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Modulating the cytokine response to treat *Helicobacter* gastritis

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Abstract

The conventional view of gastric acid secretion is that a negative feedback mechanism arises in response to high acidity, such that somatostatin keeps G-cells and parietal cells from producing more gastrin and acid, respectively. When the stomach becomes infected, for example with *Helicobacter pylori (H. pylori),* the feedback mechanism is impaired. In animal models, our laboratory has demonstrated that other types of bacteria besides *H. pylori* can cause gastritis. For example, under conditions of low acidity, gastritis is secondary to bacterial overgrowth, not production of excessive acid, thus suggesting a new paradigm for the regulation of gastric acid secretion under inflammatory conditions. Cytokines, released during the gastric inflammatory response, including IFNγ, TNFα and IL-1β stimulate the G-cell to produce gastrin. Gastrin in turn triggers the release of acid, and hypergastrinemia suppresses somatostatin, the inhibitor of acid. The overall response results in maximal gastric acid output that acts as the stomach's most important anti-microbial agent. The increased acid secretion by the stomach in the presence of *H. pylori* seems to be part of the innate immune response, in that gastrin and somatostatin are reciprocally regulated by Th1 or Th2 cytokines, respectively. In a mouse model, we showed that octreotide, a somatostatin, analog, is an efficacious treatment for *Helicobacter* gastritis. In humans, octreotide might accelerate recovery from *H. pylori* infection, reducing the duration of antibiotic therapy.

Keywords: Gastrin; Somatostatin; IFNγ; IL-4; Octreotide

1. Introduction

It is generally accepted that acid released from parietal cells located in the gastric corpus/fundus has evolved to denature ingested food and begin digestion, while the antrum begins the mechanical processing [1]. Gastrin, histamine and acetylcholine are the major secretagogues of gastric acid secretion. Gastrin stimulates acid secretion by inducing histamine release from enterochromaffin-like (ECL)-cells. Increased acidity then stimulates putative chemoreceptors on the D-cells to secrete somatostatin and block further release of gastrin and gastric acid. Thus, gastric acid secretion is regulated by a negative feedback mechanism [1].

In addition to initiating digestion, acid secretion also serves as a defense mechanism against colonization by potentially pathogenic bacteria that are ingested. We have recently confirmed this notion in a mouse model in which low acid levels result in bacterial overgrowth and gastritis [2]. This result made us reconsider the importance of acid as a defense mechanism in association with cellular immunity. Expanding on this idea further, one might speculate acid secretion as the gastric specific arm of the innate immune system.

Chronic inflammation of the gastric mucosa (chronic gastritis) is caused by *Helicobacter pylori (H. pylori)* or bacterial overgrowth in the hypochlorhydric stomach [2,3]. Infection with *H. pylori* mounts a Th1 immune response characterized by the recruitment of IFNγ -expressing T lymphocytes, and undetectable levels of Th2 cytokines [4]. An abundance of data suggest that inflammatory cytokines such as IFNγ, TNFα and IL-1β, released during bacterial infection, play a pivotal role in triggering cellular changes that contribute to gastric mucosal damage [5–8]. In particular, chronic gastritis is accompanied by reciprocal

Abbreviations: IFNγ, interferon gamma; IL-1β, interluekin-1 beta; TNFα, tumor necrosis factor alpha; IL-4, interluekin-4; G-cells, gastrin-secreting cells; D-cells, somatostatin-secreting cells; ECL-cells, enterochromaffin-like cells; *H. pylori*, *Helicobacter pylori*

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changes in the gastric neuroendocrine cell populations that regulate acid secretion. The number of gastrin-secreting G-cells increases while somatostatin-secreting D-cells decreases rendering *Helicobacter*-infected patients hypergastrinemic and often hyperacidic [9]. Recently, we have shown that the gastric immune system and acid regulatory peptides are part of an immunoregulatory circuit [5]. Thus, the focus of the following article is to review recent work that shows how modulating such an immunoregulatory circuit is a possible treatment for *Helicobacter* gastritis.

