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Authors
Kemmerly, Thomas
Kaunitz, Jonathan D

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Gastroduodenal Mucosal Defense

Thomas Kemmerly[d] and **Jonathan D. Kaunitz**[a,b,c,e,f]

[a]Greater Los Angeles Veteran Affairs Healthcare System, WLAVA Medical Center, Los Angeles, CA, 90073

[b]Department of Medicine, UCLA School of Medicine, Los Angeles, CA 90024

[c]Department of Surgery, UCLA School of Medicine, Los Angeles, CA 90024

[d]Cedars-Sinai Medical Residency Program, Los Angeles, CA 90048

[e]CURE: Digestive Diseases Research Center Department of Medicine, Los Angeles, CA, 90073 USA

[f]Brentwood Biomedical Research Institute, Los Angeles, CA, 90073 USA

Abstract

Purpose of review—To review recent developments in the field of gastroduodenal mucosal defense.

Recent findings—Research in the field of gastroduodenal mucosal defense has focused on continued elucidation of molecular mechanisms that protect the mucosa and influence healing at the cellular level. Review of literature over the past year reveals that familiar proteins and mediators such as nitric oxide, Toll-like receptors, nucleotide-binding oligomerization domain-containing proteins, β-defensins, macrophages, dendritic cells, mucins, autophagy, and the influence of aging and diet are still subjects of study, but also brings into light new processes and mediators such as dual oxidases, defense against radiation injuries, and novel proteins such as ZBP-89.

Summary—These new published findings contribute to our overall understanding of gastroduodenal defense and suggest innovative avenues of future research and possible novel therapeutic targets.

Keywords

gastrointestinal defense; mucins; innate immune system; autophagy; toll-like receptors

Address correspondence to: Jonathan D. Kaunitz, MD, Building 114, Room 217E, West Los Angeles VAMC, Los Angeles, CA 90073, +1 310 268 3879 (phone), +1 310 268 4811 (fax), jake@ucla.edu.

Conflicts of Interest:
None

Introduction

The gastroduodenal mucosa has multiple defense mechanisms to protect itself from injury due to oxidative stress, infection-induced injury due to *H. pylori*, ischemic and reperfusion injuries, and drug-induced injury primarily due to non-steroidal anti-inflammatory drugs (NSAIDs). During the past year, we have reviewed recent developments in gastroduodenal defense that focused on the mechanisms underlying many of the now well-known components of mucosal defense such as the innate immune system, antioxidants, autophagy and the molecular mechanisms underlying mucin secretion. Although some well-known molecules and mediators are discussed such as nitric oxide, Toll-like receptors, nucleotide-binding oliogmerization domain-containing proteins, β-defensins and mucin, there are new peptides, proteins and mediators to discuss.

Oxidative Stress

Oxidative stress is defined as an imbalance in the body's ability to cope with reactive oxygen species (ROS) secondary to increased production or decreased detoxification. ROS are injurious and pro-inflammatory due to DNA damage, lipid peroxidation, oxidation of amino acids, and oxidation of enzymatic co-factors. How oxidative stress affects the pathogenesis of many diseases is well established. The complex interplay among many of the factors which promote and prevent oxidative stress has, once again, been the focus of much research throughout the previous year, which we will discuss below.

The Aging Gastric Mucosa

Studies continue to examine why the aging gastric mucosa is less able to combat oxidative stress than is the young gastric mucosa. Liu *et al.* examined the gastric mucosa of male patients aged 25–40 years and 60–85 years following subtotal gastrectomy. They discovered increased resting dilation of the submucosal arterioles, decreased response to vasodilators, and decreased expression of antioxidant proteins in the elderly stomachs. The authors concluded that gastric vascular dysfunction and senescence may be associated with increased oxidative stress and decreased antioxidative defense as part of the aging process [1].

