALT)淋巴瘤密切相关[2-6]. *H pylori*呈螺旋形, 有鞭毛、适应性的酶和蛋白, 使它能在胃腔不利的酸性环境中定植和生存. *H pylori*产生的毒素和有毒素作用的酶能破坏胃黏膜屏障; *H pylori*感染还能使机体产生炎症和免疫反应, 影响胃酸、胃肠激素的分泌, 引起胃上皮细胞的凋亡, 导致一系列疾病的形成.

1 *H pylori*的形态结构特征

*H pylori*是一种革兰阴性, S形或弧形弯曲的细菌. 电镜下, 菌体的一端可见4-7条带鞘的鞭毛. 分裂时, 则两端均可见鞭毛[7,8]. *H pylori*有很强的运动能力, 可以穿透覆盖于胃黏膜上皮细胞的黏液层, 定居于胃上皮细胞表面. 1997年*H pylori* 26 695的全基因序列已测序完毕, 基因序列呈环形, 大小为1 667 867 bp, 有1 590个开放阅读框(ORFs), 占到其染色体DNA的91%[9].

2 *H pylori*对胃黏膜屏障的损害

在正常的胃黏膜上, 由黏膜上皮分泌的黏液和上皮细胞以及细胞连结组成了胃黏膜屏障. 这种屏障起着防止H^+反向弥散的作用. 1998年Goodwin *et al*[10]提出了"漏屋顶"假说, 比较形象地比喻了*H pylori*对胃黏膜屏障损害的后果. 他把胃黏膜屏障比喻为"屋顶", 它能保护其下方的黏膜组织免受胃酸("雨")的损伤, 当黏膜受到*H pylori*的损害时(形成"漏屋顶"), 就会造成H^+反向弥散(形成"泥水浆"), 导致黏膜的损伤和溃疡形成. *H pylori*的毒素和有毒性作用的酶以及*H pylori*诱导的黏膜炎症反应均能造成胃黏膜屏障的损伤.

2.1 空泡细胞毒素与细胞毒素相关蛋白 1988年Leunk *et al*[11]等发现*H pylori*肉汤培养基的上清液中含有一种相对分子质量为M_r87 000的细胞毒素, 它能使Hela细胞造成不同程度的空泡变性. 这种毒素称为空泡细胞毒素(vacuolating cytotoxin, VacA). 编码VacA的基因为vacA, vacA基因在所有的*H pylori*菌株中均存在, 但仅有50%左右的*H pylori*菌株有VacA蛋白的表达. VacA对胃上皮细胞有直接的毒性作用[12], 可造成胃黏膜的损伤和延缓胃上皮的修复. Li *et al*[13]研究表明VacA诱导的后期细胞胞吞颗粒的聚集与核周重分布是VacA致细胞空泡变性的重要机制, 有利于*H pylori*持续地定植于胃黏膜表面. 而Suzuki *et al*[14]却发现VacA能使胃黏膜凝血酶的产生增加, 而凝血酶在*H pylori*相关性上胃肠道疾病中起了积极的保护作用.

Cover *et al*[15]发现, 在VacA阳性的*H pylori*培养液中存在一种相对分子质量为M_r128 000的蛋白质, 这种物质被称为细胞毒素相关蛋白(cytotoxin associating gene protein, CagA). 编码CagA的基因为cagA, 它仅存在于60-70%的*H pylori*菌株中, 但几乎所有的cagA阳性菌株均可产生CagA蛋白. CagA是一种免疫显性抗原, 可诱导宿主产生抗CagA抗体. 但无论循环抗体或胃黏膜局部抗体, 均不能清除体内*H pylori*感染, 表明CagA为非保护性抗原.

Censini *et al*[16]对CagA阳性的CCUG17874 *H pylori*菌株进行DNA分析后, 提出cagA致病岛(pathogenicity island, PAI)的概念. CagA PAI是*H pylori*环状基因组中

40 kb长的DNA插入序列, 可编码31个推测与毒素及毒素装配和分泌机能相关的蛋白. CagA PAI可分为cagAⅠ区域和cagAⅡ区域, 其中cagAⅠ区域含cagA-cagI, cagL-cagR等开放读框, cagAⅡ区域含cagS, cagT等开放读框. CagA被认为是一新的毒素外排分泌系统, 即cagA致病岛的血清学标志之一[17]. Xiang *et al*[18]根据其cagA蛋白的有无将大多数*H pylori*临床分离菌分为两型, Ⅰ型菌: 有cagA, 表达CagA蛋白, 具有毒素活性; Ⅱ型菌: 无cagA, 不表达CagA蛋白, 无毒素活性. 研究证实cagA基因的存在是产生有活性的空泡毒素(VacA)所必须的, 并能促进细胞因子IL-8的释放及激活转录因子NF-κB, 加重胃黏膜的组织损伤, 故而目前认为含cagA基因的*H pylori*菌株是高毒株[19].

