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TOPIC HIGHLIGHT

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Helicobacter pylori gamma-glutamyl transpeptidase and its pathogenic role

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Abstract

Helicobacter pylori (*H. pylori*) gamma-glutamyl transpeptidase (GGT) is a bacterial virulence factor that converts glutamine into glutamate and ammonia, and converts glutathione into glutamate and cysteinylglycine. *H. pylori* GGT causes glutamine and glutathione consumption in the host cells, ammonia production and reactive oxygen species generation. These products induce cell-cycle arrest, apoptosis, and necrosis in gastric epithelial cells. *H. pylori* GGT may also inhibit apoptosis and induce gastric epithelial cell proliferation through the induction of cyclooxygenase-2, epidermal growth factor-related peptides, inducible nitric oxide synthase and interleukin-8. *H. pylori* GGT induces immune tolerance through the inhibition of T cell-mediated immunity and dendritic cell differentiation. The effect of GGT on *H. pylori* colonization and gastric persistence are also discussed.

Key words: *Helicobacter pylori*; Gamma-glutamyl transpeptidase; Bacterial virulence factor; Gastric epithelial cell damage; T cell-mediated immunity

Core tip: In this review, we focus on the biochemical features and physiological role of *Helicobacter pylori* (*H. pylori*) gamma-glutamyl transpeptidase and analyze the mechanisms through which gamma-glutamyl transpeptidase affects *H. pylori* gastric colonization, persistence, immune tolerance and damage to the gastric mucosa.

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INTRODUCTION

Helicobacter pylori (*H. pylori*) is a gram-negative, microaerophilic, S-shaped bacterium that colonizes approximately 50% of the world's population. *H. pylori* infection causes chronic gastritis, which is asymptomatic in the majority of carriers but may evolve into more severe disease, such as atrophic gastritis, gastric and duodenal ulcers and mucosa-associated lymphoid tissue lymphoma and gastric adenocarcinoma[1]. *H. pylori*-induced gastroduodenal disease depends on the inflammatory response of the host and on the production of specific virulence factors, such as urease, which is responsible for ammonia generation;

Table 1 Reported *Helicobacter pylori* gamma-glutamyl transpeptidase effects

Effects	Ref.
Involved in *H. pylori* colonization and persistence in the gastric mucosa	[5,6]
Hydrolysis of extracellular glutamine and glutathione to generate glutamate that is transported into the *H. pylori* cell	[8]
Highly active periplasmic deamidase involved in ammonia production	[8,20]
Significantly higher GGT activity in strains obtained from patients with peptic ulcer disease	[21]
Gastric epithelial cell death - Mitochondria-mediated apoptosis in gastric epithelial cells	[7,16,24]
Cell-cycle arrest of gastric epithelial cells	[24]
Glutathione degradation-dependent gastric epithelial cell death	[8,27]
H_2O_2 generation, nuclear factor-κB activation and interleukin-8 production in gastric epithelial cells	[21,27]
Induction of EGF-related growth factors and COX-2 in gastric epithelial cells	[15]
Induction of apoptosis and inflammation in human biliary cells	[25]
Degradation of the apoptosis-inhibiting protein survivin in gastric epithelial cells	[30]
Inhibition of T cell proliferation and induction of G1 cell cycle arrest	[9-11]
Induction of microRNA-155 in human T cells	[38]
Gastric persistence and immune tolerance	[12]

H. pylori: *Helicobacter pylori*; GGT: Gamma glutamyl transpeptidase; EGF: Epidermal growth factor; COX-2: Cyclooxygenase 2.

the vacuolating cytotoxin VacA; the cytotoxin-associated gene A product CagA; and the type Ⅳ secretion system encoded by the *cag* pathogenicity island[1-4]. Another virulence factor, gamma-glutamyl transpeptidase (GGT), has been shown to play a role in the colonization of the gastric mucosa by *H. pylori*[5,6], to induce the apoptosis of gastric epithelial cells[7,8], and to inhibit T cell proliferation and dendritic cell differentiation[9-12] (Table 1).

In this review, we focus on the biochemical features and physiological role of *H. pylori* GGT and analyze the mechanisms through which GGT plays a role in *H. pylori* infection, gastric persistence, immune tolerance and gastric mucosa damage.

BIOCHEMICAL FEATURES AND PHYSIOLOGICAL ROLE OF *H. PYLORI* GGT

GGT is a threonine N-terminal nucleophile (Ntn) hydrolase that catalyzes the transpeptidation and hydrolysis of the gamma-glutamyl group of glutathione and related compounds[13]. GGT is widely distributed in living organisms and is highly conserved, with mammalian and bacterial homologs often sharing more than 25% of their sequence identity[14]. GGT is found in all gastric *Helicobacter* species, but among the enterohepatic *Helicobacter* species, it is found only in *H. aurati*, *H. bilis*, *H. canis*, *H. muridarum* and *H. trogontum*[5,7,15,16]. The biochemical features of *H. pylori* GGT and its physiological role are summarized in Figure 1.

