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Protective effects of Cathelicidin against glomerulonephritis through promotion of host defense

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Abstract

Cathelicidin-related antimicrobial peptides are a family of polypeptides found in lysosomes of macrophages and polymorphonuclear leukocytes (PMNs). Some of these peptides can assume an alpha-helical conformation, others contain one or two disulfide bonds, still others are Pro- and Arg-rich, or Trp-rich. Higher levels of human cathelicidin antimicrobial protein (hCAP18), which are up-regulated by vitamin D, appear to significantly reduce the risk of death from infection in dialysis patients. Using in vitro and in vivo models of kidney infection, we demonstrate key antimicrobial and host immunomodulatory properties of cathelicidins. To directly assess the role of endogenous cathelicidin in the development of glomerulonephritis, WT and mCRAMP KO mice were provided with 5% DSS to induce glomerulonephritis. Some mice groups were administered with E. coli DNA I.P. Our findings showed that mCRAMP KO mice develop more severe glomerulonephritis. These data demonstrate key roles for cathelicidins in host defense against glomerulonephritis and the potential to inform the development of synthetic analogues to modulate specific host-pathogen interactions as novel antimicrobial therapeutics.

Key words: Cathelicidin, Glomerulonephritis, E. coli DNA, mCRAMP KO mice

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Introduction

Cathelicidin-related antimicrobial peptides are a family of polypeptides found in lysosomes of macrophages and polymorphonuclear leukocytes (PMNs) [1]. Some of these peptides can assume an alpha-helical conformation, others contain one or two disulfide bonds, still others are Pro- and Arg-rich, or Trp-rich [2]. Higher levels of human cathelicidin antimicrobial protein (hCAP18), which are up-regulated by vitamin D, appear to significantly reduce the risk of death from infection in dialysis patients [3].

Cathelicidin LL37 is an effector molecule of the innate immune system that is important in defense against microbial pathogens. Cathelicidins have also been proposed to play a role in

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the nonspecific defense against tumors [4], angiogenesis, and wound healing [2]. IFNα is a type I interferon that functions in antiviral, antiproliferative, and immunomodulatory activities [5].

Antineutrophil cytoplasmic antibody-associated vasculitis (AAV) is necrotizing vasculitis with few or no immune deposits that predominantly affects small vessels and is associated with antineutrophil cytoplasmic antibodies (ANCA) specific for myeloperoxidase (MPO-ANCA) or proteinase 3 (PR3-ANCA) [6]. MPO and PR3 are in the lysosomes of monocytes and the primary granules of neutrophils, and are released when neutrophils and monocytes are activated by ANCA [7].

The role of cathelicidin LL37 in pathogenesis of different human diseases has been investigated by several research groups, mostly in the field of autoimmune and autoinflammatory diseases [8]. Cathelicidin LL37 is overexpressed in inflamed skin in patients with psoriasis [9]. Human cathelicidin LL37 and its fragments inhibit HIV-1 replication and the enzymes essential to the lifecycle of HIV, including HIV reverse transcriptase, HIV protease, and HIV integrase [10]. Plasma concentrations of cathelicidin LL37 are significantly higher in active hepatitis C virus infection and inactive hepatitis B virus infection, implicating cathelicidin LL37 in certain forms of hepatitis caused by hepatitis C virus and hepatitis B virus infections [11].

Human cathelicidins are involved in mucosal immunity of the respiratory tract, gastrointestinal tract, genitourinary tract, and eye [12]. Human cathelicidin is overexpressed in head and neck squamous cell carcinoma, and is strongly correlated with radiotherapy effectiveness [13].

Materials and Methods

Animals

Homozygous wild-type (*Cnlp*$^{+/+}$, WT) and CRAMP knockout (*Cnlp*$^{-/-}$, KO) mice were generated from breeding pairs of heterozygous (*Cnlp*$^{+/-}$, HZ) 129/SVJ mice deficient in CRAMP expression [14]. All protocols were approved by the Institutional Animal Care and Use Committee of the Department of nephrology, University of Manitoba, Canada.