目前研究表明[20-22], CagA能被cagA-PAI编码的Ⅳ型分泌系统转运入宿主细胞, 并在其中被磷酸化; 磷酸化CagA聚集在细菌黏附部位的宿主细胞中, 形成圆柱状结构, 并募集细胞骨架中的肌动纤维等成分, 形成底座结构, 导致宿主细胞出现极度延伸、分散生长等类似于肝细胞生长因子作用的效应. 这些作用可能与CagA$^+$菌株致胃癌有关. 不同*H pylori*菌株CagA分子内磷酸化位点多少不一致, 其中有些菌株可缺如(J99), 而有些菌株则可因Ⅳ型分泌系统功能缺陷而无法将CagA转运入宿主细胞(26695), 这些因素都可能影响CagA磷酸化和相应功能的发挥. 这可能是CagA$^+$菌株感染与疾病关系在各地呈现复杂多样性的原因之一. Bauer *et al* [23]发现不仅细菌而且宿主细胞的因素共同决定胃黏膜上皮细胞对*H pylori*感染的反应, 从而产生不同的临床表现: 胃炎、胃溃疡或胃癌.

2.2 *尿素酶* 尿素酶产生的氨能降低黏液中黏蛋白的含量, 破坏黏液的离子完整性, 削弱屏障功能, 造成H^+反向弥散[24]. 氨还消耗需氧细胞的α-酮戊二酸, 破坏三羧酸循环, 干扰细胞的能量代谢, 造成细胞变性[25]. 有研究显示, 高浓度的氨可导致细胞的空泡变性, 其结果类似于VacA所致的空泡变性[26]. 从细菌表面脱落的尿素酶除了可使细菌逃避宿主的免疫防御机制外, 尿素酶本身还可直接造成宿主的组织损害, 或改变宿主的免疫反应[27].

2.3 *黏液酶* 胃黏液胶层的主要成分为黏蛋白, 是富含碳水化合物的高分子糖蛋白, 在胃黏液屏障中起重要的作用. 这些黏蛋白可防止胃黏膜受到化学物质(如胃酸), 各种消化酶、食物的机械磨擦和微生物因素的损害. *H pylori*能产生一种溶解黏液的酶, 体外研究显示黏液酶使猪胃黏液的黏性和弹性丧失[28]. 胃黏液的降解会促进H^+的反向弥散, 造成黏膜损害, 黏液的稠度降低有利于*H pylori*的运动, 使*H pylori*易于定植. *H pylori*感染可抑制黏蛋白的分泌, 机制尚不清楚[29], 可能为*H pylori*的分泌产物直接影响黏蛋白的基因转录, 或影响其mRNA的易位和绞接. 而Al-Marhoon *et al* [30]检测了*H pylori*阳性和阴性胃黏液层的厚度, 发现两者之间的差别无统计学意义.

2.4 *脂多糖* 层黏连蛋白是维持上皮完整性所需的一种细胞外基质, *H pylori*产生的脂多糖(LPS)能抑制宿主层黏连蛋白和嵌有脂质体的层黏连蛋白受体的结合, 造成宿主胃上皮发生渗漏, 导致胃黏膜的损害[31], 抑制程度与LPS的量呈正相关. 此外, *H pylori*还可与细胞外基质的Ⅳ型胶原、纤溶酶原和玻璃体结合蛋白等物质作用, 造成上皮下组织的损伤.

2.5 *脂酶和磷脂酶A* 正常上皮细胞膜由磷脂双分子层构成, 胃黏液中的脂质和磷脂在维持其黏性, 防止H^+反向弥散, 保持疏水性上起重要作用. *H pylori*的脂酶和磷脂酶A可分解细胞膜及黏液中的脂质和磷脂, 破坏细胞膜的完整性和黏液的屏障功能[32]. 磷脂酶A还能促使花生四烯酸的释放, 形成前列腺素和血栓素等炎症介质, 介导炎症反应. 磷脂类物质的降解产物溶血卵磷脂对细胞亦有毒性作用.