1.1. Inflammation: a trigger for the development of gastric cancer

H. pylori is a Gram-negative organism that survives in the deep mucous layer of the stomach and attaches to the epithelial cells [10]. It is estimated that half of the world's population is infected with *H. pylori,* making it perhaps the most common chronic infection of humans [11]. More than 90% of the population in the African countries and up to 50% of American populations are infected [11]. *H. pylori* has developed properties that enable it to survive and grow in the high acid conditions of the stomach. The high urease activity enables this organism to increase the pH in its surrounding environment and thus serve as a defense mechanism against gastric acid [12]. Production of ammonia increases the pH of the local environment of *H. pylori* to a level where the organism can survive [12].

Nearly 100% of infected individuals develop an acute inflammatory gastritis, which is usually asymptomatic. This immunological response is generally not sufficient to clear the infection. Unless eradicated by antimicrobial therapy, *H. pylori* infection usually persists for life. Overall, chronic *H. pylori* infection increases the risk of gastric adenocarcinoma by at least two-fold [11], and the International Agency for Cancer Research, a division of the World Health Organization, has designated the bacterium as a class I carcinogen. Although the incidence of gastric cancer rates has declined during the past century, it remains the second most common cause of death worldwide.

The addition of antimicrobial therapy to antisecretory drugs is considered the standard of care for *H. pylori*-infected patients with active or inactive peptic ulcer [13]. In developed countries, eradication therapy is successful in about 90% of cases [10]. In the developing world, eradication is more difficult due to the frequency of antibiotic resistance and the frequency of recurrent infection [14,15]. Currently in the United States, triple-drug regimens have yielded the best eradication rates [15]. These regimens usually consist of combining a proton pump inhibitor (PPI) (lanzoprazole, omeprazole etc.) with tetracycline HC1, bismuth subsalicylate and metronidazole for 10–14 days. However, when gastric acid levels decrease in the presence of a PPI, there is the risk of bacterial overgrowth that excludes *H. pylori.* In a mouse model of PPI-induced bacterial overgrowth the major species detected were *Lactobacillus*, *Enterobacter*, *Staphylococcus* and *Propionibacterium* [2].

There are at least two predominant distinct histopathologic subtypes, intestinal and diffuse, that are included in the definition of 'gastric cancer'. Intestinal type cancer predominates in high-risk populations and is preceded by a well-characterized precancerous process. The diffuse type cancer is frequent in low-risk populations and is not preceded by a well-defined precancerous process [16]. The precancerous lesions of intestinal type cancer represent a complex series of stages that results in the transformation of normal gastric mucosa to that of intestine like cells [16]. These sequential steps were first described by Pelayo Correa [17]. Fig. 1 summarizes the precursor lesions that eventually develop into intestinal type gastric cancer. The first step consists of a chronic active inflammatory response that is typically triggered by bacterial infection such as *H. pylori.* This phase is characterized by infiltration of the gastric mucosa by polymorphonuclear neutrophils. Extensive studies suggest that cytokines such as IFNγ, TNFα and IL-1β that are released during the inflammation initiate the cellular changes observed during this first phase [5,8,18–23]. The cytokines also increase gastrin-secreting G-cells and decrease somatostatin-secreting D-cells. The second phase is characterized by alterations in the epithelial cell cycle such as changes in

