Inflammation and Cancer

III. Somatostatin and the innate immune system

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Zavros, Yana, John Y. Kao, and Juanita L. Merchant. Inflammation and Cancer II. Somatostatin and the innate immune system. Am J Physiol Gastrointest Liver Physiol 286: G698–G701, 2004; 10.1152/ajpgi.00529.2003.—In the stomach, somatostatin is secreted from D cells and is a potent inhibitor of gastrin-induced acid secretion. During bacterial infection, somatostatin expression and release are suppressed. As a result, gastric infection often induces hypergastrinemia that, in turn, stimulates gastric acid secretion, the stomach’s most important antimicrobial agent. There are an abundance of data showing that inflammatory cytokines regulate somatostatin in innate and neural cells. However, it was not until recently that the immunoregulation of gastric somatostatin was studied in vivo. This theme article discusses the role of somatostatin as an immunoregulatory peptide during gastritis.

Helicobacter; gastritis; hypergastrinemia; interferon-γ; interleukin-4

Somatostatin was first identified in 1973 in the hypothalamus as growth hormone release inhibitory factor (6). In 1975, Arimura et al. (2) described the first radioimmunoassay for somatostatin. With a functioning radioimmunoassay, the tissue distribution and multiple molecular forms of somatostatin were documented. Since then, it has been revealed that somatostatin is not only produced in the hypothalamus but is present in a variety of endocrine and nonendocrine tissues. Moreover, its effect on each target cell is generally to inhibit peptide function. In the central nervous system, somatostatin acts as a neurotransmitter, whereas in peripheral tissues, it regulates endocrine and exocrine secretion and modulates motor activity in the gastrointestinal tract (17). Somatostatin also regulates hematopoietic cells involved in the immune defense pathways of several tissues including the stomach (22, 24).

In the stomach, somatostatin is the primary inhibitor of gastrin-stimulated acid secretion. Gastrin, released from antral G cells, is a major regulator of parietal cell 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 parietal cells (18). Increased acid levels then stimulate putative chemoreceptors on antral 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 involving somatostatin (17). During gastric bacterial infection, this negative feedback mechanism does not occur.

Chronic inflammation of the gastric mucosa (chronic gastritis) is caused by Helicobacter pylori or bacterial overgrowth in the hypochlorhydric stomach (5, 25). Infection with H. pylori mounts a T-helper (Th)1 immune response characterized by the recruitment of T lymphocytes expressing IFN-γ, TNF-α, and IL-1β but low levels of Th2 lymphocytes expressing IL-4 and IL-5 (15). IFN-γ-null mice do not mount an inflammatory response even after 15 mo of H. pylori infection (19). In contrast, mice deficient in IL-4 exhibit a skewed Th1 immune response (19). Thus it is believed that IFN-γ plays a pivotal role in orchestrating the mucosal damage observed during gastritis.

Chronic gastritis is also accompanied by reciprocal changes in the gastric neuroendocrine cell populations that regulate acid secretion (16). The number of G cells increases, whereas D cells decrease rendering Helicobacter-infected subjects hypergastrinemic (16). Although reciprocal changes between gastrin and somatostatin occur during bacterial colonization, the link to the immune system has been poorly defined. Recently, we have shown that the gastric immune system and acid regulatory peptides are not separate entities but rather, are part of an immunoregulatory circuit. This article summarizes the role of somatostatin in the gastric innate immune system.

Somatostatin and Its Receptor Family

Somatostatin is synthesized from a 92-amino acid preprosomatostatin precursor molecule. Mammalian preprosomatostatin is processed predominantly at the COOH-terminal segment to generate two biologically active forms, somatostatin-14 and somatostatin-28. Both bioactive forms are synthesized in unpredictable amounts by somatostatin-producing cells due to differential precursor processing. Somatostatin-14 is predominantly found in pancreatic islets, stomach, peripheral, and enteric neurons. Somatostatin-28 accounts for 20–30% of the total somatostatin in brain and is the major immunoreactive form in the small intestine (21).

Molecular characterization of rodent and human somatostatin receptors has resulted in the identification of five different receptors (sstr1–5) that all belong to the G protein-coupled receptor superfamily. They are encoded by five different genes and are highly conserved between species (for example, sstr1 of mouse and human share 99% sequence identity). Within the same species, there is a 45–61% sequence identity between different receptor subtypes. Both somatostatin-14 and somatostatin-28 bind to sstr1–4 with equal affinity. However, somatostatin-28 has a higher affinity for sstr5 (10).

All five somatostatin receptors have been identified throughout the central nervous system and endocrine and exocrine glands. However, sstr2 is the predominant receptor localized on parietal and ECL cells, suggesting that it is through this receptor that somatostatin inhibits gastric acid secretion (1). Studies using the sstr2 knockout/ lacZ knockin mice showed that the majority of epithelial cells in the
midregion of the fundus express sstr2 and were identified as parietal cells by positive H^+-K^+-ATPase immunostaining (1). In addition, ECL cells located in the fundus and pylorus also express these sstr2 receptors (1). Consistent with its location, the sstr2 knockout mouse exhibits high gastric acid secretion due to a lack of a somatostatin-induced inhibitory effect on parietal and ECL cells (13). Somatostatin also inhibits IFN-γ release from T cells (8). SSTR2 is the predominant receptor subtype expressed by granuloma lymphocytes isolated from mice with schistosomiasis infection (8). In particular, the sstr2A isoform accounts for 99% of inflammatory cell sstr2 mRNA and mediates the inhibitory effect of somatostatin on T cell IFN-γ release (8).

