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Oxidative Stress Involved Autophagy and Apoptosis in *Helicobacter pylori* Related Gastritis

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1. Introduction

Gastritis, inflammation of gastric mucosa, is a very common condition in the world wide. There is no universally accepted classification of gastritis. Early classification was based mainly on the morphology, but recently pathogenic mechanisms have also been incorporated. The Sydney system, a classification of gastritis introduced in 1990, and updated in 1995, has included both an endoscopic and histologic divisions and is designed for an unambiguous uniform reporting system. (Dixon, Genta et al. 1996)

The histologic changes of acute gastritis include hyperemia, edema, and infiltration of polymorphonuclear cells, together with variable loss of epithelium. Endoscopically, these changes can be observed as edema, petechial or submucosal hemorrhage, erosions or ulcers. A lot of factors including nonsteroidal anti-inflammatory drugs (NSAIDs) and various noxious substances may result in these acute abnormalities. Excess production of reactive oxygen species evokes oxidative stress, which can induce apoptosis and autophagy in the damaged tissue or cells. Oxidative stress induced by the NSAIDs and various noxious substances may contribute to the pathophysiologic and histopathologic alterations including autophagy and apoptosis, leading to gastritis.

The discovery of *Helicobacter pylori* has markedly improved our understanding about the nature of chronic gastritis and other important gastroduodenal diseases. (Marshall 1983; Warren 1983) *H. pylori* have been accepted as the most common cause of chronic gastritis. (Suerbaum and Michetti 2002) Colonization of gastric mucosa by *H. pylori* is always associated with persistent inflammation. Several virulence factor derived from *H. pylori* may promote these inflammatory mucosal changes. *H. pylori*-associated chronic gastritis usually accompanies with polymorphonuclear infiltration and architectural change of the gastric mucosa. There are marked mucosal cellular and systemic humoral immunologic responses. The mucosal damage seen in patients with *H. pylori* may result from both the effect of immunologic response and the bacterial toxin. Apoptosis and autophagy may contribute to cell homeostasis in gastric epithelial cells subjected to *H. pylori* infection. The combination of antioxidant and anti-adhesion materials can be attenuated the severity of gastritis.

2. Epidemiology

More than 50% of population in the world is infected with this bacterium. The prevalence of infection is increased with age and thought to be a cohort effect.
Epidemiologic studies show this infection is generally acquired during childhood and the majority of *H. pylori* transmission is through close person-to-person contact. The oral-oral, gastro-oral, or fecal-oral exposure seems the most probable explanation for infection. (Brown 2000; Amieva, El-Omar et al. 2008)

3. Pathogenesis

Bacterial factor and colonization

H. pylori infection is closely associated with chronic active type B gastritis, peptic ulcers, gastric cancer and gastric MALT lymphoma. The pre-neoplastic lesions, such as glandular atrophy and intestinal metaplasia, may consequently result from persistent chronic gastritis in some patients. The outcome of *H. pylori* infection depends on the combination of bacterial and host factors in addition to less well-defined environmental conditions.
H. pylori are one of few organisms capable of colonizing the harsh environment of the human stomach. The initial step in *H. pylori* infection is the penetration and adherence of the bacterium to mucin and epithelial cells. *H. pylori* generate large amounts of cytosolic and cell surface-associated urease. The urease helps the organism to avoid the bactericidal activity of gastric acid. *H. pylori* can use its polar flagella to migrate rapidly to a more favorable environment below the mucus layer very close to the surface of the epithelium where the pH is near neutral.
After *H. pylori* migrate to the gastric epithelium, the bacteria adhere to the surface of host cells and may damage them in order to obtain nutrients and establish persistent colonization. Several different adhesion molecules have been identified and classified as adhesins. (Boren, Falk et al. 1993) The best studied *H. pylori* adhesins are outer membrane proteins that bind carbohydrate modifications in the glycoproteins of epithelial cells. The specific bacterial gene product, BabA, act as the ligand for the fucosylated blood group antigen Lewis b receptor. (Ilver, Arnqvist et al. 1998) The SabA protein adheres to sialated glycoproteins, specifically to sialyl-Lewis-X. (Mahdavi, Sonden et al. 2002)
A segment of bacterial DNA, known as the cag pathogenicity iland (cag PAI), direct the key interaction between *H. pylori* and the host cells. Many of the genes adjacent to *cagA* encode proteins that provide a type IV secretion system (TFSS) that allows the transfer of bacterial products from pathogenic bacteria into the host cell. (Censini, Lange et al. 1996; Christie, Atmakuri et al. 2005) cag PAI plays an important role in the pathogenesis of gastritis. Patients infected with *cagA* positive strain of *H. pylori* are generally associated with increase interleukin-8 (IL-8) expression and inflammation in their gastric mucosa. (Blaser and Atherton 2004) CagA protein translocates into the cytoplasm of epithelial cell where it is tyrosine phosphorylated by host Src kinases and subsequently results in the change of cell morphology and cell function. (Higashi, Tsutsumi et al. 2002; Higashi, Tsutsumi et al. 2002)
The response of epithelial cell to *H. pylori* infection is complex and a summary of interaction with several influencing variables, such as bacterial virulence factors, the signaling linked to specific receptors, reaction of immune and hormones.
The *vacA* gene is present in all strains of this organism. However, only more than half of *H. pylori* strains are able to express the vacuolating cytotoxin (VacA). The association of the

