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EDITORIALS

Antimicrobial functions of the human cathelicidin hCAP18

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Abbreviations:

AMPs	= antimicrobial peptides
hCAP	= human cathelicidin anti-microbial protein
VD	= vitamin D
hCAP18	= human cathelicidin anti-microbial protein with molecular mass of 18 kDa
1,25-OH VD	= 1,25-dehydroxy vitamin D3
PMN	= polymorphonuclear cells
VDR	= vitamin D nuclear receptors
TLR 2	= toll-like receptors 2
LPS	= lipopolyssacharide
MIC	= minimum inhibitory concentration

ABSTRACT

*Naturally occurring antimicrobial peptides (AMP) are effectors-molecules of the **innate immune defence** system of each living cell. The cathelicidin family is a subclass of mammalian AMP, synthesized in most blood cells and epithelial tissues. These peptides display a complex role in the innate immunity through their wide antimicrobial spectrum (antibacterial, antiviral, antifungal) as well as by mediating inflammation and tissue repair mechanisms. The antiinfectious mechanism of cathelicidins is highly regulated by vitamin D receptors and it is associated with other molecules of the innate immune response (interleukins, growth factors, membrane receptors, leukotrienes). Superior to any antibiotic, cathelicidin could be considered as a prototype molecule for the synthesis of complex drugs with both antiinfectious and immunomodulatory potential.*

Key words: cathelicidin, antimicrobial peptides, innate immunity, antimicrobial

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INTRODUCTION

Antimicrobial peptides (AMPs) are effectors molecules of the innate immune system, produced by all forms of life. Once activated by infectious or non-infectious factors, these molecules play a central role in the antimicrobial defence.

The cathelicidins family is a quite ancient component of the AMPs providing a complex host defence tool. This polypeptides family, present in mammals only, consists of various members emerging from a unique and highly conserved prosequence, named "cathelin". The "cathelin" represents the inactive domain of all cathelicidins. It is activated by action of serine proteases to generate a high specific multifunctional domain. This active domain varies among species, yielding multiple peptides, with a remarkable variety of sizes, sequences, and structures.

Humans exhibit a single type of cathelicidin, "human cathelicidin anti-microbial protein" (hCAP) comprising an active C-terminal domain of 37 aminoacids, called LL-37 due to the length of 37 amino-acid residues with two leucine residues. The human hCAP is often referred to as LL37. Three research groups (Cowland, Larrick Agerberth, 1995) independently isolated the hCAP peptide. Thereafter, numerous in vitro studies have confirmed the antiinfectious role of hCAP as well as its close relation to the metabolism of vitamin D (VD) and the other mechanisms of innate immunity (1). The cellular mechanism of hCAP involves manifold actions: direct microbial lysis by a membrane effect, immune receptors binding (activation or blockage), cytokines or chemokines expressing. ❑

MOLECULAR STRUCTURE OF hCAP18

The hCAP peptide has a molecular mass of 18 kDa (hCAP18) and adopts α-helical structure with 2 disulfide bridges located between 2 molecules of cysteine (C85–C96 and C107–C124) (2). The position of the 4 cysteine molecules is well conserved between species. The hCAP18 molecule contains the inactive N-terminal domain (where cathelin is located) as well as the C-terminal antimicrobial peptide, LL37. After the hCAP18 activation, LL-37 is released into the plasma. The LL37 subsequent antimicrobial activity is dictated by the α-helical structure. The ionic composition, pH or salt environment concentration affecting α-helical structure impedes on the LL37 antibacterial activity. Thus, a higher plasma pH preserves the α-helical structure and ensures the peptide's microbicidal activity. At a lower pH (pH<2) however, the peptide is largely unfolded and inactive. The hCAP18 posses an amphiphilic structure, with a hydrophobic and a hydrophilic fragment which allows the interaction both in an aqueous environment and with lipid membranes. The positive charge of the peptide accounts for the electrostatic interaction between the cationic peptide and the negative microbial envelope. (3) ❑