H. pylori GGT is synthesized as a 60 kDa proenzyme that autocatalytically forms a heterodimer of 40 and 20 kDa subunits[5,7,14,15]. Threonine380 at the N-terminus of the small subunit is the cleavage site, and it is required for the protein's autocatalytic activity[14]. The enzymatic activity of the protein resides in the small subunit with the gamma-glutamyl binding site at the Tyr433 residue, and the Arg475 residue and the C-terminus of 20 kDa subunit contribute to catalysis[17,18]. *H. pylori* GGT possesses a signal peptide and has been isolated by two independent research groups as a secreted protein in bacterial broth culture filtrates[15,19]. Nevertheless, another research group identified *H. pylori* GGT as a periplasmic protein that is likely to associate with the membrane by ionic bonds[7].

Purified *H. pylori* GGT exhibits hydrolysis activity with very high affinities for glutamine and glutathione. *H. pylori* GGT converts glutamine into glutamate and ammonia, and converts glutathione into glutamate and cysteinylglycine, through hydrolysis[8]. Because *H. pylori* cells are unable to directly take up extracellular glutamine and glutathione, these substances are hydrolyzed into glutamate through the action of GGT, either as a secreted or periplasmic enzyme. These results indicate that the main physiological role of *H. pylori* GGT is to enable bacterial cells to use extracellular glutamine and glutathione as sources of glutamate. The resulting glutamate is then transported by a Na^+-dependent reaction into *H. pylori* cells, where it is primarily incorporated into the TCA cycle and partially used as a substrate for glutamine synthesis[8]. *H. pylori* GGT also has a physiological roles as a periplasmic deamidase and as a contributor with asparaginase to the extracellular production of ammonia[8,20]. The ammonia produced by *H. pylori* GGT can be used as a nitrogen source for bacterial cells and for resisting the acidic gastric environment. The extracellular production of ammonia, along with the consumption of extracellular glutathione and glutamine, may alter the redox balance of host cells in the gastric mucosa and render the host cells more sensitive to the toxic effects of reactive oxidizing substances, which in turn cause DNA damage and apoptosis (see below). The physiological roles exerted by *H. pylori* GGT in bacterial cells and in the host cells could provide metabolic advantages during the establishment of *H. pylori* infection. In fact, previous studies have shown that *H. pylori* GGT plays an important role in the bacterial colonization of the gastric mucosa, and *H. pylori* GGT-defective isogenic strains are unable to colonize[5] or are less efficient[6] at colonizing the gastric mucosa of mice or piglets.

EFFECTS OF *H. PYLORI* GGT ON GASTRIC EPITHELIAL CELLS

Virulence can be defined as the ability of a pathogen to damage its host[3]. Although virtually all wild-type *H. pylori* strains produce GGT, strain-to-strain variations in GGT