structure and function of VacA with the severity of disease has been demonstrated. (Cover 1996; Van Doorn, Figueiredo et al. 1999; Blaser and Atherton 2004). Specific *vacA* alleles (s1 and m1) can result in more severe disease and epithelial cell apoptosis. (Atherton, Cao et al. 1995; Cover, Krishna et al. 2003)

H. pylori strains that express outer inflammatory protein A (OipA) are also associated with increased expression of IL-8, neutrophil infiltration, and more severe clinical outcomes. (Yamaoka, Kikuchi et al. 2002)

Host response

The host response to *H. pylori* infection plays a very important role in the pathogenesis of this organism related gastrointestinal disease. The IL-1 is known as a strong inhibitor of gastric acid secretion. The genetic polymophisms of IL-1β have been demonstrated to be associated with an increased incidence of hypochlorhydria, atrophic gastritis and gastric cancer. (El-Omar, Carrington et al. 2000; Furuta, El-Omar et al. 2002) The development of gastric cancer can be related to increase IL-1 expression, more severe gastritis and greater colonization of *H. pylori*.

H. pylori infection can result in changes in epithelial cell morphology, disruption of the tight junction, production of cytokines, increased epithelial cell proliferation, and increased rates of epithelial cell death via apoptosis. (Amieva, Vogelmann et al. 2003; Naumann and Crabtree 2004; Ernst, Peura et al. 2006)

The induction and expression of genes in epithelial cells responding to *H. pylori* stimulation is regulated by several transcription factors which are controlled by a series of signaling mechanisms. The nuclear factor-kappa B (NF-$_k$B) seems to be the most studied molecule in these transcription factors. NF-$_k$B activity in *H. pylori* infected epithelium is markedly enhanced, correlating with increased secretion of IL-8 protein and infiltration of inflammatory cell. (Naumann and Crabtree 2004) The changes of cell functions, including cell profiferation, inflammation, and survival in response to *H. pylori* infection are mostly regulated by mitogen-activated protein (MAP) kinase cascades. (Keates, Keates et al. 1999)

The acid secretion is a major function of gastric epithelial cells. The net effect of *H. pylori* infection on acid secretion is related to the duration and distribution of infection and the presence of mucosal atrophy. The epithelial barrier function is altered as a consequence of both direct effects of *H. pylori* and its accompanying inflammatory response. Humans infected by *H. pylori* develop a unique inflammatory response in which infection persists despite the recruitment and activation of lymphocytes, phagocytic cells, and other immune cell populations. (Ernst, Peura et al. 2006)

It is known that *H. pylori* can induce an infiltration with T lymphocytes, plasma cells, mononuclear phagocytes and neutrophils. Furthermore, expression of cytokines such as tumor necrosis factor (TNF), IL-1, IL-6 and IL-8 is also enhanced by the infection. However, it is not well known how the immune response and the mechanisms behind it related to disease outcome. The immunoregulatory and proinflammatory cytokines induced by *H. pylori* may influence the nature of the local T cell response. It is thought that helper T (Th) cells can be divided into two subsets, Th1, and Th2. The Th1 subset promotes cell-mediated immunity by producing mainly IL-2, TNF-α, and interferon-gamma (IFN-γ), and the Th2 subset, which is important for antibody response produces IL-4, IL-5 and IL-10. Evidences in recent research have strongly suggested that T cell mediated immune response may play an important role in induction of disease in *H. pylori* infection. (Crowe, Alvarez et al. 1995; D'Elios, Manghetti et al. 1997; Mohammadi, Nedrud et al. 1997) It is still not clear whether

different outcome of the disease is modulated by the different type of T cell immune response, although some studies suggested that Th1 type dominant cellular response may be involved in the *Helicobacter* disease. (Haeberle, Kubin et al. 1997) Little is known about whether Th2 response can be protective or whether modulation of these responses can change the outcome of infection.