3 *H pylori*介导炎症和免疫反应

3.1 *炎症反应* *H pylori*一旦定植于胃黏膜上, 胃上皮细胞就会发生细胞骨架重组和酪氨酸磷酸化, 进而激活核因子NF-κB. NF-κB是一种转录因子, 可使上皮细胞或其他细胞分泌IL-8以及其他趋化因子, 趋化和激活炎症细胞, 使它们从血管内移行至胃上皮处, 导致炎症反应[24,26,33]. 此外, *H pylori*感染后中性粒细胞和巨噬细胞释放的炎性介质和细胞因子包括前列腺素、白三烯、血栓素、TNFα和各种IL等, 对胃上皮细胞有直接的细胞毒性作用. 在炎症反应中炎症细胞的迁移可破坏黏膜上皮的紧密连接, 肥大细胞脱颗粒释放的组胺, 前列腺素PGD2和白三烯能扩张血管, 增加血管的通透性, 使胃黏膜产生水肿. 炎症细胞还可产生反应性氧代谢物(ROS), 反应性氮代谢物(RNS), 损害胃黏膜[34].

3.2 *免疫反应* *H pylori*感染时胃上皮细胞可递呈抗原, 起着"非专业性"APC的作用, 可介导免疫反应[35]. APC是指能捕捉、加工和处理抗原, 并将抗原递呈给抗原特异性淋巴细胞的一类免疫细胞. T淋巴细胞激活后引起两种应答: Th1和Th2应答. Th1细胞参与细胞介导的免疫应答, 分泌IL-2、IFN-γ和TNFβ, 对宿主造成胃上皮的损伤; Th1应答释放的炎性细胞因子可增加Fas抗原的表达, 诱导上皮细胞的凋亡. Th2细胞参与黏膜表面的分泌性免疫应答和过敏反应, 分泌IL-4、IL-5、IL-6、IL-10等细胞因子, 有利于宿主消除细菌. *H pylori*感染时以Th1应答为主, *H pylori*的菌株类型, 宿主的遗传因素, 环境因素及胃黏膜上皮表达的淋巴细胞功能抗原(LFA-3)可增强Th1应答[34,36,37].

*H pylori*感染可刺激浆细胞产生局部和全身的*H pylori*特异性抗体, 参与体液免疫反应, 这种抗体多半为非分泌型IgA, 不能很好地与补体结合清除细菌,

却可造成宿主自身的损伤, 如自身抗体可造成胃上皮的损伤[38].

4 *H pylori*影响胃酸、胃肠激素的分泌

4.1 对胃酸分泌的影响 *H pylori*感染后胃酸的分泌取决于所致胃炎的类型(是胃体为主还是胃窦为主)以及胃黏膜的萎缩程度. 非萎缩性胃窦为主的胃炎可增加胃酸分泌, 其机制可能是生长抑素分泌减少, 胃泌素水平增加促使胃酸分泌增加. 萎缩性全胃炎(累及胃窦和胃体, 并以胃体为主)可导致胃酸分泌减少, 可能的机制: 胃窦部的黏膜萎缩造成G细胞数量减少, 胃泌素分泌减少; 胃体部黏膜萎缩导致壁细胞的数量减少, 使胃酸分泌减少; 胃体部的炎症损害了壁细胞的功能, 炎症产生的细胞因子可影响胃酸的分泌, 有研究证实*H pylori*感染产生的IL-1β可强有力地抑制胃酸分泌. Liu *et al* [39]报道*H pylori*感染使胃黏膜G细胞增多, D细胞减少, 从而影响胃酸的分泌. 多数*H pylori*感染者的胃黏膜萎缩很轻, 胃炎以胃窦部较为明显, 但亦影响部分胃体黏膜, 胃酸分泌没有改变[40,41]. Thong-Ngam *et al* [42]研究发现慢性胃炎中胃黏膜H^+/K^+-ATP酶的活性与*H pylori*的感染状态无关.

4.2 对胃肠激素分泌的影响

4.2.1 促胃液素 *H pylori*感染致高促胃液素血症是公认事实, 根除*H pylori*则血清促胃液素水平下降至正常范围[43,44]. 促胃液素的生理-病理意义之一, 是胃酸产生和胃酸形成. *H pylori*感染出现的高促胃液素血症为细胞素所致, TNF-α及IL-8均可刺激G细胞, 增加促胃液素的释放[45,46]. 此外, *H pylori*的脂多糖(LPS)通过抑制SS与胃黏膜上的受体结合, 减少SS在胃黏膜G细胞上的SS-受体结合, 减少SS对G细胞的抑制, 促胃液素分泌增多[47,48].

