Advances in Research on Host Defense Peptides Modulating Animal Intestinal Barrier Function: Postprint

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Abstract

Intestinal barrier function is primarily achieved by regulating the synthesis of mucins and tight junction (TJ) proteins, which is crucial for maintaining animal intestinal health and production performance. As a critical component of the innate immune system, host defense peptides (HDPs) play a vital role in mucosal defense. Deficiency of HDPs in the intestine is associated with barrier dysfunction and homeostatic dysregulation. HDPs enhance intestinal barrier function by directly inducing the expression of multiple mucins and TJ proteins. HDP-inducing compounds are capable of improving animal intestinal morphology, production performance, and feed conversion ratio. This review will comprehensively discuss the transcriptional regulation of mucins and TJ proteins by HDPs, the molecular regulatory mechanisms of intestinal barrier, and the impacts on animal production performance.

Full Text

Research Progress in Regulation of Animal Intestinal Barrier Function by Host Defense Peptides

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Abstract

Intestinal barrier function is primarily achieved through the regulation of mucin and tight junction (TJ) protein synthesis, which is crucial for maintaining intestinal health and animal performance. As an essential component of the innate

immune system, host defense peptides (HDPs) play a vital role in mucosal defense. HDP deficiency in the intestine is associated with barrier dysfunction and homeostatic disorders. HDPs enhance intestinal barrier function by directly inducing the expression of multiple mucins and TJ proteins. Compounds that induce HDPs can improve intestinal morphology, production performance, and feed conversion efficiency in animals. This review synthesizes current knowledge on the transcriptional regulation of mucins and TJ proteins by HDPs, the molecular regulatory mechanisms of intestinal barrier function, and the impacts on animal performance.

Keywords: host defense peptides; barrier function; intestinal mucosa; innate immunity; performance

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Host defense peptides (HDPs), also known as antimicrobial peptides, are essential components of the innate immune system in animals. They exhibit broad-spectrum antimicrobial activity against Gram-negative bacteria, Gram-positive bacteria, fungi, viruses, protozoa, and even cancer cells. Most HDPs are expressed at mucosal surfaces, including the gastrointestinal tract. The main families of HDPs include defensins, cathelicidins, S100 proteins, RNase A superfamily, regenerating islet-derived III (REGIII) C-type lectins, and peptidoglycan recognition proteins [**?**]. Due to their positive charge or amphipathic nature, most HDPs kill bacteria primarily by disrupting cell membranes or interacting with intracellular macromolecules. Positively charged HDPs bind to negatively charged phospholipid groups on bacterial membranes through electrostatic interactions, and their amphipathic properties facilitate insertion into target membranes, thereby compromising membrane integrity. Within cells, certain HDPs can also inhibit protein, DNA, and RNA synthesis or bind to specific targets. Beyond their antimicrobial activity, HDPs participate in regulating innate immune responses. For instance, three chicken-derived cathelicidins (fowlicidin-1, fowlicidin-2, and fowlicidin-3) directly bind to lipopolysaccharide (LPS) in the outer membrane of bacterial cell walls and can neutralize LPS-induced production of inflammatory cytokines in macrophages [**?**]. Three bovine -defensins [bovine neutrophil -defensin 3 (BNBD3), bovine neutrophil -defensin 9 (BNBD9), and bovine enteric defensin (EBD)] exhibit chemotactic activity for immature monocyte-derived dendritic cells [**?**]. Porcine cathelicidin PR-39 can inhibit NADPH oxidase activity in phagocytes and attenuate myocardial ischemia-reperfusion injury by blocking the binding of p47phox (a cytosolic component of NADPH oxidase) and thereby suppressing enzyme complex assembly [**?**]. Consequently, HDPs with potent antimicrobial activity and immunomodulatory functions are being actively developed as novel antibiotics. Recent studies have demonstrated that HDPs can directly regulate the expression of mucins, tight junction (TJ) proteins, and microbial community composition to enhance mucosal barrier integrity. This review will focus on these emerging roles of HDPs in intestinal barrier function and mucosal homeostasis.

