Antimicrobial peptides and the skin immune defense system

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Our skin is constantly challenged by microbes but is rarely infected. Cutaneous production of antimicrobial peptides (AMPs) is a primary system for protection, and expression of some AMPs further increases in response to microbial invasion. Cathelicidins are unique AMPs that protect the skin through 2 distinct pathways: (1) direct antimicrobial activity and (2) initiation of a host response resulting in cytokine release, inflammation, angiogenesis, and reepithelialization. Cathelicidin dysfunction emerges as a central factor in the pathogenesis of several cutaneous diseases, including atopic dermatitis, in which cathelicidin is suppressed; rosacea, in which cathelicidin peptides are abnormally processed to forms that induce inflammation; and psoriasis, in which cathelicidin peptide converts self-DNA to a potent stimulus in an autoinflammatory cascade. Recent work identified vitamin D3 as a major factor involved in the regulation of cathelicidin. Therapies targeting control of cathelicidin and other AMPs might provide new approaches in the management of infectious and inflammatory skin diseases. (Reprinted from J Allergy Clin Immunol 2008;122:261-6.)

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Abbreviations used
AMP: Antimicrobial peptide
1,25D3: 1,25 dihydroxy vitamin D3
25D3: 25 hydroxy vitamin D3
pDC: Plasmacytoid dendritic cell
TLR: Toll-like receptor

Antimicrobial peptides (AMPs) were first thought to act as endogenous antibiotics whose function was only to kill microbes. Today, although it is clear that AMPs act to form a chemical shield on the surface of the skin, they are also thought to trigger and coordinate multiple components of the innate and adaptive immune system.[1,2] Many cell types that permanently reside in the skin produce AMPs, including keratinocytes, sebocytes, eccrine glands, and mast cells.[3-6] Circulating cells recruited to the skin, such as neutrophils and natural killer cells, are also significant contributors to the total amount of AMPs present.[7] Cathelicidins and β-defensins are the most well characterized of the AMPs found in the skin, but a list of the known cutaneous AMPs can identify more than 20 individual proteins that have shown antimicrobial activity (Table I).[6,8-39] This extensive list of skin-derived AMPs is complicated by the nature of the experimental assays and the concentrations used to identify antimicrobial activity. Thus many molecules better known for other biologic activity, such as α-melanocyte–stimulating hormone or serine leukocyte protease inhibitor, can also be considered as functional AMPs in the skin.[8] Unfortunately, because adequate animal model systems do not always permit direct testing of the AMP activity of many of these peptides, it remains difficult to determine the primary function of a peptide that shows antimicrobial and additional biologic functions. In general, the AMPs are structurally extremely diverse but considered together only because of their antimicrobial activity.

Cathelicidins are an important AMP family in the skin because they were the first AMP[5] found in mammalian skin, and since then, the most compelling animal models that support their antimicrobial function have been compiled.[40-42] Human cathelicidin is often referred to by one of its peptide forms (LL-37) or by the nomenclature assigned to its precursor protein (hCAP18).[43,44] Peptide processing has emerged as a critical element in the control of cathelicidin activity. In its nascent form hCAP18 is thought to be inactive. On cleavage by serine proteases, the generation of the mature peptide results in multiple potential activities.[45,46] The 37-amino-acid peptide LL-37 forms an α-helix in solution and can disrupt both bacterial membranes and viral envelopes.[8] In addition, cathelicidin LL-37 shows antifungal activity.[47] Furthermore, LL-37 can interact with mammalian cells to trigger a host response. These functions have been called the *alarmin* activity of AMPs,[48] and cathelicidin peptides can act through multiple potential mechanisms. Alarmin functions include direct interactions of LL-37 with cell-surface receptors, such as the formyl-peptide receptor–like 1 or G protein–coupled receptors, resulting in direct effects on intracellular signaling pathways (Fig 1).[8,49,50] Furthermore, LL-37 was shown to influence Toll-like receptor (TLR) signaling in immune cells through interaction with the cellular membrane and epidermal growth factor receptor transactivation and to increase intracellular Ca^{2+} mobilization.[51-55] Cathelicidin also synergizes with endogenous inflammatory mediators to enhance the induction of specific inflammatory effectors through a complex mechanism involving multiple pathways.[56] As a result, cathelicidin peptides increase cell migration and secretion of chemokines and other signaling molecules from activated cells (Fig 1).[2,50] All these activities complement the role of the cathelicidins as direct antimicrobial agents, and they have

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TABLE I. Mammalian peptides with antimicrobial activity in skin (AMPs)*

