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REVIEW ARTICLE

LL-37; The Human Epithelial Antimicrobial Peptide and Innate Immunity System

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ABSTRACT

Antimicrobial peptides (AMPs) are the innate immune system effector molecules that serve to keep the integrity of the host versus potentially adverse microorganisms safe. Cathelicidins are a family of antimicrobial proteins organised in the peroxidase-negative neutrophil granules. The known biological actions reside in the C-terminal end and to become active it must be cleaved from the holoprotein. One of the members of this family is LL-37 which apply antimicrobial activity against both gram-positive and gram-negative bacteria and exhibit a wide spectrum antimicrobial activity versus many microorganism pathogen including viruses and fungi. LL-37 is a 37 amino acid generated polypeptide via extracellular cleavage of the C-terminus with the sequence as, NH2 LLGDFFRKSKEKIGKEFKRIVQRIKDFLRNLVPRTES-COOH and is cleaved from hCAP18 during healing of tissue cultured skin wounds to enhance innate immunity of body.

Keywords: Innate immunity system, Antimicrobial peptides, LL-37, Cathelicidin, Keratinocytes

The human innate immune system defend the body against the attacks of microorganisms via different defensive protocols such as complement-mediated lysis, engulfment, constitution of neutrophil extracellular snares, and release of antimicrobial peptides (AMPs). Antimicrobial peptides are important contributors of the epithelial defensive mechanism and a number of AMPs such are defensin, cathelicidin, LL-37, LLAA etc have been described as the most important contributors. Human antimicrobial peptide LL-37 is a member of cathelicidin and is derived from granulocytes. All cathelicidin-related AMPs are family of peptides found in macrophage lysosomes and polymorphonuclear leukocytes (PMNs) and also in keratinocytes. LL-37 defence the body via its diversity of immunomodulatory functions like bactericidal action, chemotaxis, chemokine sprinkle and antisepsis affect**.**

AMPs act as the effector molecules of innate immunity to keep the integrity of the host versus potentially adverse microorganisms safe. The antimicrobial peptides are conserved through progress and are palmate ranging from plants to mammals with hundreds of its described varieties (1, 2).

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Cathelicidins

Cathelicidins are groups of AMPs and first of the cathelicidin which was discovered in rabbit granulocytes as a 18 kDa pioneer protein which was able to bind the bacterial lipopolysaccharide (LPS) (3). This intriguing exclusivity prompted further investigation on the cathelicidin precursor protein, characterizing that the C-terminal end is to be ascribed for the LPS-binding activity. Moreover, this 37-amino acid peptide proved to have a widespread antibacterial affect against both gram-positive and gram negative bacteria.

LL-37

One of the cathelicidin gene family is hCAP18, which is contained of more than 20 members in different species, and is believed to be the only cathelicidin protein in humans (4, 5). In 1995, the cathelicidin protein of human was recognized and called hCAP18 (6). The discovery of this peptide signed the beginning of more than a decade of investigations on this exciting and interesting antimicrobial peptide family. LL-37, also known as hCAP18, is the C-terminal part of the only human cathelicidin identified to date called human cationic antimicrobial protein (hCAP) (7).

The C-terminus of this protein also had a 37-amino acid-long peptide with an extensive antibacterial activity (8). Later, this peptide was named LL-37, because it starts with two leucines. The holoprotein is comprised of an N-terminal fragment, cathelin, that is conserved through species and a C-terminal part, LL-37, which deliberates antimicrobial activity against both gram-positive and gram-negative bacteria (4, 9).
In humans, only a first have been known so far; among which the defensins and the hCAP18 have been implicated in epithelial defence (10-12).

Antimicrobial and cytotoxic activity of LL-37

LL-37 was initially found for its antimicrobial characteristics (13-16). It shows a wide spectrum of antimicrobial activity against viral, bacterial and fungal pathogens (17, 18) with microbicidal activity changing against various species and strains.
Table 1 gives an overview of the antimicrobial data published on a number of gram negative and gram positive bacteria, as well as on the *Candida albicans*. Antiviral activity was checked on two viruses. Only little antiviral activity by LL-37 was described for the herpes simplex virus (19). On the other hand, a decrease of virus replication was recognised for the vaccinia (smallpox) virus (20).

Significance of LL-37

Extract of wounds include antimicrobial substances, containing both LL-37, and several defensin (21). The human antimicrobial peptide hCAP18 is modulated in skin epithelium as a normal response to trauma and injury, which is agree with and affirm recent published reports (22).

In chronic non healing wounds, however, just low levels of hCAP18 are identified and immune reactive protein is missing in ulcer edge epithelium. hCAP18 is stimulated during recovery of tissue cultured skin wounds, and that re-epithelialization is prevented by antibodies against LL-37 in a dependent manner of concentration. These findings suggest that LL-37 plays a significant role in wound closure, strengthening the innate immunity of human beings (23).