Apoptosis and autophagy

Some bacterial components may reach the lamina propria where it can activate underlying phagocytosis through the damaged epithelial barrier. One of these bacterial factors is the *H. pylori* neutrophil-activating protein (Hp-NAP). This protein can promote the adhesion of neutrophil to the endothelial cells and stimulate chemotaxis of monocytes and neutrophils and production of reactive oxygen intermediates. (Satin, Del Giudice et al. 2000) Recruitment and activation of neutrophils and macrophages result in the release of various inflammatory mediators.

H. pylori urease has been shown to bind to class II major histocompatibility complex (MHC) molecules on the surfaces of gastric epithelial cells and induce apoptosis. (Fan, Gunasena et al. 2000) *H. pylori* VacA can be inserted into mitochondrial membranes where it induces cytochrome c release and activates the caspase-3-dependent cell-death signaling cascade. (Galmiche, Rassow et al. 2000) Also, Th1 cytokines induced by *H. pylori* can stimulate apoptosis through a Fas-mediate pathway by inducing expression of the cell-surface receptor Fas and Fas ligand. (Wagner, Beil et al. 1997; Jones, Day et al. 1999; Smythies, Waites et al. 2000)

The expression of inducible nitric oxide synthase (iNOS) is increased in *H. pylori* infected gastric mucosa. Nitric oxide (NO) and Superoxide (O_2^-) may be produced by infiltrating neutrophils. These reactive oxygen species (ROS) can react to form peroxynitrite which is a potent oxidant and reducing agent. Apurinic–apyrimidinic endonuclease-1 (redox factor-1) plays an important role in the regulation of redox-sensitive signaling and is expressed in epithelial cell during infection with *H. pylori*. (Ding, O'Hara et al. 2004; O'Hara, Bhattacharyya et al. 2006) The increased oxidative DNA damage by ROS is thought to play a causal role in malignant transformation. The cells which undergo apoptosis are removed by phagocytes. This engulfment of *H. pylori* infected epithelial cells by phagocytes plays an important role in the cytokine induction and the activation of host adaptive response.

An increase of chronic inflammatory cells in the gastric mucosa indicates the presence of a chronic gastritis that may result from the increased oxidative stress. Apoptosis and autophagy are two types of programmed cell death that play a critical role in tissue homeostasis and disease development. Exacerbated production of ROS in the inflamed tissue results in substantial type I programmed cell death, apoptosis, including increases in Bax/Bcl-2 ratio, caspase-3 activity, DNA fragmentation and apoptotic cell formation in the damaged tissue. (Baik, Youn et al. 1996; Smoot, Elliott et al. 2000; Chien, Lee et al. 2001; Yu, Chien et al. 2004; Yu, Lin et al. 2005)

Autophagy is type II programmed cell death and is a major lysosomal catabolic pathway for cytoplasmic macromolecules and organelles. Autophagy could be mediated by Beclin-1, a novel Bcl-2-interacting protein, to promote autophagocytosis and a cell-survival response. (Blommaart, Luiken et al. 1997; Liang, Jackson et al. 1999) Previous studies have indicated that *H. pylori*-induced gastric epithelial cell damage by increased Bax/Bcl-2-related proapoptotic cell death and decreased autophagy survival and/or repair. (Catrenich and Chestnut 1992; Lee, Yeo et al. 2004)

4. Clinical and therapeutic application

How to prevent and cure *H. pylori* infection associated with gastritis is an important issue. Nowadays the first-choice of therapy for *H. pylori* infection is one-week combination of a proton pump inhibitor and antibiotics. Following failure of the first-line treatment, second-line therapies, including alternative triple and quadruple regimens, have frequently been applied to the patients. (Chey, Wong et al. 2007; Malfertheiner, Megraud et al. 2007) Although, the current antibiotic-based therapies are generally effective, it may still fail because of the rising trend of antibiotic resistance or the low compliance. (Megraud 2004; Vakil, Megraud et al. 2007) To find out an alternative agent or mixture with preventive and therapeutic potential on *H. pylori* infection is therefore urgently required.

