Review Article

Biology, Expression, and Regulation of Host Defense Peptides: A Minireview

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Abstract | Host defence peptides (HDPs) represent a diverse group of small peptides generally consisting of less than 100 amino acid residues with a net positive charge. HDPs are synthesized preferably by phagocytes in the circulation, skin keratinocytes, and mucosal epithelial cells of the digestive, respiratory, and urogenital tracts. As important effector molecules of innate immunity, HDPs are quickly mobilized to fight off infections. In addition to direct antimicrobial activities, HDPs impact positively on wound healing, inflammation resolution, and development of adaptive immunity. Besides infection and inflammation, many HDPs were found recently to be induced by a large number of dietary compounds such as vitamins D, short-chain fatty acids, histone deacetylase inhibitors, zinc, and certain phytochemicals in humans and several other animal species such as poultry. Further investigations on the dietary modulation of HDP synthesis may lead to the development of a novel antibiotic-free approach to disease control and prevention with applications in both the livestock and poultry industry and human health.

Keywords | Host defence peptides, Antimicrobial resistance, Immune modulation, Antibiotic alternatives, Innate immunity

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INTRODUCTION

Innate immunity is the first line of host defense and crucial to protect all living organisms against microbial invasions (Linde et al., 2008; Steinstraesser et al., 2011). As critical effector molecules of the innate immune system, host defense peptides (HDPs), also known as antimicrobial peptides, have been discovered in nearly all forms of life (Zasloff, 2002; Zhang and Sunkara, 2014). HDPs are strategically expressed in leukocytes as well as mucosal epithelial cells lining the respiratory, gastrointestinal and urogenital systems of their host (Zhang and Sunkara, 2014). They are synthesized as peptide precursors and enzymatically processed to release biologically active, mature peptides (Steinstraesser et al., 2011; Zasloff, 2002). Most mature HDPs consist of 12 to100 amino acids rich in cationic residues and are largely amphipathic (Wang, 2014). They directly kill a myriad of microbes ranging from Gram-positive and Gram-negative bacteria to fungi, protozoa, parasites, enveloped viruses, and even cancerous cells. Additionally, many HDPs have a profound impact on the regulation of inflammation, wound healing, and adaptive immunity (Hilchie et al., 2013; Yeung et al., 2011). Because of these pleotropic activities, these HDPs are being actively explored as novel antimicrobials for disease control and prevention particularly against drug-resistant microbes (Hancock et al., 2012).

CLASSIFICATION OF HDPS

Nearly 2,500 HDPs have been reported in bacteria, protozoa, fungi, plants, and animals (Fjell et al., 2007; Wang et al., 2009). Based on their structures, HDPs are broadly classified into four major groups including the peptides adopting largely an α-helical, β-sheet, a loop or flexible structure (Pasupuleti et al., 2012; Yeung et al., 2011). The loop structure of HDPs is mainly due to the presence of a disulfide bond, whereas flexible structures result from enrichment of certain amino acids such as arginine, histidine, proline, and tryptophan. Cathelicidins and defensins represent two major families of HDPs found in vertebrates (Sang and Blecha, 2009; Sorensen et al., 2008; van Dijk

et al., 2011). Cathelicidins were first isolated from bovine neutrophils as cyclic dodecapeptides (Romeo et al., 1988). Since then, cathelicidins have been found in not only mammals but also in fish, snakes, and birds (Chang et al., 2006; Gennaro and Zanetti, 2000; Lynn et al., 2004; Uzzell et al., 2003; van Dijk et al., 2005; Xiao et al., 2006; Zhao et al., 2008). The name cathelicidin was coined from the presence of a highly conserved cathelin domain in the N-terminal region. The C-terminal regions of cathelicidins are highly variable among species and possess different biological functions (Gennaro and Zanetti, 2000; Kolls et al., 2008). A large group of cathelicidin genes are encoded in the porcine, ovine, and bovine genomes; however, only a single cathelicidin gene exists in rodents, dogs, primates, and humans (Steinstraesser et al., 2011; van Dijk et al., 2011). Four cathelicidin genes were found recently in chickens (Goitsuka et al., 2007; Xiao et al., 2006).