1 Overview of Animal Intestinal Barrier Function

The intestinal barrier function is achieved through two primary mechanisms: coating epithelial cells with a mucus layer and forming a selectively permeable barrier between epithelial cells. This single layer of epithelial cells in the gastrointestinal tract not only facilitates nutrient digestion and absorption but also serves as a critical defense against microbial and toxin invasion. The mucus layer, composed mainly of mucins secreted by goblet cells, acts as a physical barrier between luminal contents and the host while also aiding nutrient digestion and absorption. Alterations in mucin expression or glycosylation are commonly associated with intestinal barrier dysfunction. For example, Mucin 2 (MUC2) deficiency in mice leads to increased intestinal epithelial permeability, massive hemorrhage, gastrointestinal inflammation, and severe growth retardation [**?**]. MUC1 or MUC2 knockout mice become more susceptible to infections by *Campylobacter jejuni*, *Helicobacter pylori*, *Salmonella typhimurium*, and *Citrobacter rodentium*. Additionally, mice lacking -1,3-N-acetylglucosaminyltransferase exhibit a thinner mucus layer, increasing susceptibility to intestinal bacterial infection and dextran sodium sulfate (DSS)-induced colitis [**?**].

The primary barrier function of the gastrointestinal tract resides in epithelial cells that transport water, ions, and macromolecules through two distinct pathways: transcellular and paracellular routes. The transcellular pathway involves the active or passive movement of small molecules across epithelial cells, whereas the paracellular pathway refers to the diffusion of water, macromolecules, and immune cells between epithelial cells. In intact epithelia, the paracellular pathway determines intestinal permeability and is regulated by intercellular junctions known as tight junctions (TJs). The intestinal epithelium consists of crypts and villi composed of several distinct cell types, including intestinal stem cells, enterocytes, and specialized secretory cells such as Paneth cells, goblet cells, and enteroendocrine cells [**?**]. Intestinal stem cells differentiate into all epithelial cell lineages, while enterocytes primarily function in nutrient absorption and possess the capacity to synthesize and release HDPs and mucins. Paneth cells and goblet cells are the major producers of HDPs and mucins, respectively, whereas enteroendocrine cells secrete numerous hormones that regulate digestive functions [**?**]. All intestinal epithelial cells are connected at their lateral membranes through three major types of junctional complexes: TJs, adherens junctions, and desmosomes [**?**]. Collectively, these junctional complexes create a nearly impermeable seal between cells. In addition to their barrier function, these complexes maintain cell polarity by separating apical and basolateral membranes [**?**].

TJs are multiprotein complexes located at the most apical region of the lateral membrane, composed of transmembrane proteins and cytoplasmic plaque proteins that directly interact with the cytoskeleton. Among the three major junctional complexes, only TJs possess the ability to control selective paracellular permeability to ions, water, and small molecules [**?**]. Consequently, TJs

serve as the primary determinants of mucosal epithelial permeability.

Maintaining mucin and TJ integrity ensures proper absorption and transport of nutrients, water, and electrolytes while protecting the host from pathogens, toxins, and the intestinal microbiota. Conversely, disruption of the mucus layer and TJ complexes increases intestinal permeability, leading to enhanced bacterial translocation, exacerbated inflammation, and potentially various intestinal and systemic diseases. In livestock production, impaired intestinal barrier function compromises animal health and reduces production efficiency [**?**]. Therefore, understanding how HDPs maintain and regulate intestinal barrier function is essential for achieving optimal animal health and performance.