Nitric Oxide (NO)

NO is an important component of the gastroduodenal defense system due to its vasodilatory properties and its inhibitory effects on gastric acid secretion. It is synthesized via the inducible NO synthase (iNOS) from L-arginine. The polyamine spermine can inhibit iNOS protein expression, preventing NO production. Chatuverdi *et al.* demonstrated that spermine oxidase, a protein induced by *H. pylori* in macrophages, back-converts spermine to spermide, reducing harmful spermine concentrations and ameliorating the inhibitory effect of spermine on the innate immune system [2▪].

Dual Oxidases (DUOX)•

Dual oxidases are conserved reduced nicotinamide adenine dinucleotide phosphate oxidases that produce H_2O_2 at the epithelial surface. Their roles in cellular interactions with microbes

had not been studied in higher vertebrates. Grasberger *et al.* demonstrated that the DUOX enzyme complex prevents gastric colonization by *Helicobacter felis* in mice, restricting microbial colonization via generation of the antimicrobial oxidant H_2O_2 [3▪].

Radiation-Induced Gastrointestinal Damage *(RIGD)*

Ionizing radiation induces DNA damage in small intestinal epithelial stem cells via activation of p53 pathways, increasing production of reactive oxygen species. Ito *et al.* studied the effects of ascorbic acid administration in preventing RIGD in mice, reporting that administration of ascorbic acid 3 days prior to radiation exposure, followed by another dose 8 hours before exposure, followed by continued administration for 7 days after radiation exposure was associated with a 100% survival rate. This compared to a maximum of 20% survival rate in mice treated with ascorbic acid 3 days prior to radiation exposure, those treated with a single dose 8 hours before exposure or those treated post-exposure [4]. Blockade of p53 is not a viable strategy for prevention of RIGD since p53 maintains genomic stability. Takemura *et al.* showed that Toll-like receptor 3 (TLR3) is critical for the pathogenesis of RIGD, suggesting that its blockade may ameliorate RIGD [5].

The Innate Immune System

The innate immune system is a non-specific subsystem of the immune system that is composed of the mechanisms by which the hosts defends itself from infection in a non-specific manner. The cells and components of the innate immune system respond to pathogens in a generic manner.

Toll-like Receptors (TLRs)

Toll-like receptors are a class of membrane-spanning proteins capable of detecting microbial breach of the gastrointestinal mucosa. Salmonella flagellin, is a TLR5 ligand that induces the TLR5 pathway and the caspase-1 pathway. The TLR5 pathway attenuated intestinal inflammation but paradoxically promoted bacterial colonization in the cecum and increased systemic inflammation. The caspase-1 pathway reduced intestinal inflammation while also controlling systemic infection [6].

Sun *et al.* demonstrated that *H. pylori* stimulated bone marrow-derived dendritic cells via upregulation of TLR2. They also reported that TLR2 knockout mice had lower gastric *H. pylori* colonization with more severe gastric immunopathology compared to wild-type mice, indicating that *H. pylori* mediate immune tolerance through TLR2-derived signals and inhibits Th1 immunity, thus evading host defense [7▪]. Trevisi *et al.* report that TLR2, 3 and 4 expression in the gastric mucosa of young pigs varies in expression with location in the stomach as well as whether the piglets were suckling or weaning [8]. In a similar fashion, they demonstrated that the polymeric immunoglobulin receptor, which is responsible for the transport of secretory immunoglobulins, differed in expression according to its location in the gastric mucosa and also according to suckling or weaning status.

Intestinal epithelial cells have an innate hypo-sensitivity to bacterial products. Sham *et al.* reported that deletion of the Single Ig IL-1 Related Receptor (SIGIRR) in mice, which

negatively regulates interleukin-1 and TLR signaling, enhanced susceptibility to infection compared with wild-type mice [9▪▪].

β-Defensin

β-Defensins are antimicrobial peptides, which, as important components of the innate immune system, are implicated in the resistance of epithelial surfaces to microbial colonization. Sun *et al.* studied the effects of repeated *Campylobacter jejuni* infections in a mouse model in order to study the mechanisms of post-infectious functional bowel syndrome. They reported that repeated infections increased the number of pro-inflammatory mediators and receptors, including β-defensin and TLR-4 [10].