4.2.2 生长抑素(SS) *H pylori*感染时胃窦黏膜、胃液中的SS含量均下降, D细胞数目和SS的mRNA表达也减少; 根除*H pylori*后这些指标均恢复, 提示*H pylori*抑制SS的释放[49]. 研究表明: *H pylori*感染时胃液中TNF-α和IL-8分泌增多[50-52], TNF-α能剂量依赖地增加SS释放, 且此效应可被IL-8所增强[53]. SS对G细胞有抑制作用, SS减少时促胃液素分泌增多, 同时SS在人胃腔中有抑制*H pylori*增殖的作用[54,55]. 促胃液素刺激和SS抑制壁细胞释放胃酸, 共同保持胃酸分泌的平衡.

4.2.3 生长因子EGF及TGFα EGF和TGFα通过同一受体(即EGFr)而起作用. 它们对胃肠道的作用有促进细胞增生、溃疡愈合、抑制胃酸分泌等[56]. *H pylori*急性接触体外培养的胃黏膜细胞, 即引起细胞损伤, 并损及细胞的移行和增殖; EGF相关生长因子, 能保护胃黏膜免受损伤, 且使损伤的黏膜愈合. *H pylori*抑制EGF与其受体结合, 和抑制EGF刺激的胃细胞增殖, 是溃疡生成和难以愈合的机制[57,58]. 而最近Liu *et al*[59]报道在*H pylori*感染的慢性胃炎患者EGFr明显增高, *H pylori*感染可以促进胃黏膜细胞的增殖. Schiemann *et al*[60]报道根除*H pylori*后, 萎缩性胃炎胃黏膜中的TGFα的mRNA表达明显上调. *H pylori*感染时胃黏膜的C-myc基因蛋白和EGFr呈过分表达, 可能为胃黏膜上皮过分增殖的分子基础[61,62].

5 *H pylori*引起胃上皮细胞的凋亡

*H pylori*感染可导致胃上皮细胞的凋亡[63,64]. 有研究显示[65], *H pylori*感染者胃黏膜上有平均数为16.8%的上皮细胞发生凋亡, 主要位于胃腺的深部, 而根除感染后凋亡数下降至3. 1%. 无*H pylori*感染者仅有2.9%的上皮细胞发生凋亡, 主要位于胃腺的表浅部位. *H pylori*感染所致的细胞凋亡机制可能与以下因素有关[66]: (1) *H pylori*感染后产生的炎性细胞因子可增加Fas抗原的表达, Fas抗原是一种细胞表面的膜蛋白, 与Fas配体结合后可诱导细胞的凋亡; (2) *H pylori*可通过两种通路导致胃上皮细胞凋亡, Caspase-8在Ⅱ型通路中起了非常重要的作用; (3) 炎性细胞因子如TGFα和IFN-γ除了可直接诱导细胞凋亡外, 还可促进上皮细胞表达主要组织相容复合物Ⅱ(MHC-Ⅱ)抗原, 通过Th1应答介导的损伤造成细胞凋亡. TNF相关凋亡诱导因子(TRAIL) 和它的受体、FasL 及*H pylori*在诱导胃黏膜上皮细胞凋亡中有着复杂的相互作用[67]; (4) Das *et al*[68]用蛋白芯片技术发现*H pylori*感染后胃黏膜上皮细胞的Annexin II表达升高可能是*H pylori*引起胃上皮细胞的凋亡和增生机制之一. 胃上皮细胞的过度凋亡有利于糜烂和溃疡形成, 凋亡时程序错误或凋亡与增生不平衡则可导致肿瘤形成[69]. Hritz *et al*[70]研究表明长期的PPI治疗并没有显著地增加胃上皮细胞增殖和表皮生长因子受体的表达, 对胃上皮细胞凋亡和p53基因的表达没有影响.

总之, *H pylori*感染与胃黏膜保护的研究至今已20 a, 取得了许多可喜的成绩, 但以后的研究道路将更加坎坷; 随着后基因组时代的到来, 分子生物学高通量分析方法的广泛应用, 人类征服*H pylori*已为期不远.