Initial studies focused on the ability of somatostatin to inhibit acid secretion by suppressing adenyl cyclase/cAMP-dependent intracellular pathways. Subsequently, it was recognized that somatostatin could also act further downstream in the cell-signaling cascade. For example, one mechanism of somatostatin action involves inhibition of ERK activity, Elk-1 phosphorylation, and transcriptional activation of c-Fos and c-Jun (20). Somatostatin is also known to inhibit both basal and stimulated gastrin gene expression (3). EGF stimulation of gastrin transcription is mediated by an EGF response element (gERE) that lies between −68 and −54 in the gastrin promoter (14). Inhibition of the response by somatostatin is mediated by a cis-regulatory element located 5’ to gERE at −82 to −69 (3). The putative somatostatin response element contains the E-box CATATGG, which typically binds helix-loop-helix transcription factors (3).

GENETICALLY ENGINEERED MOUSE MODELS TO STUDY SOMATOSTATIN-INHIBITORY PATHWAYS

Originally developed to investigate the role of somatostatin as a mediator of growth hormone effects (11), somatostatin-deficient mice were found by our group to show higher circulating gastrin levels compared with wild-type mice (24). In contrast to somatostatin-deficient mice, sstr2 null mice do not show changes in circulating gastrin peptides (13). Collectively, these two results suggest that somatostatin plays a critical role in suppressing basal levels of gastrin (3) but that the inhibition of gastrin release is not mediated through the sstr2 receptor. In contrast to the sstr2-null mice, somatostatin null mice show the same basal gastric acid levels as those observed in wild-type C57BL/6 mice (24). So, in essence, the somatostatin effect on parietal cells and acid secretion occurs through sstr2, whereas the regulation of gastrin by somatostatin occurs through one of the other receptor family members. During Helicobacter felis infection in wild-type mice, we observed hypochlorhy-

![Fig. 1. Reciprocal changes in gastrin and somatostatin (SOM) release by IFN-γ from the isolated mouse gastric cells. The amount of gastrin released from gastric cells isolated from wild-type (SOM+/+) (A) and somatostatin null (SOM−/−) (B) mouse stomachs in response to treatment with 100 nM IFN-γ or IL-4 for 6, 12, 18, and 24 h. The amount of SOM released from gastric cells isolated from SOM+/+ (C) and SOM−/− (D) mouse stomachs in response to 100 nM IFN-γ or IL-4 for 6, 12, 18, and 24 h. The results are expressed as the % initial cell gastrin (350 pmol/l) or SOM (200 pmol/l) content. *P < 0.05, **P < 0.005 vs. PBS, n = 3 independent experiments performed in triplicate (24) (reproduced with permission from Proc Natl Acad Sci USA, 2003).]
IL-4 directly stimulates somatostatin release through IL-4 receptors present on canine fundic D cells (24). Furthermore, stimulation of somatostatin by IL-4 is required to reduce inflammatory T cells recruited to the stomach during Helicobacter-induced gastritis. IFN-γ 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 (24). Thus we concluded that somatostatin was both necessary and sufficient to prevent Helicobacter-induced gastritis (24). However, it is important to note that the levels of other proinflammatory cytokines (e.g., TNF-α and IL-1β) that are also elevated in the inflamed gastric mucosa were not examined in the study. Indeed, IL-1β or TNF-α has been shown to directly inhibit parietal cell function in studies using primary gastric cell preparations (23). Thus a major role of these cytokines, which are upregulated in response to bacterial infection, is likely to suppress acid secretion. The predominant Th2 cytokines elicited during helminth treatment of gastritis were IL-4, IL-10, and transforming growth factor (TGF)-β but not IL-5, IL-6, or IL-12 (9). Regulatory T cells are thought to modulate H. pylori-mediated inflammation because IL-10 null mice mount a more aggressive inflammatory response to the organism than normal mice (7, 19). However, the mechanism by which IL-10 (regulatory T cells) and TGF-β (Th3) oppose Th1-mediated inflammation has yet to be examined. Whereas experiments performed in the somatostatin-deficient mice demonstrate that somatostatin is both necessary and sufficient to resolve Helicobacter gastritis, treatment with Th2 cytokines other than IL-4 has not been investigated.

In summary, in the normal stomach, somatostatin inhibits gastrin release. However, IFN-γ removes the inhibitory influence of somatostatin by suppressing its release from the D cells during inflammation (Fig. 2A). 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 reestablished through the reduction of IFN-γ, inflammation, and, subsequently, gastrin expression (Fig. 2B). It is widely accepted that the neuropeptide somatostatin is an important regulator of the immune system in a number of tissues. However, the focus of somatostatin in the stomach has traditionally been on its ability to regulate gastric acid and gastrin secretion. In light of our recent results, we have shifted our focus from somatostatin as a regulator of acid secretion to its role as an important regulator of the innate immune system during gastritis (24). In particular, establishing a link between somatostatin and Th2 cytokines provides a possible explanation as to why Helicobacter gastritis is a Th1-predominant event. Establishing a critical link between somatostatin and the immune response may facilitate the generation of a Th2 response, development of novel therapies, and possibly vaccines.

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