Impairment of innate immunity may facilitate opportunistic infections. Kwashima *et al.* reported that a chronic illness (type 2 diabetes) in mice decreased β-defensin-3 mRNA expression. They reported that physically restrained mice and mice after administration of exogenous glucocorticoids displayed similar reductions in β-defensin mRNA expression [11▪▪]. Work by Gáscer *et al.* highlights the importance of these findings. They demonstrated that human intestinal epithelial cells expressed β-defensin in response to attempted infections with opportunistic candida species (Figure 1) [12]. Taken together, the studies support the hypothesis that chronic stress may impair β-defensin function, and thus facilitate opportunistic infection.

Nucleotide-binding oligomerization domain-containing protein (NOD)

NOD2 functions as an intracellular sensor for microbial pathogens that contributes to epithelial defense and inflammation. Two groups helped to elucidate possible mechanisms of NOD2-mediated homeostasis over the past year. Jiang *et al.* reported that *Nod2* knockout mice had significantly less intraepithelial lymphocytes than did wild-type mice [13]. Brian *et al.* confirmed that NOD2 induces microRNA-29 expression in human dendritic cells, which has diverse effects on the inflammatory cascade, most notably a suppression of interleukin-23. These studies provide valuable insight into the effects of NOD2 on host defense mechanisms [14]. The NOD-like receptor protein 3 (NLRP3) recruits multiple proteins to form the NLRP3 inflammasome which facilitates interlukin-1β maturation. Alipour *et al.* discovered that *Nlrp3* deficient mice infected with *Citrobacter rodentium* developed severe colitis. This colitis and dissemination of bacteria into the mesenteric lymph nodes were ameliorated by IL-1β administration [15▪]. They also demonstrated that IL-1β administration in wild-type mice had increased bacterial penetration and mucosal barrier disruption. The findings suggests that a balanced cytokine response is necessary for innate mucosal defense.

ZBP-89

Little is known about how enterochromaffin cells sense the luminal environment and respond to pathologic stimuli. ZBP-89 is a butyrate-inducible zinc finger transcription factor that binds to GC-rich DNA elements. Essien *et al.* investigated whether deletion of ZBP-89 from the GI tract epithelium of mice increased susceptibility to pathogens such as *Salmonella typhimurium.* They described that ZBP-89 is required for expression of the *Tph1* gene and subsequent production of serotonin (5-HT) in response to bacterial infection in

mice. *Zbp-89* knockout mice were more susceptible to developing sepsis and more prone to infection with *S typhimurium* [16▪].

Macrophages

Macrophages are immune cells that function as part of the innate immune system and as part of the adaptive immune system. During this past year, Marcial *et al.* discovered that a polysaccharide derived from *Streptococcus thermophiles*, EPS1190, significantly increases the proliferation rate of stomach lining cells while increasing macrophages phagocytosis, which increased secretion of proinflammatory cytokines [17]. Shea-Donohue *et al.* demonstrated that enteric macrophages upregulate a protease inhibitor, serpinB2, as a protection mechanism against apoptosis induced by enteric nematode infections [18▪].

Dendritic Cells

Dendritic cells are specialized antigen presenting cells that process antigens in order to present them to T-cells, acting as messengers of the innate and adaptive immune systems. Satpathy *et al.* revealed that the protein Notch2 controlled the terminal stage of dendritic cell differentiation. Their work suggests that these Notch2-dependent dendritic cells may be the source of IL-23, a vital factor in cell survival after infection with attaching-and-effacing bacteria [19].

Diet

Several research groups over the past year have investigated the influence of diet on innate antimicrobial gastrointestinal defense proteins. Zeng *et al.* determined that butyrate, a major metabolite of fiber, could induce β-defensin and the leukocyte antimicrobial peptide, protegrin, expression in pigs, suggesting that host defense-inducing food-derived molecules can serve as novel alternatives to antibiotics in augmenting innate immunity [20]. Sunkara *et al.* report that the essential cellular mediator, cyclic AMP, which poorly induces β-defensin expression in and of itself, works synergistically with butyrate to promote β-defensin expression in chickens [21].