Defensins, present in plants, invertebrates and vertebrates, are rich in cysteines and comprised of 3-4 disulfide bonds (Carvalho-Ade and Gomes, 2009; Strominger, 2009; van Dijk et al., 2008). Most vertebrate defensins consist of a signal peptide, proregion and cationic mature peptide with six conserved cysteine residues forming three intramolecular disulfide bridges creating a "defensin-like" fold (Hiemstra, 2007; Lehrer and Ganz, 2002). Based on the spacing pattern and pairing of cysteine residues, vertebrate defensins are classified into three major subfamilies namely α-, β-, and θ- defensins (Hiemstra, 2007). The disulfide bridges are formed between C1-C6, C2-C4, and C3-C5 in α-defensins, whereas C1-C5, C2-C4, and C3-C6 are paired in β-defensins, and C1-C6, C2-C5 and C3-C4 paired in θ-defensins. Triple-stranded, anti-parallel β-sheet structures are present in α- and β-defensins, while θ-defensins are composed of circular double-stranded β-sheets (Selsted, 2004; Selsted and Ouellette, 2005; Steinstraesser et al., 2011; van Dijk et al., 2008).

As important effector molecules of innate immunity, cathelicidins and defensins are produced strategically by leukocytes, skin keratinocytes, and mucosal epithelial cells of respiratory, gastrointestinal, and urogenital tracts (Brown and Hancock, 2006; Hancock and Scott, 2000). In humans, cathelicidin LL-37 is mainly found in both leukocytes and epithelial cells, while α- and θ-defensins are commonly expressed in neutrophils and paneth cells of the small intestine, and the primary source of β-defensins are mucosal epithelia and skin (Easton et al., 2009; Lehrer, 2004). HDP precursors are processed post translationally by different proteolytic enzymes to become biologically active (Auvynet and Rosenstein, 2009; Zanetti et al., 1995). For example, human α-defensin HD5 is synthesized by intestinal Paneth cells and processed by trypsin (Oppenheim, 2003). Human cathelicidin LL-37 is further processed by serine proteases like proteinase 3 in neutrophils and kallikreins 5 and 7 in the skin (Guani-Guerra et al., 2010; Sorensen et al., 2001), whereas elastase is a main enzyme responsible for cleavage of cathelicidin precursors in cattle and pigs (Panyutich et al., 1997; Scocchi et al., 1992; Zanetti et al., 1991).

ANTIMICROBIAL PROPERTIES OF HDPS

HDPs are broad-spectrum natural antibiotics that kill or suppress the growth of a wide range of bacteria, mycobacteria, fungi, parasites, and certain enveloped viruses (Bernard and Gallo, 2011). They kill microbes by physical disruption of membranes or by nonspecific inhibition of cellular transcription and translation (Yeung et al., 2011). Cationic HDPs initially accumulate and electrostatically interact with anionic membrane components such as lipopolysaccharides (LPS) of Gram-negative bacteria and lipoteichoic acid (LTA) of Gram-positive bacteria. Penetration into negatively charged phospholipids of microbial membranes resulting in membrane perturbation and leakage of intracellular contents, ultimately leading to cell death (Hale and Hancock, 2007; Zasloff, 2002). Because it is very difficult for microbes to change the overall negative charge of their membrane phospholipids, development of resistance against HDPs is extremely rare (Yeaman and Yount, 2003). Preferred disruption of microbial, but not host, membranes is believed to be due to the differences between prokaryotic and eukaryotic cell membrane properties. While the former is heavily negatively charged with high transmembrane potential (-140 mV), the latter is largely uncharged with a high cholesterol content and low transmembrane potential of approximately -15 mV (Huang et al., 2010; Yount and Yeaman, 2005). The mechanism of pore formation on microbial membranes varies among individual HDPs. Depending upon the net charge and spatial structure, HDPs permeate membranes via "barrel-stave", "toroidal-pore", "molecular electroporation", "sinking raft", or "carpet-wormhole" mechanisms (Oren and Shai, 1998; Palffy et al., 2009; van Dijk et al., 2008).

