世界华人消化杂志®
wcjd@wjgnet.com
世界华人消化杂志 2011年8月18日; 19(23): 2467-2472
ISSN 1009-3079 (print) ISSN 2219-2859 (online)

文献综述 REVIEW

蒙古沙土鼠不同幽门螺杆菌菌株感染相关性胃病的研究进展

柳云恩, 袁 媛

柳云恩, 袁媛, 中国医科大学附属第一医院肿瘤研究所暨普通外科研究所肿瘤病因与筛查研究室 辽宁省高校肿瘤病因与预防重点实验室 辽宁省沈阳市 110001
作者贡献分布: 本文综述由柳云恩完成; 袁媛教授审校.
通讯作者: 袁媛, 教授, 博士生导师, 110001, 辽宁省沈阳市, 中国医科大学附属第一医院肿瘤研究所暨普通外科研究所肿瘤病因与筛查研究室. yyuan@mail.cmu.edu.cn
电话: 024-83282292
收稿日期: 2011-07-06 修回日期: 2011-08-11
接受日期: 2011-08-12 在线出版日期: 2011-08-18

Gastric diseases in Mongolian gerbils infected with different strains of *Helicobacter pylori*

Yun-En Liu, Yuan Yuan

Yun-En Liu, Yuan Yuan, Department of Tumor Etiology and Screening, Institute of Cancer and General Surgery, Key Laboratory of Cancer Control in Liaoning Province, the First Hospital of China Medical University, Shenyang110001, Liaoning Province, China
Correspondence to: Yuan Yuan, Professor, Department of Tumor Etiology and Screening, Institute of Cancer and General Surgery, the First Hospital of China Medical University, Shenyang 110001, Liaoning Province, China.yyuan3@hotmail.com
Received: 2011-07-06 Revised: 2011-08-11
Accepted: 2011-08-12 Published online: 2011-08-18

Abstract
Helicobacter pylori (*H.pylori*) is a bacterium responsible for one of the most widespread infections found in humans. It colonizes the gastric mucosa and can result in chronic gastritis and gastric cancer. The incidence of spontaneous gastric gastritis is low in Mongolian gerbils, and spontaneous *H.pylori* infection can not be detected in this animal. Since *H.pylori*-related gastric diseases in Mongolian gerbils are very similar to those in humans, they have been considered as ideal animals to establish *H.pylori* infection models. However, different strains of *H.pylori* may induce different types of pathologic changes in Mongolian gerbils. Clarification of the pathogenic mechanisms of different strains of *H.pylori* may provide a theoretical basis for screening appropriate *H.pylori* strains and directing individualized treatment in patients with *H.pylori*-related gastric diseases. In this paper, we review the recent progress in research of gastric diseases in Mongolian gerbils infected with different strains of *H.pylori*.

Key Words: Mongolian gerbil; *Helicobacter pylori*; Pathogenic mechanism; Gastric diseases; Individualized treatment

Liu YE, Yuan Y. Gastric diseases in Mongolian gerbils infected with different strains of *Helicobacter pylori*. Shijie Huaren Xiaohua Zazhi 2011; 19(23): 2467-2472

摘要
幽门螺杆菌(*Helicobacter pylori*, *H.pylori*)感染在世界范围内高发, 他定植于人胃黏膜, 导致慢性胃炎及胃癌的发生. 蒙古沙鼠(mongolian gerbil, MG)很少患自发性胃炎, 且不是*H.pylori*的自然宿主. 人工接种*H.pylori*后, 蒙古沙鼠患*H.pylori*相关性胃病与胃病患者最相似, 是一个公认的人类胃病的动物模型. 采用不同*H.pylori*菌株感染蒙古沙鼠, 经常会导致不同的*H.pylori*相关性胃病的发生, 其原因可能与*H.pylori*致病菌株密切有关. 因此, 明确*H.pylori*的致病菌株及其机制, 可以为筛选*H.pylori*致病菌株提供理论参考, 并有利于对*H.pylori*相关性胃病患者进行个体化治疗. 本文对蒙古沙土鼠不同*H.pylori*菌株感染相关性胃疾病研究进展进行综述.

关键词: 蒙古沙鼠; 幽门螺杆菌; 致病机制; 胃病; 个体化治疗

柳云恩, 袁媛. 蒙古沙土鼠不同幽门螺杆菌菌株感染相关性胃病的研究进展. 世界华人消化杂志 2011; 19(23): 2467-2472
http://www.wjgnet.com/1009-3079/19/2467.asp

0 引言
约50%人群感染幽门螺杆菌(*Helicobacter pylori*, *H.pylori*), 其与慢性胃炎、消化性溃疡及胃癌的发生密切相关[1-4]. 绝大多数人群感染*H.pylori*后

■背景资料
蒙古沙鼠(MG)很少患自发性胃炎, 且不是*H.pylori*的自然宿主. 人工接种*H.pylori*后, 蒙古沙鼠患*H.pylori*相关性胃病与胃病患者最相似, 是一个公认的人类胃病的动物模型.