AMP	Reference
AMPs identified in resident cells	
Cathelicidins	Frohm et al (1997)[9]
	Marchini et al (2002)[10]
β-Defensins	Harder et al (1997)[11]
	Liu et al (1998)[12]
Bactericidal/permeability-increasing protein (BPI)	Takahashi et al (2004)[13]
Lactoferrin	Cumberbatch et al (2000)[14]
Lysozyme	Marchini et al (2002)[10]
Dermcidin	Schittek et al (2001)[15]
	Murakami et al (2002)[6]
Histones	Rose et al (1998)[16]
S100A15	Büchau et al (2007)[17]
RNase 7	Harder et al (2002)[18]
AMPs identified in infiltrating cells	
Cathelicidins	Gallo et al (1994)[19]
	Marchini et al (2002)[10]
α-Defensins	Harwig et al (1993)[20]
Lactoferrin	Caccavo et al (2002)[21]
Granulysin	Stenger et al (1998)[22]
Perforin	Stenger et al (1998)[22]
Eosinophil cationic protein (ECP)/RNase 3	Domachowske et al (1998)[23]
Eosinophil-derived neurotoxin (EDN)/RNase 2	Domachowske et al (1998)[24]
RANTES	Tang et al (2002)[25]
AMPs identified as proteinase inhibitors	
hCAP18/LL-37 prosequence (cathelin-like domain)	Zaiou et al (2003)[26]
Secretory leukocyte proteinase inhibitor (SLPI)/antileukoprotease	Wingens et al (1998)[27]
Elafin/skin-derived antileukoprotease (SKALP)	Simpson et al (1999)[28]
	Meyer-Hoffert et al (2003)[29]
P-cystatin A	Takahashi et al (2004)[13]
Cystatin C	Blankenvoorde et al (1998)[30]
AMPs identified as chemokines	
Psoriasin	Glaser et al (2005)[31]
Monokine induced by IFN-γ (MIG/CXCL9)	Cole et al (2001)[32]
IFN-γ–inducible protein of 10 kd (IP-10/CXCL10)	Cole et al (2001)[32]
IFN-γ–inducible T cell α chemoattractant (ITAC/CXCL11)	Cole et al (2001)[32]
AMPs identified as neuropeptides	
α-Melanocyte–stimulating hormone (α-MSH)	Cutuli et al (2000)[33]
Substance P	Kowalska et al (2002)[34]
Bradykinin	Kowalska et al (2002)[34]
Neurotensin	Kowalska et al (2002)[34]
Vasostatin-1 and chromofungin (chromogranin A)	Tasiemski et al (2002)[35]
Secretolytin (chromogranin B)	Tasiemski et al (2002)[35]
Enkelytin and peptide B (proenkephalin A)	Tasiemski et al (2002)[35]
Ubiquitin	Kieffer et al (2003)[36]
Neuropeptide Y	Lambert et al (2002)[37]
Polypeptide YY/skin-polypeptide Y	Lambert et al (2002)[37]
Catestatin	Radek et al (2008)[38]
Adrenomedullin	Allaker et al (1999)[39]

*References are limited because of space restrictions.

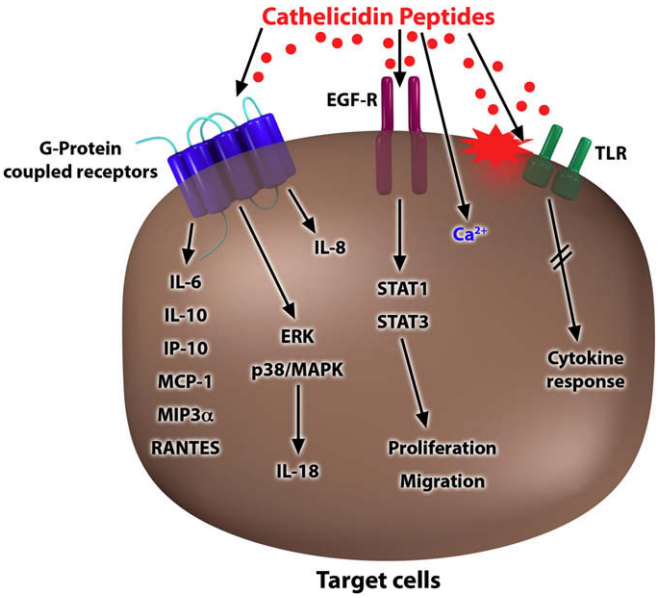

FIG 1. Models for cell activation by cathelicidins. Multiple mechanisms have been proposed for cathelicidins to stimulate a cellular response. Responses are dependent on activation of G protein–coupled receptors and transactivation of the epidermal growth factor receptor or secondary to intracellular Ca^{2+} mobilization or a change in cell membrane function, leading to alterations in receptor responses. Finally, cathelicidins can influence the function of TLRs through both direct and indirect pathways. *EGF-R*, Epidermal growth factor receptor; *IP-10*, IFN-γ–inducible protein 10; *MCP-1*, monocyte chemoattractant protein 1; *MIP3α*, macrophage inflammatory protein 3α; *ERK*, extracellular signal-regulated kinase; *MAPK*, mitogen-activated protein kinase; *STAT*, signal transducer and activator of transcription.

established their role as essential defense molecules in innate immune responses.

ROLE OF CATHELICIDIN IN INFLAMMATORY SKIN DISEASES

The presence of cathelicidin in the skin has been shown to offer increased protection against bacterial and viral infections.[40,57] In healthy skin keratinocytes express low amounts of cathelicidin. On infection or barrier disruption, cathelicidin is strongly induced.[9,58,59] However, in several common skin diseases the normal barrier against infection is diminished or the control of inflammation is abnormal. One example is atopic dermatitis. Here viral and bacterial infections perpetuate cutaneous inflammation and complicate successful therapy. Observations of the expression of AMPs of atopic patients demonstrated that the process of AMP induction was greatly reduced in lesional skin.[60] The resulting diminished antimicrobial barrier correlated with an increased susceptibility of these patients to microbial superinfections.[57,61] Diminished inducibility of cathelicidin and defensins in atopic dermatitis appears to be partially a consequence of the altered cytokine micromilieu.[57] In particular, T_H2 cytokines, such as IL-4 and IL-13, suppress the induction of AMPs and contribute to a disturbed cutaneous antimicrobial response. Thus in this disorder a decrease in the amount of AMPs released by the skin barrier contributes to disease.

Other associations of AMPs with skin diseases appear to be a consequence of host stimulatory effects rather than action as an