Multiple immune-modulatory functions of cathelicidin host defense peptides

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An essential function of innate immunity is initiating inflammatory responses to limit the spread of invading pathogens, followed by regulatory mechanisms aimed at resolving inflammation and returning the immune system to homeostasis. These meticulously regulated processes are triggered by various pathogen-associated molecular patterns or endogenous damage-associated molecular patterns. A group of natural peptides that have gained notoriety in recent years as immune-modulatory molecules contributing to both resolution of infections and inflammation, thus playing a role in maintaining homeostasis are host defense peptides (HDPs). These are gene-encoded cationic short peptides, less than 50 amino acids with an overall positive charge of +2 to +7, and ≥30% of hydrophobic residues. The two most well characterized families of HDPs in mammals are cathelicidins and defensins. We will focus on cathelicidin HDPs in this review.

Genes encoding cathelicidin HDPs have a highly conserved N-terminal cathelin domain in their precursor protein (Tomasinsig and Zanetti, 2005). This conserved cathelin domain has helped in the discovery of new cathelicidins from diverse species including non-mammalian species such as chicken, trout, and hagfish. The biological active mature mammalian cathelicidin peptides are processed from their precursor protein by proteolytic cleavage by serine proteases, e.g., proteinase 3, elastase, and kallikrein (Shinnar et al., 2003; Morizane et al., 2010). The biologically active mature cathelicidins are diverse in their sequence and structure, and can be classified into four structural groups; amphipathic α-helices (e.g., murine CRAMP), β-hairpin molecules (e.g., porcine protegrin 1), those with extended structures (e.g., bovine indolicidin), and cyclic peptides (e.g., bactenecin). Mammalian cathelicidins are found in granules of neutrophils as well as other cell types such as myeloid precursors, epithelial cells, mast cells, lymphocytes, and keratinocytes.

These peptides are expressed in a wide variety of tissues (oral cavity, skin, intestine, lungs, cervix, etc.) and found in body fluids such as plasma, breast milk, saliva, gastric juice, semen, sweat, and bronchoalveolar fluid (Nijnik and Hancock, 2009). The biologically active mature cathelicidin peptides have been demonstrated to mediate a wide range of activity from antimicrobial to immune-modulatory (discussed below). Some of the most well studied cathelicidins are human LL-37, murine CRAMP, bovine BMAP-28, and porcine PR-39.

PROTECTION AGAINST INFECTIONS

Decreased expression of cathelicidin HDPs has been associated with increased susceptibility to infections. For example, decreased expression of human cathelicidin LL-37 is linked to increased susceptibility to skin infections, frequent oral bacterial infections, severe periodontal disease, and cutaneous infections by the parasitic protozoan leishmania (Bowdish et al., 2005; Kulkarni et al., 2011). A recent study has demonstrated that the active metabolite of vitamin D induces the expression of LL-37 thus contributing to protection against tuberculosis (Jo, 2010). Similarly, the murine cathelicidin CRAMP is known to provide protection against streptococcus infections (Nizet et al., 2001). Thus, it is not surprising that research in this area was propelled by the interest of developing these peptides as alternate antibiotic-like therapy for infectious disease. However, it has been shown that the direct microbicidal activity of these peptides is often antagonized in the presence of physiological salt concentration, heparin, and serum factors (Bowdish et al., 2005). Also, microbial factors such as polysaccharides released by certain pulmonary bacterial pathogens antagonize the direct microbial killing property of these peptides (Benincasa et al., 2009). However, the fact remains that cathelicidins can indeed protect against a wide range of infections from bacteria, viruses, and parasites. As

cathelicidins have been also demonstrated to stimulate both innate and adaptive immune responses (discussed below), the ability of cathelicidins to contribute to resolution of infections is now thought to be primarily due to their role in host immunity.