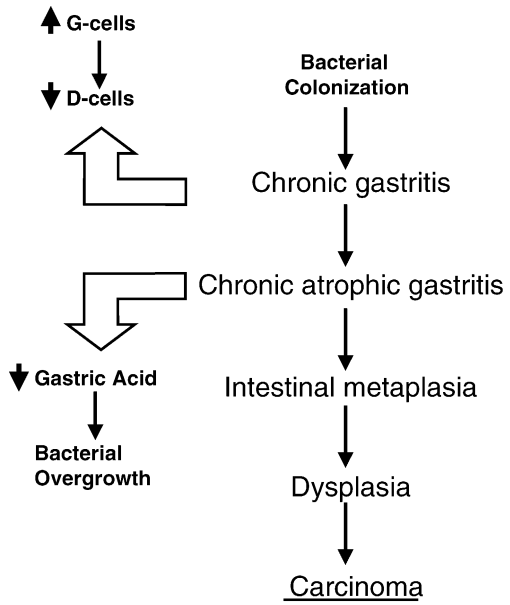

Fig. 1. Biological model for the development of human gastric cancer: the model for human gastric carcinogenesis is described as a series of sequential phases. Neoplastic transformation is initiated by an inflammatory response that is triggered by bacterial colonization. Chronic gastritis accompanied by loss of somatostatin-secreting D-cells and hypergastrinemia leads to atrophy of the acid-secreting parietal cells. Eventually the stomach loses its normal gastric phenotype and transforms to that of an intestinal cell type referred to as intestinal metaplasia that develops into intestinal type gastric carcinoma [17,59].

proliferation and apoptosis. This results in atrophy of the acid secreting parietal cells referred to as mucous gland metaplasia that is defined as the replacement of the acid-secreting parietal cells with mucous secreting cells [24]. Over time, proliferation of these mucous cells with evidence of an intestinal phenotype (intestinal metaplasia) is a major precursor lesion for gastric cancer. This eventually leads to dysplasia and cancer [17].

Chronic gastritis regardless of the etiology appears to be the most consistent early lesion leading to gastric cancer. A number of mouse models have shown that inflammation triggers neoplastic transformation [2,25,26]. We have shown in hypochlorhydric mice, due to genetically-induced gastrin deficiency, that severe inflammation develops as a consequence of bacterial overgrowth, that then resolves with antibiotics [2]. Over time persistent inflammation in the gastrin-deficient mice develops into mucous gland metaplasia, atrophic gastritis, intestinal metaplasia and eventually carcinoma (data unpublished) following the sequential series of events observed in the human model of gastric cancer [17]. In addition, a recent mouse model with expression of a mutated IL-6 receptor subtype called $gp130^{757F/F}$ resulted in over-stimulation of the IL-6-STAT3 pathway. These mice developed antral gastric cancer within two months [25,26]. Furthermore, transgenic mice simultaneously expressing COX-2 and microsomal prostaglandin E synthase (mPGES)-l in the gastric epithelium also develop metaplasia, hyperplasia and cancer triggered by macrophage infiltration [26].

1.2. The normal negative feedback mechanism regulating gastric acid secretion

In order to understand how the immune response regulates gastric acid secretion, we must first review the textbook explanation of how acid is regulated. Fig. 2 is a schematic diagram of the human stomach, showing the upper portion (corpus/fundus), which contains the acid-secreting parietal cells, and the lower portion (antrum), which is the endocrine portion. The gastrin (G)-cell resides only in the antrum and produces the acid-stimulating hormone gastrin, supposedly in response to an alkaline environment. Another endocrine regulatory cell, the D-cell, is present in both the antrum and the corpus. In the stomach, somatostatin is the primary inhibitor of gastrin-stimulated acid secretion. Gastrin indirectly stimulates acid secretion through induction of histamine release from enterochromaffin-like (ECL)-cells. Histamine subsequently stimulates gastric acid secretion through H2 receptors on the parietal cells [27,28]. Increased acid levels then stimulate putative chemoreceptors on antral D-cells to secrete somatostatin and block further release of gastrin and acid. Thus, gastric acid secretion is regulated by a negative feedback mechanism involving somatostatin [29]. During gastric bacterial infection, this negative feedback mechanism is not observed.