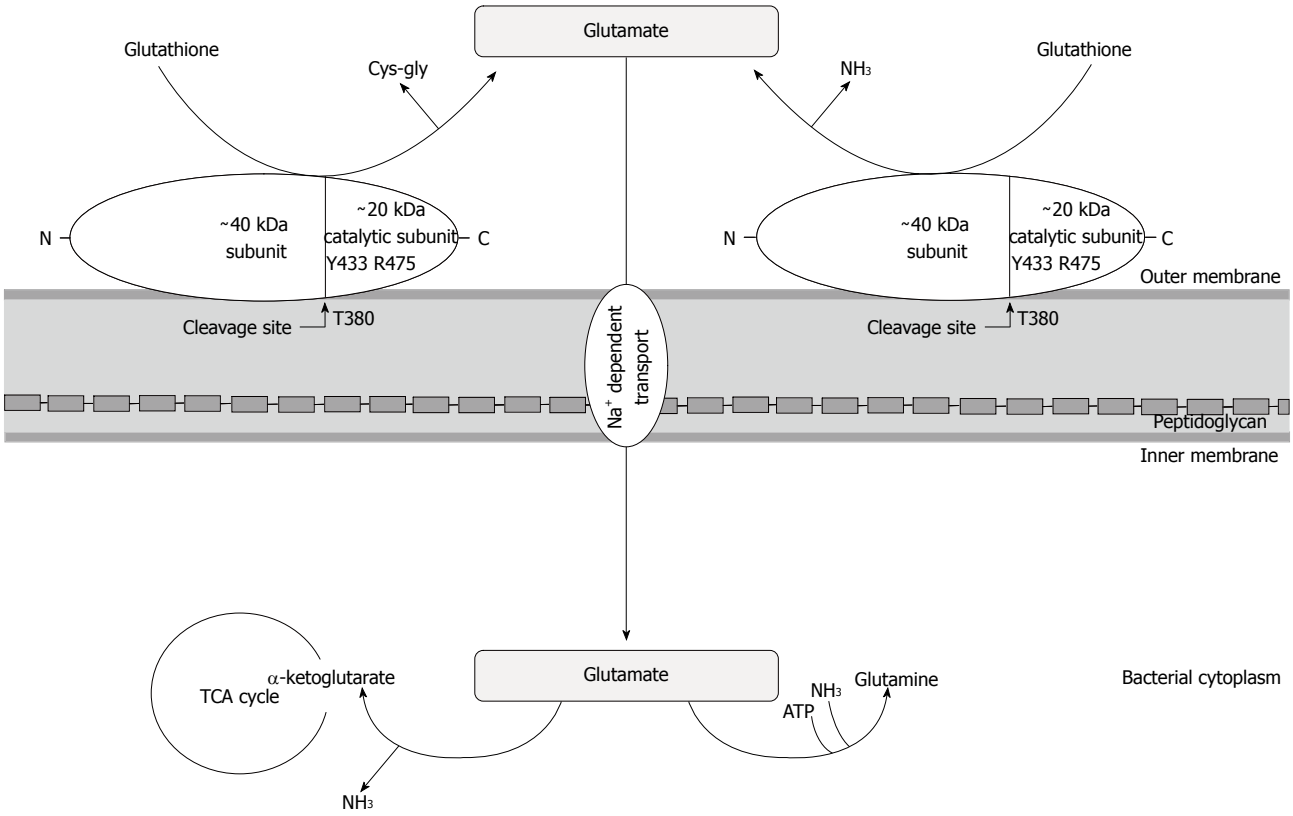

Figure 1 Biochemical features and physiological role of *Helicobacter pylori* gamma-glutamyl transpeptidase. *Helicobacter pylori* (*H. pylori*) gamma-glutamyl transpeptidase (GGT) is a secreted protein of 40 and 20 kDs subunits that converts glutamine to glutamate and ammonia, and glutathione to glutamate and cysteinylglycine. The glutamate produced is then transported into *H. pylori* cells, where it is incorporated into the tricarboxylic acid (TCA) cycle or utilized for glutamine synthesis.

level have been demonstrated among clinical isolates from patients with different disease statuses[21]. In particular, a significantly higher GGT activity has been observed in *H. pylori* isolates obtained from patients with peptic ulcer disease relative to those obtained from patients with nonulcer dyspepsia[21]. Thus, there is evidence of a direct relationship between GGT production and the development of more severe gastroduodenal diseases. This finding stresses the clinical relevance of GGT as a virulence factor in the overall *H. pylori*-induced pathogenic action. That gastric ulcer is associated with a high risk of gastric cancer[1] suggests that GGT may play an important role in *H. pylori*-induced carcinogenesis.

By favoring *H. pylori* colonization of the gastric mucosa[5,6], likely through its lymphocyte-inhibiting action[10] (see below), GGT might also act indirectly by allowing other independent virulence factors (such as CagA, VacA, *etc.*) to better exert their damaging actions against the gastric mucosa. Nevertheless, mounting evidence suggests that GGT exerts a direct damaging effect on gastric epithelial cells. The effects of *H. pylori* GGT on gastric epithelial cells are summarized in Figure 2.

Apoptosis-related effects

In 2003, Shibayama *et al*[7] demonstrated that purified *H. pylori* GGT was able to cause apoptosis in cultured gastric epithelial cells (AGS cell line) in a dose-dependent manner. This proapoptotic activity was strictly dependent on *H. pylori* GGT enzymatic activity, which was completely blocked by incubation with a glutamine analog that binds and inhibits GGT and other glutaminases. It is well-known that *H. pylori* infection induces apoptosis in gastric epithelial cells[22]. An increase in apoptosis may play a significant role in the development of pathological outcomes by disturbing the balance between the rate of new cell production and the rate of cell loss, with atrophic gastritis and gastric dysplasia (*i.e.*, gastric preneoplastic lesions) being associated with an increased rate of apoptosis[22]. Interestingly, Shibayama *et al*[7] also observed that GGT induced necrosis rather than apoptosis in a different gastric epithelial cell line (*i.e.*, KATO Ⅲ). A similar difference in the type of cell death induced among different experimental models has recently been observed for another *H. pylori* virulence factor, VacA[23]. This finding raises the key question of how and to what extent the *in vitro*-derived findings really mimic the *in vivo* situation[2]. Unlike apoptosis, necrosis results in the release of proinflammatory proteins, thereby augmenting gastric mucosal inflammation and contributing to the pathogenesis of peptic ulceration and gastric cancer[3,23].