2.1 HDPs Induce Expression of Mucin and TJ Protein Receptors

Numerous extracellular and intracellular receptors mediate the diverse physiological functions of cathelicidins and defensins in humans and mice. The human antimicrobial peptide LL-37 and murine cathelicidin-related antimicrobial peptide (CRAMP) serve as ligands for P2X purinergic receptor 7 (P2X7), formyl peptide receptor-like 1/2, glyceraldehyde-3-phosphate dehydrogenase, and sequestosome-1/p62, whereas several human and murine -defensins bind to CC chemokine receptor 2 (CCR2), CC chemokine receptor 6 (CCR6), CXC chemokine receptor 2 (CXCR2), and Toll-like receptors (TLRs) 1/2/4 [**?**]. Although epidermal growth factor receptor (EGFR) is not a direct receptor for LL-37, LL-37-induced expression of the airway mucin gene MUC5AC in lung epithelial cells appears to be mediated primarily through EGFR transactivation [**?**]. Initially, LL-37 triggers activation of tumor necrosis factor- (TNF-) converting enzyme, which sequentially cleaves the membrane-bound form of TNF- but not heparin-binding EGF; the released TNF- subsequently interacts with and phosphorylates EGFR, which activates multiple signal transduction pathways to induce MUC5AC gene expression [**?**]. In human intestinal epithelial cells, LL-37-induced expression of MUC2 and MUC3 genes involves EGFR and P2X7 but not G protein-coupled receptors [**?**]. HBD-2-induced mucin expression in human intestinal epithelial cells is partially mediated through CCR6 [**?**].

2.2 HDPs Regulate Intestinal Barrier Signaling Pathways

The mitogen-activated protein kinase (MAPK) pathway comprises three canonical signaling cascades: extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK), and p38 [**?**]. S100A7 can activate all three of these signaling cascades. ERK is rapidly phosphorylated within 2 minutes of S100A7 exposure in human skin keratinocytes, while JNK and p38 MAPK are phosphorylated within 30 minutes. p38 MAPK participates in P2X7 and EGFR activation that regulates MUC2 production in human Caco-2 cells [**?**]. Inhibition of individual MAPK signaling cascades significantly reduces transepithelial electrical resistance (TEER), indicating that all three major MAPK pathways are required. Inhibition of the ERK pathway enhances the synergistic effect of butyrate-FSK, whereas blocking JNK or p38 pathways markedly reduces avian

-defensin 9 (AvBD9) induction in chicken macrophages and jejunal explants [?]. Sodium butyrate activates the TLR2/p38 signaling pathway in bovine mammary epithelial cells, upregulating the expression of tracheal antimicrobial peptide (TAP), bovine neutrophil -defensin 5 (BNBD5), and bovine neutrophil -defensin 10 (BNBD10), thereby enhancing resistance to *Staphylococcus aureus* internalization and exerting anti-inflammatory effects [?]. Sodium butyrate induces upregulation of porcine -defensin 3 (pBD3), porcine defensin EP2C (pEP2C), porcine -defensin 128 (pBD128), porcine -defensin 123 (pBD123), and porcine -defensin 115 (pBD115) in PK-15 cells without triggering inflammatory responses. TLR2 can be activated by sodium butyrate and peptidoglycan, and blocking TLR2 expression inhibits HDP induction [?]. Post-translational modifications of TJ proteins and the status of the associated actomyosin ring significantly impact barrier permeability. Many factors alter barrier function through phosphorylation of specific TJ proteins or via activation of myosin light chain kinase (MLCK), which phosphorylates myosin light chains and causes contraction of the functional actomyosin ring, leading to opening of the paracellular pores. Determining whether and how HDPs affect post-translational modifications of TJ proteins and the transcription and activity of MLCK will be a key focus of future research.