Some strains of *Lactobacillus* and *Bifidobacterium* can inhibit *H. pylori* growth. However, probiotics do not eradicate *H. pylori* but maintain a lower level of this pathogen in the stomach.(Gotteland, Brunser et al. 2006) A vaccine can be used either propbylactically or therapeutically for *H. pylori* infection. In the mice, vaccination can result in significantly reduced *H. pylori* colonization but it cannot achieve satisfactory eradication or prevention of *H. pylori* infection. (Del Giudice, Covacci et al. 2001)

A successful *H. pylori* infection requires the penetration and adherence of the bacterium to mucin and gastric epithelial cells. *H. pylori* that adheres to gastric mucosa subsequently causes gastric epithelial cell damage and atrophy via oxidative stress and the type I apoptotic or type II autophagic programmed cell death-related pathway. Sialylated glycoconjugates are responsible for the adherence of *H. pylori* to gastric epithelium. Cumulated studies have shown that anti-adhesive therapy using 3'-sialyllactose can prevent the binding of *H. pylori* to human gastrointestinal epithelial cells and decrease *H. pylori* colonization in rhesus monkeys without side-effects. (Simon, Goode et al. 1997; Mysore, Wigginton et al. 1999)

Catechins, known as one kind of antioxidants, have been shown to possess anti-oxidative, anti-inflammatory, anti-apoptotic and cancer prevention activity. (Katiyar and Mukhtar 1996; Lin and Lin 1997; Yu, Lin et al. 2005) Besides, catechins including their major active component, epigallocatechin-3-gallate (EGCG), have antibacterial effect against *H. pylori* by inhibiting the activity of urease and VacA of this organism. (Mabe, Yamada et al. 1999; Matsubara, Shibata et al. 2003; Ruggiero, Tombola et al. 2006)

Although catechins or 3'-sialyllactose have an inhibitory effect on *H. pylori* infection in vitro, these two compounds fail to effectively control infection in animal model in vivo when each is used alone. (Mabe, Yamada et al. 1999; Mysore, Wigginton et al. 1999; Matsubara, Shibata et al. 2003) However, effective prevention and treatment of *H. pylori* infection using a combination of catechins and sialic acid in AGS cells and BALB/c mice have been shown in a recent study. (Yang, Shun et al. 2008) The combination of catechins and sialic acid showed synergistic or additive anti-*H. pylori* activity and significantly reduced iNOS expression and Bax/BCl-2-mediated apoptosis but enhanced Becline-1 mediated autophage. Pretreatment with catechins/sialic acid completely prevented *H. pylori* infection and resulted in normal histology. Post-treatment with catechins/sialic acid decreased the bacterial load and gastritis score and eradicated up to 60% of *H. pylori* infectious in a dose-dependent manner.

The rationale of this treatment model which can effectively control *H. pylori* infection includes several points. (Yang and Chien 2009) First, by reviewing the literature, we can find that monotherapy using a single drug such as PPI, bismuth salt, or antibiotics always fail to eradicate *H. pylori* in humans, although each of these drugs can work in vitro. (Bamba,

Kondo et al. 1997) Thus, dual therapy, then triple therapy, and even quadruple therapy have been recommended step by step. Second, catechins have antioxidant and anti-microbial effects (Lin and Lin 1997; Mabe, Yamada et al. 1999), whereas sialic acid has anti-adhesive and antioxidant effects. (Simon, Goode et al. 1997; Teneberg, Jurstrand et al. 2000) Together, they may have additive or synergistic effect against *H. pylori*. Third, both catechins and sialic acid can exist in the foodstuff are wildly accepted to be very safe to humans.

5. Conclusions

It is now clear that both bacterial factors and host response play a role in the pathogenesis of *H. pylori* related gastroduodenal disease. *H. pylori* infection can cause gastric mucosal injury, including oxidative stress, inflammation, and apoptosis formation but inhibit the autophagic survival response in gastric epithelial cell as indicated in **Figure 1**. A new strategy for control of *H. pylori* infection is to interfere with the interaction between the bacteria and target cells and to eradicate bacteria but not target cells at the same time. The combination of compounds with anti-adhesive, antioxidant, and anti-microbial activities may protect gastric mucosa from infection by *H. pylori* and treat its related gastritis via downregulation of apoptosis and upregulation of autophagy.

