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Review

Avian cathelicidins: Paradigms for the development of anti-infectives

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ABSTRACT

The broad-spectrum defense system based on host defense peptides (HDPs) is evolutionary very old and many invertebrates rely on this system for protection from bacterial infections. However, in vertebrates the system remained important in spite of the superposition of a very sophisticated adaptive immune system. The cathelicidins comprise a major group of HDPs in mammals. About six years ago it was first described that cathelicidins are also present in birds. Here we review the properties and biological activities of the recently discovered avian cathelicidins and their potential to be used as a paradigm for the development of anti-infectives. Like the mammalian cathelicidins, avian cathelicidins exert direct antimicrobial activities but can also selectively boost host immune responses by regulation of cytokine production and recruitment of immune cells. In addition, it was found that chicken cathelicidins bind endotoxins and dampen the endotoxin-mediated inflammatory response. Molecular dissection has allowed identification of different structural elements involved in bacterial killing and immunomodulation. These studies have enabled the design of small HDP-based antibiotics with specific functions, *i.e.* having primarily immunomodulatory or antimicrobial activities. Since the immunomodulatory effects may, to a certain degree, be species-specific, we hypothesize that poultry-specific antibiotics can be developed based on avian cathelicidins.

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1. Host defense peptides

HDPs can be defined as small peptides (10–50 amino acids in general), primarily enriched in hydrophobic and cationic amino acid residues (+2 to +9), which can display broad-spectrum antimicrobial and/or immunomodulatory activities and are widespread throughout the animal, plant and fungal kingdoms (Hancock and Sahl, 2006; Zasloff, 2002). In mammals, HDPs may be constitutively or regulatory expressed and are found at sites that routinely encounter pathogens, such as mucosal surfaces and skin, the crypts of the small intestine and within the granules of immune cells (Yang et al., 2004). HDP-containing immune cells may be attracted to the site of infection to ensure local delivery of the peptides (Froy, 2005). HDPs are important to bridge the gap between the onset of infection and sufficient clonal expansion of B and T cells necessary to mount an adequate adaptive immune response. The fact that protection against enteric Salmonellosis can be prevented by the introduction of a single HDP gene (human defensin 5) in transgenic mice indicates that even a single HDP gene can make the difference in the outcome of infection (Salzman et al., 2003). Currently, natural HDPs are increasingly being used as templates for the research and development towards new antibiotics due to their unusual broad-spectrum of antimicrobial and immunomodulatory activities. The aim of this review is to present our current knowledge on the biological functions of avian cathelicidins and to discuss possible applications in veterinary medicine.

2. Cathelicidins

Cathelicidins comprise a major group of HDPs and have been found in mammals (Zanetti, 2005), fish (Chang et al., 2006; Uzzell et al., 2003), reptiles (Zhao et al., 2008) and birds (Lynn et al., 2004; van Dijk et al., 2005; Xiao et al., 2006a). The name cathelicidin is derived from the similarity of the cathelicidin large middle domain to cathelin, a cathepsin L inhibitor originally isolated from porcine leukocytes (Ritonja et al., 1989). The number of cathelicidin variants within a species varies considerably between species, with humans, rhesus monkey, mice, rat, and guinea pig possessing only one gene, whereas eight or more cathelicidin genes have been found in pig, sheep and cattle (Braff et al., 2005; Frohm Nilsson et al., 1999; Nagaoka et al., 1997; Scocchi et al., 2009; Termén et al., 2003; Zhao et al., 2008).

2.1. Structural features

Cathelicidins are produced as inactive prepropeptides, consisting of a short signal peptide, a large cathelin-like propiece and a mature peptide. Upon release into the environment, the C-terminal mature peptide is activated by proteolytic cleavage and exerts its antimicrobial and immunomodulatory functions (Zanetti, 2005). Based on structural characteristics of their C-terminal mature HDPs, at least three subfamilies can be distinguished (Bals and Wilson, 2003; Zanetti, 2005): (i) α-helical peptides, linear peptides of 23–37 amino acid residues that adopt an amphipathic helical structure if in contact with environments mimicking biological membranes; (ii) β-hairpin peptides, short cyclic peptides (12–18 amino acid residues) formed by one or two intramolecular disulfide bridges; (iii) peptides containing an unusual proportion of one or two amino acids, such as tryptophan- (indolicidin, 13 amino acids) or proline/arginine-rich peptides. The α-helical cathelicidin peptides are the most widely spread of the three groups and found in all investigated mammalian species (Zanetti, 2005) and include all known chicken cathelicidins.

2.2. Modes of action

2.2.1. Antimicrobial activity

Mammalian cathelicidins possess potent antimicrobial activity against various bacteria, fungi, and enveloped viruses at micromolar concentrations (Zasloff, 2002). The cationic side chains of cathelicidins interact with the negatively charged components in the bacterial or fungal membrane. Subsequently, the hydrophobic side chains perturb the lipid bilayer resulting in transient pore-formation. Several models of pore formation have been suggested, *i.e.* the barrel-stave, carpet, and aggregate channel model. Microbial exposure to low peptide concentrations results in membrane permeabilization and a loss of proton motive force, while at higher concentrations complete lysis may occur. Peptides may internalize by self-promoted uptake and subsequently bind to negatively charged intracellular targets such as DNA, RNA and proteins leading to inhibition of DNA replication, protein synthesis and protein function. These mechanisms have been extensively reviewed elsewhere (Bals and Wilson, 2003; Hancock and Chapple, 1999; Nicolas, 2009; Shai et al., 2006) and will not be discussed in this review.