Hill *et al.* showed that human milk hyaluronan, a glycosaminoglycan polymer expressed in virtually all mammalian tissues, increased intracellular expression of β-defensin and subsequent resistance to salmonella [22].

Dietary intake also involves accidental ingestion of toxins such as the biotoxin okadaic acid, which accumulates in shellfish, causing diarrheal illness if ingested. Ehlers *et al.* demonstrated that the protein P-glycoprotein is critical for active efflux of okadaic acid at low doses [23]. If P-glycoprotein eliminates the effects of other toxins, it may turn out to be another important host defense component.

Dietary Zinc

Zinc, an essential mineral present in numerous proteins expressed in multiple organs across phylogeny, is essential for the function of numerous enzymes. Mei et al. studied the anti-ulcerogenic effect of a zinc-curcumin complex on the healing of acetic acid-induced gastric ulcers in rats. In ulcerated gastric mucosa, zinc-curcumin restored depressed levels of

glutathione and superoxide dismutase and also downregulated matrix metaloproteinase-9. The effect of the complex was greater than that of curcumin alone [24]. Liu et al. reported that a moderate content of dietary zinc in piglet feed was strongly pro-proliferative; it increased colonic crypt area and also increased mucus production [25].

Mucin

Mucin secretion, strongly implicated in gastroduodenal mucosal defense, serves multiple functions, including protection of the epithelial cells from digestive enzymes, acids, and abrasion from food particles, and pathogens. Mucin Muc2, a heavily O-glycosylated glycoprotein, is the primary mucin expressed in the intestine. Zarepour *et al.* report that Muc2-deficient mice had greater cecal and liver pathogen burdens, mortality rates, and barrier disruption than did wild-type mice [26].

Additional animal and clinical studies were published last year regarding the influences of medication on mucin production. Yamamoto *et al.* reported that luminal mucin concentration within the GI tract was most markedly reduced three days after administration of cisplatin, returning to baseline by day eleven (Figure 2) [27]. IIjima *et al.* reported that ten days of aspirin treatment significantly increased the rate of gastric mucus secretion with a concomitant and significant decrease in the gastric acid secretion rate /mucus secretion rate. Subjects with severe gastropathy failed to significantly increase gastric mucus concentrations and significantly decrease the gastric acid/mucus ratio [28].

Toxins also affect the concentration of mucus within the GI tract. Wan *et al.* report that Fusarium mycotoxins upregulate the secretion of MUC5AC and MUC5B, suggesting that these mucins may contribute to mucosal defense against ingested toxins [29▪▪].

Autophagy

Autophagy is a cellular degradation system for long-lived proteins, mitochondria, peroxisomes and bacteria. It is an essential component of immune homeostasis although little is known about its function in specific cell types. Chang *et al.* noted that in mice, the gastric epithelium is more resistant to shigella invasion than the intestinal epithelium. They reported the novel finding that non-inflammatory epithelial shedding, Paneth cell degranulation, and autophagy comprised a novel host defense system that they termed “epithelial barrier turnover.” [30▪▪]. The loss of autophagy-related gene 16L (ATL16L1) was associated with impaired Paneth cell function and hypersecretion of IL-1β and IL-18 from macrophages. Clues as to the genetic mechanism underlying autophagy were reported by Conway *et al.*, who demonstrated, for the first time, that ATG16L1 regulates autophagy in intestinal epithelial cells and is required for bacterial clearance [31].

