Cathelicidin Antimicrobial Peptides Block Dendritic Cell TLR4 Activation and Allergic Contact Sensitization


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Cathelicidin Antimicrobial Peptides Block Dendritic Cell TLR4 Activation and Allergic Contact Sensitization


Cathelicidins are antimicrobial peptides of the innate immune system that establish an antimicrobial barrier at epithelial interfaces and have been proposed to have a proinflammatory function. We studied the role of cathelicidin in allergic contact dermatitis, a model requiring dendritic cells of the innate immune response and T cells of the adaptive immune response. Deletion of the murine cathelicidin gene Cnlp enhanced an allergic contact response, whereas local administration of cathelicidin before sensitization inhibited the allergic response. Cathelicidins inhibited TLR4 but not TLR2 mediated induction of dendritic cell maturation and cytokine release, and this inhibition was associated with an alteration of cell membrane function and structure. Further analysis in vivo connected these observations because inhibition of sensitization by exogenous cathelicidin was dependent on the presence of functional TLR4. These observations provide evidence that cathelicidin antimicrobial peptides mediate an anti-inflammatory response in part by their activity at the membrane. The Journal of Immunology, 2007, 178: 1829–1834.

Antimicrobial peptides participate in the innate immune response through their ability to kill microbes. Their presence in cells and tissues inhibits microbial growth and provides protection against invasive infections in animal models (1–3). In addition, some of these peptides, such as cathelicidins and β-defensins, stimulate chemokine and cytokine secretion from a variety of cell types and can act through receptor-dependent mechanisms (4–6). These observations suggest that peptides with both antimicrobial and inflammatory activities exist, and that the mechanism of their protective effect may involve an ability to act both as innate human antibiotics and by their capacity to directly influence the host inflammatory response (7).

The immunomodulatory function of cathelicidin is unclear, with conflicting data showing a proinflammatory and anti-inflammatory role. The human cathelicidin peptide LL-37 has been shown to be chemotactic for monocytes, T lymphocytes, neutrophils and mast cells (5, 8, 9). Under cell culture conditions LL-37 has also been shown to stimulate chemokine and cytokine secretion from monocytes, dendritic cells (DC), and epithelial keratinocytes (10), but recent data have also shown that LL-37 can inhibit LPS induced cytokine release from monocytes (11). Given that 1) LL-37 could mediate both proinflammatory and anti-inflammatory effects in vitro and 2) the degree of proteolytic processing (12, 13) of cathelicidin peptides in tissue dictates function (10), it has remained unclear what effects cathelicidins or other antimicrobial peptides may have on inflammation in vivo.

The overexpression of cathelicidin or α-defensins in transgenic models has failed to demonstrate an increase in acute local inflammation that might be predicted by work in cultured cells (2, 3), although experiments specifically directed to detect this effect have not been reported. Therefore, to better understand the role of cathelicidins on inflammation, we analyzed the effect in mice of cathelicidin by investigating contact hypersensitivity to epicutaneously applied hapten, a model representing allergic contact dermatitis. This model is a classic type IV immunologic reaction, involving interaction of DC of the innate immune system with T cells of the adaptive immune response (14). The findings presented here, involving the in vivo studies on allergic contact dermatitis and the in vitro studies of DC function, uncover an immunosuppressive role for cathelicidins, and potentially explain the mechanism for this effect by describing a novel membrane-dependent mechanism by which antimicrobial peptides inhibit DC function.

Materials and Methods

**Mice**

Cnlp−/− mice were generated in our laboratory as previously described (1). All animal experiments were approved by the Veterans Administration of San Diego committee on animal use. C3H/He J TLR-4 mutant and C3H/HeN normal controls were purchased from Harlan laboratories.

**Bacterial products**

LPS (100 ng/ml) and peptidoglycan (1 μg/ml) were from Sigma-Genosys. *M. leprae* 19 kDa lipopeptide was a gift from M. Norgard (Texas Southwestern Medical Center, Dallas, TX).

**Peptides**

Synthetic peptides were commercially prepared and purified to >95% purity. LL-37 was the 37 aa, KR-20 the 20 aa, and mouse cathelicidin-related antimicrobial peptide (mCRAMP) the 33 aa domains of human and mouse cathelicidin, respectively (10).