Polymerase Chain Reaction

Mouse genotypes, *Cnlp*$^{-/-}$ (KO) and age-matched wild-type (WT) mice, were verified by PCR performed on tail genomic DNA, as described previously [15]. Genomic DNA was isolated from the tails of 3-to 4-week-old mice using reagents (DirectPCR Lysis Reagents; Viagen, Los Angeles, CA) and a genomic DNA isolation kit (Invitrogen, Carlsbad, CA) according to the manufacturer's specifications.

PCR was performed with reagents obtained from Invitrogen on the genomic DNA isolated from the WT and KO mice. The specific primers used were CRAMP. forward 5′-TGTTTTCTCAGATCCTTGGGAGC-3′ and reverse 5′-AATTTTCTTGAACCGAAAGGGC-3′, 241 bp; *Neo* (the knockout gene):

forward 5′-CCAGGGACTTCCATCCAGTAGAC-3′ and reverse 5′-AGACTGCCTTGGGAAAAGCG-3′, 88 bp. The PCR reaction included an initial 5-minute

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denaturation at 94°C. Amplification of the cDNA was performed for 35 cycles: denaturation, 95°C for 30 seconds; annealing, 60°C for 30 seconds; and extension, 72°C for 1 minute. A DNA ladder (HyperLadder I; Midwest Scientific, St. Louis, MO) was used as a marker (M). PCR products were visualized on 2% agarose gels by using a gel documentation system (Alpha Imager; Alpha Innotec, San Leandro, CA).

Viable Bacterial Counts

Control and challenged kidney of five mice per group (WT or KO mice) were harvested at 1, 3, 7, 14, and 21 days PI and homogenized on ice in 1 mL of sterile PBS at a pH of 7.4. For the quantitation of viable bacteria, a 100-*μ*L aliquot from the homogenate was serially diluted (10-fold dilutions) in sterile PBS. Duplicate aliquots (20 *μ*L) of each dilution, including the original homogenate, were plated onto nutrient broth agar.

Plates were incubated for 14 to 16 hours at 37°C and the number of colonies counted. The mean cfu is expressed as $\log^{10}$ number per cornea ± SEM. Data were examined statistically by using an unpaired Student's *t*-test, with $P < 0.05$ being considered significant.

Myeloperoxidase Assay

Myeloperoxidase (MPO) activity was determined by a method previously reported by [14], using the homogenate prepared as just described. Hexadecyltrimethylammonium bromide (final concentration of 0.5% wt/vol in 50 mM phosphate buffer [pH 6.0]) was added to 90 *μ*L homogenate. Samples were sonicated for 10 seconds in an ice bath and then subjected to three freeze–thaw cycles before centrifugation at 8000*g* for 20 minutes at 4°C.

Ten-microliter aliquots of the resulting supernatants were pipetted in triplicate into a flat-bottomed microtiter plate, and the enzymatic reaction was started by the addition of 90 *μ*L 0.0167% (wt/vol) *o*-dianisidine dihydrochloride and 0.002% (vol/vol) H2O2 in PBS. The change in absorbance was continuously monitored for 30 minutes at 450 nm with a plate reader and compared to a standard curve on the same plate. The standard curve was prepared from purified MPO (Calbiochem, San Diego, CA).

Results are expressed as relative units of MPO activity ± SEM (1 unit is proportional to 2 × 105 infiltrating neutrophils)43 per cornea. Data were compared statistically by unpaired Student's *t*-test with values of $P < 0.05$ being considered significant.

Enzyme-Linked Immunosorbent Assay

Homogenates prepared as described earlier were centrifuged at 4000*g* for 20 minutes at 4°C, and the resultant supernatants were immediately frozen at −80°C until required for assay. IL-1*β*, IL-6, TNF-*α*, MIP-2, KC, and VEGF levels in supernatant samples were measured in triplicate for each sample using specific ELISA kits (R&D Systems) as per the manufacturer's instructions. The data were analyzed by Student's *t*-test with values of $P < 0.05$ being considered significant.

