

Review

Cathelicidins in inflammation and tissue repair: Potential therapeutic applications for gastrointestinal disorders

William Ka Kei WU, Clover Ching Man WONG, Zhi Jie LI, Lin ZHANG, Shun Xiang REN, Chi Hin CHO*

School of Biomedical Sciences and Institute of Digestive Diseases, Faculty of Medicine, the Chinese University of Hong Kong, Hong Kong, China

Cathelicidins, a family of host defense peptides, are highly expressed during infection, inflammation and wound healing. These peptides not only have broad-spectrum antimicrobial activities, but also modulate inflammation by altering cytokine response and chemoattraction of inflammatory cells in diseased tissues. In this connection, a mouse cathelicidin has been demonstrated to prevent inflammation in the colon through enhancing mucus production and reducing production of pro-inflammatory cytokines. In addition, cathelicidins promote wound healing through stimulation of re-epithelialization and angiogenesis at injured tissues. In an animal model of gastric ulceration, the rat cathelicidin promotes ulcer healing by inducing proliferation of gastric epithelial cells both *in vitro* and *in vivo*. In conclusion, cathelicidins represent an important group of effector molecules in the innate immune system that operates a complex integration of inflammation and tissue repair in the gastrointestinal mucosa and other organs.

Keywords: cathelicidin; gastrointestinal disorder; inflammation; wound healing

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Introduction

Cathelicidins are a family of evolutionarily conserved antimicrobial peptides described in mammals, birds, fish, and reptiles. This class of pleiotropic peptides provides first-line defense against infection by promoting rapid elimination of pathogens. LL-37/hCAP18, the only cathelicidin in human, is expressed as a 18-kDa preproprotein that consists of an N-terminal signal sequence, a well conserved cathelin-like domain, and a C-terminal antimicrobial peptide domain (Figure 1). Structurally, the mature peptide LL-37, which is comprised of 37 amino acids, is characterized by a long amphipathic helix spanning residues 2–31. Noticeably, the whole molecule is curved with a train of hydrophobic side chains on the con-

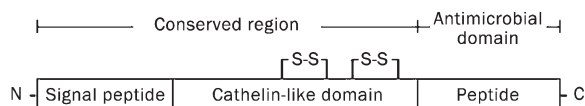


Figure 1. Schematic representation of the cathelicidin family.

cave surface^[1]. This host defense peptide is predominantly expressed in epithelia, lymphocytes and monocytes^[2,3]. LL-37 is expressed along the gastrointestinal tract. For instance, LL-37 is actively produced by surface epithelial cells, as well as chief and parietal cells in the stomach^[4]. The expression of LL-37 is also detectable in epithelial cells located at the surface and upper crypts of normal human colon^[5].

The most prominent function of cathelicidins is their ability to inhibit propagation of a diverse range of microorganisms, which occurs at micromolar range. The microbicidal action is primarily determined by their cationic and amphipathic nature in which charged residues are structurally separated from hydrophobic one, enabling the peptides to interact with the microbial membrane and initiate antimicrobial effects through membrane-permeabilization^[6].

Besides their direct antimicrobial action, recent studies have revealed the multiple functions of cathelicidins in many other activities relating to tissue repair and innate immunity. The human and porcine cathelicidins, LL-37/hCAP18 and PR-39 respectively, for examples, have been reported to modulate the activity of immune and inflammatory cells^[7,8]. Cathelicidins have also been shown to promote re-epithelialization of human skin wounds^[9] and rat gastric ulcer^[10]. In this review, we summarize the role of cathelicidins in the processes of

* To whom correspondence should be addressed.

E-mail chcho@cuhk.edu.hk

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inflammation and tissue repair with particular emphasis on those occurred in the gastrointestinal tract.

Cathelicidin and inflammation

Inflammation is a tissue response resulting from a complex integration of internal cellular reactions against a repertoire of external insults, such as chemicals, physical agents and biological challenges. It is characterized by an influx of inflammatory cells into the inflamed area and regulated by sequential and coordinated release of pro- and anti-inflammatory cytokines from these cells. In this regard, upregulation of cathelicidins during inflammation plays a modulatory role in inflammation^[11, 12].

Effects on chemotaxis and cytokine release

The initiation, maintenance, and resolution of inflammation are largely regulated by inflammatory cytokines produced by various types of inflammatory cells. There are growing evidence indicating that cathelicidins may play a role in inflammation through its ability to chemoattract some responsible cells or to alter the expression of pro-inflammatory cytokines.

