**Helicobacter pylori** infection and gastric mucosal epithelial cell apoptosis


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**ABBREVIATIONS**


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**INTRODUCTION**

Apoptosis was first described by its morphological characteristics, including cell shrinkage, plasma membrane disruption, chromat in condensation, and nuclear DNA cleavage into discrete fragments (1-3). It is a genetically-managed cell death program that may be interrupted by mutations. In fact, mutations in apoptotic routes contribute to a number of human diseases ranging from neurodegenerative disorders to tumors (4).

Other types of cell death

While apoptosis is a programmed cell death, not all programmed deaths are apoptotic. Other programmed responses contribute to clear potential cancer cells. The sequence is an irreversible cell cycle arrest program with distinct characteristics that appears to be interrupted in some tumors. Selected stimuli may induce phenotypes suggesting senescence, including mitogenic oncogene activation or ionizing radiation (5-8). For instance, an excessive shortening of terminal DNA sequences or telomeres, which may naturally occur in any replication cycle, would result in chromosomal instability, thus activating a cell cycle arrest to prevent potential mutations (9) and then leading to a common program for cell death.

In contrast to apoptosis, where cells play an active role in their own destruction, in necrosis cells undergo lysis by cytokines produced by inflammatory cells. When nuclear remnants from cells having undergone necrosis are studied by electrophoresis, a diffuse pattern may be seen, since DNA fragments are in a continuous spectrum. However, nuclear remnants from cells having undergone apoptosis exhibit an alternating band pattern—in the shape of ladder rungs—known as the ladder pattern that is an unmistakable sign that the death process studied was apoptotic in nature.

**H. pylori** and apoptosis

On the other hand, gastric mucosal infection by *Helicobacter pylori* may affect the normal balance between...
gastric epithelial proliferation and death from apoptosis, thus disregulating the normal cell cycle and initially leading to gastritis. The latter may become gastric atrophy, and then subsequently metaplasia, dysplasia and gastric cancer (10). The outcome of this process correlates with a severe reduction of the apoptotic rate in early stages (gastritis and atrophy), and with a disproportionate proliferative response in the host in more advanced stages (metaplasia and dysplasia), which may ultimately end in a malignant condition. Therefore, a definition of predictive values for genetic and biochemical markers just prior to H. pylori eradication and the long-term follow-up of patients with gastric paraneoplastic lesions may help establish preventive therapeutic options.

Objective

The aim of this paper is to review the major events involved in apoptosis, their causes at both the molecular and cellular level, and their pathologic consequences, focusing on H. pylori-induced apoptosis in gastric mucosal epithelial cells as well as on bacterial strains.

GENES INVOLVED IN APOPTOSIS

The clonation and characterization of oncogene bcl-2 established the importance of apoptosis in tumor development (11). Bcl-2 promotes cell survival by blocking programmed cell death (12-14). In transgenic mice, Bcl-2 overexpression promotes lymphoproliferation and accelerates c-Myc-induced lymphomagenesis (13,15). Together with Bcl-2, Bcl-Xl is a potent suppressor of cell death overexpressed in a number of tumor types (16). Immune reactivity rates for Bcl-2 in normal glands, metaplasia, adenoma, and adenocarcinoma have been seen to be 0, 77, 38, and 11%, respectively, which suggests Bcl-2 overexpression in premalignant lesions and Bcl-2 repression following malignant conversion, this being responsible for early events in the cancer sequence (17).

Otherwise, p53 was the first tumor suppressor gene ever described in association with apoptosis. Most human tumors exhibit mutations in the p53 gene, thus increasing chromosome viability and instability (18). The disruption of several protein p53 effectors (e.g. bax, apafl-1, and casp-9) may promote oncogenic transformation and tumor development (19-21). Mutated protein p53 has been seen to activate promoters for the following genes: Multi Drug Resistance Gene-1 (MDR-1), c-myc, interleukin-6 (IL-6), epithelial growth factor (EGF), and insulin-like growth factor-II (IGF-II), all of them associated with increased cell proliferation. In addition, several prior and subsequent components of the p53 pathway (e.g. Mdm-2, ARF, Bax) are also commonly mutated in human tumors (18).