2.3 HDPs Regulate Synthesis of Intestinal Mucins and TJ Proteins

Human -defensin-2 (HBD-2) upregulates MUC2 and MUC3 mRNA expression in human colon epithelial HT-29 cells but does not affect MUC1 or MUC5AC mRNA expression [?]. Similarly, MUC2 mRNA expression is upregulated in human colon epithelial Caco-2 cells by HBD-2, and this increased MUC2 expression subsequently promotes HBD-2 mRNA expression, suggesting a positive feedback regulatory mechanism between MUC2 and HBD-2 [?]. LL-37 enhances MUC1, MUC2, and MUC3 mRNA expression in HT-29 cells but only increases MUC3 mRNA expression in Caco-2 cells [?]. Buforin II, a 21-amino-acid HDP isolated from the stomach of Asian toads, improves intestinal barrier function in weaned piglets challenged with three enterotoxigenic *Escherichia coli* (ETEC) strains [?]. Oral administration of buforin II induces increased expression of claudin-1, occludin, and ZO-1 proteins in jejunal segments of *E. coli*-challenged piglets. Importantly, buforin II also improves intestinal morphology and growth performance while reducing bacterial shedding in fecal swabs. Additionally, cathelicidin-BF, an HDP from banded krait, induces ZO-1 protein expression in the jejunum of healthy mice and restores LPS-mediated ZO-1 damage and intestinal barrier function [?]. Furthermore, pBD-2 restores MUC1 and MUC2 mRNA expression, claudin-1, ZO-1, and ZO-2 protein expression, and colonic barrier integrity in DSS-treated mice [?].

3 Impact of HDPs on Intestinal Mucosal Homeostasis

One of the primary functions of intestinal epithelial cells is to serve as a barrier against microbial invasion. The intestinal mucosa harbors over 1,000 microbial

species, most of which are commensal bacteria that benefit the host by enhancing digestion, absorption, and vitamin synthesis while simultaneously limiting pathogen proliferation. The two most abundant bacterial phyla in human and mouse intestines are Gram-negative and Gram-positive bacteria, which together account for 70-80% of the total bacterial population. Commensal bacteria are essential for normal intestinal morphology and immune system development. Although beneficial to the host under homeostatic conditions, dysbiosis or microbial community imbalance can trigger inflammation and disrupt epithelial homeostasis.

The intestinal epithelium continuously monitors the resident microbiota through interactions between pattern recognition receptors (PRRs) and microbial-associated molecular patterns (MAMPs). PRR activation stimulates HDP and mucin synthesis and release in intestinal cells. The abundant HDPs secreted by Paneth cells and intestinal epithelial cells are retained within the mucus layer, forming a robust barrier against bacterial invasion. Studies using HDP knockout and transgenic mice have elucidated the roles of HDPs in intestinal homeostasis and immune defense. Cathelicidin CRAMP knockout mice develop colitis, with disease symptoms further exacerbated following DSS induction [**?**]. Transfer of bone marrow cells from wild-type mice to CRAMP knockout mice attenuates DSS-induced colitis. Mice carrying the human defensin 5 (HD5) transgene show enhanced resistance to oral *Salmonella typhimurium* infection. Conversely, matrix metalloproteinase 7 (MMP7) knockout mice, which cannot produce biologically active intestinal defensins, exhibit impaired clearance of intestinal pathogens. Compared to wild-type mice, HD5 transgenic mice show decreased Firmicutes and increased *Bacteroides*, whereas MMP7-deficient mice display the opposite pattern [**?**]. Furthermore, HD5 overexpression in mice leads to significantly reduced segmented filamentous bacteria in the distal small intestine and decreased Th17 cell numbers in the lamina propria, clearly demonstrating that intestinal HDPs represent key factors shaping microbial community composition and the inflammatory state of the digestive tract.

4 Effects of HDPs on Animal Growth Performance and Intestinal Morphology

Multiple studies have highlighted the beneficial effects of direct HDP supplementation on growth, intestinal morphology, and immune status in pigs. Feeding recombinant silkworm HDPs cecropin A/D significantly improved growth performance and feed conversion ratio while reducing diarrhea incidence in weaned piglets challenged with ETEC, although no significant effects on intestinal morphology or nitrogen/energy utilization were observed within 6 days [**?**]. Dietary supplementation with recombinant fusion HDPs derived from bovine lactoferrin also enhanced piglet growth performance and reduced diarrhea incidence over a 21-day period in ETEC-challenged piglets [**?**]. Administration of a mixture of four recombinant HDPs, including lactoferrin, cecropin, defensin, and plectasin,

