Toll-like Receptor 2 Ligand–Induced Protection against Bacterial Endophthalmitis

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Background. Activation of innate immunity plays a key role in determining the outcome of an infection. Here, we investigated whether Toll-like receptors (TLRs) are involved in retinal innate response and explored the prophylactic use of TLR2 ligand in preventing bacterial endophthalmitis.

Methods. C57BL/6 mice were given intravitreal injections of Pam3Cys, a synthetic ligand of TLR2, or vehicle (phosphate-buffered saline) 24 h prior to Staphylococcus aureus inoculation. The severity of endophthalmitis was graded by slit lamp, electroretinography, histological examinations, and determination of bacterial load in the retina. The expression of cytokines/chemokines and cathelicidin-related antimicrobial peptide was assessed by enzyme-linked immunosorbent assay and Western blot, respectively.

Results. Intravitreal injections of Pam3Cys up-regulated TLR2 expression in the retina of C57BL/6 mice, and Pam3Cys pretreatment significantly improved the outcome of S. aureus endophthalmitis, preserved retinal structural integrity, and maintained visual function as assessed by electroretinography in C57BL/6 mice. Furthermore, Pam3Cys pretreatment activated retinal microglia cells, induced the expression of cathelicidin-related antimicrobial peptide, and remarkably reduced the bacterial load.

Conclusions. This is the first report that highlights the existence and role of TLR2 in retinal innate immune response to S. aureus infection and suggests that modulation of TLR activation provides a novel prophylactic approach to prevent bacterial endophthalmitis.

Endophthalmitis is a potentially vision-threatening condition that requires prompt diagnosis and treatment to prevent vision loss [1]. Bacterial endophthalmitis, with an estimated incidence of 0.07%–0.3%, is one of the most severe complications of cataract surgery, a common surgical procedure performed in the aged population worldwide [2, 3]. In addition to cataract, increasing use of multiple periodic intravitreal injections of anti–vascular endothelial growth factor drugs for the treatment of age-related macular degeneration and diabetic retinopathy also predispose patients to infectious endophthalmitis [4]. The reported incidence of endophthalmitis per eye in multicenter clinical trials with anti–vascular endothelial growth factor therapy ranged from 0.7% to 1.6% [5].

Among bacterial pathogens, Staphylococcus aureus is a leading cause of severe inflammation and destruction of the retina, resulting in poor visual prognosis even with treatment [6]. The main problem with early diagnosis of endophthalmitis is that ophthalmologists can only recognize the incident after the signs of endophthalmitis become evident. To prevent such situations, surgeons prescribe the use of topical antibiotics both before and after surgery [7]. In a recent study, a fourth-generation fluoroquinolone, moxifloxacin, was shown to be effective in preventing experimental S. aureus endophthalmitis [8]. Although this class of powerful antibiotics covers a broad spectrum of organisms, they seem to be less effective against methicillin-resistant S. aureus, making prophylactic treatment ineffective [9]. Thus, in the light of an increasing incidence of endophthalmitis and antibiotic-resistant bacterial infection, the development of new adjunctive prophylactic/therapeutic modalities for preventing ocular surgery–associated staphylococcal endophthalmitis is warranted.

Although the contribution of S. aureus virulence fac-
Figure 1. Toll-like receptor 2 (TLR2) expression in Pam3Cys and Staphylococcus aureus (SA)–challenged mouse retina and retinal cells. A, The indicated cultured cells and normal C57BL/6 (B6) mouse retina were lysed for Western blot analysis with anti-TLR2 antibody. To assess the modulation of TLR2 expression by Pam3Cys treatment in vivo, 24 h after intravitreal injection of Pam3Cys (0.1 μg and 1 μg), phosphate-buffered saline (PBS) (B), and S. aureus (E) TLR2 protein expression in whole B6 mouse retina was detected using Western blot. D, Expression of TLR2 messenger RNA at 24 h after SA infection was assessed by reverse-transcriptase polymerase chain reaction (PCR) in whole retina. The band intensity of Western blot and PCR product was quantitated by densitometric analysis and normalized with their respective internal controls (ie, ERK and β-actin).

