

## Role of Immunity in Gastric Ulcer

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### ABSTRACT

Gastric ulcer is a very common global gastrointestinal disease. Despite extensive study, the mechanisms underlying the gastric mucosal injury are far from fully understood. Gastric mucosa is frequently exposed to harmful agents that may cause injury. These include exogenous factors such as alcohol, nonsteroidal anti-inflammatory drugs (NSAIDs) like aspirin and ibuprofen, *Helicobacter pylori* and ischemia-reperfusion, and endogenous factors such as gastric acid, pepsin and inflammatory cytokines. Under normal circumstances, the gastric mucosa can maintain structural integrity and protects itself against these agents through mucosal defense systems. This consists of epithelial cell lining, mucus covering and bicarbonate ions. This review provides an update on the current knowledge and recent findings related to the protective effects of gastric mucosa and immune system and its related mediators, highlighting recent advances in reduction of mucosal injury by using cytokines and other like stimulating Calcitonin Gene Related Peptide release.

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**Key words:** Gastritis; Immunity; cytokines

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### INTRODUCTION

Gastric ulcer (GU) disease results from an interplay of environmental, microbial (*Helicobacter pylori*), pharmacological (non-steroidal anti-

inflammatory drugs), excessive gastrin production (Zollinger-Ellison syndrome) and genetic factors<sup>[1,2]</sup>. In addition to that, diabetes is an independent risk factor for gastric ulcer bleeding<sup>[3]</sup>. Gastric ulcer is a lesion in the mucosa of the stomach in which acid and pepsin play a major role. It usually presents after the age of 15 and there is an important differences in the age and sex distribution of GU and relative proportion of gastric between the East and the West equally common in both sexes<sup>[4]</sup>. It is possible that the epidemiology of GU has changed with time due to improvements in hygiene, changes in lifestyle, and availability and increased use of potent antisecretory drugs as well as ulcerogenic drugs<sup>[5]</sup>.

The gastric mucosa is the most frequent site of mucosal inflammation in humans. Cellular immune function always gets disordered in the pathogenetic process of gastric ulcer, especially in the active stage, and in a relatively suppressed state<sup>[6]</sup>. T-cell network is of great significance in regulating immuno-reaction and maintaining stability of immunity in human. The mutual restraining and boosting among T-lymphocyte subsets serves to keep the dynamic equilibrium of immune function. Current immunological studies showed that the condition of cellular immunity, represented by T-lymphocytes, depends on the total number of T-cells and the distribution of its subsets<sup>[7]</sup>. Equilibrium of T-cell subsets is the key-link for keeping immune environment stable in healthy human body, as the balance of CD4 + /CD8 + ratio indicates the dominance of positive effect of cellular immunity, and the disordered T-cell subsets in patients are clues to the deprivation of immune function<sup>[8]</sup>.

The aim of this review is to collect and analyze data from past and recent literatures about the immune statuses of gastric mucosa and its alteration due to different factors that contribute in pathogenesis of gastric ulcer in order to shedding a light to treat resistance cases with immune therapy as a new method.

### GASTRIC MUCOSAL IMMUNOLOGY

From birth, antigens that include dietary antigens, normal flora and pathogens continuously challenge the gastric mucosa. Because of its extremely large surface area created by the complex involution of crypts and villi and lined by epithelial cells, the mucosa is susceptible as a site of colonization and entry for many infectious agents. The mucosal immune system must be able to recognize the foreign antigens while at the same time it must ignore commensal bacteria antigens and dietary antigens. Therefore, it is not surprising that the local immune system servicing the gastric mucosa and it is

important to human health.

### Innate Immune Defenses

An important function of mucosal immunity is that the innate immune elements aid in protecting the host from invading antigens. The innate defenses include the physical barrier provided by mucous which is secreted by goblet cells, proteolytic enzymes such as trypsin, chymotrypsin, pepsin, hydrochloric acid and bile salts. In addition to that gastric epithelial barrier that prevent the passages of bacteria due to presence of proteins (occludins, zonula occludens-1 and 2) that maintains cell to cell adhesions<sup>[9]</sup>. These proteins can be regulated by proinflammatory cytokines like gamma-interferon. This occludins seems to be diminished during inflammation and neoplasm of mucosa that leads to enhance permeability and migration of neutrophil to gastric mucosa<sup>[10]</sup>. Zinc deficiency and non steroidal anti-inflammatory drugs like aspirin lead to dysfunction of this barrier<sup>[11,12]</sup>.

Toll-like receptor (TLR) molecules play a frontline role in the defence of the host gastric mucosa against infection by microbial pathogens. These molecules have been shown to trigger innate immune responses in host cells via the recognition of highly conserved microbial structures. TLR4, which is the best-characterized of these "pathogen-recognition molecules" (PRMs), was the first to be shown to recognize a specific microbial component: the lipopolysaccharide (LPS) from Gram-negative bacteria<sup>[13]</sup>.

### Role of Chemokines

Chemokines are low molecular weight molecules that induce chemotaxis and chemokinesis of leukocytes<sup>[14]</sup>. The members of the chemokine superfamily are divided into four subfamilies based on the positions of the first cysteine molecule from the amino terminus. The CXC chemokines, such as interleukin-8 (IL-8) and GRO (growth related gene) are predominantly chemotactic for neutrophils, where as the CC chemokines, macrophage inflammatory protein-1alpha (MIP-1alpha), monocyte chemoattractant protein-1 (MCP-1), and RANTES (regulated upon activation normal T expressed and secreted), are chemotactic for monocytes and lymphocytes, and in some cases eosinophils and basophils. The CC chemokine subfamily includes only lymphotactin, which is chemotactic for lymphocytes. The fourth chemokine subfamily, called CX3C chemokine, includes only fractalkine. The production and expression of chemokines has been documented in gastric mucosa of gastric ulcer and inflammatory bowel disease<sup>[15,16]</sup>. Chemokines have been thought to be pathogenetically responsible for many of the manifestations of this disease.