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Statistical analyses

The experiments were performed in triplicate at least three separate times. Data are presented as the mean ± standard error of the mean and were analyzed using GraphPad Prism software 5 (GraphPad Software, San Diego, CA, USA). Where appropriate, either two-tailed Student's *t* tests or the Kruskal–Wallis and Mann–Whitney *U* tests were used. Differences were considered significant at $P < 0.05$.

Results

Release of LL37 and IFNα in the kidney

To assess the roles of LL37 and IFNα in renal inflammation, we evaluated the presence and localization of LL37 and IFNα in renal from Homozygous wild-type (*Cnlp*$^{+/+}$, WT) and CRAMP knockout (*Cnlp*$^{-/-}$, KO) mice. LL37 expression occurs predominantly during crescentic GN. As autoinflammatory conditions such as psoriasis can be driven by pDCs, which produce large amounts of IFNα, we next examined the expression of IFNα in the kidney tissues. Immunostaining revealed the co-localisation of IFNα and LL37 in the kidney tissues from AAV patients. However, there were only mild immunofluorescence signals stained with IFNα and LL37 in the renal tissues from patients without crescents.

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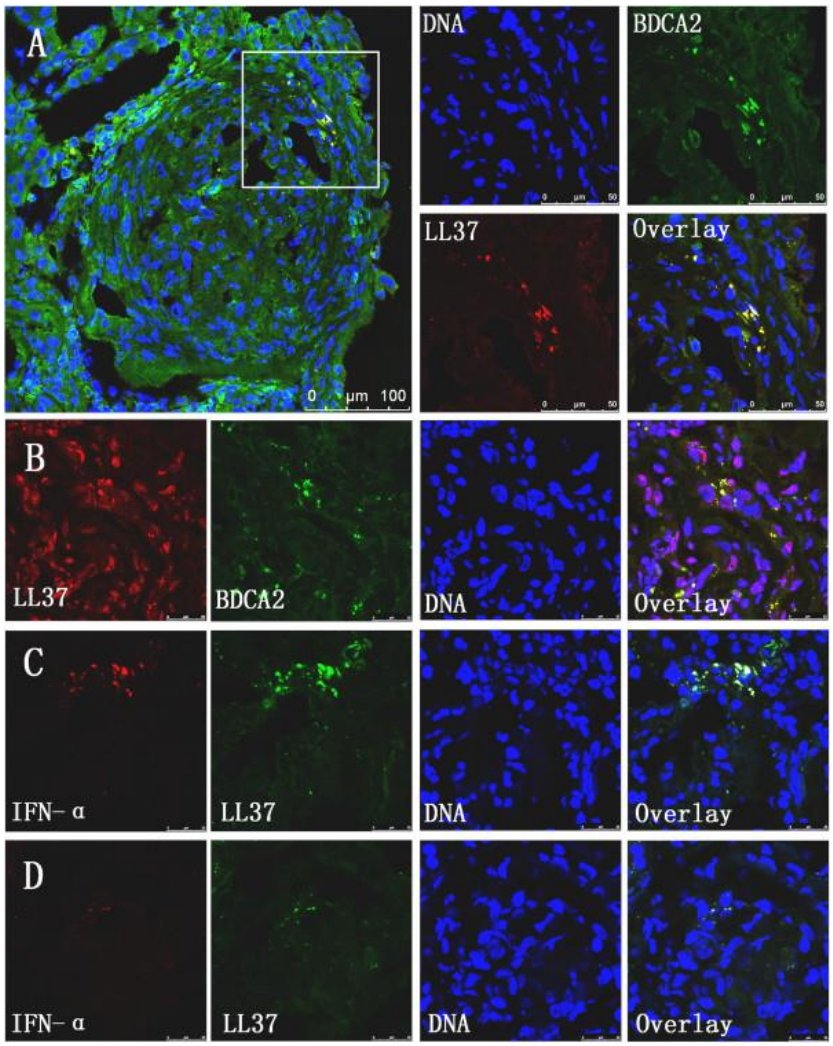

Figure 1.