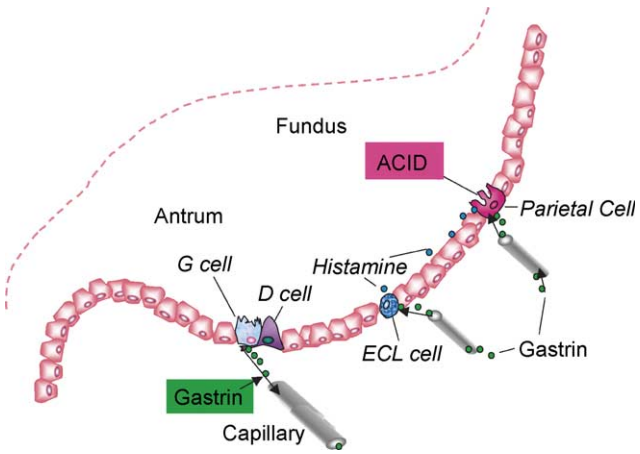

Fig. 2. Normal feedback mechanism regulating gastric acid secretion. Gastrin release from antral G-cells stimulates the release of histamine from enterochromaffin-like (ECL)-cells located in the fundus. Histamine then activates the histamine 2 (H2) receptors on the fundic parietal cells to stimulate acid secretion. Acid secretion activates chemoreceptors on antral D-cells to stimulate somatostatin secretion. Somatostatin inhibits further release of gastrin and acid secretion. During inflammation this feedback mechanism is impaired and D-cell function is suppressed resulting in elimination of the inhibitory restraint on gastrin and gastric acid. As a result, the stomach maximizes acid output in an attempt to clear bacterial infection.

1.3. Why the feedback mechanism fails during inflammation

A Th1 immune response triggered by *H. pylori* is characterized by recruitment of primarily IFNγ-expressing T lymphocytes to the stomach and low expression of Th2 cytokines such as IL-4, IL-5, IL-10 and IL-13 [30]. IFNγ-null mice do not mount an inflammatory response even after 15 months of *H. pylori* infection [6]. In contrast, IL-4 deficient mice show a skewed Th1 immune response to *H. pylori* colonization [7]. Thus, IFNγ may play an important role in initiating the mucosal damage observed during gastritis. Direct support for this hypothesis emerged from our recent in vivo mouse studies that investigated the effect of exogenous IFNγ infusion on the gastric mucosa [5]. After a seven-day infusion of IFNγ, mice show significant inflammation and develop mucous gland metaplasia, hypergastrinemia and suppressed somatostatin levels [5]. These results confirm that gastric changes observed during *Helicobacter* infection are due to a Th1-mediated gastritis.

Cytokines released during inflammation initiate a cascade of events resulting in metaplasia and neoplastic transformation of the gastric mucosa. IFNγ stimulates the release of proinflammatory cytokines such as tumor necrosis factor alpha (TNFα) and interleukin-1 beta (IL-1β. In vitro studies using canine antral G-cells and fundic canine and rabbit D-cells demonstrated that TNFα and IL-1β stimulate the release and gene expression of gastrin while inhibiting somatostatin secretion [5,8,18–23]. More recently, using isolated mouse gastric cells, we showed that IFNγ stimulates the release of gastrin in part by suppres-

sing somatostatin secretion [5]. In contrast, the Th2 cytokine IL-4 significantly stimulates somatostatin release that results in suppression of gastrin secretion [5]. Somatostatin plays a major role in the negative feedback mechanism that suppresses gastric acid. It is clear that suppression of somatostatin results in the failure of the normal feedback mechanism to proceed. Thus, it is important to determine the mechanism by which somatostatin is suppressed during gastritis.