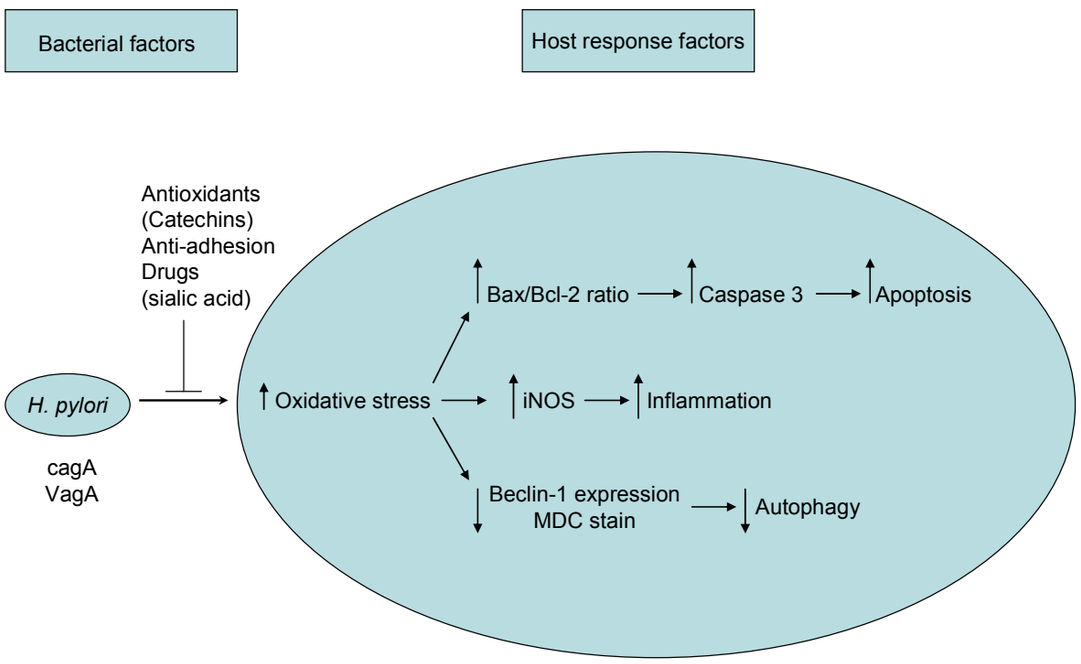


Fig. 1. Possible pathways of *H. pylori* invade gastric epithelium via a upregulation in oxidative stress, inflammation and apoptosis and a downregulation in autophagy. The combination of antioxidants and anti-adhesion drug may reduce *H. pylori*-induced gastritis.

6. References

Amieva, M. R., E. M. El-Omar, et al. (2008). "Host-bacterial interactions in Helicobacter pylori infection." Gastroenterology 134(1): 306-323.

Amieva, M. R., R. Vogelmann, et al. (2003). "Disruption of the epithelial apical-junctional complex by Helicobacter pylori CagA.[see comment]." Science 300(5624): 1430-1434.

Atherton, J. C., P. Cao, et al. (1995). "Mosaicism in vacuolating cytotoxin alleles of Helicobacter pylori. Association of specific vacA types with cytotoxin production and peptic ulceration." Journal of Biological Chemistry 270(30): 17771-17777.

Baik, S. C., H. S. Youn, et al. (1996). "Increased oxidative DNA damage in Helicobacter pylori-infected human gastric mucosa." Cancer Research 56(6): 1279-1282.

Bamba, H., Y. Kondo, et al. (1997). "Minimum inhibitory concentration of various single agents and the effect of their combinations against Helicobacter pylori, as estimated by a fast and simple in vitro assay method." American Journal of Gastroenterology 92(4): 659-662.

Blaser, M. J. and J. C. Atherton (2004). "Helicobacter pylori persistence: biology and disease." Journal of Clinical Investigation 113(3): 321-333.

Blommaart, E. F., J. J. Luiken, et al. (1997). "Autophagic proteolysis: control and specificity." Histochemical Journal 29(5): 365-385.

Boren, T., P. Falk, et al. (1993). "Attachment of Helicobacter pylori to human gastric epithelium mediated by blood group antigens.[see comment]." Science 262(5141): 1892-1895.

Brown, L. M. (2000). "Helicobacter pylori: epidemiology and routes of transmission." Epidemiologic Reviews 22(2): 283-297.