GENETIC STRUCTURE OF hCAP18

The 2kb CAMP gene, comprising 4 exons and 3 introns, encodes the hCAP18. Exons1-3 encodes the signal peptide and the cathelin domain, whereas the 4th exon indicates the site to be cleaved and generate the active peptide LL-37. The CAMP gene was sequenced and localized on chromosome 3 (3p21) in the proximity of other genes with similar functions such as: the gene for "Macrophage colony-stimulating factor 1", an antiviral cytokine, the gene for "Hepatocyte growth factor like-protein", a multifunctional factor needful in tissue repair and angiogenesis, the gene for "Collagen VII alpha-1 polypeptide", a protein responsible for tissular integrity and the gene for "Natural killer-tumour recognition", a molecule involved in the activity of T killer lymphocytes. According to a study hCAP18 up-regulates 49 genes, controlling the expression of many chemokins or chemokins receptors (CXCR-4, CCR2) and of some cytokines (IL 8) (4). CAMP transcription is enhanced during bacterial, viral, fungal or protozoa infection. 1,25-dehydroxy vitamin D3 (1,25-OH VD) is also a powerful inductor of cathelicidin mRNA transcription. (5) ❑

SYNTHESIS AND REGULATION OF THE hCAP18 RELEASE

The hCAP18 is synthesized in a wide number of cells. In healthy subjects, hCAP18 plasma level ranges between 50-80 ng/ml, a significant amount of which is released by blood cells: polymorphonuclear cells (PMN),

monocytes, lymphocytes and mastocytes. The hCAP18 is also secreted in epithelial cells like keratinocytes or the cells of digestive, respiratory and genital endothelia. The hCAP18 is permanently synthesized and stored as a preproprotein. Following antigenic cell stimulation, the precursor is enzymatically cleaved to the terminal peptide LL37, the biologically active domain. LL37 is released into the plasma, extracellular space or into various secretions (saliva, milk, and sudoripary secretion, seminal and amniotic fluid). The hCAP18 exerts a crucial role in the rapid innate defence through the permanent synthesis in sentinel cells (such as contact cells of epithelia and endothelia) as well as the rapid release into the plasma by blood cells, after specific stimulation.

VD mediates the hCAP18 synthesis through the vitamin D nuclear receptors (VDR) expression. A high number of microbial molecules (like lipoteichoic acid, peptidoglycans and atypical lipopolyssacharides from *Leptospira* and *Porphyromonas gingivalis* species, lipomannan from mycobacteria family, various viral or fungic antigens) activate Toll-like receptors 2 (TLR 2).These ubiquitous receptors of innate immunity trigger a VD mediated response, via hormonally active 1,25-OH VD. The 1,25-OH VD interacts with VDR, thus activating the CAMP gene for expressing hCAP18. Repressing or enhancing the VDR expression was demonstrated to alter the level of hCAP18. In addition, in the presence of infectious stimuli, the level of VD also up-regulates the expression of TLR2, enabling an increased response to the TLR activation. Certain polymorphisms of the gene encoding TLR2 or VDR lead to serious sepsis infections with Gram positive bacteria or mycobacterial infections. This evidence places VD as the most important factor in the regulation of hCAP18 and could explain the antimicrobial action attributed to this vitamin. (6,7) ❑

THE ACTIONS OF hCAP18

The hCAP18 possesses multiple but insufficiently documented actions. Its "in vivo" interaction with other molecules of the innate immune system, such as defensins, chemokins, interleukins and growth factors is extremely complex. However, "in vitro" experiments are incapable of offering a complete study of this molecule so far (8). Various studies have reported the following actions of hCAP18:

- the antimicrobial activity (9);
- the chemotactic PMN, monocytes, lymphocytes and mastocytes activity (10);
- the antitoxic activity by binding to the lipopolyssacharide (LPS) endotoxin of Gram negative bacilli (4);
- the activation of epithelia cells during trauma and skin infections succeeded by cutaneous reepithelization (11);
- the histamine release from the mast cells (12);
- the angiogenesis (13);
- the stimulation of gene expression (4);
- the regulation of dendritic cell differentiation (14). ❑

THE ANTIINFECTIOUS ACTIONS OF hCAP18

The antimicrobial action is prompt and unselective against bacteria, viruses and fungi. The hCAP18 exhibits different actions at different concentrations: the lowest concentration for the antibacterial effect towards Gram positive bacteria is of 0, 75μM, while the antibacterial level required towards the Gram negative bacteria, is over 5 μM. Chemotactic activity was observed at a concentration of 10μM. Above 15μM the hCAP18 is cytotoxic for body cells and need to be rapidly inactivated by binding to the plasma lipoproteins (apolipoprotein A). The hCAP18 antibacterial effect is related to the environment physical and chemical conditions and is also enhanced by an imunomodulatory and chemotactic associated activity (15).