Wild protein p53 is also directly or indirectly involved in the regulation of genes associated with growth factors, in the regulation of cytoskeleton-forming proteins, in the regulation of genes involved in cell adhesion, in cell cycle arrest, in the repression of cell metabolism genes, and in the maintenance of chromosome integrity following DNA damage (22). Studies in p53-defective mice have demonstrated that endogenous protein p53 may play a role in apoptosis. It was also seen that p53 was necessary for radiation-induced cell death in the thymus, but not for glucocorticoid-induced cell death (23,24). Thus, the role of protein p53 in apoptosis is indirectly linked to DNA damage, and is dependant upon the stimulus (radiation) and tissue (thymocytes). Stimuli capable of p53 activation to promote apoptosis include hypoxia and mitogenic oncogenes. Should mutations occur in some of the genes associated with cancer, they may suppress apoptosis. For example, a malfunction in the Fas/CD95 pathway, which controls the number of cells in the immune system by clearing them through apoptosis, may lead to lymphoproliferative disorders and even cancer (25).

Another critical pathway implies signaling through phosphoinositol-3 (PI-3) kinase, which is activated by Ras and repressed by PTEN, a tumor suppressor. Ras activation and PTEN loss are both usual in human tumors (26). A variety of signals may trigger apoptosis. Extracellular triggers include growth factor depletion, hypoxia, radiation, and lost cell-matrix interaction. Intracellular mechanisms include DNA damage from defective cell cycle checkpoints, endogenous toxins, telomerase (enzyme in charge of telomere replication) malfunction, and inappropriate proliferation signaling because of oncogenic mutations (27). In some cases an apoptotic signal counteracts an antiapoptotic signal. For instance, IGF-I promotes cell survival through the PI-3 kinase pathway, and IGF-I or other growth factor depletion may trigger a “depletional death” (28). In contrast, other stimuli imply true proapoptotic factors—for example, some forms of cell stress may activate protein p53, which promotes apoptosis through molecules such as Bax, a proapoptotic protein belonging in the Bcl-2 class (20,21,29).

APOPTOSIS MECHANISMS

Better known apoptosis pathways are those starting at “death receptors” such as Fas/CD95 or TNFR1 and 2. The binding of TNF-α to TNFR1 results in a recruitment of TRADD (TNFR death domain) messenger molecules through interactions between proteins known as intracellular “death domains” (DD). If TRADD recruits a receptor interacting protein (RIP) and TNFR-associated factor 2 (TRAF2), the activation of nuclear factor κB (NF-κB) ensues, which suppresses apoptosis as induced by TNF-α (30). In contrast, the recruitment of FADD (Fas-associated death domain) by Fas or by TNFR1 (in the latter case also through TRADD) results in apoptosis through the activation of the protease caspase 8, thus initiating a pro-
tease cascade leading to apoptosis (31). Caspases are cysteine proteases that are expressed as inactive proenzymes; these associate with effectors allowing their activation, and their action is to selectively cleave proteins by an aspartate residue (32,33).

Some cytokines or DNA damage are signals for cell death through mitochondria. This pathway is a target for a number of oncogenic mutations affecting the function of members in the Bcl-2 family. These may modulate mitochondrial function through transition pores (MTP), whose TNF-induced aperture leads to a sharp increase in mitochondrial membrane Ca2+ permeability, which releases cytochrome c (34). Cytosolic cytochrome c may interact with apoptotic protease activation factor (Apaf-1) and procaspase 9 to initiate a protease cascade leading to apoptosis (35-37).

Selected messenger molecules alter the frequency of apoptosis induction by proapoptotic signals. For instance, cytokines such as IL-6 may suppress p53-induced apoptosis (38).

On the other hand, the PI-3 kinase pathway is involved in cell survival via extracellular cytokine receptors, which activate a kinase cascade involving PI-3 kinase and leading to the phosphorylation and inactivation of proapoptotic molecules such as Bad (another member in the Bcl-2 family) and caspase 9 (39,40). In contrast, PTEN, which acts as a lipid phosphatase, inactivates the Bcl-2 family, thus repressing this pathway (41,42). PTEN-induced apoptosis by proapoptotic signals. For instance, cytokines such as IL-6 may suppress p53-induced apoptosis (38).