Catrenich, C. E. and M. H. Chestnut (1992). "Character and origin of vacuoles induced in mammalian cells by the cytotoxin of Helicobacter pylori." Journal of Medical Microbiology 37(6): 389-395.

Censini, S., C. Lange, et al. (1996). "cag, a pathogenicity island of Helicobacter pylori, encodes type I-specific and disease-associated virulence factors." Proceedings of the National Academy of Sciences of the United States of America 93(25): 14648-14653.

Chey, W. D., B. C. Wong, et al. (2007). "American College of Gastroenterology guideline on the management of Helicobacter pylori infection." American Journal of Gastroenterology 102(8): 1808-1825.

Chien, C. T., P. H. Lee, et al. (2001). "De novo demonstration and co-localization of free-radical production and apoptosis formation in rat kidney subjected to ischemia/reperfusion." Journal of the American Society of Nephrology 12(5): 973-982.

Christie, P. J., K. Atmakuri, et al. (2005). "Biogenesis, architecture, and function of bacterial type IV secretion systems." Annual Review of Microbiology 59: 451-485.

Cover, T. L. (1996). "The vacuolating cytotoxin of Helicobacter pylori." Molecular Microbiology 20(2): 241-246.

Cover, T. L., U. S. Krishna, et al. (2003). "Induction of gastric epithelial cell apoptosis by Helicobacter pylori vacuolating cytotoxin." Cancer Research 63(5): 951-957.

Crowe, S. E., L. Alvarez, et al. (1995). "Expression of interleukin 8 and CD54 by human gastric epithelium after Helicobacter pylori infection in vitro." Gastroenterology 108(1): 65-74.

D'Elios, M. M., M. Manghetti, et al. (1997). "T helper 1 effector cells specific for Helicobacter pylori in the gastric antrum of patients with peptic ulcer disease." Journal of Immunology 158(2): 962-967.

Del Giudice, G., A. Covacci, et al. (2001). "The design of vaccines against Helicobacter pylori and their development." Annual Review of Immunology 19: 523-563.

Ding, S.-Z., A. M. O'Hara, et al. (2004). "Helicobacter pylori and H2O2 increase AP endonuclease-1/redox factor-1 expression in human gastric epithelial cells." Gastroenterology 127(3): 845-858.

Dixon, M. F., R. M. Genta, et al. (1996). "Classification and grading of gastritis. The updated Sydney System. International Workshop on the Histopathology of Gastritis, Houston 1994." American Journal of Surgical Pathology 20(10): 1161-1181.

El-Omar, E. M., M. Carrington, et al. (2000). "Interleukin-1 polymorphisms associated with increased risk of gastric cancer.[erratum appears in Nature 2001 Jul 5;412(6842):99]." Nature 404(6776): 398-402.

Ernst, P. B., D. A. Peura, et al. (2006). "The translation of Helicobacter pylori basic research to patient care." Gastroenterology 130(1): 188-206; quiz 212-183.

Fan, X., H. Gunasena, et al. (2000). "Helicobacter pylori urease binds to class II MHC on gastric epithelial cells and induces their apoptosis." Journal of Immunology 165(4): 1918-1924.

Furuta, T., E. M. El-Omar, et al. (2002). "Interleukin 1beta polymorphisms increase risk of hypochlorhydria and atrophic gastritis and reduce risk of duodenal ulcer recurrence in Japan.[erratum appears in Gastroenterology 2002 Sep;123(3):957 Note: Sugimurra Haruhiko [corrected to Sugimura Haruhiko]]." Gastroenterology 123(1): 92-105.

Galmiche, A., J. Rassow, et al. (2000). "The N-terminal 34 kDa fragment of Helicobacter pylori vacuolating cytotoxin targets mitochondria and induces cytochrome c release." EMBO Journal 19(23): 6361-6370.

Gotteland, M., O. Brunser, et al. (2006). "Systematic review: are probiotics useful in controlling gastric colonization by Helicobacter pylori?" Alimentary Pharmacology & Therapeutics 23(8): 1077-1086.

Haeberle, H. A., M. Kubin, et al. (1997). "Differential stimulation of interleukin-12 (IL-12) and IL-10 by live and killed Helicobacter pylori in vitro and association of IL-12 production with gamma interferon-producing T cells in the human gastric mucosa." Infection & Immunity 65(10): 4229-4235.

Higashi, H., R. Tsutsumi, et al. (2002). "Biological activity of the Helicobacter pylori virulence factor CagA is determined by variation in the tyrosine phosphorylation sites." Proceedings of the National Academy of Sciences of the United States of America 99(22): 14428-14433.