1. The role of hCAP18 in bacterial infections

The direct antimicrobial action of hCAP18 requires a minimum inhibitory concentration (MIC) ranging between 1-50μm depending on the tested species. Moreover, the action of hCAP18 against bacteria has been better observed in Gram positive species. MIC was shown to vary between 1-32μM for the following streptococci: group A Streptococcus (16 μM), group B Streptococcus (32 μM), group C Streptococcus (16 μM) (16). However, in vitro tests on Gram negative bacteria revealed a MIC between 12-50 μM as follows: P. aeruginosa-12.5 μM, E. coli-25 μM and K. pneumoniae-50 μM. Some highly resistant species of P. aeruginosa, E. coli and S. aureus proved sensitive to hCAP18 (9). In addition, other species of resistant

E. faecalis and S. epidermidis were found susceptible to hCAP18 (17). The hCAP18 can bind to the lipoteichoic acid as well as to the lipoarabinomannan, preventing the activation of macrophages in staphylococcal infections and tuberculosis (4). Unfortunately, due to the various employed methods and differences in the pH and ionic media, the tests results remains difficult to assess and to compare. Furthermore, is hard to evaluate in these tests the immune mechanisms triggered by hCAP18. Thus, we make allowance of increasing chemotactism and large blood cells migrations during inflammatory process, which may raise the hCAP18 level much over the basal concentration. In rare cases certain proteolytic enzymes of resistant bacteria (18) could destroy hCAP18 as well as other AMPs. Table 1 shows the pathogenic agents sensitive to the hCAP18 actions in various "in vitro" experiments.

Bacteria: *E. coli, P. aeruginosa, K. pneumoniae, Shigella genus*, *S. typhimurium, S. aureus* (methicilinoresistant *species included*), the group A, group B and group C of *Streptococcus spp., L. monocytogenes, Enterococcus species* (including *vancomycin–resistant enterococci*), *Actinobacillus, Capnocytophaga, Porphyromonas, Prevotella, H. pylori, N. meningitidis*
Viruses: *Human immunodeficiency virus, Herpes simplex virus, Human papilloma virus, Vaccinia virus, Lentiviruses, Adenoviruses*
Fungi, protozoa and Chlamydia: *Candida albicans, T. cruzi, Ch. trachomatis, Ch. pneumoniae*

TABLE 1. Pathogenic agents sensitive to the hCAP18 actions

In addition to its bactericidal effect, hCAP18 is able to neutralize LPS produced by Gram-negative bacteria, protecting against endotoxic shock through three possible mechanisms (19):

- blocking the release of α-TNF at CD14 lymphocytes level (a crucial effect in various experiments);
- blocking other compounds of the inflammatory process like nitric oxide, tissue factor, prostaglandins (PGE2), chemokines, etc.;
- inhibiting TLR4 dendritic cells receptors, thus preventing their activation and response to the LPS.

Neutralization of LPS is expected at a minimum concentration of 12.5μg/ml.

The major hCAP18 antibacterial role was proved on mice depleted for CAMP gene (knockout mice) often suffering from keratoconjunctivitis (20), sepsis, meningitis (21) or cutaneous (22), gastrointestinal (23) and urinary (24) infections. A change in the level of hCAP18 has been observed on humans, in some skin infections like psoriasis, rosaceea, and atopic dermatitis (25, 26) and also in respiratory and urinary infections (27, 24).The congenital absence of defence peptides (hCAP18 and defensins) in human leads to Kosmann syndrome (severe congenital neutropenia). This is transmitted according to a recessive autosomal pattern and consists in a deficiency of mature mielocytes to express hCAP18 and defensins (28). In such cases a normal number of PMN still is not enough to prevent severe recurrent infections and periodontitis (29).

2. The role of hCAP18 in viral infections

The hCAP18 directly interacts with viral receptors (30), lipid membranes, viral envelope and viral DNA (31). Furthermore, its immune modulating action is accompanied by the up-regulating action of the interferon and chemokins (32). These mechanisms prevent the cell virus entrance and viral synthesis simultaneous with infected cells lysis. The antiviral actions are difficult to assess in experiments due to the difficulty to explore the complex immune modulating action played by hCAP18 in the antiviral defence.