MATERIAL AND METHODS

Bacterial strain and reagents. S. aureus (strain RN 6390) was maintained in tryptic soy broth (Sigma-Aldrich). Bacterial lipopeptide Pam3Cys-Ser-(Lys)₄ hydrochloride (Pam3Cys), a synthetic lipopeptide that acts as an exclusive TLR2 agonist, was purchased from Calbiochem.

Infection procedure and clinical examination. Female C57BL/6 mice (aged 8 weeks) were intravitreally injected in the left eye with different amounts of Pam3Cys reconstituted in sterile phosphate-buffered saline (PBS) or PBS alone as a sham control (1 μL volume). The intravitreal injections were performed using a 33-gauge needle (Hamilton Company). After 24 h, mice were challenged with or without 5000 colony forming units (cfu) of S. aureus per eye in 1 μL PBS via intravitreal inoculation. The right eye of each mouse was left untreated/uninfected and served as an internal control. Clinical examinations were performed by an ophthalmologist in a blinded fashion with use of slit lamp microscopy. The ocular disease was graded, and clinical scores from 0 to 4.0 were assigned using the scale described elsewhere [25, 26]. Mice were treated in compliance with the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research and all procedures were approved by the Institutional Animal Care and Use Committee of Wayne State University.

Enzyme-linked immunosorbent assay (ELISA) assay for cytokines/chemokines. At the desired time point after TLR2 li-
Figure 2. Intravitreal injection of Pam3Cys prevents the development of endophthalmitis and preserves retinal architecture. A, C57BL/6 mice (5 per group) were administered phosphate-buffered saline (PBS) or indicated concentrations (μg/eye) of Pam3Cys by intravitreal injection. After 24 h, eyes were inoculated with 5000 colony forming units of Staphylococcus aureus (SA) (RN6390). A clinical score (range, 0–4) of Pam3Cys-pretreated and PBS-injected mice on 1, 2, and 3 days postinfection (dpi) was assigned for each infected eye by an ophthalmologist and presented as mean clinical scores. Analysis of variance was performed to compare all groups at 2 (P < .001) and 3 dpi (P < .001), and a nonparametric Mann-Whitney U test was performed to compare each Pam3Cys treatment to the PBS group (**P < .001). Eyes pretreated with the indicated concentration of Pam3Cys or PBS control were enucleated at 3 dpi. Light microscopy examination (B) and histopathological analysis (C) were performed on representative eyes. Hematoxylin and eosin–stained retinal tissue of PBS-pretreated and SA-infected mice showed massive infiltration as well as destruction of retinal architecture (C, left panel); histology of Pam3Cys-pretreated and SA-infected mice showed intact retinal architecture (C, center and right panel). Original magnification, 2.5× (whole eyes) and 20× (retina).

gland or bacterial inoculation, eyes were enucleated. Sensory retina and retinal pigment epithelial–choroid complex was carefully isolated, placed in 150 μL of lysis buffer, and sonicated on ice for 15 s. The lysate was centrifuged at 21,000 g for 15 min at 4°C, and MIP-2 and IL-1β levels in the supernatant were determined with a mouse-specific ELISA kit (R&D Systems) and normalized to total protein, according to the manufacturer’s protocol.