A LINK BETWEEN H. PYLORI, APOPTOSIS, AND CELL PROLIFERATION

H. pylori is the main cause of chronic gastritis and peptic ulcer, and has been categorized as a type-I carcinogen based on seroepidemiologic evidence (43-46). H. pylori colonizes the gastric mucosa by adhering to the epithelial tissue without ever penetrating epithelial cells (47-49). H. pylori has been seen to induce apoptosis in patients with gastroduodenal ulcer and gastritis (50-55). Some authors have seen greater than five-fold increases in the number of apoptotic cells in patients with duodenal ulcer versus those observed following H. pylori eradication (56). In vitro studies have shown that apoptosis is induced in tumor cell lines incubated with H. pylori (57), as is a cell cycle arrest between phases G1 and S (58).

Both apoptosis and cell proliferation are increased in precancer lesions (atrophy, metaplasia, dysplasia) in the presence of H. pylori infection (59). A disregulation of genes controlling apoptosis and hence homeostasis between apoptosis and cell proliferation may ultimately lead to tumor development (60).

The gastric mucosal degeneration process is initiated by inflammation, and results in a destruction (atrophy) of gastric glands, their replacement by an intestinal-like epithelium (intestinal metaplasia), and progression to dysplasia (the earliest manifestation of a neoplasm that may be seen under a microscope) (61).

If the H. pylori-infected mucosa is invaded by an inflammatory cell infiltrate, glands become separated and compressed, and may falsely resemble atrophy (61). Of course, when glands are destroyed and then substituted for by another tissue (metaplastic epithelium or fibroblasts plus cell matrix), and they actually disappear (true atrophy), pathophysiological consequences are similar, and acid production decreases thus resulting in hypochlorhydria. Only atrophy characterized by intestinal metaplasia and fibrosis, and hence by a true loss of glands has been associated with the development of gastric cancer; cases of apparent atrophy may even show gland regeneration and a functional recovery of acid production (61).

Other authors reported that in premalignant lesions or gastric carcinoma increased cell proliferation is no longer associated with H. pylori from a certain point in time on, since eradication induces no reversal (51,62), which suggests a potential association with a disregulated cell growth due to genetic changes during intestinal metaplasia, including an activation of proto-oncogenes such as k-ras, expression and release of gastrin and other cell growth factors, and suppression of suppressor genes such as p53 (63,64). These mitogenic peptides, including the epithelial growth factor (EGF), hepatocyte growth factor (HGF, responsible for both epithelial and non-epithelial tumors), and transforming growth factor α (TGF-α), are synthesized in the gastric mucosa, especially following H. pylori-induced damage, interact with surface receptors on epithelial cells, and induce the expression of oncogenes c-myc, c-jun and c-fos, which stimulate cell growth (65). A mutated k-ras causes an overexpression of mutated p53 protein followed by a phosphorylation and activation of MAP-kinases, thus enhancing tumor growth.

Gastrin, which is mainly synthesized by G cells at the gastric mucosa, is another factor involved in H. pylori-related carcinogenesis. Upon secretion to the gastric lumen in response to these bacteria, this hormone may stimulate H. pylori growth and G cells to release further gastrin, thus blocking the expression of gene p21 (66) –regulated by p53 and involved in cell cycle arrest and apoptosis – and overexpressing the mutated p53 protein (62). H. pylori eradication before surgery in patients with gastric cancer is followed by a sharp drop in plasma gastrin, luminal gastrin, and cancer tissue gastrin levels (67).

The Fas/Fas-ligand system is involved in apoptosis as induced by H. pylori in epithelial cells and lamina propria cells (57,68-70). In a study the expression of FasL mRNA was higher in T-cells of infected patients versus healthy subjects, which suggests that local T-cells may induce apoptosis through Fas/FasL (71). In addition, the
Fig. 1.- Apoptosis-related transduction routes as mediated by TNFR, Fas, or mitochondria. Receptor-mediated death and mitochondria-mediated routes are two major apoptotic routes. Receptor activation results in the recruitment of adaptor proteins. The recruitment of the Fas-associated death domain (FADD) by Fas or the tumor necrosis factor receptor (TNFR) via the TNFR-associated death domain (TRADD) activates caspase 8. Another apoptotic route begins in mitochondria. Cytochrome c is released into the cytosol and activates caspase 9. The activation of caspase 8 or caspase 9 results in the activation of the caspase cascade. The nuclear factor κB (NF-κB) route is also initiated via TRADD and TNFR-associated factors (TRAFs). NIK: NF-κB-inducing kinase; IKK: IκB kinase-α and IκB kinase-β; ROS: reactive oxygen species.

