Pharmacology & Therapeutics 178 (2017) 132–140

Contents lists available at ScienceDirect

Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/pharmthera

Associate editor: S. Enna

Antimicrobial peptides: Role in human disease and potential as immunotherapies

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ARTICLE INFO

Available online 21 April 2017

Keywords:
Antimicrobial peptides (AMPs)
Synthetic peptides
Antibiotic resistance
Immune modulation
Infectious diseases
Inflammation
Vitamin D
Host-directed therapy

ABSTRACT

Antimicrobial peptides (AMPs) have evolved through billions of years as part of our innate immune system. These agents are produced by various cells throughout the human body and play important roles in our ability to respond to infections. In this review, we outline evidence linking AMP expression with a range of inflammatory and autoimmune human diseases. Finally, we highlight the promise of endogenous AMP induction for the treatment of disease (i.e., host-directed therapy) and briefly mention the different peptide drugs that are currently undergoing clinical trials.

Contents

Abbreviations: APDs, aroylated phenylenediamines; CD14, cluster of differentiation 14; CF, cystic fibrosis; COPD, chronic obstructive pulmonary disease; CXCL, chemokine (C-X-C motif) ligand; G-CSF, granulocyte-colony stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; hBD, human beta-defensin; HNP, human neutrophil peptide; IBD, inflammatory bowel disease; ICDs, immature phagocytic and dendritic cells; IL, interleukin; LPS, lipopolysaccharide; LTA, lipoteichoic acid; MDP, muramyl dipeptide; NF-κB, nuclear pathway kappa B; NOD2, Nucleotide-binding oligomerization domain-containing protein 2; PAMPs, pathogen-associated molecular patterns; PBA, 4-phenylbutyrate; PRRs, pattern recognition receptors; TLRs, toll-like receptors; VDR, vitamin D receptor.

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1. Introduction

Antimicrobial peptides (AMPs), also called host defense peptides (HDPs) for their immunomodulatory properties, are produced by virtually all organisms known on Earth. So far, >2500 such peptides have been identified. Although AMPs display a diversity of primary and secondary structures, they share certain commonalities, such as their overall positive charge due to their many Arg and Lys amino acid residues, and the presence of ~50% hydrophobic amino acids within their

http://dx.doi.org/10.1016/j.pharmthera.2017.04.002
0163-7258/

sequence that facilitate their interaction with membranes and further translocation into cells.

AMPs are capable of killing a broad range of microorganisms, including bacteria, fungi, parasites and viruses (Silva et al., 2016). Recently, a subset of these peptides and their synthetic derivatives have also been shown to act as potent inhibitors of microbial biofilms, which are associated with the majority (about two-thirds) of all infections in humans, and exhibit increased tolerance to treatment with numerous clinically available antibiotics (Anunthawana, de la Fuente-Núñez, & Hancock, 2015; Haney, Mansour, Hilchie, de la Fuente-Núñez, & Hancock, 2015). AMPs have also been shown to control the function of host cells and tissues involved in the host immune response, for instance by modulating the inflammatory response while boosting immunity by increasing the recruitment recruitment of leukocytes to the site of infection (Silva et al., 2016).

AMPs constitute excellent templates for the production of novel synthetic optimized agents with enhanced potency. However, the use of naturally occurring AMPs as therapeutic agents has some limitations that need to be overcome. These include lack of stability (particularly in vivo), potential toxicities of some AMPs (either towards host cells or in animal models), and their relatively large size (>20 aa), which increases overall production and manufacturing costs limiting the potential of these drugs as therapeutics. Rational design and computational biology strategies have been used to optimize the biological functions of AMPs in an attempt to eliminate adverse effects against host cells while retaining activity against target microbes (Fjell, Hiss, Hancock, & Schneider, 2011). Rational design of AMPs has also been used to reduce production costs by generating shorter primary structures without affecting biological function (Deslouches et al., 2013).

2. Natural AMPs and human diseases: roles in innate and adaptive immunity responses

Natural AMPs belong to an evolutionarily ancient and diverse group of molecules that are important components of the innate immune system (Nijnik & Hancock, 2009). As outlined earlier, AMPs are mostly cationic (net charge generally +2 to +9, due to excess Lys and Arg residues), short (10–50 amino acids), amphipathic molecules with heterogeneous structures and multiple modes of action (Wang & Wang, 2004). The role of AMPs in innate immunity is complex and includes protecting the host from infections through their rapid and broad-spectrum antimicrobial activity and immunomodulatory functionalities (Ganz, 2003). Indeed, AMPs are produced by virtually all organisms reported to date, and constitute an effective, rapid and non-specific first line of defense against invading pathogens. Interestingly, in humans these bioactive peptides can be generated by the cleavage of pro-peptides. Indeed, various researchers have demonstrated that endogenous human peptides can be generated by cleavage of other proteins belonging, for example, to the complement system or the coagulation cascade, which have also been shown to play important roles in host defense against pathogens (Nordahl et al., 2004; Papareddy, Kalle, et al., 2010; Papareddy, Rydengård, et al., 2010), or may be included within the structure of proteins or precursors, which may be defined as “cryptic” (Gaglione et al., 2017; Pane et al., 2016, 2017). The main feature of these peptides is the presence of a heparin-binding region, which has been used as a template to search for sequences that may correspond to new endogenous peptides (Andersson et al., 2004; Baglia, Badellino, Ho, Dasari, & Walsh, 2000; Shimazaki et al., 1998). Various other AMPs have been found in humans with a primary role in host protection against microbial infections (Wang, 2014). AMPs have been found in a wide variety of tissues or exposed surfaces including the skin (Bardan, Nizet, & Gallo, 2004), eyes (McDermott, 2004), oral cavity (Dale & Fredericks, 2005), ear (Bøe et al., 1999), airway (Bals, Wang, Zasloff, & Wilson, 1998), lung (Agerberth et al., 1999), female reproductive tract (King, 2000), cervical-vaginal fluid (Stock et al., 2009), intestines (Cash, Whitham, Behrendt, & Hooper, 2006), and urinary tract (Bates et al., 2004), in addition to other tissues and organs of the human body.