In addition to direct disruption of membranes, certain HDPs, particularly α- and θ-defensins, suppress viral proliferation by acting as collectins. For example, retrocyclins (primate θ-defensins) bind to glycoproteins (gp41 and gp120) of HIV as well as CD4 of host immune cells and prevent viral entry by blocking the conformational change of gp41, which is required for attachment and fusion of viruses with host cells (Penberthy et al., 2011). Similarly, human α-defensins (HNP1, -2, and -3) bind to envelop glycoprotein B of herpes simplex virus to suppress viral entry into the host cells (Hazrati et al., 2006). Because of these diverse interactions with microbes, it is extremely difficult for microbes to develop resistance against HDPs.

ANTIINFLAMMATORY EFFECTS OF HDPS

Besides antimicrobial properties, HDPs suppress inflammation and protect the host from excessive production of proinflammatory mediators triggered by microbial products. HDPs are capable of neutralizing bacterial endotoxins, inhibiting proinflammatory cytokine production, inducing antiinflammatory cytokines, and preventing activation of classical and lectin complement cascades (Choi et al., 2012; Easton et al., 2009; Groeneveld et al., 2007). For example, human cathelicidin LL-37 binds to and neutralizes LPS and LTA, thereby abolishing the production of proinflammatory cytokines such as TNF-α, IL-1β, and IL-6, while also stimulating the expression of antiinflammatory cytokines such as IL-10 (Mookherjee et al., 2006; Mookherjee and Hancock, 2007; Ruan et al., 2013; Scott et al., 2011; Suphasiriroj et al., 2013). In addition, LL-37 inhibits IFN-γ-induced cell activation, proliferation, and production of proinflammatory and Th1-polarizing cytokines and antibodies in antigen- presenting cells (Nijnik et al., 2009). In a murine infection model, LL-37 protects mice from septic shock induced by *Pseudomonas aeruginosa* (Kirikae et al., 1998). It also promotes secondary necrosis of apoptotic neutrophils without causing loss of membrane integrity or provoking inflammatory response of macrophages (Li et al., 2009b). Likewise, chicken cathelicidin fowlicidin-1 prevents LPS-induced production of nitric oxide and TNF-α (Bommineni et al., 2010). Porcine cathelicidin PR-39 inhibits the production of reactive oxygen species, while bovine cathelicidin BAMP-28 induces apoptosis of activated lymphocytes (Brown and Hancock, 2006).

Similar to cathelicidins, defensins also inhibit production of proinflammatory cytokines by binding to microbial membranes, surface adhesins, and bacterial toxins as well as by surpressing their attachment to host cells (Kohlgraf et al., 2010). For example, human α-defensin HNP1 attenuates LPS-mediated production of proinflammatory cytokines such as IL-1β from monocytes (Shi et al., 2007). HNP2 and HNP3 reduce production of several proinflammatory cytokines including IL-1 β, IL-6, IL-8 and TNF-α from LPS-stimulated human monocyte-derived macrophages (Miles et al., 2009). Human β defensin(HBD)-3 also abrogates the induction of IL-6, and TNF-α from human myeloid dendritic cells stimulated with *Porphyromonas gingivalis* (Pingel et al., 2008). Moreover, there is evidence that expression of human α- and β-defensins is reduced in inflammatory diseases like Crohn's disease, emphasizing the role of defensins in regulation of inflammation (Guani-Guerra et al., 2010; Salzman, 2010).