■同行评议者
王江滨, 教授, 吉林大学中日联谊医院消化内科; 王振宁, 教授, 中国医科大学附属第一医院肿瘤外科

■研发前沿
深入研究不同*H.pylori*菌株特有的致病基因和毒素蛋白, 同时深入研究MG的宿主因素, 并探讨两者之间的交互作用.

无任何症状[5], 少数人患*H.pylori*相关性胃炎及溃疡, 极少数发展为*H.pylori*相关性胃癌. 为了探究不同的临床结局是否与*H.pylori*的致病菌株相关, 亟待建立一个与人类胃病类似的动物模型. Yokota等[6]首次报道了蒙古沙鼠(Mongolian gerbil, MG)感染*H.pylori*后, 胃黏膜发生轻微的炎细胞浸润. MG患自发性胃炎机率很低, 且不是*H.pylori*自然宿主. 人工接种*H.pylori*后, MG发生*H.pylori*相关性胃病与人类胃病最类似. 研究发现将*H.pylori*接种到MG体内, 胃黏膜发生萎缩或肠化生等病变[7,8]. 而Cao等[9]用*H.pylori*诱导MG黏膜发生了神经内分泌起源的类癌. 此外, Kuo等[10]在MG体内诱发了胃癌. 相反, Toyoda等[11]采用相同*H.pylori*菌株感染MG, 并未观察到任何胃部肿瘤发生. 因此, 不同*H.pylori*菌株感染MG, 经常会产生截然不同的临床结局, 其原因可能与菌株自身致病性密切相关. 因此, 明确*H.pylori*致病菌株及其机制, 可以为筛选*H.pylori*致病菌株提供理论参考, 并有利于对*H.pylori*相关性胃病患者进行个体化治疗. 本文对蒙古沙土鼠不同*H.pylori*菌株感染相关性胃疾病进行综述.

1 *H.pylori*相关性胃炎

Ikeno等[12]用ATCC43504菌株接种MG, 2 wk后, 镜下未见任何组织学改变; 4 wk后, 胃黏膜明显变薄, 移行带壁细胞和主细胞消失, 幽门出现轻-中度炎细胞浸润; 26 wk后, 出现溃疡, 肠化生和增生性息肉等病变. Honda等[13]用相同菌株感染MG, 6 wk后, 幽门部即发生溃疡, 并持续到18 wk, 溃疡穿透黏膜下层和肌层, 部分浸润到肝脏和胰腺, 6 mo后, 胃小弯发生萎缩性胃炎和肠化生, 12-18 mo, 肠化生演变为发育异常. 使用相同菌株感染同一品系MG, 病变的严重程度和出现的时间却大相径庭, 其原因可能与菌株毒力大小有关, 众所周知, 任何菌株原代培养时致病性最强, 随着不停的传代培养, 菌株毒力明显下降[14], 因而, 在这种情况下可能导致同一菌株致病性显著不同. 研究发现ATCC43504菌株是一个高致病性菌株[15], 其为研究*H.pylori*致病基因及毒力大小提供了实验模型, 并为评价其他菌株的毒力提供了标准.

Yan等[16]用2×10^9 CFU/mL NCTC11637菌株接种MG, 6 wk后, MG胃黏膜发现轻度的炎症细胞浸润. Takahashi等[17]用相同菌株接种MG, 20 wk后, MG发生了出血性胃炎和溃疡等病变. 结果提示, 与ATCC43504菌株相比, NCTC11637菌株的毒力明显降低, 两种菌株的致病性存在较大差别, 两种菌株属于同一家族, 且均表达$cagA^+vacA^+$[18,19], 因此, 除公认的致病基因($cagA^+vacA^+$)外, ATCC43504菌株可能存在独特的致病基因, 使其具备较强的致病能力.

Watanabe等[20]用TN2GF4菌株(胃溃疡分离株)接种MG, 26 wk后, MG发生了重度活动性胃炎、溃疡和肠化生等病变. Ohkusa等[21]用TN2GF4和ATCC43504菌株分别接种MG, 12 wk后, MG发生了胃炎和溃疡, 然而, 感染TN2GF4菌株的MG发生十二指肠炎和肠化生的风险更高. 肠化生是慢性胃炎常见表现形式, 且肠化生与肠型胃癌发生密切相关[22,23], 此外, TN2GF4菌株单独诱导MG发生高分化腺癌的机率高. 结果提示TN2GF4菌株可能较ATCC43504具有更强的致病能力.