Cathelicidins can regulate leukocyte migration and infiltration. To date, cathelicidins from four different mammals including bovine^[13], porcine^[7], human^[2, 8, 14], and mice^[15] have been reported to function as leukocyte chemoattractants. They chemoattract neutrophils, monocytes, mast cells, and T-cells to inflammatory sites at sub-antimicrobial concentrations^[7]. The chemotactic activity of human and mouse cathelicidins are mediated by the engagement of the peptides with the formyl peptide receptor-like 1 (FPRL1), a G protein-coupled, seven-transmembrane cell receptor found on macrophages, neutrophils, and subsets of lymphocytes^[8, 15]. Moreover, these peptides participate in inflammation by activating mast cells to release histamine through calcium mobilization^[14, 16]. LL-37 also induces secretion of interleukin (IL)-8 in airway epithelial cells, leading to increased infiltration of neutrophils and amplification of inflammatory signal. The activation of epithelial cells has been suggested to be mediated through a sequential activation of molecular events, including induction of matrix metalloproteinases (MMP) activities, cleavage of membrane-anchored ligands of epidermal growth factor receptor (EGFR), and the subsequent transactivation of EGFR by these ligands^[17]. *In vivo* study further suggests that this peptide stimulates macrophages to produce chemokines which in turn chemoattract additional cells to the inflamed sites^[18].

Apart from recruiting inflammatory cells, cathelicidins moderate inflammation by altering the expression of various cytokines. The findings by Braff *et al*^[19] show that LL-37 promotes the mRNA expression of numerous inflammatory mediators, including IL-8, cyclooxygenase-2 (COX-2), pro-IL-1 β , and IL-6 by keratinocytes. The ability of LL-37 to increase pro-inflammatory mediators released from keratinocytes may have a critical impact on the initial phase of cutaneous inflammation. Cathelicidins also enhance IL-1 β processing and release from monocytes. Activation of the P2X₇ receptor, a member of the P2X family of nucleotide-gated channels, expressed on non-

cytic cells like monocytes and macrophages is involved in this action^[20]. On the other hand, cathelicidins promote phagocytic clearance of damaged and pathogen-infected cells present at inflammatory sites while minimize undesired inflammatory response^[21, 22].

Effect on mucus secretion and other biological events in inflammatory bowel disease

Increasing evidence suggests that abnormal mucus secretion is the hallmark for the pathogenesis of several diseases. Mucus hypersecretion is one of the major causes of inflammatory airway diseases like chronic bronchitis, asthma and cystic fibrosis^[23]. On the contrary, marked reduction in the colonic mucus have also been reported in ulcerative colitis (UC)^[24, 25]. However, the mechanisms regulating these changes are still not understood. The importance of mucus alteration in the initiation or perpetuation of UC has been widely studied over decades. During the active stage of UC, the mucus layer is severely disrupted and discontinuous with a 60%–70% decrease in thickness^[26]. This is linked to the depletion of goblet cells and downregulation of mucin production which could be influenced by immunological or bacterial factors during inflammation. *In vitro* study has revealed that pro-inflammatory cytokines IL-1, IL-6 or tumor necrosis factor (TNF)- α can cause an increased synthesis of MUC2 and other secretory mucins whereas incubation of individual cytokine additionally results in decreased and altered glycosylation in human goblet cell-like cells^[27]. The elevated number of bacteria detected within the colonic mucus layer of UC patients poses another threat to the intestinal mucosa. These findings reinforce the idea that enhancing the mucosal barrier could be an important therapeutic strategy in treating patients with inflammatory bowel diseases.

Our recent study demonstrated that mouse cathelicidin (mCRAMP) given intrarectally in mice could attenuate dextran sulfate sodium (DSS)-induced colitis through the preservation of the mucus layer during inflammation^[28]. This was accompanied with an up-regulation of the MUC1, MUC2, MUC3, and MUC4 genes expression. Interestingly, MUC2 is the most predominantly expressed secretory mucin in the colon^[29], which could be stimulated through a mitogen-activated protein kinase (MAPK) pathway^[30]. Concordantly, our study showed that application of MAPK inhibitor could completely block the increase of MUC1 and MUC2 expression as well as mucus synthesis induced by cathelicidin^[31]. However, the identify of receptor that mediates the stimulatory effect of cathelicidin on colonic mucus secretion remains unclear. To this end, FPRL-1 and P2X₇, both of which are putative receptors of LL-37, have been reported to be expressed in cultured colon epithelial cells^[32, 33].