Expression of LL37, IFNα and BDCA2 in anti-neutrophil cytoplasmic antibody-associated vasculitis patients with crescentic glomerulonephritis. (A), (B) Representative images showing the co-localisation of LL37 (red) and BDCA2, a marker of plasmacytoid dendritic cells (green), in the glomeruli of frozen renal biopsy sections after immunofluorescence staining. (C) Co-localisation of interferon alpha (IFNα; red) and LL37 (green) in renal biopsy sections from anti-neutrophil cytoplasmic antibody-associated vasculitis (AAV) patients with crescentic glomerulonephritis (GN). (D) Co-localisation of IFNα (red) and LL37 (green) in renal biopsy sections from AAV patients without crescentic GN.

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Autoantibodies to LL-37 and raised serum levels of LL-37 but no correlation with disease parameters in SLE

We investigated the presence of autoAbs to LL-37 in Homozygous wild-type (*Cnlp*$^{+/+}$, WT) and CRAMP knockout (*Cnlp*$^{-/-}$, KO) mice. We detected significantly higher levels of IgG autoAbs to LL-37 in SLE sera compared to healthy controls ($p<0.001$) (sensitivity 18,62%, specificity 97,01%), but not in RA (Fig. 1A). Specificity of the anti-LL-37 antibodies was confirmed by inhibition of the reactivity when sera were preincubated with LL-37 (Fig. 1B). Together with anti-LL-37 autoAbs, also serum levels of LL-37 peptide were raised in 13,91% of patients with SLE and in 11,63% of patients with RA but not in sera from healthy donors (Fig. 1C).

However, in contrast to previous reports [3], the levels of autoAbs to LL-37 in sera of the two cohorts tested did not correlate to either clinical or laboratory disease parameters of SLE, such as SLEDAI, anti-dsDNA autoAbs, CRP, IFNα (Fig. 1D), or organ involvement (data not shown). Moreover, no correlation was shown in individuals with SLE over the course of the disease between anti-LL-37 and change in SLEDAI. In line with that, there was no significant correlation of serum levels of LL-37 peptide and disease activity (Fig. 1E), organ involvement, or treatment (not shown). Serum levels of LL-37 peptide did also not correlate with anti-LL-37 autoAbs.

M1 Binds Immature Cathelicidin to Block Antimicrobial Peptide Generation

To examine whether M1 sequestration of LL-37 is functional in an infection context, we performed pulldown analysis using whole lysates from neutrophils, the major producers of the human defense peptide (Sørensen et al., 2001). Surprisingly, the major cathelicidin form detected was uncleaved hCAP18 (Figure 2A). This was confirmed by FACS analysis, where recombinant hCAP18 bound the GAS surface in an M1-dependent manner (Figure 2B, 2C). Surface plasmon resonance confirmed a high differential affinity of M1 protein to both LL-37 and hCAP-18. Compared to M49 protein, calculated K_d values for M1 indicated 53-fold stronger binding to LL-37 (1.18 μM vs. 62.67 μM) and 10-fold stronger binding to hCAP-18 (0.92 μM vs. 9.07 μM) (Figure 2D)