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3 Abbreviations used in this paper: DC, dendritic cell; BMDC, bone marrow-derived DC; NHK, normal human keratinocyte; mCRAMP, mouse cathelicidin-related antimicrobial peptide.

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FIGURE 1. Cathelicidin deficiency decreases allergic contact sensitization in mice. a, Cathelicidin-deficient (Cnlp<sup>−/−</sup>) and wild-type (Cnlp<sup>+/+</sup>) littermates were sensitized with 2% DNFB on their flanks and challenged 7 days later by application of 0.1% DNFB or vehicle alone. Separate mice were not sensitized with DNFB to assess primary irritation on the ear due to DNFB. Ear thickness measurements are shown 24 h after challenge. b, Measurement of cell recruitment in ears of experiments described in a. Leukocyte counts were performed in three random high-power fields (HPF; magnification, ×400). c, BALB/c mice were injected on flank with mCRAMP or PBS before sensitization by topical application of DNFB over site of injection. Seven days later mice were challenged and swelling measured as in a. d, Measurement of cell recruitment in ears of experiments described in c. Leukocyte counts were performed in three random high-power fields (HPF; original magnification, ×400). Cells were >90% neutrophils as determined by staining with GR-1 and CD3. Data shown represent mean ± SD. Mice (n = 9) in each group for three independent experiments.

Preparation of purified DC populations
Bone marrow-derived DC (BMDC) were from BALB/c mice. Cells were negatively selected using rat anti-mouse CD127, TER 119, Gr-1, CD45R/220, and CD3e (BD Pharmingen). Cells were plated in RPMI (Irving Scientific) containing 20 ng/ml recombinant murine GM-CSF (BD Pharmingen). Cells were 85–90% CD11c positive by FACS on day 7. For peripheral blood derived DC, human monocytes were seeded in complete RPMI 1640 medium with human rIL-4 and human rGM-CSF for 1 wk (15, 16). CD-40, CD-80, and CD-86 expression was evaluated by FACS at the VA San Diego Research FACS core facility using respective Abs directly conjugated with PE (BD Pharmingen).

Quantitative Real-Time PCR
In brief, 0.5 µg of extracted RNA (RNA Easy; Qiagen) was amplified with the Retroscript kit (Ambion) using the ABI Prism 7000 (Applied Biosystems). GAPDH and TLR4 probe and primers were added together for multiplex analysis.

Immunofluorescence microscopy
BMDC were stained with 1 µl/ml anti-CD54 Ab (ICAM-1) (200 µg/ml; Cedarlane Laboratories) and FITC rat-anti-mouse (1/400) Abcam. Normal human keratinocytes (NHK) were stained with mouse anti-EGFR Ab and goat anti-mouse AlexaFluor 488.

Scanning electron microscopy
Cells were fixed in 2% glutaraldehyde for 3 h on ice, and stained in 1% OsO<sub>4</sub>. Images were acquired using a Hitachi S-2700 Scanning Electron Microscope.

Allergic contact dermatitis
Allergic dermatitis was induced by topical application of DNFB (2,4-dinitrofluorobenzene; Sigma-Aldrich) on the back as described (17). Ear thickness was measured using a micrometer, (Mitutoyo) (18). For evaluation of the effect of excess cathelicidin, 0.04 ml of mCRAMP (GLL-33 aa peptide) in PBS (100 µM) or PBS alone was injected intradermally. After 15 min mice were sensitized with 5 µl of 1% DNFB at the injection site.

Cytokine measurements
Mouse IL-6 and IL-1β ELISA were as instructed (BD OptEIA; BD Pharmingen). Human DC cytokine release was also quantified using Multiplex analysis (Linco Research). MIP-2 ELISA kit was from R&D Research.

Statistical analysis
In all results shown, data are expressed as the mean of at least triplicate measurements ± SD and are representative of at least three independent experiments. The paired Student’s t test was used and values of p < 0.05 considered significant.