AMPs exert various biological functions within the immune system (innate and adaptive), including recruiting cells, inducing or modulating pro-inflammatory responses, stimulating cell proliferation, promoting wound healing, modifying gene expression, and killing cancer cells (Choi, Chow, & Mookherjee, 2012; Lai & Gallo, 2009; Steinstraesser, Kraneburg, Jacobsen, & Al-Benna, 2011). To date, the most thoroughly characterized mechanism of AMP activity within the immune system is the antagonistic effect they exert on the endotoxin lipopolysaccharide (LPS) of the outer membrane of Gram-negative bacteria. LPS is known to stimulate to stimulate the secretion of pro-inflammatory cytokines and, in severe cases, can lead to endotoxic shock (Mueller, Lindner, Dedrick, Schromm, & Seydel, 2005). Inhibition of LPS-induced cellular responses is a well-established property of several AMPs; however, the exact underlying mechanism has not yet been fully elucidated. In addition, peptides are capable of eliminating extracellular LPS through direct interactions with this molecule (Scott, Vreugdenhil, Buurman, Hancock, & Gold, 2000). Indeed, several studies have suggested that peptide binding to LPS leads to an aggregated LPS structure complex that can induce a series of cellular responses (Mueller et al., 2005). Some peptides also interfere with processes such as LPS ligation, thus preventing interactions between LPS and its receptor (Rosenfeld, Papo, & Shai, 2006; Scott et al., 2000). It has also been observed that certain AMPs can block interactions between the differentiation pool 14 (cluster of differentiation 14-CD14) and LPS, thus inhibiting subsequent release of proinflammatory cytokines (Rosenfeld et al., 2006; Scott et al., 2000). Human cathelicidin LL-37 and β-defensin represent classical examples of AMPs with immunomodulatory activity, as both peptides are capable of repressing LPS-induced responses, and target the nuclear pathway kappa B (NF-κB) (Mookherjee et al., 2006; Semple et al., 2011). Examples of interconnections between AMPs and human diseases are shown in Fig. 1

2.1. Skin infectious diseases

The skin has the largest surface area and is the most exposed of any organ of the body. Despite the effective protection provided by the skin barrier against external hazards, infections caused by bacteria, fungi or viruses are still very common. These infections often result from a break in the integrity of the skin, which enables pathogen entry into the dermis and subsequent establishment of the infection (O'Dell, 1998).

As mentioned earlier, AMP production constitutes one of the early mechanisms by which the host immune system provides protection against invaders. In fact, the skin plays a fundamental role in keeping pathogens at bay, as it is the first barrier of mammalian defense. Certain AMPs have been shown to be constitutively expressed in the skin (Rieg, Garbe, Sauer, Kalbacher, & Schittek, 2004), while others are induced following infection by microbes or skin lesion (Kreuter et al., 2006). Over the past decades, numerous studies have demonstrated the roles of different AMPs in the context of infectious and inflammatory diseases of the skin. Examples include psoriasis (Christophers & Henseler, 1987), atopic dermatitis (Ong et al., 2002), rosacea (Yamasaki et al., 2006), Kostmann syndrome (Pütsep, Carlsson, Boman, & Andersson, 2002), severe congenital neutropenia (Kostmann, 1956), lupus erythematosus (Frohm et al., 1997), nickel contact hypersensitivity (Frohm et al., 1997), erythema toxicum neonatorum (Marchini et al., 2002), lesions of acne vulgaris (Chronnell et al., 2001), folliculitis (Oono, Huh, Shirafuji, Akiyama, & Iwatsuki, 2003), scleroderma (Kreuter et al., 2006), cutaneous T-cell lymphoma (Escher et al., 2006), basal cell carcinoma (Gambichler et al., 2006), viral infection (Conner, Nern, Rudisill, O'Grady, & Gallo, 2002), and skin wounds (Gallo et al., 1994; L. Zhang et al., 2015).

Several studies in the last two decades have further reported on the role of AMPs as an important defense mechanism in the skin. These