Las rutas de transducción de la apoptosis mediadas por TNFR, Fas, o la mitocondria. La muerte mediada por receptores y las rutas mediadas por las mitocondrias son las dos principales rutas apoptóticas. La activación de los receptores resulta en el reclutamiento de proteínas adaptadoras. El reclutamiento del Fas asociado a la muerte celularmediado por TNFR, Fas o por el receptor del Factor de Necrosis Tumoral (TNFR) a través del TNFR asociado a la muerte comienza con la activación de caspasas 8. Otra ruta apoptótica comienza en la mitocondria. El citocromo-c es liberado al citosol y activa a la caspasa-9. La activación de la caspasa-8 o de la caspasa-9 conduce a la activación de la cascada de caspasas. La ruta del factor nuclear κB (NF-κB) también se inicia a través de TRADD y de los factores asociados a TNFR (TRAF). NIK: kinasa inductora de NF-κB; IKK: IkB kinasa-α e IkB kinasa-β; ROS: especies reactivas de oxígeno.
expression of FasL mRNA is also increased in gastric epithelial cells during *H. pylori* infection, which suggests that apoptosis may also be induced by epithelial cells themselves in addition to T-cell FasL, thus bringing about their own death and that of neighboring epithelial cells (69). An interaction of *H. pylori* with the main histocompatibility complex II (MHC II) as an apoptosis induction receptor in gastric epithelial cells has also been seen (72).

### Oxidative damage by *H. pylori* and apoptosis

Oxygen radicals (superoxide ion and hydrogen peroxide) derived from *H. pylori*-activated neutrophils are factors that may damage the gastric mucosa (73-78). A positive association between reactive oxygen species (ROS) production and *H. pylori*-related infection and histologic damage has been described (79). Cell protection against ROS results from the activation of ROS-sequestering enzymes, including superoxide dismutase (SOD), catalase, and glutathione peroxidase.

Some authors, using the AGS epithelial cell line, found that when exposed to ROS in the absence of *H. pylori*, cell survival was reduced by 84%. On the other hand, if such cells were exposed to ROS after incubation with *H. pylori*, survival was reduced to 73 and 39% for cagA+ and cagA− strains, respectively. SOD activity was also measured, and was seen to be higher in cells incubated with cagA+ strains versus cagA− strains, but only the expression of the cytokine-induced Mn-SOD was increased, with a modest increase in the constitutive CuZn-SOD. Similarly, higher levels of catalase and glutathione peroxidase activity have been reported for cagA+ strains. This increased activity of enzymes suppressing potential DNA-damaging agents following exposure to cagA+ strains is probably a cause of increased cell survival following exposure to ROS (80).

Using 8-hydroxyguanidine as an oxidative damage marker in the DNA of gastric mucosal cells, *H. pylori*-positive patients would exhibit a higher presence of hydroxylated guanine in their DNA versus subjects with no *H. pylori* infection (81). This indicates that the damage induced in DNA by *H. pylori* infection in early gastritis may bring about its transformation into gastric cancer (80).

On the other hand, chloramine (NH₄Cl) is a toxic oxidizing agent produced within the gastric mucosa by *H. pylori* invasion. In neutrophils, the enzyme myeloperoxidase catalyzes chloride oxidation by H₂O₂ into HClO. The latter reacts with the NH₄⁺ resulting from *H. pylori* metabolism and becomes NH₃Cl, which is highly toxic due to its lipophilic and low molecular weight characteristics—it may easily cross the cell plasma membrane. *In vitro* studies have shown that apoptotic rates and chromatin condensation levels increase significantly more following treatment of gastric cells with NH₃Cl versus NH₄⁺ or HClO (83).

MTP and caspase 3 activation has been witnessed in cells exposed to NH₃Cl; these release cytochrome c (84), which forms a complex with Apaf-1 and procaspase 9, activates the latter, and initiates the caspase cascade—including caspases 3, 6, and 7—thus giving rise to the apoptotic process. In addition to NH₃Cl, other molecules produced by *H. pylori*, including cytotoxin VacA (85) or lipopolisaccharide, may induce apoptosis (86).