IMMUNOMODULATORY ACTIVITIES OF HDPS

HDPs have the capacity to directly kill pathogens, but their antimicrobial activity is often diminished in biological fluids in the presence of monovalent and divalent cations, serum, and polyanionic molecules like glycosaminoglycans (Bowdish et al., 2005). Several HDPs, albeit with extremely weak or no antibacterial activities, have been found to still protect the host from infections, implying a host defense role other than directly killing bacteria (Brown and Hancock, 2006; Jenssen and Hancock, 2010; Yeung et al., 2011). In fact, HDPs promote diverse immunomodulatory functions by stimulating the production of chemokines and cytokines, and by regulating complement activation, promoting wound healing, and by acting as chemoattractants (Pundir and Kulka, 2010; van Dijk et al., 2011; Yeung et al., 2011). For example, Human β-defensins (HBD1 and HBD3) chemoattract immature dendritic cells and memory T cells, while human α-defensins are chemotactic to naïve T cells (Auvynet and Rosenstein, 2009). Similarly, HNP1-3 and HBD3-4 stimulate migration of neutrophils and monocytes, whereas LL-37 and HNP1-3 are chemotactic to mast cells and induce degranulation to release histamine and prostaglandin-2, respectively (Auvynet and Rosenstein, 2009). HDPs also induce production of various pro-inflammatory cytokines such as IL-1β, TNF-α and IL-6 as well as chemokines such as IL-8 and monocyte chemotactic protein-1 from mononuclear phagocytes and epithelial cells (Auvynet and Rosenstein, 2009; van Dijk et al., 2009).

In addition to modulation of host immunity, HDPs enhance wound healing. HDPs promote re-epithelialization, angiogenesis and vascularization by inducing proliferation of epithelial cells and vascular endothelial cells and chemoattracting fibroblasts and macrophages (Steinstraesser et al., 2011). LL-37 was shown to enhance the closure of wounds in human corneal epithelial cells and in high-glucose-attenuated porcine corneal epithelial cells (Yin and Yu, 2010). HDPs enhance synthesis of growth factors and cytokines in keratinocytes and epithelial cells that are essential for wound repair (Yeung et al., 2011). For example, human LL-37 and HBDs enhances IL-18 secretion from keratinocytes (Niyonsaba et al., 2005). HBD2 and HBD-3 are also actively involved in re-epithelialization of damaged skin (Steinstraesser et al., 2008). Porcine PR-39 is involved in wound healing by increasing the expression of extracellular matrix proteoglycans such as syndecan-1 and 4, which are important for activation of many growth factors (Gallo et al., 1994). Given such an array of immunomodulatory properties of HDPs, it is highly desirable to harness these properties for antimicrobial therapies to boost host immunity without directly acting on microbes,

thereby minimizing the risk of developing resistance (Finlay and Hancock, 2004).

TRANSCRIPTIONAL REGULATION OF HDPS

HDP Regulation in Humans

Expression of many HDPs can be induced in response to infection and inflammation. Human cathelicidin LL-37 expression is induced in response to Gram-negative bacteria such as *Salmonella enterica* serovar Dublin, and enteroinvasive *Escherichia coli* in human colonic epithelium (Hase et al., 2002), *Helicobacter pylori* in human gastric epithelial cells (Hase et al., 2003), and *Pseudomonas aeruginosa* in corneal epithelium (Gao et al., 2010). Likewise, the synthesis of LL-37 is increased in response to Gram-positive bacteria including *S. aureus* in keratinocytes (Midorikawa et al., 2003), *Mycobacterium* species in human alveolar macrophages, monocytes, neutrophils and epithelial cells (Mendez-Samperio et al., 2008; Rivas-Santiago et al., 2008), LPS and LTA in sinus epithelial cells (Nell et al., 2004), flagellin in corneal epithelial cells (Gao et al., 2010). On the other hand, *Shigella dysenteriae*, *Vibrio cholera* (Islam et al., 2001) and *Nisseria gonorrhoeae* (Bergman et al., 2005) downregulate LL-37 expression in intestinal epithelial cells. In addition, stressors like injury (Dorschner et al., 2001), endoplasmic reticulum stress (Park et al., 2011), and inflammatory disorders (Frohm et al., 1997) also enhance LL-37 expression in keratinocytes. Moreover, various proinflammatory cytokines (IL-1α, IL-6, and IL-17) (Erdag and Morgan, 2002; Lande et al., 2007; Peric et al., 2008) and growth factors (insulin-like growth factor 1 and transforming growth factor-α and -β1) (Sorensen et al., 2003) promote LL-37 expression in skin epithelial cells, while proinflammatory cytokines display no effect on colonic epithelium (Hase et al., 2002). IL-10 and IL-13 also suppress LL-37 expression in the skin (Kolls et al., 2008), and IL-18 stimulates LL-37 expression in colonic epithelial cells (McDonald et al., 2006).

