

Cathelicidin A Unique Host Defense Peptide for Gastric Disorders

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Antimicrobial peptides (AMPs) or host defense peptides, e.g. defensins and cathelicidins, are considered as endogenous antibiotics which act as a primary defense against bacteria and other pathogens. They have been confirmed as an essential part of the immune system. Cathelicidins are a family of evolutionarily conserved pleiotropic precursor proteins characterized by an N-terminal signal peptide, the cathelin prosequence, followed by a highly variable C-terminal antimicrobial domain. Humans and mice express only one cathelicidin protein, named hCAP18 and Cathelicidin-Related Anti-Microbial Protein (CRAMP) respectively. In humans, cleavage of hCAP-18 is required for the release of the bioactive peptide, namely LL-37. Expression of cathelicidin is found in epithelial cells of the intestine, airway, genitals, ocular surface and skin where the cathelicidin peptides form the first layer of defense against bacteria. Human neutrophils, Natural Killer (NK) cells, and mast cells constitutively express the cathelicidin protein and other cells of the innate immune system are also known to express cathelicidin, like dendritic cells, monocytes and macrophages. In normal stomachs, the expression of the peptide is restricted to differentiated surface of various types of cells including epithelial cells, chief cells and parietal cells and is also present in the gastric secretion [1].

Consistent with its function as a host defense peptide, cathelicidin exhibits microbicidal activity against a broad spectrum of microorganisms, such as Gram-positive and Gram-negative bacteria [2] and parasites. Recent findings reveal that cathelicidin is up-regulated in the gastric secretion and epithelium inflamed by *H. pylori* infection. *In vitro* experiments also show that cathelicidin is bactericidal for several strains of *H. pylori*, including SD4, SD14, and SS1, suggesting that cathelicidin may play a role in the protection against *H. pylori* infection in the stomach [3].

Cathelicidins play a role in inflammation through chemo attraction as well as stimulation and modulation of cytokine release from cells of the innate and adaptive immune system. LL-37 expressed by infected epithelial cells can directly chemoattract cells of the innate immune system such as monocytes, neutrophils, and dendritic cells and also certain subpopulations of T cells of the adaptive immune system [4,5]. At or around the site of infection, LL-37 indirectly attracts more innate immune cells by inducing secretion of IL-8 from macrophages, fibroblasts [6] and epithelial cells [7,8]. This chemokine helps attracting more neutrophils to fight against infection together with LL-37. In this regard LL-37 is able to stimulate and modulate their immunological actions, resulting in a balanced production and release of pro- and anti-inflammatory cytokines in inflamed tissues [9].

It is noted that once the infection is cleared, tissues damaged by the microbe or the action of the immune system need to be repaired. The pro-healing action of cathelicidins has been reported and is mediated by their angiogenic effect and the stimulatory action on migration and proliferation of epithelial cells, along with their modulatory function in inflammation in the stomach [10,11].

Human cathelicidin LL-37 is strongly expressed in skin epithelium during wound healing and antibodies to this peptide inhibit post-wounding re-epithelialization [12]. By acting as a pro-migratory factor, LL-37 induces keratinocytes migration [13]. In addition to their pro-

migratory action, cathelicidins are known to have a direct stimulatory effect on epithelial cell proliferation [12,14]. Induction of angiogenesis by cathelicidin further highlights its potential role in wound repair [15]. LL-37 is able to recruit endothelial progenitor cells to the site of wound healing, induce their proliferation and promote angiogenesis [16]. We have demonstrated for the first time that the rat cathelicidin rCRAMP is involved in tissue repair in the stomach [10]. To this end, ulceration upregulates the expression of rCRAMP in the gastric mucosa. Further induction of rCRAMP expression by plasmid-based gene therapy accelerates ulcer healing by promoting angiogenesis and cell proliferation in the gastric mucosa. Moreover, rCRAMP directly stimulates proliferation of cultured rat gastric epithelial cells through transforming growth factor γ -dependent transactivation of epidermal growth factor and its related signaling pathway [10].

Emerging evidence indicates that LL-37 plays a prominent and complex role in carcinogenesis. Studies on the action of LL-37 in cancer report contradictory results. It has been shown that LL-37 is increased in ovarian, breast and lung cancers [17]. During *H. pylori*-associated gastric carcinogenesis the expression of LL-37 is deregulated [3]. Immunochemical staining of LL-37 revealed that the expression of LL-37 was down-regulated in gastric hyperplastic polyps, tubular adenomas, and adenocarcinomas [3,18]. After *H. pylori* infection, LL-37 is markedly up-regulated in the epithelium and gastric secretion. Such upregulation could not be detected in patients with *H. pylori*-independent gastric inflammation. Our recent study suggests that LL-37 may function as a putative tumor-suppressing peptide in gastric carcinogenesis [18]. We found that exogenous LL-37 inhibits proliferation and induces G0/G1-phase cell cycle arrest in gastric cancer cells. Furthermore, depletion of endogenous LL-37 by RNA interference stimulates gastric cancer cell DNA synthesis. Indeed the direct anticancer activity of LL-37 on gastric cancer needs further investigation both in animals and humans.

In conclusion, cathelicidin plays multiple roles in gastric mucosae. It could eradicate *H. pylori* infection and modulates the inflammatory responses and carcinogenesis in the stomach. It may also promote tissue repair through defined mechanisms of action in the gastric epithelium. It is envisaged that the direct delivery of this host defensive peptide to the targeted site in the stomach represents the future goal of treatment for gastric disorders in man.

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