### Cytokines released in response to *H. pylori* infection and its related inflammatory response

The host’s *H. pylori*-stimulated inflammatory/immune response leads to a release of cytokines by Th1 cells, including TNF-α, interferon γ (INF-γ) or IL-2, which enhance apoptosis (57,69,72). This response is mediated by the Fas system (87), results in caspase 3 and 8 activation following DNA fragmentation, and increases MHC II expression and binding to *H. pylori* (88). In contrast, cytokines produced by Th2 cells, including IL-10, prevent apoptosis (89).

### Regulation of the IL-8 gene

IL-8 is a lymphocyte- and neutrophil-activating chemotactic cytokine secreted by gastrointestinal epithelial cells in response to bacterial infection (90) that establishes a chemotactic gradient towards the epithelial surface.

The human IL-8 gene has several binding sites within its promoter—one for NF-kB and two nearby loci for the binding of proteins c-Fos and c-Jun, which together make up transcription factor AP-1. NF-kB is a cytoplasmic transcription factor, the activation and regulation thereof being closely regulated by a protein family designated IκB—to be found non-covalently bound to NF-kB—preventing its translocation to the nucleus. Through signaling molecules such as TNF-α, there is a pathway leading to IκBα and IκBβ phosphorylation, and IκBα proteosomal degradation; this releases NF-kB, which migrates to the nucleus where it regulates the expression of a number of genes, including those involved in inflammation and cell survival (91).

Two inducible kinases, IκB kinase-α and IκB kinase-β (IKK-α and IKK-β), phosphorylate IκBα in response to proinflammatory cytokines (92), which are in turn phosphorylated and activated by the NF-kB-inducing kinase (NIK), itself activated through proteins associated with TNF-α and IL-1 receptors (93), TRAF2 and TRAF6, respectively. Since NF-kB stimulation requires no protein synthesis, it allows effective action on target genes, including IL-8 (91).

NF-kB activation is followed by an increased expression of mRNA and IL-8 protein (94,95). The ability of *H. pylori* to activate NF-kB in vivo has been corroborated *in vitro*, since activated NF-kB is present in epithelial cells.
from infected patients (95). Mitogen-activated protein kinases (MAPK) are mediators in the H. pylori-dependant activation of NF-κB and IL-8 expression. Signal transduction takes place down a cascade of MAPK kinase phosphorylations: extracellular signal-regulated kinase 1 and 2 (ERK1/2), p38, and c-Jun amino-terminal kinase (JNK). Since MAPKs activate both NF-κB and AP-1, and the IL-8 gene has binding domains for both, NF-κB activation has been researched and seen to be inadequate for IL-8 expression, with the implication of AP-1 being required (96).

ERK activation by a MAPK kinase (MEKK1) leads to Elk-1 phosphorylation, which together with JNK allows c-fos and c-jun transcription, their products making up AP-1. MEKK1 and NIK may each seemingly activate IkB by phosphorylation, thus releasing NF-κB (92,93).

**Relationship between H. pylori genotype and pathogenicity**

H. pylori cagA+ strains induce high levels of inflammation and more severe gastritis when compared to cagA− strains, in addition to a higher risk of gastric cancer or peptic ulcer, and greater cell proliferation (56,91,97). CagA+ strains have been seen to notably increase IL-8 expression, hence inducing a more profound inflammatory response versus cagA− strains (91). The exposure of cell cultures to cagA+ strains has been seen to result in an initial increase – followed by a decrease – of p53 and p21 protein expression, whereas cagA− strains stimulate a continuous increase (98). In addition, the expression of Bcl-2 is increased in cells exposed to cagA+ strains, and diminished in cagA− strains (98). Therefore, apoptosis seems to initially increase and subsequently decrease in cagA+ strains, with a persistent increase in cell proliferation. In this regard cagA+ strains have been suggested to induce mainly apoptosis, whereas proliferation would correlate to cagA− strains (56).

However, other authors disagree with such observations, and state that both strains induce apoptosis with no differences between them (58,99,100). Some authors have investigated H. pylori cagA−-induced apoptosis in cell cultures, and found an increased expression of Bax, a pro-apoptotic protein in the Bcl-2 family, and a suppression of anti-apoptotic Bcl-2 (91,104). However, cagA disruption does not affect NF-κB, MAP-kinase or IL-8 activation (94,105,106), thus suggesting the presence of a different factor injected into the host cell.