Neutrophil-derived human α-defensins are mostly constitutively expressed but inducible in a few cases such as pulmonary tuberculosis, septicemia, and bacterial meningitis (Ashitani et al., 2002; Ashitani et al., 2000; Panyutich et al., 1993). Similarly, IL-18 and viral infections like hepatitis C increase α-defensin expression in intestinal cells and in peripheral blood mononuclear cells, respectively (Aceti et al., 2006; McDonald et al., 2006). HBD1 expression is primarily constitutive, but induced by LPS, and IFN-γ in certain antigen-presenting cells, and repressed by *Shigella dysenteriae*, *Vibrio cholera* and bacterial exotoxins (Chakraborty et al., 2008; Duits et al., 2002; Islam et al., 2001). The expression of HBD2-4 is upregulated by various stimulants including bacteria, and bacterial products, and cytokines such as IL-1α, IL-1β, IL-22, IL-17A, TNF-α, and IFN-γ in keratinocytes (Harder et al., 2004). HBD2 and HBD3 are also inducible in *Campylobacter jejuni*-treated intestinal epithelial cells (Zilbauer et al., 2005). Viral infections including HIV-1 and Rhinovirus-16 enhance HBD2 and HBD3 expression in epithelial cells (Lehrer, 2004). *Cryptosporidium parvum* upregulates HBD2, but down-regulates HBD1 with no effect on HBD3 expression in colonic epithelial cells (Zaalouk et al., 2004).

Apart from infection and stress, human LL-37 is also induced by several dietary factors including short-chain fatty acids, flavones, zinc, and vitamin D_3. For example, short-chain fatty acids such as butyrate and propionate induce LL-37 expression in human intestinal and hepatic cells as well as lung epithelial cells by acting as histone deacetylase (HDAC) inhibitors (Kida et al., 2006; Schauber et al., 2004; Schauber et al., 2003). Other HDAC inhibitors including 4-phenylbutyrate and trichostatin (TSA) are also able to augment LL-37 expression in epithelial and monocytic cells (Schauber et al., 2004; Schauber et al., 2003; Steinmann et al., 2009). Other fatty acids including valerate, hexanoate and heptanoate appear to be more potent in inducing LL-37 than butyrate in human colonic and monocytic cells (Jiang et al., 2013). Besides fatty acids, vitamin D_3 stimulates LL-37 synthesis in lung epithelial cells, keratinocytes, and monocytes, but not in colonic epithelial cells (Hansdottir et al., 2008; Peric et al., 2009; Schauber et al., 2006; Schauber et al., 2008). In addition, zinc has the capacity to enhance LL-37 expression in human intestinal epithelial cells (Talukder et al., 2011). LL-37 expression is also augmented by various cyclic adenosine monophosphate (cAMP) signaling agonists in mucosal epithelial cells (Chakraborty et al., 2009).

Human neutrophil α-defensins are induced by 2-arachidonoyl-glycerol and arachidonic acid and the induction is correlated with increased antimicrobial activities of neutrophils against *E. coli*, *S. aureus*, herpes simplex virus (HSV)-1, and respiratory syncytial virus (RSV) (Chouinard et al., 2013). Human HBD1 expression is mostly constitutive in response to infection, but can be modulated by dietary compounds such as apicidin, butyrate, depudecin, MS-275 and valproic acid in human lung epithelial cell lines through inhibition of HDAC1 (Kallsen et al., 2012). Another HDAC inhibitor and butyrate analog, 4-phenylbutyrate stimulates the expression of HBD1, but not HBD2-4 in human lung epithelial cells (Steinmann et al., 2009). However, 4-phenylbutyrate fails to induce HBD1 in monocytic cells in the same study (Steinmann et al., 2009), suggesting that HDP regulation is both gene- and cell-specific.

HDAC inhibitors such as TSA, butyrate, and sulforaphane are also capable of enhancing HBD2 expression in human colonic epithelial cells (Schwab et al., 2008). Free fatty ac-

ids such as lauric acid, palmitic acid, and oleic acid enhance the antimicrobial activity of sebocytes against *Propionibacterium acnes* by upregulation of HBD2 (Nakatsuji et al., 2010). Zinc and several probiotic bacterial strains have also been found to upregulate HBD2 expression (Di Cagno et al., 2010; Putaala et al., 2010; Schlee et al., 2008). It is likely that probiotics and prebiotics stimulate bacterial fermentation of short-chain fatty acids, which in turn promote HDP synthesis, host immunity, and disease resistance.