P38α

P38 mitogen-activated protein kinases, a class of proteins responsive to stress stimuli, are implicated in cell differentiation, apoptosis and autophagy. P38α protects against attaching and effacing bacteria by regulating T-cell recruitment, but its exact impact on immune responses had been unclear. Shim *et al.* reported that mice deficient in p38α in T-cells, but

not in macrophages or dendritic cells had an impaired ability to clear *Citrobacter rodentium* infection. These mice also had decreased inflammatory cytokine expression and T-cell recruitment, which could be rescued with exogenous interferon-γ administration. The investigators concluded that a p38α-mediated inflammatory response is necessary for intestinal host defense against attaching and effacing bacteria [32▪▪]. Caballero-Franco *et al.* reinforced the importance of p38α in the intestinal epithelium as they reported that loss of p38α aberrantly activates multiple signalling proteins with resultant exaggerated epithelial proliferation, inadequate differentiation, and sensitivity to apoptosis [33].

Conclusion

Well-studied proteins and mediators such as nitric oxide, Toll-like receptors, nucleotide-binding oliogmerization domain-containing proteins, β-defensins and mucins are further implicated in the mechanism of gastroduodenal defense. Newly discovered proteins and mediators such as ZBP 89, p38α, and serpin B2 have been implicated as well. Enhanced knowledge of these defense mechanisms will help in the development of novel interventions targeted at maintaining the integrity of the GI mucosa.

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Key bullet points

- Throughout the past year, further steps have been taken towards understanding the mechanisms behind the initiation of the inflammatory cascade which results in gastroduodenal mucosal damage.
- Several studies throughout the past year have addressed the mechanisms by which the damaged gastrointestinal mucosa repairs itself
- Mucin, with its many isoforms, plays a critical role in maintaining the integrity of the gastroduodenal mucosa.
- Specific dietary factors which influence gastroduodenal mucosal defense have been identified over the past year, leading to further avenues of potential research.