6 参考文献

1 Marshall BJ, Warren JR. Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. *Lancet* 1984; 1: 1311-1315

2 Vandenplas Y. *Helicobacter pylori* infection. *World J Gastroenterol* 2000; 6: 20-31

3 Hou P, Tu ZX, Xu GM, Gong YF, Ji XH, Li ZS. *Helicobacter pylori* vacA genotypes and cagA status and their relationship to associated diseases. *World J Gastroenterol* 2000; 6: 605-607

4 Pinto-Santini D, Salama NR. The Biology of *Helicobacter pylori* Infection, a Major Risk Factor for Gastric Adenocarcinoma. *Cancer Epidemiol Biomarkers Prev* 2005; 14: 1853-1858

5 庄小强, 林三仁. 幽门螺杆菌与胃癌的研究进展. 世界华人消化杂

志 2000; 8: 206-207
6 Morgner A, Bayerdorffer E, Neubauer A, Stolte M. Gastric MALT lymphoma and its relationship to Helicobacter pylori infection: management and pathogenesis of the disease. *Microsc Res Tech* 2000; 48: 349-356
7 张振华, 杜佩英, 俞爱琴. 幽门弯曲菌超微结构及其与胃黏膜上皮的关系. 上海第二医科大学学报 1989; 9: 2277-2812
8 Good win CS, Armstrong JA. Microbiological aspects of *Helicobacter pylori* (*Campylobacter pylori*). *Eur J Clin Microbiol Infect Dis* 1990; 9: 1-13
9 Tomb JF, White O, Kerlavage AR, Clayton RA, Sutton GG, Fleischmann RD, Ketchum KA, Klenk H pylori, Gill S, Dougherty BA, Nelson K, Quackenbush J, Zhou L, Kirkness EF, Peterson S, Loftus B, Richardson D, Dodson R, Khalak HG, Glodek A, McKenney K, Fitzegerald LM, Lee N, Adams MD, Hickey EK, Berg DE, Gocayne JD, Utterback TR, Peterson JD, Kelley JM, Cotton MD, Weidman JM, Fujii C, Bowman C, Watthey L, Wallin E, Hayes WS, Borodovsky M, Karp PD, Smith HO, Fraser CM, Venter JC. The complete genome sequence of the gastric pathogen *Helicobacter pylori*. *Nature* 1997; 388: 539-547
10 Goodwin CS, Duodenal ulcer, *Campylobacter pylori*, and the "leaking roof" concept. *Lancet* 1988; 2: 1467-1469
11 Leunk RD, Johnson PT, David BC, Kraft WG, Morgan DR. Cytotoxin activity in broth culture filtrates of *Campylobacter pylori*. *J Med Microbiol* 1988; 26: 93-99
12 Figueiredo C, Machado JC, Yamaoka Y. Pathogenesis of *Helicobacter pylori* Infection. *Helicobacter* 2005; 10 Suppl 1:14-20
13 Li Y, Wandinger-Ness A, Goldenring JR, Cover TL. Clustering and redistribution of late endocytic compartments in response to *Helicobacter pylori* vacuolating toxin. *Mol Biol Cell* 2004; 15: 1946-1959
14 Suzuki Y, Gabazza EC, Imoto I, James RF, Hirayama T, Wada A, Horiki N, Nakamura M, Inoue H, Kuroda M, Ogura A, Taguchi Y, Yano Y, Taguchi O, Suzuki K, Adachi Y. Vacuolating cytotoxin A is associated with increased thrombin generation in gastric mucosa. *Helicobacter* 2005; 10: 323-331
15 Cover TL, Dooley CP, Blaser MJ. Characterization of and human serologic response to proteins in *Helicobacter pylori* broth culture supernatants with vacuolizing cytotoxin activity. *Infec Immun* 1990; 58: 603-610
16 Censini S, Lange C, Xiang Z, Crabtree JE, Ghiara P, Borodovsky M, Rappuoli R, Covacci A. Cag, a pathogenicity island of *Helicobacter pylori*, encodes type Ⅰ specific and disease associated virulance factors. *Proc Natl Acad Sci USA* 1996; 93: 14648-14653
17 Atherton JC, *H pylori* virulence factors. *Br Med Bull* 1998; 54: 105-120
18 Xiang Z, Censini S, Bayeli PF, Telford JL, Figura N, Rappuoli R, Covacci A. Analysis of expression of cagA and vacA virulence factors in 43 strains of *Helicobacter pylori* reveals that clinical isolates can be divided into two major types and that cagA is not nessary for expression of the vacuolating cytotoxin. *Infect Immun* 1995; 63: 94-98
19 Yokoyama K, Higashi H, Ishikawa S, Fujii Y, Kondo S, Kato H, Azuma T, Wada A, Hirayama T, Aburatani H, Hatakeyama M. Functional antagonism between *Helicobacter pylori* CagA and vacuolating toxin VacA in control of the NFAT signaling pathway in gastric epithelial cells. *Proc Natl Acad Sci USA* 2005; 102: 9661-9666
20 Odenbreit S, Puls J, Sedlmaier B, Gerland E, Fischer W, Haas R. Translocation of *Helicobacter pylori* CagA into gastric epithelial cells by type Ⅳ secretion. *Science* 2000; 287: 1497-1500
21 Segal ED, Cha J, Lo J, Falkow S, Tompkins LS. Altered states: involvement of phosphorylated CagA in the induction of host cellular growth changes by *Helicobacter pylori*. *Proc Natl Acad Sci USA* 1999; 96: 14559-14564