Aside from increasing mucus production, experimental evidence shows that LL-37 significantly reduces the increased number of fecal microflora in UC animals. Treatment with mCRAMP (a mouse cathelicidin) also suppresses the induction of apoptosis by DSS^[28]. All these actions could contribute to the protective action of cathelicidin in UC (Figure 2) in which

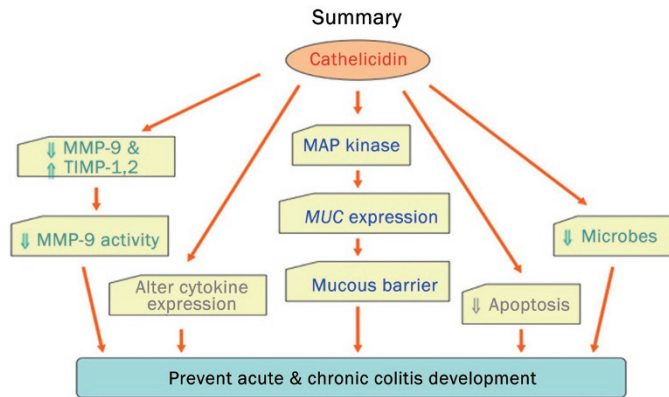


Figure 2. Proposed mechanism of action for cathelicidin to prevent colonic inflammation induced by dextran sodium sulfate in mice.

this peptide could serve as a novel therapeutic option.

Stimulatory effect on wound healing

Wound healing requires an orchestrated integration of complex cellular events involving inflammation, tissue regeneration, and scar formation^[34]. Recent finding suggests that LL-37 is involved in healing of human skin wounds. Cathelicidins are strongly expressed in skin epithelium during wound healing. In addition, its expression is low or absent in chronic ulcer epithelium. Current evidence supports that the pro-healing action of cathelicidins is mediated by their angiogenic effect and the stimulatory action on migration and proliferation of epithelial cells, alongside with their modulatory function in inflammation.

In the context of tissue repair, cathelicidin is strongly expressed in skin epithelium during wound healing and antibodies to this peptide inhibit post-wounding re-epithelialization^[35]. In addition, cathelicidin expression is low or absent in chronic skin ulcers^[36]. The ability of cathelicidin to induce angiogenesis further highlights its potential role in wound repair^[37]. The pro-healing effects of cathelicidin may be mediated through modification of growth-factor/receptor interactions and angiogenesis^[38–40]. Definitive proof of the involvement of these mechanisms in wound healing, however, has not yet been obtained.

Re-epithelialization of wound requires an orderly process of epithelial cell migration and proliferation, which is regulated by the expression of growth factors and the activation of specific intracellular signaling pathways^[41]. Recent findings suggest that cathelicidins may play an important role in these cellular processes. Human cathelicidin LL-37 is highly expressed in healing skin epithelium and treatment with antibodies raised against LL-37 inhibits re-epithelialization as demonstrated by an *ex vivo* wound healing model consisting exclusively of cultured human skin^[9]. By acting as a pro-migratory factor, LL-37 induces keratinocytes migration^[42]. It has been proposed that the pro-migratory action of LL-37 is mediated through MMP-dependent ectodomain shedding of heparin-binding-EGF-like growth factor (HB-EGF) and the subsequent

transactivation of EGFR and the downstream STAT3 pathway. Transfecting keratinocyte with a dominant-negative mutant of STAT3 abolishes LL-37-induced migration, suggesting that STAT3 pathway downstream of EGFR transactivation is centrally involved in the pro-migratory action of LL-37^[42]. In parallel to the above finding, LL-37 induces airway epithelial cells NCI-H292 migration in an EGFR-dependent manner^[43].

Aside from their pro-migratory action, cathelicidins are known to have a direct stimulatory effect on epithelial cell proliferation. In this respect, anti-LL-37 antibodies delay wound healing and reduce the proliferation marker Ki67 in cultured human skin, suggesting that LL-37 may promote cutaneous wound closure by stimulating epithelial cell proliferation^[9]. Similarly, LL-37 induces airway epithelial cells NCI-H292 proliferation via a GPCR-, EGFR-, and ERK-dependent pathway^[43]. All these findings suggest that cathelicidins may be a putative growth factor for epithelial cells.