不同菌株致病性存在较大差别, 即使同一家族来源的菌株致病性也千差万别, 其原因何在? Ohnita等[24]发现携带$cagPAI^+$菌株诱导MG发生溃疡、萎缩、肠化生和增生性息肉, 而$cagPAI^-$菌株仅见黏膜糜烂和轻度炎细胞浸润, 但cagPAI并未影响菌株的定植能力. *H.pylori*菌株感染周期和定植密度可以促进细胞增殖, 从而发挥致癌作用[25]. 此外, $cagPAI^+$能激活转录因子NF-κB, NF-κB通过刺激IL-8的产生而促进胃黏膜细胞的增殖, 从而导致MG发生*H.pylori*相关性胃炎[26,27]. IL-1β是急性炎症最特征的细胞因子之一, MG感染*H.pylori*后, IL-1β表达水平升高, 4 wk时, 达到高峰, 然后迅速降低. IL-4, IL-6和IL-10是慢性炎症最具特征的细胞因子, 这些细胞因子在*H.pylori*感染8-24 wk达到高峰, 他们与胃癌的发生密切相关[28]. 因此, 当对*H.pylori*感染患者进行筛选时, 可以通过检测细胞因子的表达水平, 即可大致判断菌株的感染时间, 从而为临床治疗*H.pylori*相关性胃炎提供重要参考.

2 *H.pylori*相关性胃癌

Honda等[13]用ATCC43504菌株感染MG, 18 mo后, 2/5(40%)动物发展为高分化胃癌, 其中1例来源于肠化生部位, 另外1例也与肠化生密切相关, 未见低分化腺癌. 而Hirayama等[29]用ATCC43504菌株接种MG, 24 mo后, 18/56只MG发生了类癌, 1/56发展为低分化腺癌. Zheng等[30]用ATCC43504和161菌株(中国胃癌患者分离株)感染MG, 84 wk后, 18%(3/17)感染了ATCC43504菌株的MG发生了高分化癌, 而感染161菌株的MG

发生了1例胃癌. 结果提示, 使用相同菌株感染MG, 可以导致胃癌发生率明显不同, 其原因何在? 首先, *H.pylori*感染时间明显不同, 而*H.pylori*感染时间是胃癌形成的必要条件, 长期*H.pylori*感染可以刺激黏膜细胞增生[31]; 其次, MG饲养条件及来源不同, 实验动物对条件要求较为苛刻, 不同条件下动物自发病变发生率明显不同; 再次, 菌株的传代次数, 不同实验使用的菌株传代次数不可能完全一致, 有的可能是原代培养, 有的菌株可能传过若干代, 菌株毒力无法保证, 因而导致结果不同.

Sugiyama等[32]用致癌物MNU和ATCC43504菌株共同感染MG, 20 wk后, 36.8%(7/19)的动物发生了腺癌和印戒细胞癌, 其中高、低分化腺癌各1例, 印戒细胞癌5例. Cao等[33]分别在*H.pylori*菌株感染的早、中和晚期给予MG致癌物MNU, 52 wk后, 3个阶段胃癌的发生率分别为60%(12/20), 18.4%(2/11)和10%(2/20), 结果提示在菌株感染早期给予致癌物容易导致胃癌的发生. Tokieda等[34]用相同菌株和致癌物MNNG接种MG, 52 wk后, 单用*H.pylori*感染的MG未发生腺癌, 而单用MNNG致癌物则诱发17.6%动物发生了腺癌, 致癌物和*H.pylori*联合作用在24 wk即有1例发生高分化腺癌, 52 wk后, 66.7%(4/6)的动物发生了高分化腺癌. Shimizu等[35]用相同菌株和不同剂量的致癌物MNNG分别接种MG, 50 wk后, MNNG(300 mg)和*H.pylori*联合导致12(44.4%)的动物发生高分化腺癌, 而MNNG(60 mg)和*H.pylori*联合作用, 导致6(24.0%)动物发生印戒细胞癌. 结果提示, 不同浓度致癌物与*H.pylori*联合使用, 导致MG发生的胃癌类型和发生率与单用*H.pylori*均存在显著差别, 单独*H.pylori*感染只能诱导出高分化腺癌, 而未见其他类型癌产生. 因此, 有研究认为*H.pylori*可能在胃癌发生过程中只是起到促进作用, 而并非启动作用[36].