Results
Cathelicidin modifies allergic contact hypersensitivity in vivo
To examine whether the endogenous expression of cathelicidin alters inflammation in vivo, and distinguish this activity from their antimicrobial action, we examined mice with a targeted deletion of the cathelicidin gene Cnlp in a model with minimal contribution from microbial elements, allergic contact dermatis to DNFB. Mice were either sensitized with DNFB or exposed to vehicle control, then after 7 days challenged with DNFB vs vehicle control and ear thickness measured 24 or 48 h later. In this model, the application of vehicle alone is known to cause a small increase in ear thickness due to mild irritation. In nonsensitized mice, there was approximately a 2-fold increase in ear thickness after DNFB challenge, with no differences seen between the two different mouse strains. Surprisingly, given prior reports of the proinflammatory effects of cathelicidins, mice lacking cathelicidin (Cnlp<sup>−/−</sup>) demonstrated a significantly larger increase in ear swelling compared with wild type controls (Fig. 1). These data indicate an anti-inflammatory activity for cathelicidin, that the endogenous expression of cathelicidin, independent of its antimicrobial activity, inhibited the immune inflammatory events required for the generation of allergic contact dermatitis. However, measurement of the cellular infiltrate in ears of sensitized mice showed that despite an increase in swelling, Cnlp<sup>−/−</sup> mice had a 4-fold decrease in cell infiltrate, suggesting that endogenous cathelicidin may act in several ways, influencing both allergic sensitization and cell recruitment.

To examine this potential anti-inflammatory role for cathelicidin we performed experiments to study the effect of exogenous administration of excess cathelicidin on the DNFB allergic response. Mice were locally treated with a single intradermal injection of mCRAMP on the flank immediately before sensitization at that site with DNFB. These mice showed a large reduction in ear swelling upon challenge compared with the control group (Fig. 1c). This decrease in ear edema correlated with a reduction in cell recruitment (Fig. 1d). In parallel experiments, topical application of mCRAMP on the ear during the elicitation phase showed no observable effect (data not shown). Thus, the administration of excess cathelicidin supported the conclusion...
FIGURE 2. Cathelicidin decreases DC responsiveness to LPS. a, FACs analysis of CD40, CD80, and CD86 expression. Cells were assayed before treatment (baseline), after exposure to LPS (100 ng/ml) or after 2 h pretreatment with CRAMP (10 μM), peptide removed, then followed by LPS (100 ng/ml). Data represent mean values of FACs analysis of at least 10,000 cells. b, Real-time RT-PCR of TLR-4 mRNA. Cells were pretreated with mCRAMP (10 μM) or PBS for 2 h, peptide removed, then treated with LPS (100 ng/ml) for 1 h. c, Mouse DC cytokine production. Cells were treated with LPS alone (100 ng/ml) (shaded bars) or pretreated with either 10 μM (■) or 25 μM (▲) mCRAMP. d, Human peripheral blood-derived DC cytokine release. Cells were pretreated with human cathelicidin LL-37 (10 μM) for 2 h, peptide removed, then treated for 22 h with LPS (100 ng/ml).

FIGURE 3. Cathelicidins block IL-6 DC responsiveness to LPS but not to TLR2 ligands. a, Human peripheral blood derived DC were treated with LL-37 (1 μM or 10 μM) for 2 h, peptide removed, then exposed to 19 kDa (5 μg/ml) or LPS (100 ng/ml) for 22 h. b, Mouse BMDC were treated with mCRAMP for 2 h, peptide removed, then treated with LPS (100 ng/ml) or peptidoglycan (1 μg/ml) for 22 h. c, Mouse BMDC were treated with mCRAMP (10 μM), LL-37 (10 μM) or D-LL-37 (10 μM) for 2 h, peptide removed, then treated with LPS (100 ng/ml) for 22 h. Cells without peptide treatment (0) are shown with and without 100 ng/ml LPS. d, Mouse BMDCs were treated with LL-37 (10 μM) or KR-20 (10 μM) for 2 h, peptide removed, then treated with LPS (100 ng/ml) for 22 h. Data shown represent mean ± SD. n = 3 in two independent experiments; * p < 0.01.
The effects observed on inhibition in response to a TLR4 ligand prompted us to assess whether the lack of responsiveness in DC pre-treated with cathelicidin was TLR4 specific. Pretreatment of DC with cathelicidin did not inhibit TLR2/TLR1 activation by the 19 kDa lipopeptide, but rather increased responsiveness (Fig. 3a). Similarly, mCRAMP did not block but rather increased IL-6 release by BMDC challenged with peptidoglycan (Fig. 3b). In addition, DC treated with cathelicidin showed a slight increase in TLR2 expression (data not shown). Thus, cathelicidin treatment of both human and mouse DC selectively and specifically inhibits TLR4 activation.

