Antimicrobial Peptides: An Emerging Approach to Treating Colitis

Diana Hoang-Ngoc Tran and Hon Wai Koon*

Center for Inflammatory Bowel Diseases, Division of Digestive Diseases, David Geffen School of Medicine, the University of California Los Angeles, Los Angeles, CA 90095, USA

*Corresponding author: Hon Wai Koon, Assistant Professor, Center for Inflammatory Bowel Diseases, Division of Digestive Medicine, The University of California Los Angeles, Los Angeles, USA, Tel. (310) 825-9742; E-mail: hkoon@mednet.ucla.edu

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Introduction

Antimicrobial peptides are endogenous peptides typically expressed on mucosal surfaces, such as the mouth, intestines, and respiratory tract. These mucosal surfaces are typically in close contact with the external environment and microbiota. Over the last decade, the role of antimicrobial peptides in colitis has become increasingly apparent, and some antimicrobial peptides show promise as future therapeutic approaches to treat colitis. Pharmaceutical companies and laboratories are developing clinically useful versions of antimicrobial peptides with high efficacy, robust chemical stability, and excellent safety profile.

Cathelicidin

Cathelicidin is a 37-amino acid antimicrobial peptide called LL-37 in humans and mCRAMP in mice [1]. It may directly kill bacteria by pore formation on the cell membrane [2]. On the other hand, cathelicidin mediates an anti-inflammatory effect by binding to endotoxin lipopolysaccharide and neutralizing its toxicity [3]. Recent evidence shows that cathelicidin may bind to the bacterial sensor formyl peptide receptor-like 1 (FPRL1) and mediate its chemotactic activity in immune cells [4]. In the colonic mucosa of inflammatory bowel disease patients, cathelicidin mRNA expression is increased in ulcerative colitis (UC) patients but not Crohn’s disease (CD) patients [5]. However, this increase does not correlate with local inflammatory activities in the colonic tissues.

In mice, the lack of endogenous cathelicidin also contributes to exacerbation of DSS-mediated colitis [6]. Intracolonic administration of cathelicidin peptide or oral administration of cathelicidin-expressing bacteria reduces colonic inflammation in mice after exposure to dextran sulfate (DSS) [7,8]. These findings suggest the protective role of cathelicidin in colitis.

Cathelicidin may also play a role in inhibiting colitis-associated intestinal fibrosis in Crohn’s Disease patients. Around 10-20% of Crohn’s disease patients develop stricture or intestinal fibrosis that has no established way for prevention or reversal [9]. The current last resort option is surgery, which can affect the quality of life. A recent report shows that intracolonic cathelicidin peptide administration effectively inhibits intestinal fibrosis in mice caused by exposure to trinitrobenzene sulfonic acid and Salmonella [10]. This study also reveals that cathelicidin can inhibit fibrogenic gene (collagen) expression in fibroblasts directly via an ERK-dependent mechanism. Another study demonstrates that cathelicidin can inhibit epithelial-mesenchymal transition (EMT) [11]. Inhibition of EMT eventually reduces the generation of fibroblasts, the cellular source of fibrogenesis.

Colonic expression of cathelicidin is also increased in C. difficile-infected patients. In mice infected with C. difficile, intracolonic administration of cathelicidin peptide inhibits colitis [12]. Unfortunately, it is difficult to translate these important bench-side findings to clinical bedside application because cathelicidin can be degraded in body fluid and cause hemolysis [13-15]. Alternatively, N8 Medical Inc. has recently developed cathelicidin mimic CSA13 that shows superior antimicrobial capability [13,14]. Its non-peptide nature makes CSA13 resistant to degradation, and CSA13 does not cause a significant hemolysis in human red blood cells [16]. However, its efficacy in colitis and its safety profile in vivo still need further investigations.

Lactoferrin

Lactoferrin is a glycoprotein originally found in milk [17]. In IBD patients, fecal lactoferrin is a novel non-invasive biomarker of IBD with high sensitivity and specificity [18]. Deficiency of lactoferrin augments azoxymethane- and DSS-mediated colitis-associated colorectal dysplasia in mice [19]. Oral feeding of lactoferrin significantly reduces DSS-mediated colitis in rats [20]. Despite promising preclinical findings, lactoferrin has not been used to treat IBD patients in clinical trials. The reason of this is that some IBD patients (13-29%) develop anti-lactoferrin autoantibodies [21]. The clinical significance of the autoantibodies is unclear but may potentially neutralize the therapeutic effect of lactoferrin.

Elafin

Elafin consists of 117 amino acids and possesses antimicrobial and anti-protease activities [22,23]. Colonic Elafin mRNA expression is increased in UC patients, but not CD patients and healthy control subjects [24]. Another study shows that elafin is typically found in colonic epithelial cells of UC patients [25]. In terms of therapeutic potential of elafin, elafin-expressing food grade lactic acid bacteria significantly inhibit DSS-mediated acute colitis and CD4CD45RBhi-mediated chronic colitis in mice [26]. However, it is not known whether elafin is useful in clinical applications.

Clinical applications of antimicrobial peptides in treating colitis

Up to now, no clinical trial directly utilizes antimicrobial peptides in treating colitis. However, a Phase II randomized, double-blind, placebo-controlled clinical trial has shown the positive therapeutic role of butyrate in treating shigellosis [27]. Butyrate enema induced LL-37 expression in the rectum and reduced shigellosis-mediated rectal tissue damage and inflammatory responses, suggesting the therapeutic effect of cathelicidin in colitis. On the other hand, another randomized double-blind controlled trial shows that bovine lactoferrin significantly reduces longitudinal prevalence and severity of diarrhea caused by...
norovirus, *E. coli*, and Shigella in children [28]. An ongoing clinical trial has recruited 25,875 American men and women to study whether a vitamin D3 supplement can increase plasma cathelicidin levels and affect the risk of infectious diseases (NCT01758081). In fact, vitamin D2 supplement reduces C-reactive protein (CRP) levels and erythrocyte sedimentation rate (ESR) of adult IBD patients [29]; however, the LL-37 levels of these patients in this clinical trial were not reported.

In summary, antimicrobial peptides are novel and potentially useful approaches to treating various forms of colitis. One approach is to induce expression of cathelicidin by butyrate or vitamin D. Another approach may be the development antimicrobial peptide mimics. Some of the endogenous antimicrobial peptides may also serve as biomarkers for indicating disease activity of colitis.

References