Watanabe等[20]用TN2GF4菌株(胃溃疡患者分离株)接种MG, 26 wk后, MG出现重度活动性胃炎、溃疡和肠化生, 62 wk后, 37%(10/27)的动物发生了高分化腺癌. Ogura等[37]用分别用TN2(WT)和TN2△vacA菌株接种MG, 该菌株与TN2GF4菌株属于同一家族, 23 wk后, TN2(WT)菌株分别诱导25%(1/4)和25%(1/4)动物发生了高分化腺癌和类癌, 而TN2△vacA菌株在接种28周后, 分别有25%(1/4)和17.86%(5/28)的动物发生了高分化腺癌和类癌. 结果提示, 同一家族中不同菌株致病能力差别显著, 同一菌株野生型和突变株致癌性也千差万别, TN2GF4家族菌株可能是一个高致癌性菌株家族.

此外, Romero-Gallo等[38]用7.13(溃疡患者分离株)菌株接种MG, 14 wk后, 33%MG发生了高分化腺癌, 18 wk后, 50%的MG发生高分化腺癌, 该菌株不仅能迅速诱发胃癌, 还随接种时间的延长, 胃癌发生率显著增加. Franco等[39]则将7.13菌株及oipA$^-$突变株接种MG, 24 wk后, 7.13(WT)菌株诱发44%的MG发展为高分化腺癌, 而oipA$^-$菌株仅能导致27%动物发展为腺癌. 结果提示oipA$^-$突变明显降低了7.13菌株致病能力, 从而降低了胃癌的发生率和减轻了病变的严重程度, 同时oipA$^-$基因缺失也极大的降低了胞质或核内B-catenin易位能力, 影响了核内细胞信号传导途径[40], 从而降低了胃癌发生率. 此外, oipA能导致重度*H.pylori*感染, 同时引起IL-6和IL-11表达水平升高, 最终能增加*H.pylori*相关性胃病的发病风险[41]. 然而, 他的子代菌株B128仅能导致MG发生轻度溃疡和胰腺炎[42]. 研究发现7.13菌株和B128菌株的主要区别在于OioA$^-$基因位于7.13菌株编码框架内部, 而由于在5’端富含CT区域插入2个bp, OioA$^-$基因位于B128菌株编码框架外部, 从而导致其转录过早终止[43]. 此外, 7.13菌株感染MG后, 不同炎症因子表达各不相同, 6-12 mo, TNF-α mRNA表达水平达到顶峰, IL-17 mRNA表达水平则在感染12 mo后达到顶峰, 结果提示7.13菌株处于慢性感染阶段, 同时发现, IL-17, IL-18和TNF-α mRNA等细胞因子在7.13菌株野生株中的表达水平显著高于oipA$^-$突变株[44,45], 说明oipA$^-$基因可能决定胃黏膜炎症细胞因子的表达, 从而对胃癌的发生起决定作用. 结果表明同一家族不同菌株致病基因可能存在较大差别, 这种差别可能会导致菌株的致病能力存在显著差异[46], 从而可能严重影响同一家族菌株的致癌性.

3 结论

不同*H.pylori*菌株感染MG均能成功建立与人类*H.pylori*相关性胃病类似的动物模型[47-49], 然而, 不同菌株感染MG通常会导致不同的病理变化(表1), 即便是来源于同一家族的菌株或同一菌株的突变株, 感染MG结局也大不相同. 因此, 为了更清楚的研究*H.pylori*致病机制, 我们有必要深入研究不同*H.pylori*菌株特有的致病基因和毒素蛋白, 同时深入研究MG的宿主因素, 并探讨

■创新盘点
本文对蒙古沙鼠不同*H.pylori*感染相关性胃病进行综述, 并剖析了不同菌株的致病特点及其机制.

■应用要点
本文可以为临床筛选*H.pylori*致病菌株提供理论参考，对*H.pylori*相关性胃病患者进行个体化治疗有一定的参考价值.