Cathelicidin peptides directly and selectively alter receptor motility

To next explore how cathelicidin may be altering DC TLR-4 function, we examined the structure-function relationships of the cathelicidin peptides. Cathelicidin has been suggested to stimulate leukocyte recruitment and cytokine release in a receptor-specific manner (5, 21, 22). Thus, if a high-stringency receptor interaction was required to inhibit LPS activation of DC, structural modifications would be expected to eliminate this response. Cathelicidin synthesized with D-amino acids (D-37), and cathelicidin orthologs with major sequence differences from species not native to the host cells, were used to test this effect. Although diverse, these peptides all maintained an overall cationic, amphipathic and α-helical configuration and are potent antimicrobials. Cathelicidins with these diverse structures were equally potent in blocking LPS-induced IL-6 release (Fig. 3c). However, shorter forms of LL-37 with similar charge and antimicrobial potency did not inhibit LPS activation of DC (Fig. 3d). This suggested that either the effects were receptor-independent or that the interaction with a putative receptor was due to less stringent interaction with the receptor or the membrane-receptor complex.

Cathelicidins are known to interact with bacterial membranes, and TLR4 function requires the membrane-dependent association of a receptor complex including, TLR4, CD14 and MD2 (23). We therefore investigated whether the ability of cathelicidin to block TLR4 activation involved alterations in the DC membrane that might interfere with the assembly of this receptor complex. The abundance of TLR4 at the DC surface precluded direct observation of this receptor. Therefore, surrogate cell surface receptors that are abundantly expressed were examined following cathelicidin exposure to determine whether the movement and assembly of proteins in the cell membrane was impaired. DC treated with LL-37 showed complete inhibition of their surface proteins to be aggregated as measured by Ab mediated capping of ICAM-1. (Fig. 4, a and b). These effects occurred at concentrations of cathelicidin that were previously seen to be nontoxic as determined by LDH or propidium iodide exclusion, and which enabled normal responsiveness to TLR-2 ligands. The degree of this effect was similar to that observed for cells fixed in paraformaldehyde (Fig. 4c). Consistent with differences in lipid composition, keratinocytes did not show such profound effects (Fig. 4, d–f). In addition, a direct effect on DC membrane structure was detected by scanning electron microscopy (Fig. 4, g and h). Examination of DC revealed multiple membrane blebs but again, keratinocytes showed minimal perturbations by LL-37 (Fig. 4, i and j). Although these techniques are indirect measures of membrane fluidity, and membrane fluidity was not directly measured by these approaches, the combined evidence of inhibition of membrane as seen by alterations in receptor mobility, and membrane structure perturbations, provide a possible mechanism to explain how cathelicidin inhibits TLR4 function.

Functional TLR4 is required for cathelicidin to modify allergic contact hypersensitivity

To summarize, our data suggest that the endogenous production of cathelicidin downmodulates allergic contact dermatitis in vivo, that the addition of exogenous cathelicidin inhibits allergic contact dermatitis in vivo, and given that allergic contact dermatitis requires functional DC, we showed that cathelicidin specifically inhibits TLR4 activation of DC by altering DC membrane function.
When considered together, these data raised the question whether the ability of cathelicidin to inhibit allergic contact dermatitis was dependent on TLR4 signaling. To examine this, DNFB allergic contact experiments were repeated in mice lacking functional TLR4 (C3H/HeJ) (Fig. 5). Under control conditions in which PBS alone was administered, the absence of functional TLR4 resulted in a small but not significant increase in the final DTH response. Importantly, in the absence of fully functional TLR4, exogenously administered cathelicidin lost the capacity to block sensitization. This demonstrates that the ability of exogeneous cathelicidin and perhaps endogenous cathelicidin to inhibit the DTH response in vivo involves TLR4 signaling, providing a mechanistic link between the in vivo observations involving allergic contact dermatitis and the in vitro experiments on DC function.