In vitro, GGT-induced apoptosis has been shown to occur *via* the so-called "intrinsic" (*i.e.*, mitochondria-dependent) pathway with the release of cytochrome *c* in the cytosol and the activation of caspase-9 and -3. These caspases are critical components of the apoptotic machinery and are associated with the up-regulation of proapop-

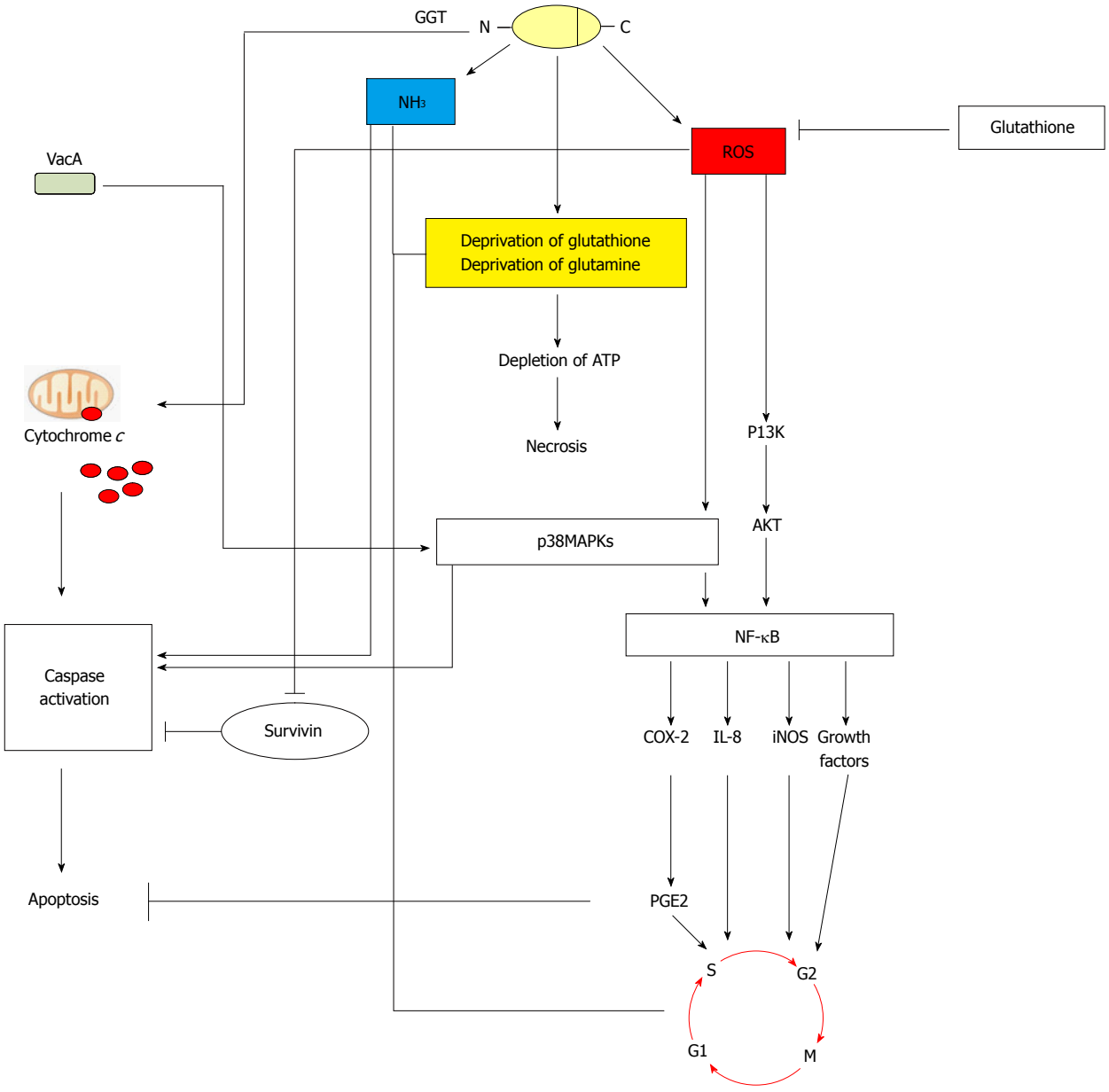

Figure 2 Effects of *Helicobacter pylori* gamma-glutamyl transpeptidase on gastric epithelial cells. *Helicobacter pylori* (*H. pylori*) gamma-glutamyl transpeptidase (GGT) causes consumption of mucosal glutamine and glutathione, production of ammonia and generation of ROS. These products induce caspase activation and apoptosis, ATP-depletion and necrosis, and cell-cycle arrest at G1-S phase in gastric epithelial cells. The effect of vacuolating cytotoxin (VacA) on caspase activation and apoptosis of gastric epithelial cells is also shown. *H. pylori* GGT may also inhibit apoptosis and induce proliferation through p38 MAPKs, AKT and NF-κB activation and subsequent COX-2, iNOS, growth factors and interleukin-8 (IL-8) induction. ROS: Reactive oxygen species; p38 MAPK: p38 mitogen-activated protein kinase; PI3K: Phosphatidylinositide 3-kinase; AKT: AKT kinase; NF-κB: Nuclear factor κB; COX-2: Cyclo-oxygenase 2; iNOS: Inducible nitric oxide synthase; PG: Prostaglandin.

totic members of the Bcl-2 protein family (such as Bax) and the downregulation of antiapoptotic proteins of the same family (Bcl-2 and Bcl-xL)[24]. It is worth noting that similar results have been found recently using human cholangiocarcinoma cells (KKU-100 cell line) as an *in vitro* cell model, in which *H. pylori* GGT was also found to increase both the level of *iNOS* gene expression and the secretion of interleukin (IL)-8[25]. Based on these results, Boonyanugomol *et al*[25] suggested that *H. pylori* GGT might be involved in the development of hepatobiliary tract cancer by altering cell kinetics and promoting biliary cell inflammation. However, this intriguing hypothesis remains highly speculative given that, as stressed above, the *in vivo* biological plausibility and clinical counterpart of the *in vitro* findings are still far from being confidently ascertained.

Apoptosis-independent antiproliferative effects

Another research group found that recombinant *H. pylori* GGT showed an apoptosis-independent inhibitory effect on AGS cell proliferation in a dose-dependent manner, although the minimum required protein concentration was 25 times higher than the concentration needed to inhibit the proliferation of human T cells[16]. The dis-