22 Bourzac KM, Guillemin K. *Helicobacter pylori*-host cell interactions mediated by type IV secretion. *Cell Microbiol* 2005 ; 7: 911-919
23 Bauer B, Moese S, Bartfeld S, Meyer TF, Selbach M. Analysis of cell type-specific responses mediated by the type IV secretion system of *Helicobacter pylori*. *Infect Immun* 2005; 73: 4643-4652
24 Hazell SL, Lee A. Campylobacter pyloridis, urease, hydrogen ion back diffusion, and gastric ulcer. *Lancet* 1986; 2: 15-17
25 Marshall BJ, *Helicobacter pylori*. *Am J Gastroenterol* 1994; 89: S116-S128
26 Xu JK, Goodwin CS, Cooper M, Robinson J. Intracellular vaculization caused by the urease of *Helicobacter pylori*. *J Infect Dis* 1990; 161: 1302-1304
27 Windsor hm, O'Rourke J. Bacteriology and taxonomy of *Helicobacter pylori*. *Gastroenterol Clin North Am* 2000; 29: 633-648
28 Sarosiek J, Bilski J, Murty VL, Slomiany A, Slomiany BL. Colloidial bismuth subcitrate (De-Nol)inhibits degradation of gastric mucus by *Campylobactor pylori* protease. *Am J Gastroentetol* 1989; 84: 506-510
29 Byrd JC, Yunker CK, Xu QS, Sternberg LR, Bresalier RS. Inhibition of gastric mucin synthesis by *Helicobacter pylori*. *Gastroenterology* 2000; 118: 1072-1079
30 Al-Marhoon MS, Nunn S, Soames RW. Effects of $cagA^+$ and cagA- strains of *Helicobacter pylori* on the human gastric mucus layer thickness. *J Gastroenterol Hepatol* 2005; 20: 1246-1252
31 Slomiany BL, Piotrowski J, Sengupta S, Slomiany A. Inhibition of gastric mucosal laminin receptor by *Helicobacter pylori* lipopolysaccharide. *Biochem Biophys Res Comm* 1991; 175: 963-970
32 Slomiany BL, Nishikawa H, Piotrowski J, Okazaki K, Slomiany A. Lipolytic activity of *Campylobacter pylori*: Effect of sofalcone. *Digestion* 1989; 43: 33-40
33 Brandt S, Kwok T, Hartig R, Konig W, Backert S. NF-kappaB activation and potentiation of proinflammatory responses by the *Helicobacter pylori* CagA protein. *Proc Natl Acad Sci USA* 2005; 102: 9300-9305
34 Go MF, Crowe S E. Virulence and pathogenicity of *Helicobacter pylori*. *Gastroenterol Clin North Am* 2000; 29: 649-670
35 Zevering Y, Jacob L, Meyer TF. Naturally acquired human immune responses against *Helicobacter pylori* and implication for vaccine development. *Gut* 1999; 45: 465-474
36 Blanchard TG, Czinn S J. Immunology of *Helicobacter pylori* and prospects for vaccine. *Gastroenterol Clin North Am* 2000; 29: 671-685
37 Bamford KB, Fan X, Crowe SE, Leary JF, Gourley WK, Luthra GK, Brooks EG, Graham DY, Reyes VE, Ernst PB. Lymphocytes in the human gastric tissue during *Helicobacter pylori* have a T helper cell 1 phenotype. *Gastroenterology* 1998; 114: 482-492
38 Rathbone BJ, Wyatt JI, Worsley BW, Shires SE, Trejdosiewicz LK, Heatley RV, Losowsky MS. Systemic and local antibody responses to gastric campylobacter pyloridis in non-ulcer dyspepsia. *Gut* 1986; 27: 642-647
39 Liu Y, Vosmaer GD, Tytgat GN, Xiao SD, Ten Kate FJ. Gastrin (G) cells and somatostatin (D) cells in patients with dyspeptic symptoms: *Helicobacter pylori* associated and non-associated gastritis. *J Clin Pathol* 2005; 58: 927-931
40 McColl KE, El-Omar E, Gillen D. *Helicobacter pylori* gastritis and gastric physiology. *Gastroenterol Clin North Am* 2000; 29: 687-703
41 McColl KE, El-Omar E, Gillen D. Interactions between *Helicobacter pylori* infection, gastric-acid secretion and antisecretary therapy. *Bri Med Bull* 1998; 54: 121-138
42 Thong-Ngam D, Tangkijvanich P, Sampatanukul P, Prichakas P, Mahachai V, Tosukowong P. Direct measurement of gastric H+/K+-ATPase activities in patients with or without *Helicobacter pylori*-associated chronic gastritis. *World J Gastroenterol* 2005; 11: 3514-3517
43 Maconi G, Lazzaroni M, Sangaletti O, Bargiggia S, Vago L, Porro GB. Effect of *Helicobacter pylori* eradication on gastric histology, serum gastrin and pepsinogen Ⅰ levels, and gastric emptying in patients with gastric ulcer. *Am J Gastroenterol* 1997; 92: 1844-1848
44 Ohkusa T, Takashimizu I, Fujiki K, Araki A, Honda K, Shimoi