Higashi, H., R. Tsutsumi, et al. (2002). "SHP-2 tyrosine phosphatase as an intracellular target of Helicobacter pylori CagA protein." Science 295(5555): 683-686.

Ilver, D., A. Arnqvist, et al. (1998). "Helicobacter pylori adhesin binding fucosylated histo-blood group antigens revealed by retagging." Science 279(5349): 373-377.

Jones, N. L., A. S. Day, et al. (1999). "Helicobacter pylori induces gastric epithelial cell apoptosis in association with increased Fas receptor expression." Infection & Immunity 67(8): 4237-4242.

Katiyar, S. K. and H. Mukhtar (1996). "Tea consumption and cancer." World Review of Nutrition & Dietetics 79: 154-184.

Keates, S., A. C. Keates, et al. (1999). "Differential activation of mitogen-activated protein kinases in AGS gastric epithelial cells by cag+ and cag- Helicobacter pylori." Journal of Immunology 163(10): 5552-5559.

Lee, K.-M., M. Yeo, et al. (2004). "Protective mechanism of epigallocatechin-3-gallate against Helicobacter pylori-induced gastric epithelial cytotoxicity via the blockage of TLR-4 signaling." Helicobacter 9(6): 632-642.

Liang, X. H., S. Jackson, et al. (1999). "Induction of autophagy and inhibition of tumorigenesis by beclin 1." Nature 402(6762): 672-676.

Lin, Y. L. and J. K. Lin (1997). "(-)-Epigallocatechin-3-gallate blocks the induction of nitric oxide synthase by down-regulating lipopolysaccharide-induced activity of transcription factor nuclear factor-kappaB." Molecular Pharmacology 52(3): 465-472.

Mabe, K., M. Yamada, et al. (1999). "In vitro and in vivo activities of tea catechins against Helicobacter pylori." Antimicrobial Agents & Chemotherapy 43(7): 1788-1791.

Mahdavi, J., B. Sonden, et al. (2002). "Helicobacter pylori SabA adhesin in persistent infection and chronic inflammation." Science 297(5581): 573-578.

Malfertheiner, P., F. Megraud, et al. (2007). "Current concepts in the management of Helicobacter pylori infection: the Maastricht III Consensus Report." Gut 56(6): 772-781.

Marshall, B. J. (1983). "Unidentified curved bacilli on gastric epithelium in active chronic gastritis." Lancet i: 1273-1275.

Matsubara, S., H. Shibata, et al. (2003). "Suppression of Helicobacter pylori-induced gastritis by green tea extract in Mongolian gerbils." Biochemical & Biophysical Research Communications 310(3): 715-719.

Megraud, F. (2004). "H pylori antibiotic resistance: prevalence, importance, and advances in testing." Gut 53(9): 1374-1384.

Mohammadi, M., J. Nedrud, et al. (1997). "Murine CD4 T-cell response to Helicobacter infection: TH1 cells enhance gastritis and TH2 cells reduce bacterial load." Gastroenterology 113(6): 1848-1857.

Mysore, J. V., T. Wigginton, et al. (1999). "Treatment of Helicobacter pylori infection in rhesus monkeys using a novel antiadhesion compound.[see comment]." Gastroenterology 117(6): 1316-1325.

Naumann, M. and J. E. Crabtree (2004). "Helicobacter pylori-induced epithelial cell signalling in gastric carcinogenesis." Trends in Microbiology 12(1): 29-36.

O'Hara, A. M., A. Bhattacharyya, et al. (2006). "Interleukin-8 induction by Helicobacter pylori in gastric epithelial cells is dependent on apurinic/apyrimidinic endonuclease-1/redox factor-1." Journal of Immunology 177(11): 7990-7999.

Ruggiero, P., F. Tombola, et al. (2006). "Polyphenols reduce gastritis induced by Helicobacter pylori infection or VacA toxin administration in mice." Antimicrobial Agents & Chemotherapy 50(7): 2550-2552.

Satin, B., G. Del Giudice, et al. (2000). "The neutrophil-activating protein (HP-NAP) of Helicobacter pylori is a protective antigen and a major virulence factor.[see comment]." Journal of Experimental Medicine 191(9): 1467-1476.