crepancies between these results and those of Shibayama *et al*[7] have tentatively been attributed to the different methodologies. In particular, only stress conditions such as serum starvation seem to sensitize AGS cells to GGT-dependent apoptosis[16]. Kim *et al*[26] investigated the effect of *H. pylori* GGT on cell cycle regulation of AGS cells in serum-containing medium. Although the changes were less marked than those in serum-deprived cells, the investigators confirmed the previously observed apoptotic action of GGT and found, in addition, that GGT caused cell cycle arrest at the G1-S phase transition[26]. Cell cycle arrest was associated with altered expression of specific cell cycle regulatory proteins, namely the down-regulation of cyclin E, cyclin A, cyclin-dependent kinase (Cdk) 4 and Cdk 6, and the up-regulation of the Cdk inhibitors p27 and p21. Thus *H. pylori* GGT seems to act as a brake at the G1 to S phase transition, thereby disrupting the normal function of several components of the cell cycle which also lead to apoptosis[26].

GGT-activated molecular pathways in gastric epithelial cells

The mechanisms by which the enzymatic activity of *H. pylori* GGT leads to gastric epithelial cell damage have been carefully investigated by several groups[8,15,20,27]. In mammalian cells, glutathione is synthesized in the cytosol where it reaches mM levels and functions as a redox buffer to detoxify oxidizing molecules. Glutathione may be translocated out of cells, where it serves as a substrate for mammalian cell GGT that is integrated into the plasma membrane using its active site. Because of GGT, the gamma-glutamyl moiety of glutathione is transferred to other amino acids along with the formation of gamma-glutamyl amino acids to be subsequently taken up by the cell; this sequence of events is the so-called "gamma-glutamyl cycle". Because the K_m for the hydrolysis reaction catalyzed by *H. pylori* GGT is much lower than that of the reaction catalysed by human GGT, gastric epithelium colonization by *H. pylori* would result in the exhaustive hydrolysis of epithelial cell glutathione[8]. If either the glutathione supply or its synthesis fails to compensate for its *H. pylori* GGT-dependent hydrolysis, the redox balance of the gastric cell will be impaired. The reduced cytosolic concentration of glutathione makes the epithelial cells more sensitive to the toxic effects of oxidizing molecules, making them more prone to DNA damage, cell cycle alterations, apoptosis and carcinogenesis. Moreover, because glutathione synthesis is an ATP-dependent process, its enhanced degradation by *H. pylori* GGT would also cause increased compensatory energy consumption by the epithelial cells, which in turn would result in impaired cell viability and proliferation. The hydrolytic activity of *H. pylori* GGT also exhibits a very high affinity for glutamine, an important nutrient for the gastric mucosa. Extracellular glutamine depletion by bacterial GGT at the *H. pylori* colonization site would result in the impairment of both the cytoprotective properties of gastric epithelial cells and the immune function of recruited inflammatory cells, for which glutamine is an important respiratory fuel source[8]. In addition, GGT-dependent glutamine hydrolysis is associated with the production of ammonia[8,20], which is well-known not only for its high toxicity to human cells[28] but also for greatly increasing the cytotoxic action of another pivotal *H. pylori* virulence factor, namely the VacA toxin[29].