### Dendritic cells

Dendritic cells (DCs) play an important role as antigen-presenting cells that direct the nature of the adaptive immune response. Subtypes are differentiated by lineage, tissue, marker expression and function. Their function in promoting regulatory T cells in the gut to maintain immunologic homeostasis is well documented. Dendritic cells are present in the gastric mucosa of healthy subjects and are more prevalent and more activated in the inflamed gastric mucosa. These cells showed increased levels of CD11c, CD86 and CD83, and to secrete proinflammatory cytokines, particularly interleukin (IL)-6 and IL-8. These cells leads to activation of adaptive CD4 T helper cell responses that are important in the pathogenesis of chronic gastritis<sup>[17,18]</sup>. In addition to DC, the antigens that enter the stomach can transport across mucosal barrier through specialized microfold cell (M cell), play an important role in the genesis of both mucosal

and systemic immune responses by delivering antigenic substrate to the underlying lymphoid tissue where immune responses start<sup>[19]</sup>.

## CALCITONIN GENE-RELATED PEPTIDE

The major function of the gastric mucosal barrier is to prevent diffusion of acid from the lumen into the mucosa and to defend mucosa against acid erosion. Besides the gastric mucosal barrier, there is an endogenous substances help defend the gastric mucosa against inflammatory injury like calcitonin gene-related peptide (CGRP), a principal transmitter in capsaicin-sensitive sensory nerves, is a protective substance for gastric mucosa<sup>[20]</sup>. CGRP, a polypeptide with 37 amino acid residues, is a major neurotransmitter from capsaicin-sensitive sensory nerves. The main site of CGRP synthesis is the dorsal root ganglion (DRG), which contains the cell bodies of capsaicin-sensitive sensory neurons<sup>[21]</sup>. The CGRP polypeptide has a half-life of approximately 10 min, where it is cleaved and inactivated by neutral endopeptidase, trypsin and chymotrypsin<sup>[22]</sup>. The mature CGRP is transported to nerve endings of the peripheral capsaicin-sensitive sensory nerves to exert physiological functions. It is a predominant neurotransmitter from capsaicin-sensitive sensory nerves, which are widely distributed in the gastrointestinal system. These sensory nerves are reported to be involved in the protection of gastric mucosa against damage by various stimuli. In addition to increase in gastric mucosal blood flow, the beneficial effects of CGRP on gastric mucosa include inhibition of gastric acid secretion, prevention of cellular apoptosis and oxidative injury. The synthesis and release of CGRP is regulated by the capsaicin receptor which is known as transient receptor potential vanilloid subfamily member 1 (TRPV1) and the agonists of TRPV1 have the potential for gastric mucosal protection. So far, multiple TRPV1 agonists, including capsaicin, capsiate, anandamide and rutaecarpine are reported to exert beneficial effects on gastric mucosal injury induced by various stimuli. Therefore, the TRPV1/CGRP pathway represents a novel target for therapeutic intervention in human gastric mucosal injury<sup>[23]</sup>.

## NETWORK OF T CELL RESPONSE AND CYTOKINES PRODUCTION

Gastric epithelial cells (GEC) are thought to play a major role in the host response due to their strategic location between luminal Ag and resident intraepithelial and lamina propria T cells. In addition to their well-characterized contribution to the host response via the secretion of multiple cytokines, GEC may function as APCs due to their constitutive expression of class II MHC molecules, and this expression is increased during infection and inflammation<sup>[24]</sup>. In addition to that GEC expressed a costimulatory molecules such as CD80, CD86 and B7-H1 (programmed death-1 ligand 1), a member of B7 family of proteins associated with T cell inhibition, suggests their role in local Ag presentation<sup>[25]</sup>. Host gastric cellular immune response is an important determinant of the outcome of infection and inflammation. Infected individuals express proinflammatory cytokines in their gastric mucosa (IFN-gamma, IL-8), and gastric mucosa is infiltrated with proinflammatory Th1-biased lymphocytes as well as neutrophils and other inflammatory cell types<sup>[26]</sup>. CD4+ Th cells are necessary and sufficient for induction of severe gastritis and they are identifiable by strong expression of the CD45RB marker. CD4-depleted cells and CD4+ CD45RB<sup>low</sup> cells do not induce gastritis, DTH, or bacterial suppression<sup>[27]</sup>. Thus, cellular rather than humoral immunity determines the outcome of gastritis. Several studies have shown that failure of Ig production has no effect on either gastritis or bacterial colonization but the absence

of immune cells eliminates gastritis, suggesting that cellular rather than humoral immune response determines gastritis<sup>[28]</sup>. Cytokines had an important role in gastritis like IFN-gamma had an important role in induction of gastritis<sup>[29]</sup>. In addition to that, gastric mucosal cytokines are important in induction of gastritis<sup>[30]</sup>. Interleukin-18 (IL-18), a cytokine that promotes Th1 responses, is processed to the active mature protein by caspase-1<sup>[31]</sup>. Thus, imbalance between Th1 and Th2 cytokines secretion, enhance gastric inflammation and progression to ulceration. This may shed a light to treat gastric ulceration using immune modulator drugs especially ulcers that resist treatment by conventional medication<sup>[32]</sup>.

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