**Changes in the expression of enzymes related to inflammation as caused by H. pylori infection**

Cyclooxygenases (COX) catalyze the conversion of arachidonic acid into prostanoids such as prostaglandin E2 (PGE₂), which protect the gastric mucosa against apoptosis, thus increasing cell proliferation (107,108). Two isoenzymes exist: COX-1 and COX-2, the first one being constitutive and the second one inducible in case of lesion (107-110).

Non-steroidal anti-inflammatory drugs (NSAIDs) are amongst the most widely used drugs worldwide. Classic or nonspecific NSAIDs inhibit both COX isoenzymes, and their benefits are to a greater or lesser extent associated with lesions induced in the gastrointestinal tract (111).

On the other hand, the relationship between NSAIDs and H. pylori infection has not been elucidated, and a synergic association, antagonic association, or absolute independence on the gastroduodenal mucosa have all been postulated (112).

Gastrointestinal tract cells, including macrophages, neutrophils, myofibroblasts and endothelial cells, have been shown to express COX-2 in inflammation (107,113-115). Specifically, H. pylori-related gastritis has been seen to induce its expression depending upon bacterial strain (113,115-123), which may partly explain its distinct pathogenic potential (123,124). Infection by H. pylori cagA+ strains has been seen to overexpress COX-2 in patients with gastric cancer (123). In addition, some studies have demonstrated that organism eradication is associated with a decrease in COX-2 gastric expression (116,121,125).

Another molecule –nitric oxide (NO)– has been seen to play a role in the protection of the gastric mucosa by increasing blood flow and inhibiting leukocyte adhesion to the endothelium (126). The normal gastric mucosa contains no inducible NO synthase (iNOS) enzyme, but its expression increases in patients with H. pylori-related gastritis (116).

Both iNOS and COX-2 are induced by cytokines such as IL-1β, TNF-β or INF-γ, phorbol esters and growth factors in general, as well as bacterial polysaccharides (127-129). The induction of IL-1β by bacterial products has been seen to stimulate PG synthesis in a number of tissues (130), while increased PGs have also been witnessed in subjects with no clinical signs of infection (131). Cells treated with IL-1β have been shown to exhibit a decline and subsequent recovery of the NF-κB inhibitor protein IκBα, which suggests that treatment with IL-1β activates NF-κB (132).

On the other hand, the effect of mutated p53 on COX-2 expression and PGE₂ production has been investigated.
using in vitro experiments, and cells with wild-type p53 were found to produce 90% less PGE2, than cells with mutated p53, and to completely suppress COX-2 expression (133). Wild-type p53 also blocks the induction of COX-2 promoter activity by phorbol esters (133).

It is important to note that NO is mutagenic (134,135), and its metabolites, including nitrosamines, are involved in gastric carcinogenesis (136). COX-2 products have also been shown to be both mutagenic (137) and carcinogenic (138,139). Several binding sites for transcription factors have been identified within the COX-2 gene promoter, including two for NF-κB that regulate COX-2 transcription (132).

The extent of expression for both genes has been seen to be higher in tissues from patients with gastritis and concomitant H. pylori infection than in tissues of patients with gastritis and no H. pylori infection, whereas the level of constitutive cyclooxygenase COX-1 was approxi- mately identical in all tissues (116). Consistent with the fact that H. pylori colonization is greater in the antrum versus the gastric body (140, 141), the extent of expression of both iNOS and COX-2 has been seen to also be considerably higher in the antrum. However, it should be noted that a recent study showed inflammation levels that were not significantly higher in the antrum versus the gastric body, which suggests a direct effect of H. pylori on the induction of expression for both genes (116).

CONCLUSIONS

In summary, a number of conclusions may be drawn, which are discussed below:

—Apoptosis is a process of programmed cell death under genetic control that may be altered by a number of factors, including oxidative stress, ionizing radiation, hypoxia, etc.; these may ultimately lead to mutations in oncogenes regulating the apoptosis/cell proliferation process, which may throw gastric homeostasis out of balance and lead to the development of tumors.

—Another factor that may alter the balance between apoptosis and proliferation, specifically at the gastric mucosa, is H. pylori infection. The outcome may be a dramatically increased apoptosis rate, which may lead to gastritis or ulcer, or result in increased cell proliferation and reduced apoptosis, which may potentially progress to metaplasia, dysplasia, and eventually adenocarcinoma.