表 1 不同*H.pylori*菌株感染MG胃癌类型

年代	菌株	沙鼠周龄(wk)	致癌物	试验周期: 胃癌发生率*n*(%)	胃癌类型(*n*)	研究者
1998	ATCC-43504	5	无	18 mo: 2/5(40)	高分化腺癌	Honda等[13]
1998	ATCC-43504	7	MNU	20 wk: 7/19(36.8)	高分化腺癌(1); 低分化腺癌(1); 印戒细胞癌(5)	Sugiyama等[32]
1999	ATCC-43504	不明	无	24 mo: 19/112(19.96)	类癌(18/56); 高分化腺癌(1/56)	Hirayama等[29]
1999	ATCC-43504	5	MNNG	24 wk: 1/2(50); 52 wk: 4/6(66.7)	高分化腺癌(5)	Tokieda等[34]
1999	ATCC-43504	7	MNNG	50 wk: MNNG(300 mg) 12(44.4); 50 wk: MNNG(60 mg)6 (24)	高分化腺癌(8); 低分化癌(4)印戒细胞癌(6)	Shimizu等[35]
2000	TN2 (WT)	5	无	23 wk: 2 /8(25.00)	类癌(1/4); 高分化腺癌(1/4)	Ogura等[37]
2000	TN2△vacA	5	无	28 wk: 6/22(27.27)	类癌(5/18); 高分化腺癌(1/4)	Ogura等[37]
2000	TN2GF4(溃疡分离株)	不明	无	62 wk: 10/27(37)	高分化腺癌(10)	Watanabe等[20]
2004	ATCC-43504	不明	无	84 wk: 2/11(18.18)	高分化腺癌(2)	Zheng等[30]
2004	161(胃癌分离株)	不明	无	84 wk: 1/6(16.67)	高分化腺癌(1)	Zheng等[30]
2008	7.13oipA$^-$	4	无	24 wk: 27	高分化腺癌	Franco等[39]
2008	7.13(WT)	4	无	24 wk: 44	高分化腺癌	Franco等[39]
2008	7.13(溃疡分离株)	4-8	无	14 wk: 33; 18 wk: 50	高分化腺癌	Romero-Gallo等[38]

两者之间的交互作用[50], 从而为更深入研究不同*H.pylori*相关性胃病的致病机制提供理论基础.

4 参考文献

1 Plummer M, van Doorn LJ, Franceschi S, Kleter B, Canzian F, Vivas J, Lopez G, Colin D, Muñoz N, Kato I. Helicobacter pylori cytotoxin-associated genotype and gastric precancerous lesions. *J Natl Cancer Inst* 2007; 99: 1328-1334

2 Motta CR, Cunha MP, Queiroz DM, Cruz FW, Guerra EJ, Mota RM, Braga LL. Gastric precancerous lesions and Helicobacter pylori infection in relatives of gastric cancer patients from Northeastern Brazil. *Digestion* 2008; 78: 3-8

3 Batista SA, Rocha GA, Rocha AM, Saraiva IE, Cabral MM, Oliveira RC, Queiroz DM. Higher number of Helicobacter pylori CagA EPIYA C phosphorylation sites increases the risk of gastric cancer, but not duodenal ulcer. *BMC Microbiol* 2011; 11: 61

4 Kato M, Asaka M. Recent knowledge of the relationship between Helicobacter pylori and gastric cancer and recent progress of gastroendoscopic diagnosis and treatment for gastric cancer. *Jpn J Clin Oncol* 2010; 40: 828-837

5 Taddesse G, Habteselassie A, Desta K, Esayas S, Bane A. Association of dyspepsia symptoms and Helicobacter pylori infections in private higher clinic, Addis Ababa, Ethiopia. *Ethiop Med J* 2011; 49: 109-116

6 Yokota K, Kurebayashi Y, Takayama Y, Hayashi S, Isogai H, Isogai E, Imai K, Yabana T, Yachi A, Oguma K. Colonization of Helicobacter pylori in the gastric mucosa of Mongolian gerbils. *Microbiol Immunol* 1991; 35: 475-480

7 Hagiwara T, Mukaisho K, Nakayama T, Sugihara H, Hattori T. Long-term proton pump inhibitor administration worsens atrophic corpus gastritis and promotes adenocarcinoma development in Mongolian gerbils infected with Helicobacter pylori. *Gut* 2011; 60: 624-630

8 Wiedemann T, Loell E, Mueller S, Stoeckelhuber M, Stolte M, Haas R, Rieder G. Helicobacter pylori cag-Pathogenicity island-dependent early immunological response triggers later precancerous gastric changes in Mongolian gerbils. *PLoS One* 2009; 4: e4754

9 Cao L, Mizoshita T, Tsukamoto T, Takenaka Y, Toyoda T, Cao X, Ban H, Nozaki K, Tatematsu M. Development of carcinoid tumors of the glandular stomach and effects of eradication in Helicobacter pylori-infected Mongolian gerbils. *Asian Pac J Cancer Prev* 2008; 9: 25-30