HDP Regulation in other Species Including Poultry

Mouse cathelicidin CRAMP expression is enhanced in the skin in response to injury and mild UV irradiation and in mast cells by LPS stimulation (Dorschner et al., 2001; Hong et al., 2008; Li et al., 2009a). Mouse intestinal α-defensins (cryptidins) are also induced in response to *Toxoplasma gondi* via TLR9-dependent pathway (Foureau et al., 2010). Mouse β-defensin 3 (MBD3) are augmented in the esophagus and tongue by *E. coli*, and MBD2 expression are triggered in the skin by UV irradiation (Ahrens et al., 2011). In contrast, MBD1 expression is inhibited by *Cryptosporidium parvum* (Burd et al., 2002; Hong et al., 2008; Zaalouk et al., 2004). In rats, neuropathogenic *E. coli* enhances the expression of intestinal α-defensins (Birchenough et al., 2013), and methicillin-resistant *Staphylococcus aureus* enhanced the rat β-Defensin 3 (RBD3) expression in the lung (Wu et al., 2011). In response to intestinal ischemia or injury, RBD2 is stimulated in the lung as well (Liu et al., 2009). Similarly, *Actinobacillus actinomycetemcomitans* increases RBD1 and RBD2 expression in gingival epithelia (Kurland et al., 2006). Testicular and epididymal β-defensins are enhanced in rats treated with LPS (Biswas and Yenugu, 2013, 2011). In rabbits, oral supplementation of butyrate or 4-phenylbutyrate alleviates clinical symptoms of dysentery in shigellosis infections through upregulation of cathelicidin expression in the colon and lung epithelia (Raqib et al., 2006; Sarker et al., 2011).

Like their mammalian counter parts, porcine cathelicidins such as protegrins and PR-39 show an increased expression in porcine bone marrow cells in response to different *Salmonella* strains, LPS, and IL-6 (Wu et al., 2011; Zhang et al., 1997). In addition, PR-39 is increased in mucosal and lymphatic tissues of the respiratory tract in pigs chronically, but not acutely infected with *Actinobacillus pleuropneumoniae* (Hennig-Pauka et al., 2012). Porcine β-defensin 2 (PBD2) expression is enhanced in intestinal epithelial cells exposed to live *Salmonella*, but not heat-killed or colistin-treated bacteria (Veldhuizen et al., 2006). Likewise, *Salmonella enteritidis* infection stimulates PBD1 gene expression (Veldhuizen et al., 2006; Veldhuizen et al., 2009), while PBD1 is upregulated and PBD2 is down-regulated in intestinal epithelial cells treated with *Fusarium* toxin (Wan et al., 2013). Treatment of primary tracheal epithelial cells with LPS or canine respiratory coronavirus or parainfluenza virus has led to a decreased expression of several canine β-defensins (Erles and Brownlie, 2010).

In ruminant animals, *E. coli* or LPS stimulation of neutrophils results in an increased production of bovine cathelicidin Bac-5 (Tomasinsig et al., 2002). Furthermore, bovine HDPs such as TAP, LAP, and BBD5 are upregulated in response to infections, particularly in the mammary, lung, and uterine tissues (Meade et al., 2014). Several bovine β-defensins are also increased in response to inflammation and infection (Das et al., 2008; Russell et al., 1996; Stolzenberg et al., 1997). Similarly, *S. aureus* or LPS treatment of umbilical endothelial cells potentiates the expression of bovine LAP, BBD1 and BBD4 through autocrine production of TNF-α (Alva-Murillo et al., 2012b). Intrauterine infusion of *E. coli* in goats results in up-regulation of β-defensin 2 gene expression (Shao et al., 2012), whereas infection of intestinal epithelial cells with *Eimeria spp* leads to down-regulation of the goat β-defensin 2 gene (Ibarra-Velarde and Alcala-Canto, 2007). In sheep, SBD1 is increased with parainfluenza virus type 3 infection and decreased by *Mannheimia haemolytica*, with no difference in gene expression observed with SBD2 (Ackermann et al., 2004).

