The Critical and Multifunctional Roles of Antimicrobial Peptides in Dermatology

Toshiya Takahashi, MD, PhD, Richard L. Gallo, MD, PhD*

KEYWORDS

• Antimicrobial peptides • Cathelicidin • Defensins • Immunology • Rosacea • Psoriasis • Atopic dermatitis

KEY POINTS

- Antimicrobial peptides (AMPs) not only kill bacteria but also control inflammation and other host responses.
- The main AMPs that are secreted in skin are cathelicidin and human β-defensins.
- Cathelicidin and β-defensins are 2 of many families of antimicrobial peptides in the skin that increase in response to injury.
- In psoriatic and rosacea skin, AMPs are overexpressed and promote inflammation. On the other hand, in atopic dermatitis, some AMPs fail to be appropriately induced and enable infection.
- Control of the expression and action of AMPs can be of therapeutic benefit for skin diseases.

INTRODUCTION

Skin is the physical and immunologic armor of the body. Both the physical and immune defense system of the skin combine to accomplish functions essential to life, including preventing invasion by pathogenic microbes such as bacteria, fungi, viruses, and parasites, and maintaining homeostasis with commensal microorganisms. Antimicrobial peptides and proteins (AMPs) have an essential role in this immunologic armor and enable epithelial surfaces to cope with many microbial challenges. They are evolutionarily ancient innate immune effectors that are produced by almost all plants and animals.[1] More than 1800 AMPs have been identified and more than 20 AMPs have been found in skin.[2] They typically are small (12–50 amino acids residues), have positive charge and amphipathic structure,[2] features that allow them to interact with negatively charged phospholipid head groups and hydrophobic fatty acid chains of microbial membranes, and kill some organisms by disrupting the microbial membrane and release of cytosol components.[3,4]

However, AMPs are not only natural antibiotics. Recently, common human skin disorders such as rosacea, psoriasis, and atopic dermatitis (AD) have been linked to an abnormality of AMPs. These skin diseases cannot be attributed only to microorganisms. Contrary to the term antimicrobial, AMPs not only directly kill or inhibit the growth of microorganisms[5] but also modify host inflammatory responses by a variety of mechanisms, including action as chemotactic agents, angiogenic factors,

Funding Sources: R.L. Gallo receives funding from the NIH through grants R01AI116576, R01AR064781, R01AI052453, R21AR0675478, U19AI117673 and P01HL107150.
Conflict of Interest: None.
Department of Dermatology, University of California, San Diego, La Jolla, CA 92093, USA
* Corresponding author.
E-mail address: rgallo@ucsd.edu

Dermatol Clin 35 (2017) 39–50
http://dx.doi.org/10.1016/j.det.2016.07.006

Abbreviations and acronyms

AD	Atopic dermatitis
AMP	Antimicrobial peptide
DAMPs	Danger or Damage-associated molecular patterns
FPRL1	Formyl peptide receptor-like 1
hBD	Human β-defensin
HIV	Human immunodeficiency virus
IFN	Interferon
IL	Interleukin
KLK	Kallikrein
MCET	Mast cell extracellular trap
mDC	Myeloid dendritic cells
pDC	Plasmacytoid dendritic cell
PSMγ	Phenol-soluble modulin-γ
Th cells	T-helper cells
TLR	Toll-like receptor
TNF	Tumor necrosis factor
UV	Ultraviolet
VDRE	Vitamin D response element

and regulators of cell proliferation.[2] This article summarizes how they participate in human skin diseases and what the knowledge of AMPs will do for clinical dermatology.

ANTIMICROBIAL PROTEIN FUNCTION: BASIC

Key AMPs of the skin's repertoire are the cathelicidins, the first AMP discovered in mammalian skin[6] and β-defensins.[7] The single cathelicidin gene (*CAMP*) encodes a precursor protein, hCAP18 in humans.[8] This protein can be alternatively cleaved to generate several active AMPs, including the 37-amino-acid peptide LL-37.[9] In contrast to cathelicidin, approximately 90 β-defensin genes have been identified in mice and humans. Both cathelicidins and β-defensins are antimicrobial against a diverse range of skin pathogens, including gram-negative and gram-positive bacteria, fungi, viruses, and parasites.[2] In normal skin, keratinocytes produce various AMPs at lower levels to defend the skin barrier,[10] whereas cathelicidin precursor protein and mature peptide are the most abundantly expressed by resident mast cells.[11] Mast cells normally occupy positions around blood vessels and store large amounts of cathelicidin in preformed granules. This localization places the AMPs derived from mast cells in an ideal position to resist infections after skin injury and inoculation with pathogens.[12] Moreover, AMPs has been detected in mast cell extracellular traps (MCETs).[13] Once inflamed, skin produces cathelicidin through increased expression of CAP18 by keratinocytes, adipocytes,[14] and increased local deposition by recruited neutrophils.[15–17]

Though many AMPs target essential cell wall or cell membrane structures through enzymatic or nonenzymatic disruption, AMPs can also function as potent immune regulators by signaling through chemokine receptors and by inhibiting or enhancing Toll-like receptor (TLR) signaling.[18] AMPs seem to function not only under stimulus from pathogen-associated molecular patterns but also as triggered by danger-associated or damage-associated molecular patterns, including urea[19] and nucleic acids.[20] This means that AMPs are not only antimicrobial.

The expression, secretion, and activity of most AMPs are tightly controlled. Cathelicidins are synthesized as propeptides. Serine proteases are responsible for the processing of cathelicidins into various sizes. In neutrophils, the propeptide is removed by proteinase 3,[21] whereas processing is carried out by kallikreins (KLKs, also known as stratum corneum tryptic enzyme) in keratinocytes.[22] Interestingly, the antimicrobial activity of cathelicidin peptides differs by their size.[23] Processing mechanisms generate the active forms of AMPs in skin and the mechanism is useful to prevent potential harmful effects of these proteins on mammalian cell membranes.[24] A particularly surprising observation came with the recognition that the human cathelicidin gene is under transcriptional control of a vitamin D response element (VDRE).[25,26] Following skin injury or infection, 25(OH)D3 is hydroxylated by the enzyme cytochrome p450, 27B1 (CYP27B1) to $1,25(OH)_2D3$, and this is stimulated locally by activation of TLR2 or local cytokines such as tumor necrosis factor (TNF) or type I interferons (IFNs).[27,28] This local enzymatic event enables rapid induction of CAMP expression through binding of $1,25(OH)_2D3$ to the VDRE. These observations suggest that AMP expression could be influenced by serum vitamin D level,[29] dietary vitamin D,[30] or vitamin D generated by exposure of the skin to sunlight.[31] This implies that the nutritional environment is probably a source of important signals that control AMP expression. Conversely, LL-37 also transactivates epidermal growth factor receptor and downstream signaling in epithelial cells.[32,33]

Similarly, β-defensins are expressed as propeptides; however, the processing mechanism remains to be established.[34]

ANTIMICROBIAL PROTEIN FUNCTION IN VIVO

AMPs not only provide resistance to infection by killing bacteria but may also determine microbiota composition and limit access of the microbiota to