to weaned piglets across five different farms improved growth performance and feed conversion ratio while decreasing diarrhea incidence [**?**]. Similarly, supplementation with synthetic HDPs (AMP-A3 or P5) during a 4-week trial improved nutrient digestibility, intestinal morphology, and growth performance in weaned piglets without significantly affecting serum immunoglobulin A (IgA), IgG, or IgM levels [**?**]. Additionally, AMP-A3 and P5 appeared to reduce potentially harmful *Clostridium* titers and coliform counts in the ileum, cecum, and feces [**?**]. In piglets challenged with the mycotoxin deoxynivalenol, feeding a combination of two HDPs and a probiotic yeast improved intestinal morphology and feed conversion ratio [**?**]. In most of these trials, HDPs were comparable to antibiotics in promoting pig growth, improving feed efficiency, and enhancing intestinal morphology. Dietary AMP-A3 supplementation increased body weight and improved feed conversion ratio in broiler chickens, with production performance similar to that of broilers fed the antibiotic avermectin [**?**]. Intestinal morphology in broilers can also be improved by increasing small intestinal villus height and the villus height-to-crypt depth ratio. Supplementation with yeast broth containing recombinant cecropin A/D enhanced intestinal morphology and feed conversion ratio in broilers, with a trend toward improved growth performance during a 4-week trial [**?**]. Cecropin A/D also reduced total aerobic bacterial counts in jejunal and cecal contents of 42-day-old chickens. Collectively, these animal trial results demonstrate the benefits of HDP supplementation and justify the use of dietary HDPs as a rational antibiotic alternative strategy for promoting animal growth and disease control.

5 Compounds that Induce HDP Synthesis

Due to their susceptibility to enzymatic degradation and the high production costs of synthetic or recombinant forms, direct HDP supplementation in animal diets may lack biological efficacy and economic feasibility. Recently, several classes of small-molecule compounds, such as butyrate, have been identified as HDP inducers that enhance bacterial clearance in animals without triggering inflammatory responses. Dietary supplementation with these simple HDP-inducing compounds or their combinations has proven to be a novel approach for replacing conventional low-cost antibiotics in animal production. Feed supplementation with 0.1% butyrate significantly increased intestinal HDP expression in chickens while reducing cecal *Salmonella enteritidis* titers by nearly 10-fold relative to the experimental infection dose [**?**]. In chicken HD11 macrophages and primary monocytes, HDP induction correlates negatively with free fatty acid chain length, with short-chain fatty acids being most effective, followed by medium-chain and long-chain fatty acids with diminishing efficacy [**?**]. Three short-chain fatty acids—acetate, propionate, and butyrate—exert powerful synergistic effects on enhancing HDP gene expression in chicken cells. Compared to individual short-chain fatty acid supplementation, combining all three in drinking water further reduces cecal *S. enteritidis* infection in chickens. Importantly, short-chain fatty acids enhance HDP gene expression without stimulating pro-inflammatory interleukin-1 production. Butyrate alleviates clinical symptoms

of hemolytic uremic syndrome (HUS) and partial inflammation induced by *E. coli* O157:H7 in pigs and upregulates HDP expression through histone acetylation modifications [**?**]. Acetate, propionate, butyrate, and hexanoate can all reduce *S. aureus* infection in bovine mammary epithelial cells and upregulate TAP and BNBD5 gene expression [**?**]. However, the efficacy of these HDP-inducing compounds in promoting animal growth, intestinal health, and microbial community balance requires further validation in ruminant trials.

6 Conclusion

Disruption of the intestinal barrier leads to animal disease and reduced production efficiency, making understanding of intestinal barrier function and its regulatory mechanisms crucial for ensuring sustainable development of animal agriculture. With potent antimicrobial and immunomodulatory capabilities, HDPs have demonstrated a novel capacity to directly regulate intestinal barrier function. Aberrant HDP synthesis commonly results in intestinal barrier dysfunction, and diseases characterized by compromised barrier integrity are often associated with reduced HDP synthesis, highlighting the potential of HDPs for enhancing intestinal health and animal performance. While synthetic peptides have been applied to treat human diseases, their use in livestock production remains prohibitively expensive. HDP-inducing compounds or exogenous recombinant HDPs have emerged as effective strategies for disease prevention and treatment in animals and may potentially replace antibiotic use in livestock production in the future.

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