In avian species, HDPs are also differentially expressed in response to infectious agents and inflammatory mediators (Cuperus et al., 2013; Zhang and Sunkara, 2014). For example, several chicken cathelicidins are augmented in response to *S. typhimurium* in cecal tonsils, and down-regulated by *Camphylobacter jejuni* in peripheral blood leukocytes and *Eimeria praecox* in small intestine (Akbari et al., 2008; Meade et al., 2009; Sumners et al., 2011). Chicken β-defensins are also regulated by *Haemophilus paragallinarum* in the trachea (AvBD3) and by *Salmonella typhimurium* (AvBD1, 2, 5, and 6) in cecal tonsils (Akbari et al., 2008; Zhao et al., 2001).

Dietary compounds has also been found to regulate HDPs expression in non-human species. For example, fatty acids such as butyrate, propionate and hexanoate have been shown to increase the expression of several bovine β-defensins in primary mammary epithelial cells and inhibit both internalization and infection of *Staphylococcus aureus* (Alva-Murillo et al., 2012a). In contrast, the expression of bovine LAP, TAP, and BBD4 is decreased in rumen epithelia when infused with butyrate (Baldwin et al., 2012). Oleic acid induces MBD4 in the hair follicle sebaceous glands of ear skin in mice (Nakatsuji et al., 2010). Lysozyme-digested probiotics increases mouse CRAMP expression in macrophages and protects rats against sepsis (Bu et al., 2006). Free fatty acids with 3-8 carbons are able to induce porcine HDPs such as PBD2, PBD3, PEP2C, and protegrins in intestinal epithelial cells, alveolar macrophages, and primary monocytes (Zeng et al., 2013). PBD2 is induced in the

ileum of pigs administered with a probiotic, *Lactobacillus rhamnosus* (Li et al., 2012).

In animal agriculture, particularly in poultry, organic acids including butyrate and propionate have been used for decades and shown an overall improved resistance to *S. enteritidis* (Van Immerseel et al., 2006) and *Clostridium perfringens* (Timbermont et al., 2010). Many antibacterial mechanisms of organic acids have been proposed, including a reduction of intestinal pH, direct antibacterial activities, and suppression of bacterial attachment to host intestinal cells (Gantois et al., 2006; Van Immerseel et al., 2004; Van Immerseel et al., 2003; Van Immerseel et al., 2006). Augmenting HDP synthesis and host immunity has also been proposed as a new mode of action of organic acids, which often contain short-chain fatty acids that have been revealed to be strong inducers of chicken HDPs both *in vitro* and *in vivo* (Sunkara et al., 2011; Sunkara et al., 2012). A combination of three short-chain fatty acids, namely butyrate, acetate and propionate, could synergistically induce chicken HDP expression and clearance of *Salmonella* in the cecum of chickens (Sunkara et al., 2012). A phytochemical, forskolin, also synergizes with butyrate in enhancing chicken HDP expression both *in vitro* and *in vivo* (Sunkara et al., 2012; Sunkara et al., 2014).

CONCLUSIONS

HDPs are important effector molecules of innate immunity, possessing a myriad of beneficial functions with potent antimicrobial, antiinflammatory, and immunomodulatory activities. HDPs are mobilized quickly in response to infection and inflammation. A growing body of evidence suggests that dietary factors including vitamin D_3, short-chain fatty acids, zinc, certain amino acids, and phytochemicals are capable of inducing HDP synthesis in humans and other animal species like cattle, pigs, sheep and poultry, suggesting the potential of using these HDP-inducing compounds for immune augmentation and disease resistance. Dietary modulation of the endogenous HDP synthesis may be further explored as a novel antibiotic-free strategy for disease prevention and control for both human and animal health including poultry.

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CONFLICTS OF INTEREST

The authors have declared no conflict of interest.

AUTHOR'S CONTRIBUTION

Lakshmi Tulasi Sunkara and Amanda Renee Curits drafted the manuscript and Guolong Zhang drafted and revised the manuscript.

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