Analysis of retinal function. Scotopic electroretinogram was used to track retinal function during the course of endophthalmitis. Electroretinograms were recorded following bilateral mydriasis and 4 h of dark adaptation. Silver/nylon fiber recording corneal electrodes (DTL Plus Electrodes; Diadnosis) were used. Reference needle electrodes were placed in both ears, and a ground needle electrode was placed in the tail. Responses were acquired using data acquisition software from the UTAS visual diagnostic system and amplified using the UBA-4204 amplifier (LKC Technologies). Ganzfeld light stimulus was used to present eight 10-ms flashes, with light intensities increasing from 0.0001 to 100 cd-s/m². The electroretinogram a-wave was measured as an amplitude between the electroretinogram baseline and the first negative peak, and the electroretinogram b-wave was measured as an amplitude between the first negative peak and the first positive peak.

Bacterial load and histopathological analysis. At 3 days postinfection, eyes were enucleated and rinsed in sterile PBS. Individual eyes were disrupted and homogenized with metal beads in a tissue lyser (Qiagen) in 1 mL PBS for 2 min at maximum speed. The homogenates were serially diluted, and aliquots (100 μL) were plated onto StaphChromo agar plates (BD Biosciences) and incubated overnight at 37°C. For histological study, eyes were enucleated, fixed in 10% formalin for 24 h, and subjected to sectioning and staining with hematoxylin and eosin.

Antibacterial activity and cathelicidin-related antimicrobial peptide (CRAMP) expression. The antibacterial activity of conditioned media derived from microglia (BV-2 cell line) challenged with Pam3Cys was tested against S. aureus, as described elsewhere [27]. Two mL of conditioned media was inoculated with 100 cfu of S. aureus, the cultures were incubated at 37°C for 8 h, and bacterial growth was monitored by measuring optical density at 600 nm. The accumulation of TNF-α and CRAMP in the same media was determined by ELISA and dot-blot [27].

Statistical analysis. An unpaired, 2-tailed Student t test was used to determine statistical significance for data from the cytokine ELISA and bacterial count. A nonparametric Mann-Whitney U test was performed for clinical score, and multiple group comparison was performed using analysis of variance (ANOVA).

RESULTS

TLR2 is expressed in the retina and retinal cells. As a first step to understand the role of TLRs in the retina, we assessed the expression of TLR2, a major cell surface pattern recognition receptor for gram-positive bacteria. Figure 1A shows that TLR2
is expressed in the whole mouse retina and in several types of cultured, non-neural retinal cells, including retinal pigment epithelium (ARPE-19), Muller cells (rMC-1), and microglia (BV2).

To determine whether the TLR2-expressing retina recognizes and responds to TLR2 ligand, we challenged the mouse retina with a synthetic TLR2 ligand Pam3Cys, S. aureus, or PBS (vehicle control) by intravitreal injection. Western blot analysis revealed that exposure of the mouse retina to Pam3Cys (0.1 and 1 μg/eye) resulted in an increase in the levels of TLR2 (Figure 1B and 1C). In contrast, intravitreal inoculation of S. aureus decreased the expression of TLR2 both at the messenger RNA (mRNA) (Figure 1D) and protein levels (Figure 1E and 1F) in C57BL/6 mouse retina. Taken together, these results suggest that the retina is capable of recognizing and responding to S. aureus via TLR2.

**Intravitreal injection of Pam3Cys protects mice from S. aureus endophthalmitis.** Having shown that the retina expresses TLR2 and is responsive to its agonist, we next investigated whether TLR2 ligand can enhance the innate immunity of the retina. We adapted a C57BL/6 mice model of S. aureus–induced endophthalmitis [25, 28] and confirmed that mice receiving 5000 cfu of S. aureus by intravitreal injection showed a complete destruction of the retina (clinical score, 4.0). To assess the protective effect of TLR2 activation on the development of staphylococcal endophthalmitis, mice were given intravitreal injections of Pam3Cys 24 h prior to challenge with 5000 cfu of S. aureus. As shown in Figure 2A, no significant difference was observed in clinical scores in the control versus Pam3Cys-treated groups (P > .05) at 1 day postinfection. At 2 days postinfection, the average clinical scores of 1.2 (0.5 μg), 1.0 (0.25 μg), and 0.4 (0.1 μg) for the Pam3Cys-pretreated mice were significantly lower than for the PBS-pretreated control mice, which demonstrated an average clinical score of 2.6. At 3 days postinfection, 60% (3 of 5) of the control eyes scored 4.0 and 80% (4 of 5) of eyes pretreated with 0.1 μg of Pam3Cys scored 0, suggesting a Pam3Cys pretreatment–mediated protection. Overall, clinical scores of all Pam3Cys treated groups were significantly lower than the control both at 2 and 3 days postinfection (P < .001, by ANOVA).