hCAP18 and other AMPs inhibit the human immunodeficiency virus (HIV) replication through three mechanisms: by direct HIV inactivation (33), by interfering with HIV replication at the CD4 T lymphocytes level (34) and by binding to the gp120 receptor and preventing the intracellular HIV passage (35). The hCAP18 could play a significant role out from the first stages of HIV infection by protecting the intestinal epithelium during HIV enteropathy, an important event in the future outcome of the HIV disease. As a result of the premature intestinal permeability in HIV infection, frequent microbial translocations are to be expected. This exposes HIV patients to repeated intestinal diseases and to a subsequent continuous antigenic stimulation. Consequently this may conduct to a high LPS level in the bloodstream of these patients. Local peptides like hCAP18, by inactivating LPS at the gastrointestinal mucosa and tissue repair actions, enable HIV enteropathy remission and prevent the CD4 T lymphocytes to be destroyed in the early stages of the disease. Using hCAP18 to relieve HIV enteropathy could be therefore

considered as a possible supportive treatment of this infection. At the same time hCAP18 ensures HIV patients protection at the level of the genital and respiratory mucosa, reducing the number of opportunistic infections. Despite these favourable results, hCAP18 appears to require high concentrations for its modulating effect in lentiviruses infections or for its virulicidal potential (for example the half maximal inhibitory concentration IC_{50} needed in wild HIV strains is of 88 μg/ml while immune modulation requires concentrations of over 30-50 μg/ml).

High levels of hCAP18 and defensins have been reported in human papillomavirus infections like condyloma acuminatum and verruca vulgaris, two infections with a high neoplastic conversion risk (36). The hCAP18 synthesis was also experimentally proved in keratinocytes which had previously been infected with vaccinia virus, a poxvirus (37), in H. simplex virus infections (38) or in lentivirus infected cells (39).

However, additional studies are required to understand the action of hCAP18 in other viral infections.

3. The role of hCAP18 in mycobacterial infections

Epithelial cells and alveolar macrophages serve as the first line of defence in tuberculosis. Mycobacterial infections of these cells induces AMPs, including hCAP18, which posses a mycobactericidal role by directly permeating the mycobacteria cell membrane. hCAP18 synthesis in *M. tuberculosis* infections was experimentally proved in several types of cells (epithelial cells, neutrophils, alveolar macrophages and monocyte-derived macrophages) (40). Another experiment proved that hCAP18 is induced by epithelial cells after *M. bovis* BCG stimulation as well. hCAP18 is also supposed to be prematurely released during acute *M. tuberculosis* infection and does not seem to be of any importance in the late immunity.

4. The role of hCAP18 in fungal infections

hCAP18 is induced in keratinocytes during infections with dermatiphytes such as *Trichophyton, Epidermophyton, Microsporum* or in potentially invasive fungal infections ***(Candida albicans)***. Only a few studies have so far investigated the role of hCAP18 in fungal infections. Hence, mostly superficial skin infections have been associated with the hCAP18 presence in keratinocytes and in sudoral secretion (41). ❑

CLINICAL USE OF hCAP18

The AMPs study is still at the beginning. hCAP18 could be considered as a candidate in antimicrobial therapy owing to its wide bactericidal spectrum (including high resistant species), chemotactic potential and immunomodulatory activity. By comparison with the hCAP18 complex actions, the synthetic antibiotics are unable to induce the immune mechanisms, having only a selective and limited microbial spectrum. Skin infections and septic shock prevention are the two most important hCAP18 applications at the present. One promising usage would be associated hCAP18-antibiotic treatment, which would add an immune modulating potential to the antibacterial role. Unfortunately the correlations of hCAP18 with the rest of immune mechanisms are insufficiently studied. Recent studies regarding the high level of hCAP18 in tumoral cells like pulmonary (42), ovarian (43) and breast (44) neoplasia or in inflammatory diseases like arthritis (45), atherosclerosis (46) or dermatitis, urges to caution and even raises questions on the beneficial effects of this peptide. ❑

CONCLUSION

The hCAP18 is a defensive peptide present in humans only, with a complex antiinfectious and immune modulating potential. hCAP18 synthesis is triggered in infections, inflammations and traumatic lesions. The hCAP18 actions initiates both antiinfectious and tissue repair mechanisms. Due to the large antimicrobial spectrum, the hCAP18 plays a central prophylactic role, preventing infections at the site of all the epithelial tissues (respiratory, cutaneous, intestinal, and genital). Depending on the receptor with which it interacts in the antiinfectious process, hCAP18 promotes inflammation as a defence factor, or has a protective anti-inflammatory action – such is the case of sepsis induced by the LPS of Gram-negative bacteria. The tight link already proven, between the hCAP18 synthesis and VDR, could modify the status of VD, advancing it as an essential defence factor of the innate immune system. ❑

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