K, Sakurazawa T, Horiuchi T, Suzuki S, Ariake K, Ishii K. Changes in serum pepsinogen gastrin, and immunoglobulin G antibody titers in *Helicobacter pylori*-positive gastric ulcer after eradication of infection. *J Clin Gastroenterol* 1997; 25: 317-322
45 Beales IL, Post L, Calam J, Yamada T, Delvalle J. Tumour necrosis factor alpha stimulates gastrin release from canine and human antral G cells: possible mechanism of the *Helicobacter pylori*-gastrin link. *Eur J Clin Invest* 1996; 26: 609-611
46 Beales I, Blaser MJ, Srinivasan S, Calam J, Perez-Perez GI, Yamada T, Scheiman J, Post L, Del Valle J. Effect of *Helicobacter pylori* products and recombinant cytokines on gastrin release from cultured canine G cells. *Gastroenterology* 1997; 113: 465-471
47 Piotrowski J, Slomiany A, Slomiany BL. *Helicobacter pylori* lipopolysaccharide inhibition of gastric somatostatin receptor: effect of sucralfate. *Biochem Mol Biol Int* 1997; 42: 545-551
48 Piotrowski J, Skrodzka D, Slomiany A, Slomiany BL. Reversal of gastric somatostatin receptor inhibition by *Helicobacter pylori* lipopolysaccharide with ebrotidine and sulglycotide. *Gen Pharmacol* 1997; 28: 705-718
49 Yamashita K, Kaneko H, Yamamoto S, Konagaya T, Kusugami K, Mitsuma T. Inhibtory effect of somatostatin on *Helicobacter pylori* proliferation *in vitro*. *Gastroenterology* 1998; 115: 1123-1130
50 Xuan J, Deguchi R, Yanagi H, Ozawa H, Urano T, Ogawa Y, Fukuda R, Kojima S, Nishina M, Sudo H, Kijima H, Koga Y, Takagi A. Relationship between gastric mucosal IL-8 levels and histological gastritis in patients with *Helicobacter pylori* infection. *Tokai J Exp Clin Med* 2005; 30: 83-88
51 Xing CZ, Guo XL, Xu HM, Yuan Y. The relationship between *helicobacter pylori* infection and IL-8 expression in remnant stomach mucosa. *XiBao Yu FenZi MianYiXue ZaZhi* 2005; 21: 503-505
52 Beswick EJ, Das S, Pinchuk IV, Adegboyega P, Suarez G, Yamaoka Y, Reyes VE. *Helicobacter pylori*-induced IL-8 production by gastric epithelial cells up-regulates CD74 expression. *J Immunol* 2005; 175: 171-176
53 Beales I, Calam J, Post L, Srinivasan S, Yamada T, DelValle J. Effect of transforming growth factor alpha and interleukin 8 on somatostatin release from canine fundic D cells. *Gastroenterology* 1997; 112: 136-143
54 Calam J. The somatostain-gastrin link of *Helicobacter pylori* infection. *Ann Med* 1995; 27: 569-573
55 Calam J. *Helicobacter pylori* and hormones. *Yale J Biol Med* 1996; 63: 39-49
56 陈元方, yamada T主编. 胃肠肽类激素基础与临床. 北京: 北京医科大学中国协和医科大学联合出版社, 1997: 304-316
57 Tunio AM, Holton J, Hobsley M. Gastric juice epidermal growth factor concentration and *Helicobacter pylori* in patients with duodenal ulcer. *Br J Surg* 1995; 82: 1204-1206
58 Seto K, Hayashi-Kuwabara Y, Yoneta T. Vacuolation induced by cytotoxin from *Helicobacter pylori* is mediated by the EGF receptor in Hela cells. *FEBS Lett* 1998; 431: 347-350