—To conclude, the relationship between H. pylori strain genotype and the organism’s pathogenic potential remains unclear, albeit a number of papers report an association of cagA+ strains with reduced apoptosis and the development of neoplastic processes on the one hand, and an association of cagA− strains with a higher-than-normal apoptotic rate on the other hand. In contrast, other authors draw opposite conclusions when failing to demonstrate differences in apoptotic rates between H. pylori cagA+ and cagA− strains, or to show that cagA+ strains indeed give rise to higher apoptotic rates, this being the reason why this association remains a highly controversial topic.

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REFERENCES

1. Kerr JF, Wyllie AH, Currie AR. Apoptosis: a basic biological phe-
nomenon with wide-ranging implications in tissue kinetics. Br J
2. Kerr JF, Winterford CM, Harmon BV. Apoptosis. Its significance in
non-apoptotic morphological changes in neurons of the mouse hip-
campus following transient hypoxic-ischemia. Neurosci Res
1999; 33: 49-55.
4. Thompson CB. Apoptosis in the pathogenesis and treatment of dis-
5. Linke SP, Clarkin KC, Di Leonardo A, Tsou A, Wahl GM. A re-
versible, p53-dependent G0/G1 cell cycle arrest induced by ribonu-
cleotide depletion in the absence of detectable DNA damage. Genes
Premature senescence involving p53 and p16 is activated in re-
ponse to constitutive MEK/MAPK mitogenic signaling. Genes Dev
7. Serrano M, Lin AW, Mccurraeh ME, Beach D, Lowe SW. Oncoge-
ric ras provokes premature cell senescence associated with accumu-
fibroblasts induced by oncogenic Raf. Genes Dev 1998; 12: 2997-
3007.
1999; 187: 100-11.
10. Nardone G, Staubino S, Rocco A, Mezza E, D’Armiesto FP, Isabau-
to L, et al. Effect of Helicobacter pylori infection and its eradica-
tion on cell proliferation, DNA status, and oncogene expression in pa-
Silieri N, et al. Effect of Helicobacter pylori infection, age and ep-
ithelial cell turnover in a general population at high risk for gastric
12. Vaux DL, Cory S, Adams JM. Bcl-2 gene promotes haemopoietic
cell survival and cooperates with c-myc to immortalize pre-B cells.
JP, et al. bcl-2-immunoglobulin transgenic mice demonstrate ex-
tended B cell survival and follicular lymphoproliferation. Cell 1989;
57: 79-88.
Bcl-2 is an inner mitochondrial membrane protein that blocks pro-
15. Strauss A, Harris AW, Bath ML, Cory S. Novel primitive lymphoid
tumours induced in transgenic mice by cooperation between myc
17. Nakamura T, Nomura S, Skai T. Expression of Bcl-2 oncprotein in
gastrointestinal and uterine carcinomas and their premalignant le-
18. Wallace-Boeddeker RR, Lowe SW. Clinical implications of p53 muta-


70. Wang J, Fan X, Brook EG. Gastric T cells damage the epithelium during H. pylori infection through interactions between Fas receptor and Fas ligand. Gastroenterology 1999; 116: A842 (abstract).
108. Gisbert JP, Pajares JM. Cyclooxygenase-2 (COX-2) y lesiones gas-

trodenales. ¿Alguna relación con Helicobacter pylori? Una re-


109. Lanas A, Martín-Mola E, Ponce J, Navarro F, Puque JM, Blanco FJ.

Clinical strategy to prevent the gastrointestinal adverse effects of nonsteroidal anti-inflammatory agents. Gastroenterol Hepatol 2003; 

110. Halter F, Tarnawski AS, Schmassmann A, Peskar BM. Cyclooxyge-
nase-2-implications on maintenance of gastric mucosal integrity and ulcer healing: controversial issues and perspectives. Gut 2001; 49: 
443-53.

111. Hawkey CJ. Non-steroidal anti-inflammatory drugs and peptic ul-

112. Gisbert JP, Boixeda D, Martín de Argila C, García Plaza A. Le-

siones gastrodenales y antiinflamatorios no esteroides: ¿Qué papel desempeña Helicobacter pylori en esta relación? Rev Esp En-

ferm Dig 1998; 90: 655-64.