ROLE IN IMMUNE-MEDIATED INFLAMMATORY DISORDERS

Altered expressions of cathelicidins have also been reported in auto-inflammatory or auto-immune diseases. Human LL-37 is found to be suppressed in atopic dermatitis and Crohn's disease (Ong et al., 2002; Wehkamp et al., 2007), but shown to be elevated in systemic lupus erythematosus (SLE) and rheumatoid arthritis (Paulsen et al., 2002; Sun et al., 2011). It has been proposed that LL-37 can complex with self DNA activating dendritic cells to contribute to the pathogenesis of SLE (Lande et al., 2011). Whereas, in psoriasis it has been hypothesized that LL-37 can act both as an effector and a regulator (Kanda et al., 2010). Furthermore, a recent study has shown that LL-37 can interfere in the activation of inflammasome contributing to suppression of pro-inflammatory responses in psoriasis (Dombrowski et al., 2011). Consistent with this, it has been hypothesized that LL-37 can protect against auto-immune diseases, which may be in part mediated by vitamin D (Bartley, 2010). Even though studies have demonstrated that altered cathelicidin expression is associated with chronic inflammatory auto-immune diseases, clarification of their specific roles in immune-mediated inflammation will require further investigations. Research in the last decade has established that cathelicidins mediate a wide range of immune functions including promotion of barrier repairs, chemokine and cytokine production, modulation of dendritic cell differentiation, and T-cell polarization, as well as demonstrate potent anti-sepsis and anti-inflammatory properties (discussed below). Elucidating the differential effects

of pro- and anti-inflammatory functions mediated by these peptides resulting in both immune activation and control of inflammation represents an exciting area of research.

CATHELICIDIN-MEDIATED IMMUNE ACTIVATION

A primary innate immune function mediated by cathelicidins is the facilitation of immune cell recruitment, either by direct chemoattractant properties or indirectly by inducing the production of chemokines. For example, human LL-37 and porcine PR-39 are direct chemoattractants for neutrophils, monocytes, T-cells, mast cells, etc. (Yang et al., 2001; Niyonsaba et al., 2002; Tjabringa et al., 2006). In addition, cathelicidins such as LL-37 can also promote chemotaxis by inducing the production of chemokines, e.g., MCP-1, RANTES, Gro-α, and IL-8 from both immune cells and other cell types such as epithelial cells and gingival fibroblasts (Mookherjee et al., 2006; Montreekachon et al., 2011). LL-37 also up-regulates the expression of chemokine receptors such as CXCR4, CCR2, and IL-8RB in macrophages (Scott et al., 2002). Mediating recruitment of leukocytes and thus aiding in phagocytosis to enhance clearance of pathogens is one of the critical innate immune functions of cathelicidin peptides. Furthermore, cathelicidins such as LL-37 synergistically enhances anti-infective immune responses in the presence of certain critical cytokines such as IL-1β and GM-CSF (Yu et al., 2007). Other innate immune activating properties of cathelicidins are (i) mediating protection against mycobacterium by promoting autophagy in macrophages (Yuk et al., 2009), (ii) prolonging the life span of neutrophils by inducing the expression of anti-apoptotic protein BcL-X$_L$ and inhibiting caspase-3 activity, thus enhancing phagocytosis by neutrophils (Nagaoka et al., 2006), and (iii) enhancing epithelial wound healing (Carretero et al., 2008).

Cathelicidins such as human LL-37 appear to be a link between the innate and adaptive immune responses by influencing dendritic cell activation and polarization of T-lymphocytes (Davidson et al., 2004; Bandholtz et al., 2006). LL-37 up-regulates the endocytic capacity of dendritic cells and enhances the secretion of cytokines that aid in the polarization of a Th1 immune response (Davidson et al., 2004). Apart from influencing the initiation of the adaptive immune response, recent studies have shown that cathelicidins also have a direct impact on lymphocytes. For example, murine CRAMP can directly alter T- and B-cell responses, promote and regulate humoral and cellular antigen-specific adaptive immune responses (Kurosaka et al., 2005; Kin et al., 2011). Overall, cathelicidins have a direct effect on immune cells influencing both innate and adaptive immunity against pathogenic attack. Most of the above mentioned immunity-related activity mediated by cathelicidins can be described as pro-inflammatory functions required for resolution of infections. However, these peptides also exhibit anti-inflammatory properties, thus playing a significant role in balancing inflammation and maintaining homeostasis.