**Discussion**

The ability of cathelicidin to function as an antimicrobial peptide is required for optimal host defense against infection both in vitro and in vivo (1, 24, 25). However, recent in vitro studies indicate that cathelicidin can also modulate host inflammatory responses. Here we provide evidence in vivo that cathelicidin has an anti-inflammatory role in host immunity. In a mouse model of allergic contact dermatitis, cathelicidin down-regulated inflammation. Furthermore, by studying both cultured DC and TLR4−/− mice, we provide evidence to indicate that one of the possible mechanisms by which cathelicidin exerts an anti-inflammatory effect is by inhibiting TLR4 signaling through an alteration of cell membrane function. Together these data indicate that cathelicidin has dual functions in innate immunity, mediating antimicrobial activity and down-regulating inflammation.

A novel aspect of the present study was the investigation of the inflammatory role of cathelicidin in vivo. This was accomplished by investigating allergic contact dermatitis in mice, a classic type IV immunologic reaction involving the interaction between DC of the innate immune system and T cells of the adaptive immune response (14). Furthermore, this model allows the study of inflammation, without the context of infection, an ideal model given the antimicrobial activity of cathelicidin. The striking observation in the present study was that allergic contact dermatitis was significantly enhanced in the absence of cathelicidin, using the Cnlp−/− mouse, and inhibited by the exogenous introduction of recombinant cathelicidin during the sensitization phase. The application of CRAMP during elicitation had no effect, therefore suggesting that cathelicidin acts during sensitization, an observation consistent with examination of DC function. To our knowledge, these data provide the first in vivo evidence that cathelicidin modulates inflammation, clearly demonstrating an anti-inflammatory effect on delayed-type hypersensitivity.

Much work using cell culture models has shown that cathelicidins can alter host immune responses including stimulating proinflammatory events (5, 8–10), and recent evidence mediating potentially anti-inflammatory events (11). The complexity of cell types studied, the culture conditions used and opposite effects observed from the same laboratory (11), have made it difficult to draw conclusions regarding the inflammatory function of cathelicidins in vivo. Our data are clear—cathelicidin possesses potent anti-inflammatory activity, inhibiting allergic contact dermatitis. The data indicate the following: 1) cathelicidin mediates an anti-inflammatory response to allergic contact dermatitis in vivo; 2) cathelicidin can mediate an anti-inflammatory response on DC via TLR4 in vitro; and 3) TLR4 mediates an anti-inflammatory response to exogenous but not endogenous cathelicidin in vivo. Differences between endogenous and exogenous cathelicidin effects may be due to the local concentrations of cathelicidin and/or to the way it was given in vivo. Therefore, the levels of cathelicidin induced in inflammation, and in particular the local tissue concentrations may affect the mechanism of action.

Our data provide linked evidence that cathelicidin exerts selective inhibitory effects on allergic inflammation and DC function, indicating that cathelicidin inhibits TLR4 activation and alter cell membrane function. Furthermore, we found that cathelicidin specifically inhibited TLR4-induced DC maturation, including inhibiting up-regulation of CD40, CD80, and CD86, as well as inhibiting cytokine release in vitro. Therefore, cathelicidins, by inhibiting these key functional aspects of the innate immune system in instructing the adaptive T cell response, would be expected to block the induction of a type IV immunologic reaction such as allergic contact dermatitis. Importantly, these in vitro data were connected to the in vivo model by demonstrating that the anti-inflammatory activity of exogenous cathelicidin required TLR4 signaling, thus showing physiologic relevance of our in vitro studies. The requirement for TLR4 signaling suggests that cathelicidin acts directly on the innate immune system, not by binding to the hapten in the allergic contact dermatitis model.