113. Tatsuguchi A, Sakamoto C, Fukuda Y, Wada K, Akamatsu T, 

Tsukui T, et al. Induction of cyclooxygenase-2 in mesothelial cells in 

peritonitis caused by perforated ulcers-an immunohistochemical 

study in humans. Aliment Pharmacol Ther 2000; 14 (Supl. 1): 58-

63.

114. Wallace J. Distribution and expression of cyclooxygenase (COX) 

isozymes, their physiological roles, and the categorization of non-

116-66; discussion 167-175.

115. Jackson LM, Wu KC, Mahida YR, Jenkins D, Hawkey CJ. Cy-

clooxygenase (COX-1) and 2 in normal, inflamed, and ulcerated hu-


116. Fu S, Ramanujam KS, Wong A, Fantry GT, Drachenberg CB, James 


93.

117. Franco L, Talamini G, Carra G, Doria D. Expression of COX-1, 

COX-2, and inducible nitric oxide synthase protein in human gastric 

antrum with Helicobacter pylori infection. Gastrointest Endosc 


118. Xie QW, Cho HJ, Calaycay J, Munford RA, Swiderek KM, Lee 

TD, et al. Cloning and characterization of inducible nitric oxide syn-


119. Lowenstein CJ, Glatt CS, Bredt DS, Snyder SH. Cloned and ex-

pressed macrophage nitric oxide synthase contrast with the brain 


120. Arias-Negrete K, Keller K, Chadee K. Proinflammatory cytokines 


121. Mitchell MD, Romero RJ, Avila C, Foster JT, Edwin SS. 

Prostaglandin production by amnion and decidual cells in response 

to bacterial products. Prostaglandins Leukot Essent Fatty Acids 


al. Amniotic fluid interleukin-1 in spontaneous labor at term. J 


123. Allport VC, Slater DM, Newton R, Bennett PR. NF-kappaB 

and AP-1 are required for cyclo-oxygenase 2 gene expression by 

amnion epithelial cell line (WISH). Mol Hum Reprod 2000; 6: 

561-5.

124. Subbaramaiiah K, Altorki N, Chung WJ, Mestre A, Dan-

nenberg AJ. Inhibition of cyclooxygenase-2 gene expression by 


125. Wink DA, Kasprzak K, Marchetti TM, Elespuru RK, Misra M, 

Dunams TM, et al. DNA deaminating ability and genotoxicity of ni-


126. Arias-Negrete S, Keller K, Chadee K. Proinflammatory cytokines 

and AP-1 are required for cyclo-oxygenase 2 gene expression 

in amnion epithelial cell line (WISH). Mol Hum Reprod 2000; 6: 

561-5.

127. Plummer SM, Hall M, Faux SP. Oxidation and genotoxicity of fe-

tucan-12 are potentiated by prostaglandin H synthase. Car-


128. Mitchell MD, Romero RJ, Avila C, Foster JT, Edwin SS. 

Prostaglandin production by amnion and decidual cells in response 

to bacterial products. Prostaglandins Leukot Essent Fatty Acids 


129. Arias-Negrete S, Keller K, Chadee K. Proinflammatory cytokines 


130. Mitchell MD, Romero RJ, Avila C, Foster JT, Edwin SS. 

Prostaglandin production by amnion and decidual cells in response 

to bacterial products. Prostaglandins Leukot Essent Fatty Acids 


131. Plummer SM, Hall M, Faux SP. Oxidation and genotoxicity of ni-


132. Subbaramaiiah K, Altorki N, Chung WJ, Mestre A, Dan-

nenberg AJ. Inhibition of cyclooxygenase-2 gene expression by 


133. Wink DA, Kasprzak K, Marchetti TM, Elespuru RK, Misra M, 

Dunams TM, et al. DNA deaminating ability and genotoxicity of ni-


134. Wink DA, Kasprzak K, Marchetti TM, Elespuru RK, Misra M, 

Dunams TM, et al. DNA deaminating ability and genotoxicity of ni-


135. Nanney L, Shibut T, Ponnappan K, Natsuaki M, Nishikawa K, 

Nakanishi H, et al. DNA deaminating ability and genotoxicity of ni-


136. Nanney L, Shibut T, Ponnappan K, Natsuaki M, Nishikawa K, 

Nakanishi H, et al. DNA deaminating ability and genotoxicity of ni-