59 Liu ZX, Chen BW, Yang GB, Zhang XQ, Jia BQ. Effect of *Helicobacter pylori* on gastric mucosal cell proliferation in gastritis. *Beijing DaXue XueBao* 2004; 36:297-299
60 Schiemann U, Konturek J, Assert R, Rembiasz K, Domschke W, Konturek S, Pfeiffer A. mRNA expression of EGF receptor ligands in atrophic gastritis before and after *Helicobacter pylori* eradication. *Med Sci Monit* 2002; 8: CR53-CR58
61 高晋华, 梁后杰, 刘为纹. 幽门螺杆菌清除前后胃黏膜C-myc蛋白和表皮生长因子受体的变化. 世界华人消化杂志 1999; 7: 1018-1019
62 Joh T, Kataoka H, Tanida S, Watanabe K, Ohshima T, Sasaki M, Nakao H, Ohhara H, Higashiyama S, Itoh M. *Helicobacter pylori*-Stimulated Interleukin-8 (IL-8) promotes cell proliferation through transactivation of epidermal growth factor receptor (EGFR) by disintegrin and metalloproteinase (ADAM) activation. *Dig Dis Sci* 2005; 50: 2081-2089
63 Xu H, Chaturvedi R, Cheng Y, Bussiere FI, Asim M, Yao MD, Potosky D, Meltzer SJ, Rhee JG, Kim SS, Moss SF, Hacker A, Wang Y, Casero RA Jr, Wilson KT. Spermine oxidation induced by *Helicobacter pylori* results in apoptosis and DNA damage: implications for gastric carcinogenesis. *Cancer Res* 2004; 64: 8521-8525
64 Basak C, Pathak SK, Bhattacharyya A, Pathak S, Basu J, Kundu M. The secreted peptidyl prolyl cis,trans-isomerase H pylori0175 of *Helicobacter pylori* induces apoptosis of gastric epithelial cells in a TLR4- and apoptosis signal-regulating kinase 1-dependent manner. *J Immunol* 2005; 174: 5672-5680
65 Moss SF, Calam J, Agarwal B, Wang S, Holt PR. Induction of gastric epithelial apoptosis by *Helicobacter pylori*. *Gut* 1996; 38: 498-501
66 Ledig S, Wagner S, Manns MP, Beil W, Athmann C. Role of the receptor-mediated apoptosis in *Helicobacter pylori* in gastric epithelial cells. *Digestion* 2004; 70:178-186
67 Martin JH, Potthoff A, Ledig S, Cornberg M, Jandl O, Manns MP, Kubicka S, Flemming P, Athmann C, Beil W, Wagner S. Effect of *H pylori* on the expression of TRAIL, FasL and their receptor subtypes in human gastric epithelial cells and their role in apoptosis. *Helicobacter* 2004; 9: 371-386
68 Das S, Sierra JC, Soman KV, Suarez G, Mohammad AA, Dang TA, Luxon BA, Reyes VE. Differential protein expression profiles of gastric epithelial cells following *Helicobacter pylori* infection using ProteinChips. *J Proteome Res* 2005; 4: 920-930
69 Leite KR, Darini E, Canavez FC, Carvalho CM, Mitteldorf CA, Camara-Lopes LH. *Helicobacter pylori* and cagA gene detected by polymerase chain reaction in gastric biopsies: correlation with histological findings, proliferation and apoptosis. *Sao Paulo Med J* 2005; 123: 113-118
70 Hritz I, Herszenyi L, Molnar B, Tulassay Z, Pronai L. Long-term omeprazole and esomeprazole treatment does not significantly increase gastric epithelial cell proliferation and epithelial growth factor receptor expression and has no effect on apoptosis and p53 expression. *World J Gastroenterol* 2005; 11: 4721-4726

电编 张勇 编辑 菅鑫妍 审读 张海宁