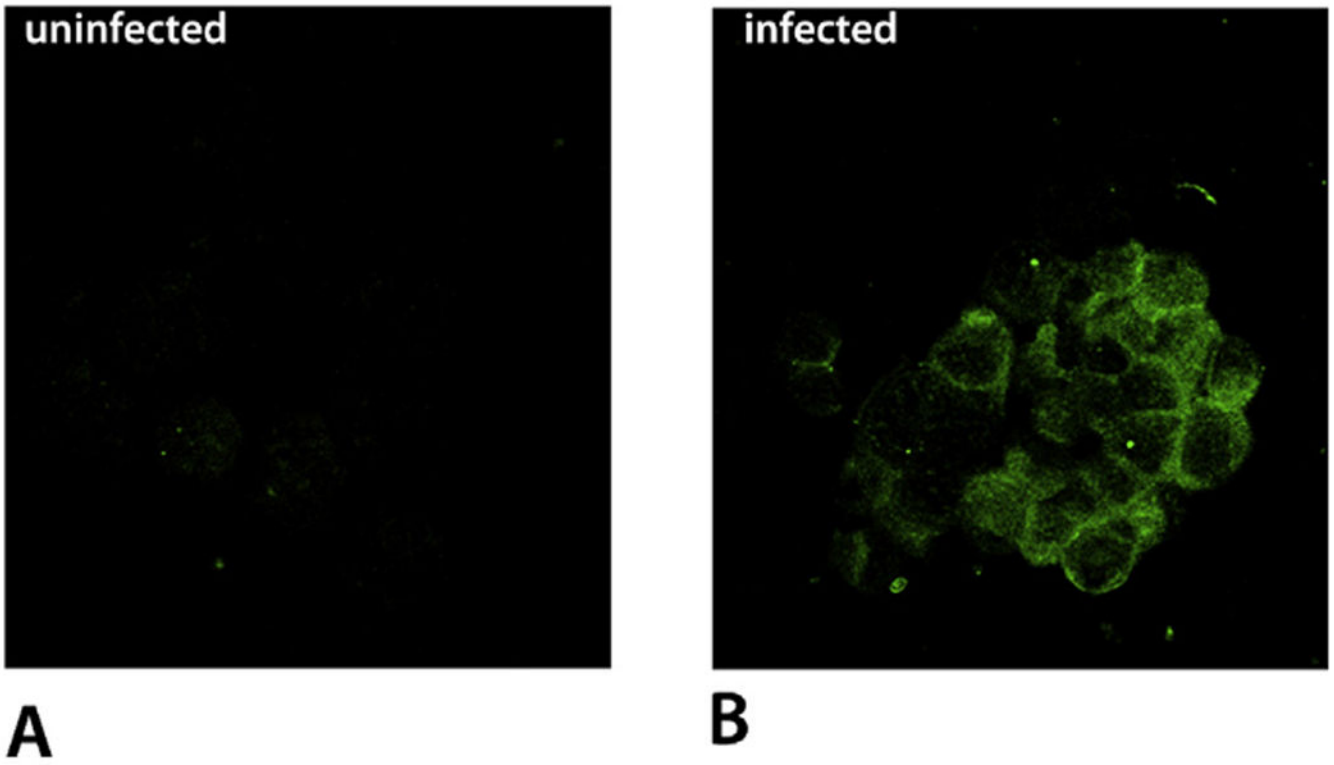

Figure 1.

Figure 1A: Baseline β-Defensin expression of human intestinal epithelial cells without infection. Figure 1B: Immunoflourescent labeling of *in vitro* intestinal epithelial cells 24 hours after infection with *Candida albicans*. Adapted from [12]

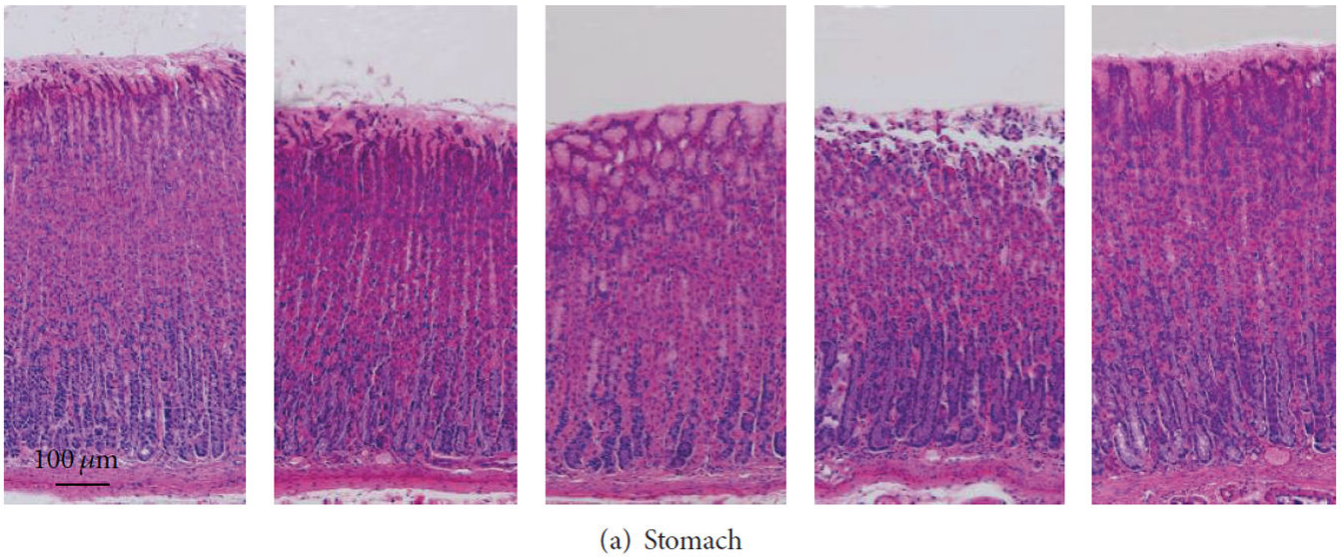

Figure 2.

Appearance of gastric mucosa 0, 1, 3, 7 and 11 days following systemic cisplatin administration. This demonstrates the nadir of gastric mucus on day 3 followed by full recover on day 11. Adapted from [27]