Histamine, released from the enterochromaffin-like (ECL)-cells, stimulates gastric acid secretion by acting at the H2 receptors on the parietal cells. Histamine also augments gastric acid secretion by eliminating the inhibitory effect of somatostatin on the G- and parietal cells [31,32]. Studies using enriched suspensions of fundic ECL-cells isolated from rat and rabbit show that histamine is capable of inhibiting its own synthesis and release via H3 autoreceptors [28,33]. Moreover, histamine suppresses somatostatin secretion in isolated mouse stomach and rat fundic mucosa via H3 receptors [31,32]. *N*-α-methyl histamine is a histamine metabolite, which is produced in the stomach of *H. pylori* infected patients [34]. In mice, *N*-α-methyl histamine was shown to stimulate both acid secretion and gastrin secretion [34–36] while suppressing somatostatin release [31,32]. We have shown that gastrin infused into gastrin-deficient mice is sufficient to suppress somatostatin [37]. Therefore, since inflammation increases gastrin and gastrin stimulates histamine release [5,8, 18–23], it is likely that gastrin suppresses somatostatin by releasing histamine [27,28]. Elevated histamine levels, in turn, suppresses somatostatin via H3 receptors on D-cells.

1.4. Hypergastrinemia and H. pylori-induced carcinogensis

Gastrin, a hormone released from antral G-cells, was first characterized by its ability to stimulate acid secretion. In addition to its role as a regulator of acid secretion, gastrin also stimulates proliferation of the gastric mucosa [38,39]. It is believed that hypergastrinemia in response to *H. pylori* infection is an important factor influencing the development of gastric cancer [3]. Recently, genetically engineered mouse models that overexpress gastrin peptide have permitted analysis of the role of gastrin in the development of gastric cancer. The insulin-gastrin (INSGAS) transgenic mouse overexpresses the human gastrin gene in β-cells of the islet pancreas [39]. The resulting hypergastrinemia in the INS-GAS mouse stimulates proliferation of the gastric acid-secreting mucosa. With advanced age (1–2 years), these mice spontaneously develop corpus atrophy and subsequently cancer in the fundus [39,40]. Moreover, infection with *H. felis* accelerates the progression to gastric cancer [41]. Collectively, these studies suggest that *Helicobacter* synergizes with hypergastrinemia to accelerate the malignant transformation.

Nevertheless, it is important to note that there are several mouse models that also spontaneously develop gastric cancer independent of *Helicobacter* infection. These models tend to develop cancer in the antrum of the stomach. Such murine models include genetically engineered mice in which the TFF1, Smad4 or RUNX3 genes have been deleted [42–45]. Expression of a mutated form of the IL-6 receptor subunit gp130$^{757F/F}$ has also been found to cause gastric cancer in the antrum [25]. Interestingly, both the gp130$^{757F/F}$ and TFF1 mouse models are hypogastrinemic [25,42]. Furthermore, we find that the gastrin-deficient mice, also spontaneously develop antral gastric cancer (unpublished observation). Therefore, overall hypergastrinemia and *Helicobacter* infection are not the only factors that cause malignant transformation in the stomach. In fact bacterial infection and hypergastrinemia may be merely triggers for a sequence of pathophysiologic changes resulting in neoplastic transformation of the gastric mucosa.

1.5. Novel treatments for H. pylori infection

The role of somatostatin in modulating an immune response has been studied in the spleens of mice infected with Schistosoma mansoni [46–48]. The parasite generates a Th2 immune response by inducing granuloma-based macrophages to secrete IL-4 and somatostatin [49]. It was shown that IL-4 released from granulomas blocks IFNγ expression [47,48]. We have shown recently that a similar immunoregulatory circuit exists in the stomach by infusing IL-4 and preventing *Helicobacter*-induced gastritis, a response mediated by the release of somatostatin and suppression of IFNγ expression [5].

Normalizing the balance between Th1 and -2 immune responses is a mechanism proposed to resolve tissue damage and associated complications at mucosal surfaces [46]. Coinfection of mice with both *Helicobacter* and a helminth (*Heligmosomoides polygyrus)* was sufficient to attenuate the Th1 immune response normally generated by the bacteria [46]. Parasitic and helminth infections activate a Th2 immune response, raising the possibility that counterbalancing a Th1-mediated infection with a Th2 cytokine might be sufficient to prevent *Helicobacter* gastritis.