10 Kuo CH, Hu HM, Tsai PY, Wu IC, Yang SF, Chang LL, Wang JY, Jan CM, Wang WM, Wu DC. Short-term celecoxib intervention is a safe and effective chemopreventive for gastric carcinogenesis based on a Mongolian gerbil model. *World J Gastroenterol* 2009; 15: 4907-4914

11 Toyoda T, Tsukamoto T, Takasu S, Shi L, Hirano N, Ban H, Kumagai T, Tatematsu M. Anti-inflammatory effects of caffeic acid phenethyl ester (CAPE), a nuclear factor-kappaB inhibitor, on Helicobacter pylori-induced gastritis in Mongolian gerbils. *Int J Cancer* 2009; 125: 1786-1795

12 Ikeno T, Ota H, Sugiyama A, Ishida K, Katsuyama T, Genta RM, Kawasaki S. Helicobacter pylori-induced chronic active gastritis, intestinal metaplasia, and gastric ulcer in Mongolian gerbils. *Am J Pathol* 1999; 154: 951-960

13 Honda S, Fujioka T, Tokieda M, Gotoh T, Nishizono

A, Nasu M. Gastric ulcer, atrophic gastritis, and intestinal metaplasia caused by Helicobacter pylori infection in Mongolian gerbils. *Scand J Gastroenterol* 1998; 33: 454-460
14 Radin JN, González-Rivera C, Ivie SE, McClain MS, Cover TL. Helicobacter pylori VacA induces programmed necrosis in gastric epithelial cells. *Infect Immun* 2011; 79: 2535-2543
15 Chang CC, Chen SH, Lien GS, Lee YJ, Lou HY, Hsieh CR, Fang CL, Pan S. Anti-Helicobacter pylori therapy significantly reduces Helicobacter pylori -induced gastric mucosal damage in Mongolian gerbils. *World J Gastroenterol* 2005; 11: 982-985
16 Yan J, Luo YH, Mao YF. Establishment of Helicobacter pylori infection model in Mongolian gerbils. *World J Gastroenterol* 2004; 10: 852-855
17 Takahashi S, Fujita T, Yamamoto A. Role of cyclooxygenase-2 in Helicobacter pylori- induced gastritis in Mongolian gerbils. *Am J Physiol Gastrointest Liver Physiol* 2000; 279: G791-G798
18 Baek HY, Lim JW, Kim H. Interaction between the Helicobacter pylori CagA and alpha-Pix in gastric epithelial AGS cells. *Ann N Y Acad Sci* 2007; 1096: 18-23
19 Chen Y, Wang Y, Xu W, Zhang Z. Analysis on the mechanism of Helicobacter pylori-induced apoptosis in gastric cancer cell line BGC-823. *Int J Mol Med* 2005; 16: 741-745
20 Watanabe T, Tada M, Nagai H, Sasaki S, Nakao M. Helicobacter pylori infection induces gastric cancer in mongolian gerbils. *Gastroenterology* 1998; 115: 642-648
21 Ohkusa T, Okayasu I, Miwa H, Ohtaka K, Endo S, Sato N. Helicobacter pylori infection induces duodenitis and superficial duodenal ulcer in Mongolian gerbils. *Gut* 2003; 52: 797-803
22 Tsukanov VV, Butorin NN, Maady AS, Shtygasheva OV, Amelchugova OS, Tonkikh JL, Fassan M, Rugge M. Helicobacter pylori Infection, Intestinal Metaplasia, and Gastric Cancer Risk in Eastern Siberia. *Helicobacter* 2011; 16: 107-112
23 Das KM. Lack of clinical usefulness of Das-1 monoclonal antibody and mucin expression as risk markers of gastric carcinoma in patients with gastric intestinal metaplasia. *Am J Clin Pathol* 2010; 133: 980
24 Ohnita K, Isomoto H, Honda S, Wada A, Wen CY, Nishi Y, Mizuta Y, Hirayama T, Kohno S. Helicobacter pylori strain-specific modulation of gastric inflammation in Mongolian gerbils. *World J Gastroenterol* 2005; 11: 1549-1553
25 Cao X, Tsukamoto T, Nozaki K, Tanaka H, Cao L, Toyoda T, Takasu S, Ban H, Kumagai T, Tatematsu M. Severity of gastritis determines glandular stomach carcinogenesis in Helicobacter pylori-infected Mongolian gerbils. *Cancer Sci* 2007; 98: 478-483
26 Yanai A, Maeda S, Shibata W, Hikiba Y, Sakamoto K, Nakagawa H, Ohmae T, Hirata Y, Ogura K, Muto S, Itai A, Omata M. Activation of IkappaB kinase and NF-kappaB is essential for Helicobacter pylori-induced chronic gastritis in Mongolian gerbils. *Infect Immun* 2008; 76: 781-787