Simon, P. M., P. L. Goode, et al. (1997). "Inhibition of Helicobacter pylori binding to gastrointestinal epithelial cells by sialic acid-containing oligosaccharides." Infection & Immunity 65(2): 750-757.

Smoot, D. T., T. B. Elliott, et al. (2000). "Influence of Helicobacter pylori on reactive oxygen-induced gastric epithelial cell injury." Carcinogenesis 21(11): 2091-2095.

Smythies, L. E., K. B. Waites, et al. (2000). "Helicobacter pylori-induced mucosal inflammation is Th1 mediated and exacerbated in IL-4, but not IFN-gamma, gene-deficient mice." Journal of Immunology 165(2): 1022-1029.

Suerbaum, S. and P. Michetti (2002). "Helicobacter pylori infection.[see comment]." New England Journal of Medicine 347(15): 1175-1186.

Teneberg, S., M. Jurstrand, et al. (2000). "Inhibition of nonopsonic Helicobacter pylori-induced activation of human neutrophils by sialylated oligosaccharides." Glycobiology 10(11): 1171-1181.

Vakil, N., F. Megraud, et al. (2007). "Eradication therapy for Helicobacter pylori." Gastroenterology 133(3): 985-1001.

Van Doorn, L. J., C. Figueiredo, et al. (1999). "Geographic distribution of vacA allelic types of Helicobacter pylori." Gastroenterology 116(4): 823-830.

Wagner, S., W. Beil, et al. (1997). "Regulation of gastric epithelial cell growth by Helicobacter pylori: offdence for a major role of apoptosis." Gastroenterology 113(6): 1836-1847.

Warren, J. R. (1983). "Unidentified curved bacilli on gastric epithelium in active chronic gastritis." Lancet i: 1273.

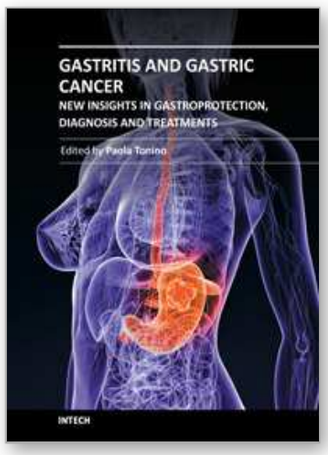
Yamaoka, Y., S. Kikuchi, et al. (2002). "Importance of Helicobacter pylori oipA in clinical presentation, gastric inflammation, and mucosal interleukin 8 production." Gastroenterology 123(2): 414-424.

Yang, J.-C. and C.-T. Chien (2009). "A new approach for the prevention and treatment of Helicobacter pylori infection via upregulation of autophagy and downregulation of apoptosis." Autophagy 5(3): 413-414.

Yang, J. C., C. T. Shun, et al. (2008). "Effective prevention and treatment of Helicobacter pylori infection using a combination of catechins and sialic acid in AGS cells and BALB/c mice." Journal of Nutrition 138(11): 2084-2090.

Yu, H. J., C. T. Chien, et al. (2004). "Hypoxia preconditioning attenuates bladder overdistension-induced oxidative injury by up-regulation of Bcl-2 in the rat." Journal of Physiology 554(Pt 3): 815-828.

Yu, H. J., B. R. Lin, et al. (2005). "Sympathetic vesicovascular reflex induced by acute urinary retention evokes proinflammatory and proapoptotic injury in rat liver." American Journal of Physiology - Renal Physiology 288(5): F1005-1014.



Gastritis and Gastric Cancer - New Insights in Gastroprotection, Diagnosis and Treatments

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This book is a comprehensive overview of invited contributions on Helicobacter pylori infection in gastritis and gastric carcinogenesis. The first part of the book covers topics related to the pathophysiology of gastric mucosal defense system and gastritis including the gastroprotective function of the mucus, the capsaicin-sensitive afferent nerves and the oxidative stress pathway involved in inflammation, apoptosis and autophagy in H. pylori related gastritis. The next chapters deal with molecular pathogenesis and treatment, which consider the role of neuroendocrine cells in gastric disease, DNA methylation in H. pylori infection, the role of antioxidants and phytotherapy in gastric disease. The final part presents the effects of cancer risk factors associated with H. pylori infection. These chapters discuss the serum pepsinogen test, K-ras mutations, cell kinetics, and H. pylori lipopolysaccharide, as well as the roles of several bacterial genes (cagA, cagT, vacA and dupA) as virulence factors in gastric cancer, and the gastrokine-1 protein in cancer progression.

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