While IFNγ (Th1 cytokine) causes gastric mucosal damage and changes in the neuroendocrine cell population, we find that IL-4 (Th2 cytokine) blocks the inflammatory response caused by *Helicobacter* through restoration of somatostatin levels in the stomach [5]. IL-4 directly stimulates somatostatin release through IL-4 receptors present on canine D-cells [5]. Furthermore, stimulation of somatostatin by IL-4 is required to reduce inflammatory T-cells recruited to the stomach during *Helicobacter*-induced gastritis. IFNγ-expression, hypergastrinemia and bacterial colonization were also inhibited by IL-4. However, the inhibition did not occur in IL-4 infused somatostatin-deficient mice infected with *Helicobacter* [5]. Thus, we

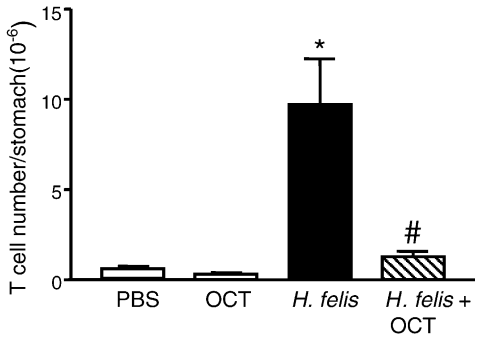

Fig. 3. Octreotide (OCT) resolves *H. felis* gastritis. The number of T-cells (CD3+) after a two-month *H. felis* infection was analyzed by FACS. Shown is the mean ± S.E.M. for eight mice. $^{*}P < 0.05$ versus OCT alone treated mice, $^{\#}P < 0.05$ versus *H. felis* treated mice (unpaired *t*-test, Reproduced with permission from PNAS [5]).

concluded that somatostatin was both necessary and sufficient to prevent *Helicobacter*-induced gastritis [5]. These results raised the intriguing possibility that somatostatin or its anlogs could directly suppress *Helicobacter* gastritis. Therefore, we attempted to treat *Helicobacter*-infected mice with the somatostatin analog octreotide that has a significantly longer serum half-life than somatostatin (hours rather than minutes). Healthy animals were infected with *Helicobacter felis* for two months, then injected daily for four weeks with octreotide. Octreotide treatment reduced T-cell numbers by 80% indicating reduced inflammation (Fig. 3). Octreotide also reduced *Helicobacter* colonization, IFNγ expression and plasma gastrin levels. Interestingly, reduced somatostatin levels returned to baseline correlating with the resolution of the infection [5]. Therefore, octreotide and other somatostatin analogs may be relevant and useful in treating *Helicobacter* infections in humans, preventing further mucosal damage and facilitating the generation of a Th2 response with effective antibody production [5].

Establishing homeostasis between the Th1 and Th2 immune response to fight disease has been studied in a number of conditions including Crohn's disease, ulcerative colitis and inflammatory bowel disease [50,51]. A number of studies have explored the applications of probiotic bacteria in the prevention and treatment of these gastrointestinal conditions. Lactic acid reducing bacteria and their pro-bioactive secreted substances have been beneficial in the gastrointestinal tract. For example, genetically modified *Lactobacillus lactis* secreting interleukin 10 has been examined as a treatment for inflammatory bowel disease [50]. In addition, TNFα that plays an important role in the pathogenesis of intestinal inflammation in Crohn's disease, is reduced by *Lactobacillus casei* and *Lactobacillus bulgaricus* [51]. Therefore, probiotic bacteria can modulate the local production of proinflammatory cytokines. The effects of such probiotic bacteria in the treatment of *Helicobacter* gastritis requires further investigation.