27 Yang C, Ling H, Zhang M, Yang Z, Wang X, Zeng F, Wang C, Feng J. Oxidative stress mediates chemical hypoxia-induced injury and inflammation by activating NF-κb-COX-2 pathway in HaCaT cells. *Mol Cells* 2011; 31: 531-538
28 Yamaoka Y, Yamauchi K, Ota H, Sugiyama A, Ishizone S, Graham DY, Maruta F, Murakami M, Katsuyama T. Natural history of gastric mucosal cytokine expression in Helicobacter pylori gastritis in Mongolian gerbils. *Infect Immun* 2005; 73: 2205-2212
29 Hirayama F, Takagi S, Iwao E, Yokoyama Y, Haga K, Hanada S. Development of poorly differentiated adenocarcinoma and carcinoid due to long-term Helicobacter pylori colonization in Mongolian gerbils. *J Gastroenterol* 1999; 34: 450-454
30 Zheng Q, Chen XY, Shi Y, Xiao SD. Development of gastric adenocarcinoma in Mongolian gerbils after long-term infection with Helicobacter pylori. *J Gastroenterol Hepatol* 2004; 19: 1192-1198
31 Gonzalez-Obeso E, Fujita H, Deshpande V, Ogawa F, Lisovsky M, Genevay M, Grzyb K, Brugge W, Lennerz JK, Shimizu M, Srivastava A, Lauwers GY. Gastric hyperplastic polyps: a heterogeneous clinicopathologic group including a distinct subset best categorized as mucosal prolapse polyp. *Am J Surg Pathol* 2011; 35: 670-677
32 Sugiyama A, Maruta F, Ikeno T, Ishida K, Kawasaki S, Katsuyama T, Shimizu N, Tatematsu M. Helicobacter pylori infection enhances N-methyl-N-nitrosourea-induced stomach carcinogenesis in the Mongolian gerbil. *Cancer Res* 1998; 58: 2067-2069
33 Cao X, Tsukamoto T, Nozaki K, Tanaka H, Shimizu N, Kaminishi M, Kumagai T, Tatematsu M. Earlier Helicobacter pylori infection increases the risk for the N-methyl-N-nitrosourea-induced stomach carcinogenesis in Mongolian gerbils. *Jpn J Cancer Res* 2002; 93: 1293-1298
34 Tokieda M, Honda S, Fujioka T, Nasu M. Effect of Helicobacter pylori infection on the N-methyl-N'-nitro-N-nitrosoguanidine-induced gastric carcinogenesis in mongolian gerbils. *Carcinogenesis* 1999; 20: 1261-1266
35 Shimizu N, Inada K, Nakanishi H, Tsukamoto T, Ikehara Y, Kaminishi M, Kuramoto S, Sugiyama A, Katsuyama T, Tatematsu M. Helicobacter pylori infection enhances glandular stomach carcinogenesis in Mongolian gerbils treated with chemical carcinogens. *Carcinogenesis* 1999; 20: 669-676
36 Tatematsu M, Tsukamoto T, Mizoshita T. Role of Helicobacter pylori in gastric carcinogenesis: the origin of gastric cancers and heterotopic proliferative glands in Mongolian gerbils. *Helicobacter* 2005; 10: 97-106
37 Ogura K, Maeda S, Nakao M, Watanabe T, Tada M, Kyutoku T, Yoshida H, Shiratori Y, Omata M. Virulence factors of Helicobacter pylori responsible for gastric diseases in Mongolian gerbil. *J Exp Med* 2000; 192: 1601-1610
38 Romero-Gallo J, Harris EJ, Krishna U, Washington MK, Perez-Perez GI, Peek RM. Effect of Helicobacter pylori eradication on gastric carcinogenesis. *Lab Invest* 2008; 88: 328-336
39 Franco AT, Johnston E, Krishna U, Yamaoka Y, Israel DA, Nagy TA, Wroblewski LE, Piazuelo MB, Correa P, Peek RM. Regulation of gastric carcinogenesis by Helicobacter pylori virulence factors. *Cancer Res* 2008; 68: 379-387
40 Yamaoka Y. Mechanisms of disease: Helicobacter pylori virulence factors. *Nat Rev Gastroenterol Hepatol* 2010; 7: 629-641
41 Sugimoto M, Ohno T, Graham DY, Yamaoka Y. Helicobacter pylori outer membrane proteins on gastric mucosal interleukin 6 and 11 expression in

■同行评价
本文对蒙古沙鼠幽门螺杆菌相关性胃病的研究进展进行了综述, 有一定的参考价值和意义.