Flahou *et al*[27] recently confirmed that incubating AGS with *H. pylori* GGT resulted in cell apoptosis. However, they also observed that the supplementation of GGT-treated cells with glutathione strongly enhanced the degree of cell death and resulted in the induction of oncosis/necrosis and not apoptosis. This effect was preceded by increased extracellular H_2O_2 concentrations, which caused lipid peroxidation. These authors concluded that the GGT-mediated degradation of glutathione results in the generation of pro-oxidant products, in turn leading to epithelial cell death, which will be caused by apoptosis or necrosis depending on the amount of extracellular glutathione available as GGT substrate[27]. Indeed, the type of *in vitro* H_2O_2-induced cell death is known to depend on the concentration of this reactive oxygen species (ROS), with the higher concentrations inducing necrosis rather than apoptosis[27]. Like mammalian GGTs, *H. pylori* GGT-mediated extracellular glutathione catabolism produces ROS (such as H_2O_2) by thiol-dependent iron reduction, and this production is increased with the addition of exogenous Fe^{3+} and, conversely, inhibited by treatment with the iron chelator desferrioxamine[21]. Interestingly, it was recently observed[30] that this type of GGT-dependent pathway seems to play a key role in the *H. pylori*-induced loss of the apoptosis-inhibiting protein survivin in gastric epithelial cells by triggering enhanced proteasomal degradation of the protein. The loss of survivin may thus contribute to the increased cell death induced by *H. pylori* GGT.

As demonstrated both in AGS gastric cancer cells and in primary non-transformed gastric epithelial cells, the increased production of H_2O_2 by *H. pylori* GGT also leads to the activation of nuclear factor-κB and the up-regulation of IL-8 which is known to play a major role in the inflammation-associated mucosal injury induced by *H. pylori*[21]. Gong and coworkers[21] also found that *H. pylori* GGT caused oxidative DNA damage, which can be counteracted by preincubation with the H_2O_2 inhibitor N-acetylcysteine, suggesting a key role for H_2O_2 generation in GGT-dependent DNA damage. However, Toller *et al*[31] found that GGT was apparently not involved in DNA double-strand breaks caused by *H. pylori* in primary and transformed murine and human epithelial/mesenchymal cells, suggesting that *H. pylori* GGT did not contribute to the genetic instability and chromosomal aberrations observed during gastric carcinogenesis.

Upregulation of EGF-related peptides and COX-2

The molecular cross-talk between *H. pylori* and human gastric mucosa leading to gastric inflammation and cancer involves also the increased expression of epidermal

growth factor (EGF)-related peptides and the activation of the EGF receptor signal transduction pathway as well as upregulation of the expression of cyclooxygenase (COX)-2, the inducible isoform of the enzyme responsible for prostaglandin production[1,2,15]. Our group[15] demonstrated that GGT is the virulence factor responsible for the *in vitro* up-regulation of both EGF-related peptides and COX-2 in human gastric epithelial cells. This finding was supported by observations showing that all such effects were counteracted by the selective GGT inhibitor acivicin and that an *H. pylori* isogenic mutant strain defective in GGT did not exert any effect on either EGF-related peptides or COX-2 expression[15]. Apparently, a common signal transduction pathway that relies on the activation of phosphatidylinositol-3 kinase and p38 kinase, but not MAP kinase kinase, triggers the GGT-dependent effects on the cell expression of both EGF-related peptides and COX-2. Notably, the GGT-induced up-regulation of EGF-related peptides and COX-2 mRNA expression was significantly inhibited by treatment with desferrioxamine, which inhibits the formation of ROS generated by cysteinylglycine in the presence of transition metals[15]. This last finding suggests that *H. pylori* GGT may trigger a proinflammatory and procarcinogenic mucosal response *via* oxidative stress in gastric mucosal cells.