The effect on TLR4 activation was selective and not due to nonspecific toxic effects because response to TLR2 ligands remained intact. Different cathelicidin peptides produced the same effect independent of their stereospecificity, species-specificity and even independent from their antimicrobial activity. KR-20, a postsecretory processed form of human cathelicidin, had enhanced antimicrobial activity but did not inhibit DC activation. Cathelicidin peptides in the form of LL-37 or mCRAMP induced a block in DC responsiveness that could not be readily explained by either binding of the peptide to LPS itself or by DC toxicity. Although we cannot exclude that the DC has incorporated a nonlethal amount of cathelicidin into its membrane systems that complexes LPS preventing effective delivery to TLR4 and other LPS binding proteins required for a cellular response. This alternative explanation fails to explain the ability of cathelicidin to block a linear carbohydrate (hyaluronic acid). Thus, the selective interaction of cathelicidin peptides with DC membrane structure could explain why cell treated with this peptide loose responsiveness to LPS. Taken together, these data compel further study of the role of cathelicidins in the adaptive immune response, and suggest that alternate mechanisms of action, such as selective cell responses based on the membrane activity of the peptide, should be explored. At present it is unclear whether the significant membrane alterations in DC is responsible for the in vivo observations. Nevertheless, our findings propose a novel mechanism by which differences dictated by membrane function could explain why cathelicidin inhibits chemokine release from DC but stimulates CXC chemokine release in keratinocytes (10) because DC membrane lipid composition is distinct from that of keratinocytes (26–28).

Precedence exists for a link between TLR4 and contact dermatitis in observations that TLR4 can activate INKT cell and B-1 cell collaboration in the production of Ab responses capable of recruiting Ag-specific T cells (29, 30). However, it is unclear from the current investigation why the TLR4 deficiency in C3HeJ did not decrease DNBC-induced contact dermatitis (Fig. 5). A role for TLR4 in contact dermatitis is supported here by our observations that C3HeJ mice are no longer suppressed by exogenous cathelicidin. Further evidence for a link between the contact dermatitis and TLR4 has been found through observations that C57BL/10ScCr mice containing a double mutation in both TLR4 and IL-12Rb2 lack an allergic contact dermatitis response to TNCB, yet single mutations in either TLR4 or IL-12Rb2 have no effect (31). These observations are consistent with our findings that C3HeJ mice have normal DNFB response. However, the function of TLR4 in the contact dermatitis response is clearly complex and remains to be elucidated.

One possible explanation for the previously reported apparent opposite effect of cathelicidin in vitro, that is a proinflammatory
activity (32), may be the level of inflammation in the model system. In an active inflammatory environment, such as allergic contact dermatitis or TLR-induced DC maturation in vitro, cathelicidin has an anti-inflammatory effect, perhaps to down-modulate the immune response from causing tissue injury. This phenomenon has been previously suggested for the porcine cathelicidin PR-39 and its action to inhibit NADPH oxidase in neutrophils (33, 34). In the absence of inflammation or a proinflammatory stimulus, cathelicidin may have little or a mild proinflammatory effect (32). In support of this idea, our data indicated that the presence of murine cathelicidin mCRAMP did not alter inflammation in nonsensitized mice in vivo and that Cnlp−/− mice showed less cell infiltration despite greater ear swelling after allergic challenge. Thus, the data of Fig. 1a showing increased ear swelling in Cnlp−/− mice are consistent with the capacity of cathelicidin peptides to block DC function during sensitization while the data of Fig. 1b showing a decrease in cellular infiltrate in these same mice are consistent with the loss of chemotactic activity attributed to cathelicidins. The further analysis of other inflammatory and noninflammatory processes should provide additional insight into the immunoregulatory role of cathelicidin in immune homeostasis and in disease.

A lack of cathelicidin antimicrobial peptides has been associated with an increase in microbial growth in both mouse models of invasive infection and in isolated cell culture systems (1, 24, 25). In addition, a lack of cathelicidin and other antimicrobial peptides correlates with increased infections in patients with atopic dermatitis or Kostman syndrome (19, 35). This observations provide compelling evidence that cathelicidins act as innate antibiotics to kill or inhibit microbes. The present study also provides in vivo and in vitro evidence that cathelicidin has anti-inflammatory properties, down-regulating innate immune responses. It is therefore reasonable to consider the therapeutic use of cathelicidin, or modulators of cathelicidin expression, in clinical diseases such as atopic dermatitis where both antimicrobial and anti-inflammatory agents are traditionally used.

Disclosures
The authors have no financial conflict of interest.

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