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. Furthermore, rCRAMP directly stimulates proliferation of cultured rat gastric epithelial cells^[10]. This action is mediated through transforming growth factor α (TGF α)-dependent transactivation of EGFR and the downstream signaling mediator ERK1/2 to induce proliferation of gastric epithelial cells (Figure 3). In accord with these findings, cathelicidin has been reported to promote proliferation and migration of human airway epithelial cells as well as cutaneous wound repair. In addition, the human homolog LL-37 is known to directly induce proliferation and formation of vessel-like structures in cultured endothelial cells^[32]. Mice deficient in cathelicidin also exhibit significantly decreased vascular structures and delayed wound closure^[36, 37, 44]. All these

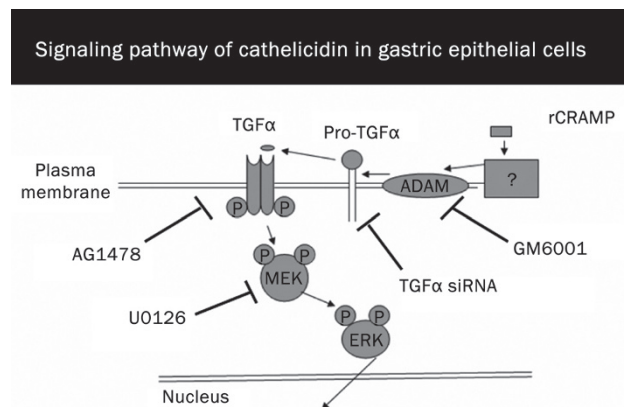


Figure 3. The proposed signaling pathway for cathelicidin to promote proliferation of rat gastric epithelial cells. AG1478: epidermal growth factor receptor kinase inhibitor; U0126: kinase (ERK) kinase (MEK)-specific inhibitor; GM6001: matrix metalloproteinase inhibitor; TGF α siRNA: small interfering RNA targeting rat TGF α .

findings suggest that cathelicidin is an important endogenous mitogenic and pro-angiogenic factor in tissue repair (Figure 4). However, there is no evidence so far showing that cathelicidin acts through similar mechanisms to promote healing during the recovery of inflammation in the colon^[28].

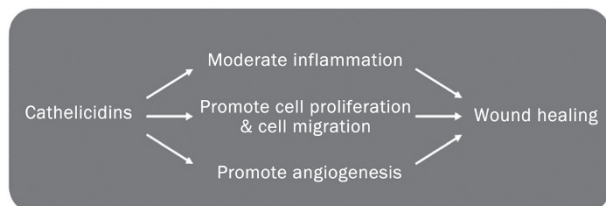


Figure 4. The biological actions of cathelicidin in wound healing.

Conclusion

Cathelicidins are a family of antimicrobial molecules of the innate immune system that have multifunctional roles in the regulation of inflammation and wound healing (Figure 2 and 3). The human cathelicidin LL-37 seems to display both pro- and anti-inflammatory properties in which it modulates chemotaxis and cytokine responses of inflammatory cells. LL-37 also stimulates angiogenesis and re-epithelialization, both of which are essential for wound healing. With respect to its signaling pathways, the pharmacological action of cathelicidins in these cellular responses is mediated by GPCR and specially FPRL-1 in its chemotactic and angiogenic action. Transactivation of EGFR is also involved in the mediation of its mitogenic and pro-migratory effects on epithelial cells. Taken together, cathelicidins are important endogenous angiogenic, mitogenic, and pro-migratory peptides with microbicidal action and regulatory effects on inflammation in which all these functions converge to its pro-healing effect in wound tissues.

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Abbreviations

DSS: dextran sulfate sodium; EGFR: epidermal growth factor receptors; FPRL1: formyl peptide receptor-like 1; IL: interleukin; HB-EGF: heparin-binding-EGF-like growth factor; MAP: mitogen-activated protein; mCRAMP: mouse cathelicidin; MMP: matrix metalloproteinases; rCRAMP: rat cathelicidin; TGF α : transforming growth factor α ; TNF: tumor necrosis factor; UC: ulcerative colitis

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