EFFECTS OF *H. PYLORI* GGT ON T CELL-MEDIATED IMMUNITY

Mounting evidence indicates that *H. pylori* GGT may modulate T cell-mediated immunity and contribute to immune evasion during *H. pylori* infection. Gerhard *et al*[9] first demonstrated that the inhibition of T cell proliferation by *H. pylori* is mediated by a low-molecular weight protein secreted by the bacterium. The same research group identified *H. pylori* GGT as the secreted bacterial protein that induces cell cycle arrest in the G1 phase of T cells and suppresses T cell proliferation[10]. They also identified the disruption of Ras- but not PI3K-dependent signaling by *H. pylori* GGT as the cause of the G1 arrest, and it also suppressed T cell proliferation[10].

VacA toxin has also been identified as an additional bacterial virulence factor that can efficiently block T cell proliferation by inducing G1/S cell cycle arrest[32,33] and inhibiting the activation of nuclear factor of activated T cells (NFAT), a transcription factor acting as a global regulator of immune response genes[32,34]. Interestingly, impairment of the mitochondrial function has been suggested as an additional mechanism involved in the VacA-induced blockade of $CD4^+$ T cell proliferation[35]. A similar action in the T cell mitochondria might also be hypothesized for GGT, accounting for its proven capacity to damage epithelial cell mitochondria. VacA and GGT released from the bacteria in the gastric mucosa may directly contact intraepithelial T cells or penetrate the mucosa-associated lymphoid tissue (MALT) through the opening of tight junctions brought about by *H. pylori*[36]. Notably, *H. pylori* has also been demonstrated to be able to penetrate the gastric epithelium *in vivo* reaching the underlying lamina propria where it directly contacts immune-inflammatory cells[37].

Because *H. pylori* is a cholesterol auxotroph and needs to extract this nutrient from host cells, the inhibitory effects of VacA and GGT on the proliferation of human $CD4^+$ T cells is also modulated by the ability of *H. pylori* to form cholesterol alpha-glucosides[11]. In further support of the roles of VacA and GGT on the inhibition of T cells, it has recently been demonstrated that VacA and *H. pylori* GGT positively regulate the expression of the non-protein-coding microRNA (miRNA) miR-155 and the master T cell regulator Foxp3 in human lymphocytes through a cAMP-dependent pathway[38].

Both VacA and GGT from *H. pylori* may also affect T cell activity in an indirect manner by reprogramming dendritic cells to promote the differentiation of naive T cells into T regulatory (Treg) cells[12]. Treg cell differentiation in response to *H. pylori* infection requires the direct interaction of naive T cells with "tolerogenic" dendritic cells that have been exposed to *H. pylori*, either in the gastric mucosa or in gastric or mesenteric lymph nodes[39,40]. Dendritic cells that have been exposed to *H. pylori* fail to induce T_H1 and T_H17 type T cell responses *in vitro* and *in vivo*; instead, such dendritic cells preferentially induce the expression of the Treg cell-specific transcription factor FOXP3, the surface marker CD25 and the anti-inflammatory cytokine IL-10 in naive T cells[12]. This action may contribute to gastric persistence and immune tolerance during infection, and it may independently potentiate the evasion of the immune response generated by the apoptosis of human monocytes in the presence of *H. pylori* expressing functional *cag* pathogenicity island[41]. The immune response evasion might also be due to the induction of COX-2 in gastric epithelial cells by *H. pylori* GGT[15], which has been shown to suppress the T_H1 polarization of T cell response to *H. pylori*[42].

The effects of *H. pylori* GGT on T cell-mediated immunity could represent the biological basis of observations in animal models, showing an important role for GGT in *H. pylori* colonization[5,6]. Because *H. pylori* has been classified as a type I carcinogen[1], the inhibition of immune responses caused by *H. pylori* GGT might also be an important factor in the induction of malignant MALT lymphoma and adenocarcinoma of the stomach. The effects of *H. pylori* GGT on T cell-mediated immunity are summarized in Figure 3.

CONCLUSION

H. pylori produces a combination of virulence factors that damage the gastric mucosa and subvert the host immune response to allow persistent colonization of the challenging environment of the human stomach. In this review, we focussed on *H. pylori* GGT, a bacterial protein that inhibits cell proliferation and induces the apoptosis of gastric epithelial cells through different pathways involving ammonia and ROS production. This action may