1.6. The use of somatostatin analogs for the treatment of Helicobacter-induced gastritis

The short-half life of somatostatin makes it unsuitable for routine treatment. For this reason, various somatostatin analogs have been developed and used in clinical practice. Octreotide is a long acting somatostatin analog that is routinely used for the treatment of acromegaly [52]. In addition, octreotide is also used for the treatment of upper gastrointestinal bleeding associated with peptic ulcer disease [53] and eradication of *H. pylori* colonization [54]. The production of the octapeptide somatostatin analog lanreotide has been shown to have a prolonged-release and has also been used to treat acromegaly [52]. However, the long-term effects of these somatostatin analogs include gallstone development and chronic hypoacidity that result in gastric inflammation [55,56]. Moreover, the exact mechanism of action of these analogs are not well defined and often an infusion will target cells other than those in the stomach and thus provides the rationale for the development of more specific somatostatin analogs.

Neuroendocrine tumors often arise from enterochromaffin cells and are widely distributed in small intestine, lung, pancreas, colon and stomach. Interestingly, the majority of these neuroendocrine tumors express somatostatin receptors, providing the basis for treatment of these tumors with somatostatin analogs that will respond to the inhibitory actions of somatostatin [57]. Recently, the introduction of SOM-230 from Novartis is a compound, which binds with high-affinity to somatostatin receptor subtypes 1, 2, 3 and 5 with a favorable half-life of 24 h. SOM-230 is currently under investigation as a possible treatment for Graves' ophthalmopathy but its effects on *Helicobacter*-induced gastritis have yet to be tested [58]. It is also important to note that somatostatin is but one therapeutic option. Our study raises the possibility of using other counter-regulatory cytokines as useful therapies [5] that may stimulate somatostatin, but this remains to be tested.

2. Summary

In the normal stomach, somatostatin inhibits gastrin and acid release. However, IFNγ removes the inhibitory effect of somatostatin by suppressing D-cell function during inflammation (Fig. 4A). Systemic administration of a synthetic analog of somatostatin, such as octreotide, or infusion of the Th2 cytokine IL-4 increases the circulating levels of somatostatin. The Th1/Th2 equilibrium is re-established through reduction of IFNγ, inflammation and subsequently gastrin expression (Fig. 4B). In light of our recent work, we have shown that the gastric immune system and acid regulatory peptides are not separate entities but rather, are part of an immunoregulatory circuit. In particular, establishing a link between somatostatin and the immune response may facilitate the generation of a Th2

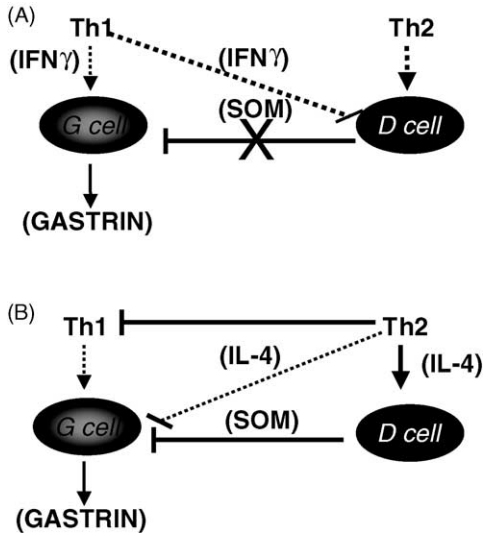

Fig. 4. Model for immune regulation of gastrin and somatostatin secretion. (A) Gastrin is stimulated by the release of IFNγ during a Th1 immune response to bacterial colonization. IFNγ down-regulates the release of somatostatin by inhibiting the D-cell and stimulating gastrin release (dotted line shown representing both direct and indirect pathways). This result relieves the inhibitory effect of somatostatin on gastrin. (B) Somatostatin is released in response to IL-4 and can mediate the resolution of *Helicobacter*-induced gastritis by suppressing Th1 immune cells. The inhibitory effect of IL-4 on the G-cell occurs acutely by stimulating the release of somatostatin. However, in the absence of somatostatin (SOM/mice), a delayed inhibitory effect of IL-4 on the G-cell was revealed (dotted line shown representing both direct and indirect pathways the G-cell). (Reproduced with permission from PNAS). [5]

response, development of novel therapies and possibly vaccines for the treatment of *Helicobacter* gastritis.

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