Mongolian gerbils. *J Gastroenterol Hepatol* 2011 Jun 16 *[Epub ahead of print]*
42 Rieder G, Karnholz A, Stoeckelhuber M, Merchant JL, Haas R. H pylori infection causes chronic pancreatitis in Mongolian gerbils. *World J Gastroenterol* 2007; 13: 3939-3947
43 Farnbacher M, Jahns T, Willrodt D, Daniel R, Haas R, Goesmann A, Kurtz S, Rieder G. Sequencing, annotation, and comparative genome analysis of the gerbil-adapted Helicobacter pylori strain B8. *BMC Genomics* 2010; 11: 335
44 Sugimoto M, Ohno T, Graham DY, Yamaoka Y. Gastric mucosal interleukin-17 and -18 mRNA expression in Helicobacter pylori-induced Mongolian gerbils. *Cancer Sci* 2009; 100: 2152-2159
45 Futagami S, Hiratsuka T, Suzuki K, Kusunoki M, Wada K, Miyake K, Ohashi K, Shimizu M, Takahashi H, Gudis K, Kato S, Tsukui T, Sakamoto C. gammadelta T cells increase with gastric mucosal interleukin (IL)-7, IL-1beta, and Helicobacter pylori urease specific immunoglobulin levels via CCR2 upregulation in Helicobacter pylori gastritis. *J Gastroenterol Hepatol* 2006; 21: 32-40
46 Kawai M, Furuta Y, Yahara K, Tsuru T, Oshima K, Handa N, Takahashi N, Yoshida M, Azuma T, Hattori M, Uchiyama I, Kobayashi I. Evolution in an oncogenic bacterial species with extreme genome plasticity: Helicobacter pylori East Asian genomes. *BMC Microbiol* 2011; 11: 104
47 Senkovich OA, Yin J, Ekshyyan V, Conant C, Traylor J, Adegboyega P, McGee DJ, Rhoads RE, Slepenkov S, Testerman TL. Helicobacter pylori AlpA and AlpB Bind Host Laminin and Influence Gastric Inflammation in Gerbils. *Infect Immun* 2011; 79: 3106-3116
48 Fox JG, Kuipers EJ. Long-term proton pump inhibitor administration, H pylori and gastric cancer: lessons from the gerbil. *Gut* 2011; 60: 567-568
49 Ohno T, Vallström A, Rugge M, Ota H, Graham DY, Arnqvist A, Yamaoka Y. Effects of blood group antigen-binding adhesin expression during Helicobacter pylori infection of Mongolian gerbils. *J Infect Dis* 2011; 203: 726-735
50 Shin CM, Kim N, Lee HS, Lee DH, Kim JS, Jung HC, Song IS. Intrafamilial aggregation of gastric cancer: a comprehensive approach including environmental factors, Helicobacter pylori virulence, and genetic susceptibility. *Eur J Gastroenterol Hepatol* 2011; 23: 411-417

编辑 李薇 电编 何基才

ISSN 1009-3079 (print) ISSN 2219-2859 (online) CN 14-1260/R 2011年版权归世界华人消化杂志

• 消息 •

《世界华人消化杂志》参考文献要求

本刊讯 本刊采用“顺序编码制”的著录方法, 即以文中出现顺序用阿拉伯数字编号排序. 提倡对国内同行近年已发表的相关研究论文给予充分的反映, 并在文内引用处右上角加方括号注明角码. 文中如列作者姓名, 则需在“Pang等”的右上角注角码号; 若正文中仅引用某文献中的论述, 则在该论述的句末右上角注码号. 如马连生[1]报告……, 潘伯荣等[2-5]认为……; PCR方法敏感性高[6-7]. 文献序号作正文叙述时, 用与正文同号的数字并排, 如本实验方法见文献[8]. 所引参考文献必须以近2-3年SCIE, PubMed,《中国科技论文统计源期刊》和《中文核心期刊要目总览》收录的学术类期刊为准, 通常应只引用与其观点或数据密切相关的国内外期刊中的最新文献, 包括世界华人消化杂志(http://www.wjgnet.com/1009-3079/index.jsp)和*World Journal of Gastroenterology*(http://www.wjgnet.com/1007-9327/index.jsp). 期刊: 序号, 作者(列出全体作者). 文题, 刊名, 年, 卷, 起页-止页, PMID编号 ; 书籍: 序号, 作者(列出全部),书名, 卷次, 版次, 出版地, 出版社, 年, 起页-止页.