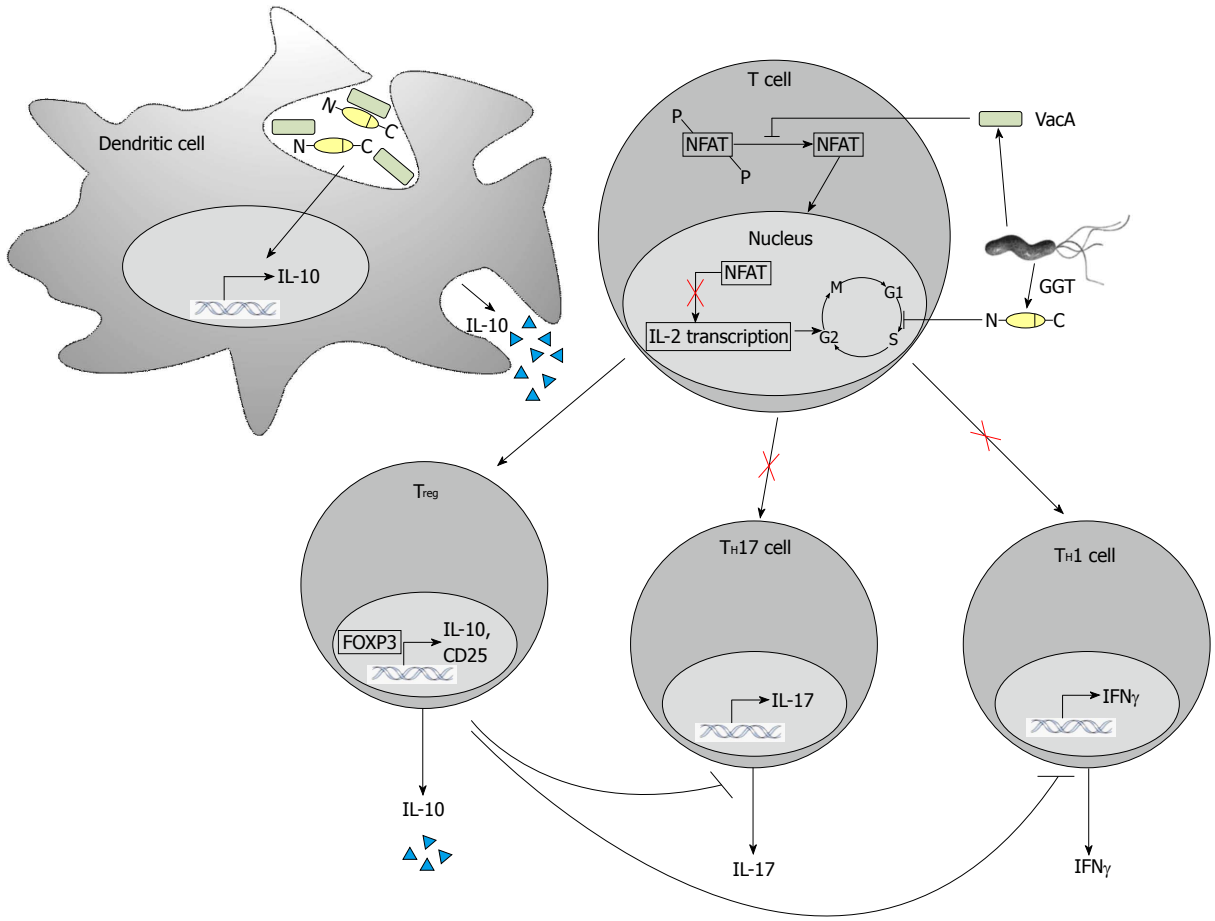

Figure 3 Effects of *Helicobacter pylori* gamma-glutamyl transpeptidase on T cell-mediated immunity. *Helicobacter pylori* gamma-glutamyl transpeptidase (GGT) and VacA inhibit T cell proliferation and differentiation to T helper 1 (T_H1) and T_H17. They also prevent T cell immunity by reprogramming dendritic cells to produce interleukin-10 (IL-10) and IL-18 and promote the differentiation of naive T cells into T regulatory (Treg) cells that further suppress T_H1 and T_H17 effector functions. FOXP3: Forkhead box P3; NFAT: Nuclear factor of activated T cells; IFN-γ: Interferon gamma.

contribute to gastric injury during *H. pylori* infection. Interestingly, *H. pylori* GGT may also stimulate the expression of antiapoptotic factors and factors that protect against cell damage, such as COX-2 and prostaglandins, EGF-related growth factors and iNOS, which could heal gastric mucosa but may also play a procarcinogenic role during infection. The effects exerted by *H. pylori* GGT may depend on the level of GGT expression and/or on the concomitant expression of other bacterial virulence factors. Instead, the effect of *H. pylori* GGT on the inhibition of T cell immunity and dendritic cell maturation may favor colonization and bacterial persistence in the gastric mucosa. The evasion of the immune response by *H. pylori* GGT may also play a role during gastric carcinogenesis. Increased knowledge of the molecular mechanisms underlying *H. pylori* infection may lead to the recognition of potential intervention targets to prevent the progression of chronic gastritis to atrophic gastritis and gastric cancer.

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