CONTROL OF INFLAMMATION BY CATHELICIDINS

Peptides such as LL-37 and CRAMP have been demonstrated to confer protection in animal models of pathogenic sepsis (Cirioni et al., 2006), and have anti-inflammatory effects in "sterile" inflammatory diseases such as ulcerative colitis (Wong et al., 2012). Consistent with this, cathelicidin knock out mice show increased inflammatory responses compared to wild type (Morioka et al., 2008). Recent studies have also shown that synthetic cationic peptides derived from cathelicidins can indeed suppress inflammation in infection models (Scott et al., 2007) and in immune-mediated inflammatory models (Turner-Brannen et al., 2011).

Mechanistic studies have demonstrated that cathelicidins intervene at multiple points within the inflammatory cascade to suppress inflammation in a targeted fashion. For example, human and bovine cathelicidins alter the TLR-to-NF-κB pathway in the presence of exogenous inflammatory stimuli (e.g., endotoxin) and selectively suppress specific pro-inflammatory cellular responses such as TNF-α, TNFAIP2, IL-1β, and NFκB1 (Mookherjee et al., 2006). In contrast, anti-inflammatory mediators such as IL-10, TNFAIP3, NF-κB inhibitor NFκBIA are enhanced by these peptides (Mookherjee et al., 2006; Brown et al., 2011). It has also been shown that LL-37 can inhibit cellular immune responses triggered by IFN-γ, which is a key cytokine for polarization of Th1-responses (Nijnik et al., 2009). Another mechanism of inflammatory control demonstrated for cathelicidin peptides, e.g., PR-39, is by proteosome-mediated degradation of IκBα and subsequent inhibition of activation of NF-κB (Bao et al., 2001).

Intracellular uptake has been shown to be important for immunomodulatory activity of cathelicidins (Lau et al., 2005). This is mediated either by putative surface receptors (De et al., 2000; Lau et al., 2005) or by atypical endocytic pathways followed by interaction with intracellular receptor, e.g., GAPDH (Mookherjee et al., 2009). Specific receptor interaction for cathelicidin peptides and how this influences different immune-modulatory functions is yet to be completely resolved. The molecular mechanism of the anti-inflammatory activity of cathelicidins appears to be very complex, requires intracellular uptake, interaction with either putative surface or intracellular receptors, leading to the alteration of various signaling pathways (e.g., NF-κB, p38 and JNK MAPK, PI3K) with different kinetics.

The overall result of immunomodulatory functions of cathelicidin HDPs is the net balancing or control of inflammation without compromising immune responses that are required for resolution of infections. This duality or pro- and anti-inflammatory biological activities of these peptides has made them attractive agents to be explored as therapeutics. The distinct advantages of developing cathelicidins and their derivatives as therapeutics are (i) the ability to control inflammation without compromising the immune functions required to clear infections, and (ii) the unlikelihood of developing microbial resistances against these peptides, since most of these peptides influence the immune system under physiological conditions to control infections rather than direct microbicidal activity (Afacan et al., 2012).

SUMMARY

Cathelicidins have been defined to play multiple roles in immunity contributing to both resolution of infections and inflammation. The molecular mechanisms governing the multiple functions of these peptides in immunity is very complex, involving various signaling pathways and multiple transcription factors, and is influenced by

the cellular environment and extracellular signals. Moreover, the process of endocytic uptake or interaction with specific receptors and how this mediates the diverse immunomodulatory functions of cathelicidins is not completely understood. However, evidence in the last decade revealing the duality of pro- and anti-inflammatory functions of cathelicidins, resulting in the promotion of immune responses required for resolution of infections and at the same time controlling inflammation, has captured the interest of biomedical researchers. Consequently, there has been a keen interest in the development of these peptides, in particular their synthetic derivatives as therapeutics; as antimicrobials, anti-inflammatory agents, adjuvants, and in wound healing. The challenges however are limited pharmacokinetic or toxicology data, bioavailability, and high manufacturing costs. Establishing the immune-regulatory properties of HDPs such as cathelicidins and exploring their potential as immunomodulatory therapeutics represents an exciting avenue of research that is growing rapidly.

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