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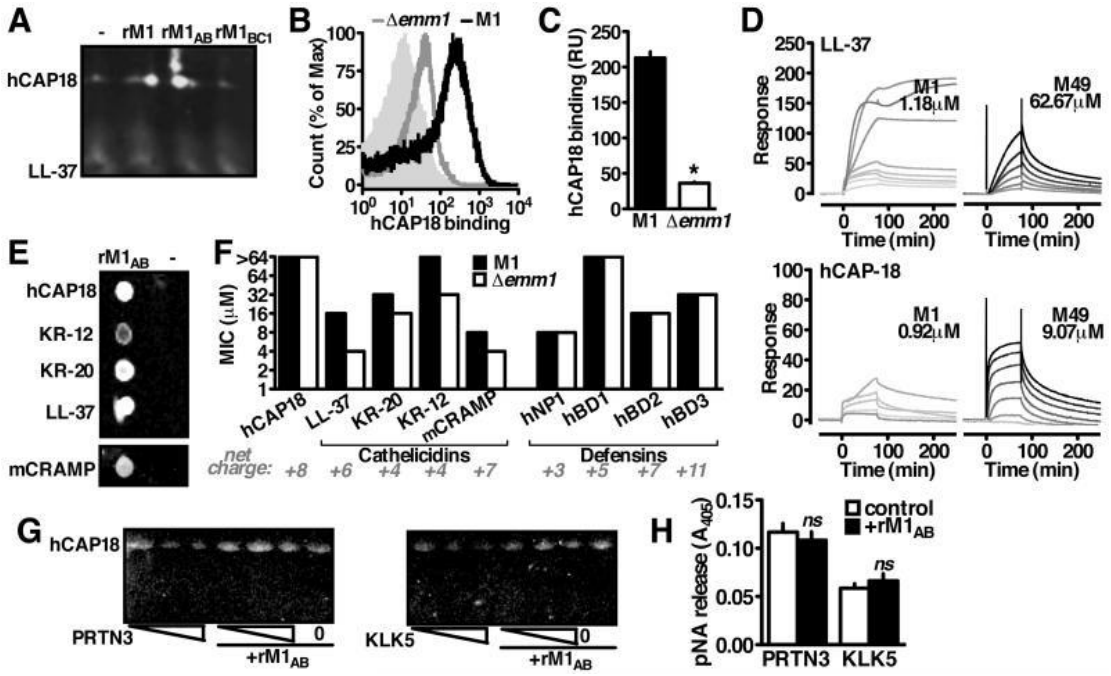

Figure 2.

M1 Binds Immature Cathelicidin to Block Antimicrobial Peptide Generation

(A) Interaction between rM1 and cathelicidin from neutrophil lysate by pulldown analysis and Western blot using anti-LL-37 antibody. (B, C) FACS detection of recombinant hCAP18 on the bacterial surface with anti-LL-37 antibody indicates Δ*emm1* GAS binds significantly less hCAP18 than wild-type GAS. (D) Representative sensorgrams from surface plasmon resonance analysis of M1 or M49 protein binding to immobilized LL-37 or hCAP18. Greyscale indicates concentration of M protein analyte in two-fold dilutions starting from 80 M (black) to 78.125 nM (lightest grey), starting from 5 μM (M1-LL-37), 80 μM (M49-LL-37), 1.25 μM (M1-hCAP18), or (D) 80 μM (M49-hCAP18). (E) Pulldown analysis with rM1 as bait for full-length (hCAP18) or truncated (LL-37, KR-20, KR-12, mCRAMP) forms as shown by dot blot probed with anti-LL-37 antibody (B). (F) Resistance of wild-type and Δ*emm1* GAS to full-length cathelicidin and the antimicrobial peptides from the cathelicidin (LL-37, KR-20, KR-12, mCRAMP) and defensin (hNP1, hBD1, hBD2, hBD3) families. (G) Cleavage of recombinant hCAP18 by increasing amounts of proteinase-3 (PRTN3) or kalikrein-5 (KLK5) (1, 2, 5 enzymatic units) in the presence or absence of rM1, as visualized by Western blot with anti-LL-37 antibody. (H) Enzymatic activity of proteinase-3 or kalikrein-5 in the presence of rM1. Figures are representative of at least 3 independent experiments.

In addition to binding LL-37 and hCAP18, M1 also bound the peptides KR-20 and KR-12 (Figure 2E), the most active processed forms of cathelicidin expressed by keratinocytes in human skin (Yamasaki et al., 2006). This activity was not limited to human cathelicidin, as the active murine form, mCRAMP, was also bound (Figure 2E). Consistent with binding cathelicidin family peptides, M1 protected GAS from killing by KR-20, KR-12, LL-37, and mCRAMP, but not from the similarly charged defensin-family peptides α-defensin-1 (hNP1), β-defensin-1 (hBD1), β-defensin-2 (hBD2), and β-defensin-3 (hBD3) (Figure 2F).