Structure characteristics of LL-37

LL-37 is a 37 amino acid cationic peptide produced by extracellular cleavage of the C-terminus of the 18-kDa hCAP18 protein by serine proteases of the kallikrein family in keratinocytes (24) and neutrophils proteinase 3 (25, 26) as shown in Figure 1. It has been shown that LL-37 is produced via cleavage of hole length hCAP18 and has abundant immunomodulatory action depending on contexts of environmental and cellular. The 18-kDa propeptide hCAP18 is generated and stored in granules. Following stimulation by flammatory signals, hCAP18 is released into the extracellular

surroundings and proteinase 3 in neutrophils cleaved it and kallikrein of the keratinocytes (green dots) and the N-terminal 37 amino acid form the α helical conformation of LL-37 peptide that then be dimerizes and trimerizes in solution. Exposure to LL-37 consequence in recruitment of inflammatory cells, suggestion of M1 macrophages, and stimulus of inflammatory responses like as inflammasome function. However, LL-37 has powerful antiinflammatory affects like as neutralization of TLR4 activation by LPS, down regulation of inflammatory cytokine responses, and inhibiting invasion, offensive and inflammatory responses to pathogenic microorganism. (39)

The sequence of LL-37 is NH2 LLGDFFRKSKEKIGKEFKRIVQRIKDFLRNL VPRTES-COOH. Its positive charge allows it to preferentially related with negatively charged phospholipid membranes (32). More, it supposes a primarily α-helical conformation during membrane interactions terminating in unilateral separation of its hydrophobic residues (33). This permits for membrane penetration, formation and organization of transmembrane pores and bacterial lysis (34, 35). Cellular membranes associated and affiliate with cholesterol, including those found in mammals, are preserve from the pore-forming affects of LL-37 (36); otherwise, this result can be dominate by higher concentrations of this peptide (37).

LL-37 is capable of forming aggregates and mass in solution and lipid bilayers thus, unlike other AMPs, keep safe from proteolytic degradation.

Conclusion

In the past decade, the biological investigations of AMPs, comprising the cathelicidin LL-37, has consequently increased. Currently, it is well established that LL-37 is an antibacterial and immunomodulatory factor by varying membrane dynamics via binding to intracellular targets.

Table 1. Compilation of reported antimicrobial properties of LL-37 (7)

Organism	LL-37 activity	Reference
Gram Positive Bacteria		
Streptococcus		
Group A	1–16 μM	(22)
Group B	≥32 μM	(22)
Group C	16 μM	(22)
Staphylococcus aureus	>32 μM	(22)
Enterococcus faecalis	30 μg/ml	(12)
Staphylococcus epidermidis	7.6 μg/ml	(14)
Listeria monocytogenes	1.5 μg/ml	(14)
Enterococcus faecium	0.7 μg/ml	(14)
Lactobacillus acidophilus	19 μM	(27)
Bacillus subtilis	2.7 μg/ml	(14)
Bacillus megaterium	0.2 μM	(9)
Gram Negative Bacteria		
Escherichia coli	>32 μM	(22)
Pseudomonas aeruginosa	16 μg/ml	(12)
Actinobacillus actinomycetemcomitans	10 μg/ml	(16)
Salmonella typhimurium	3.5 μg/ml	(15)
Salmonella minnesota	0.2 μg/ml	(15)
Burkholderia cepacia	79 μg/ml	(14)
Capnocytophaga ochracea	11 μg/ml	(16)
Klebsiella pneumoniae	4.2 μg/ml	(15)
Proteus mirabilis	5.7 μg/ml	(14)
Stenotrophomonas maltophilia	1.9 μg/ml	(14)
Proteus vulgaris	2.5 μg/ml	(14)
Capnocytophaga sputigena	7.5 μg/ml	109
Capnocytophaga gingivalis	9 μg/ml	(16)
Salmonella serovar dublin	2.8–6.0 μM	(28)
Spirochaete		
Leptospira interrogans	144–225 μg/ml	(29)
Borrelia spp.	450 μg/ml	(29) and (30)
Treponema pallidum	450 μg/ml	(29)and (31)
Yeast		
Candida albicans	>20 μg/ml	[15]

Some natural AMPs, such as LL-37, after being investigated at clinical level, will hopeful supply a new option of treatment and cure against infections. In many immunocompetent cells a complicated array of responses upon LL-37 treatment may also supply a new alternative for immunomodulatory molecules. As a result of its function on keratinocytes, LL-37 may be used as a pleiotropic factor against infection and as a wound healing improvement in situations such as acute and drastic burn wound (38). New LL-37 therapeutic intervention pathway is valuable for future investigations.

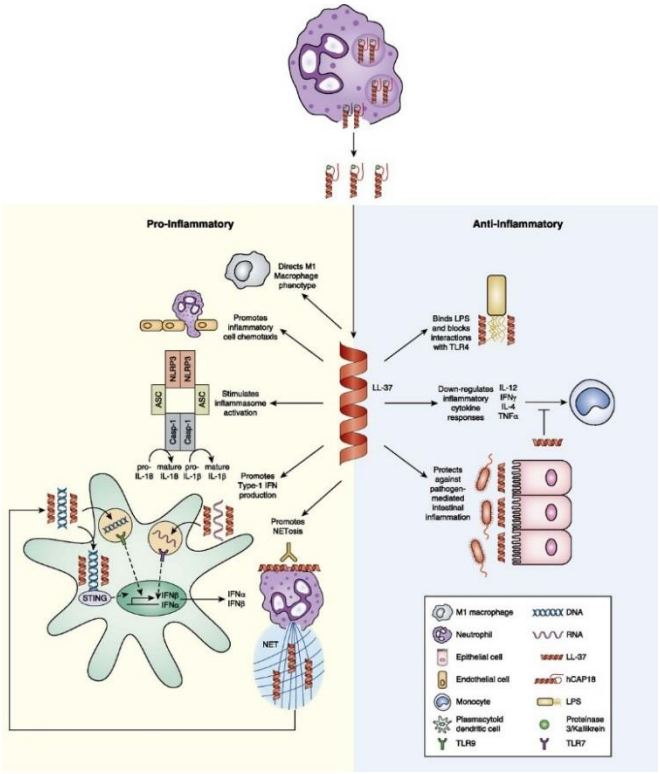

Figure 1. Production Mechanism of LL-3.

Conflict of Interest:

There is no any conflict of interest with any person or organization regarding this manuscript.

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