Unprocessed hCAP18 lacked antimicrobial activity (Figure 2F), consistent with previous reports that only the cleavage products are active (Zaiou et al., 2003). Antimicrobial binding and killing are coupled properties of its cationic charge (Lai and Gallo, 2009), so it was surprising immature cathelicidin interacted with the bacterium without toxicity.

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M1 protein binding of immature cathelicidin suggested that possibility that the proteolytic maturation of cathelicidin into antimicrobial peptides could be altered. Indeed, M1 inhibited hCAP18 processing by neutrophil proteinase-3 (PRTN3) [16] and keratinocyte kallikrein-5 (KLK5) (Yamasaki et al., 2006) (Figure 2G). M1 did not inhibit proteinase-3 or kallikrein-5 processing of another substrate (Figure 2H), indicating that M1 is not acting broadly as protease inhibitor. Instead, this suggests that hCAP18 is protected from proteolytic activation when complexed with M1, allowing GAS to inhibit the generation of antimicrobial peptides

Discussion and conclusion

The innate immune system provides organisms with a rapid, non-specific first line of defense against colonization by pathogenic microorganisms. The components of innate immunity include the barrier function of the skin, reduced pH of the stomach, the sweeping motion of the cilia in the airway to remove inhaled pathogens, and chemical defenses which include host defense peptides [17].

These gene-encoded defense molecules, initially known as antimicrobial peptides (AMPs), are a diverse collection of peptides that participate in several aspects of innate immunity, and may also provide the basis for the design of novel therapeutic agents. Numerous reviews have been written on the diversity of these peptides, their structure and activities *in vitro* and *in vivo*, and genetics and gene regulation (see, for example [18].

While the antibiotic properties of secretions were observed as early as Fleming [19], the presence of broad-spectrum antimicrobial activity in blood cells was first described in the 1950s [8]. Subsequently, it was discovered that phagocytic cells produce intracellular cationic AMPs in response to infection [21], as did innate immune cells in insects [20]). In 1983, Lehrer and Selsted purified two AMPs with three intralinked cysteines from rabbit lung macrophages, which were later named defensins [22]. Subsequent examination of different cell types, including those of the myeloid lineage and epithelium have uncovered a wide variety of AMPs both from mammals as well as amphibians [23].

In previous studies, involucrin reactivity has primarily been shown in granular layer keratinocytes and in the inner stratum corneum; involucrin has also been detected in cytoplasmic granules of both the suprabasal epidermis and cultured cells [7]. Further, lamellar granule-associated protein (LGP) is expressed in coordination with the cornified cell envelope precursor proteins involucrin and loricrin during epidermal development [26]. hCAP18/LL-37 colocalization with involucrin suggests that cathelicidin is stored in granules, possibly lamellar bodies, and that cathelicidin expression increases during keratinocyte differentiation. Of note, keratinocytes cultured as monolayers and stimulated to differentiate solely by increasing calcium concentration do not increase cathelicidin expression relative to cells grown in low calcium conditions [9]. Keratinocytes must be cultured as three-dimensional skin constructs in order to achieve terminal differentiation and to form lipid profiles that resemble *in vivo* skin [27].

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In addition to the diseases mentioned above, reports exist of potential roles for LL-37 in other autoimmune disorders. LL-37 may have a potentially protective role in the development of sarcoidosis, as transcript levels are repressed in more severe disease. This is ascribed to TNFα effects, which negatively affect LL-37 expression in alveolar macrophages [27].

Additionally, nasal secretions from patients with granulomatosis with polyangiitis (formerly known as Wegener's) colonized with *Staph aureus*, a potentially pathogenic bacteria in this disease, show significantly elevated levels of LL-37 [28]. However, whether the elevated levels of this peptide are pro-inflammatory or protective in this disease remain to be determined. Inconclusion, these data demonstrate key roles for cathelicidins in host defense against glomerulonephritis and the potential to inform the development of synthetic analogues to modulate specific host-pathogen interactions as novel antimicrobial therapeutics.

Competing interests

The authors declare that they have no competing interests.

Ethics Statement

The study was approved by the ethics committees at the Department of Cell Biology and Biochemistry, Tech University Health Sciences Center, Texas, USA

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