As shown by light microscopy (Figure 2B), PBS-pretreated mice exhibited dense opacity and clear signs of severe inflammation and infection at 3 days postinfection. In contrast, the eyes that were pre-exposed to Pam3Cys were clear with no sign of infection or inflammation (score 0). Histopathological analysis (Figure 2C) revealed that, in PBS-pretreated eyes, infection caused complete destruction of the retina with heavy inflammatory infiltrates (Figure 2C, left panel). In contrast, pre-exposure of the retina to Pam3Cys preserved retinal structural integrity and reduced tissue damage associated with S. aureus infection (Figure 2C, center and right panel). Thus, TLR2-ligand pretreatment protects the retina from tissue damage caused by S. aureus in C57BL/6 mice.
variance was performed for all groups at 3 dpi ( ). Indicated bacterial load was determined by serial dilution plate count. Analysis of eye. At the indicated days postinfection (dpi), the whole eyes were enucleated under sterile conditions, homogenized in 1 mL of PBS, and the bacterial load was determined by serial dilution plate count. Analysis of variance was performed for all groups at 3 dpi \( (P < .01) \). Indicated \( P \) values were generated using paired Student’s \( t \) test.

**Pam3Cys pretreatment maintains retinal function.** The foregoing results demonstrate that Pam3Cys pretreatment diminished the pathology of staphylococcal endophthalmitis at the tissue level. To determine whether Pam3Cys pretreatment also preserves retinal function in the infected eyes, we measured scotopic electroretinogram responses in PBS- and Pam3Cys-pretreated and \( S. aureus \)-infected mice. Representative electroretinogram traces at a flash intensity of 6 dB (10 cd·s/m\(^2\)) are shown in Figure 3. Electroretinogram response showed normal a-wave (the response generated from photoreceptors) and b-wave (the response generated from the inner retina, mostly the bipolar and Muller cells) in the PBS- and Pam3Cys-pretreated eyes without infection (data not shown). Control mice that received sterile PBS intravitreal injections prior to \( S. aureus \) inoculation demonstrated the loss of retinal function with a significant decrease in both a-wave (90%) and b-wave (94%) amplitudes (Figure 3A and 3C) at 3 days postinfection. Remarkably, mice pretreated with Pam3Cys maintained their normal electroretinogram findings with no significant decrease in a- or b-wave amplitude (Figure 3B and 3C). Taken together, these results suggest that the intravitreal injection of Pam3Cys at low doses preserves electroretinogram findings during bacterial infection.

**Pam3Cys pretreatment reduced the bacterial load in C57BL/6 mice eyes.** The observation that Pam3Cys-pretreated eyes were protected from endophthalmitis suggests an enhanced bacterial clearance in these eyes. We next assessed the effect of Pam3Cys pretreatment on bacterial load in the eyes. As shown in Figure 4, at 1 days postinfection there were an average of \( 5 \times 10^5 \) cfu/eye in the control mice and \( 2 \times 10^4 \) cfu/eye in Pam3Cys-pretreated mice, which represents a 15-fold difference from the control and a 2.5-fold reduction from the total number of bacteria injected into the vitreous. At 2 days postinfection, mean bacterial loads of \( 5 \times 10^4 \) and \( 3 \times 10^4 \) cfu/eye were detected in control mice and Pam3Cys-pretreated mice, respectively. More strikingly, at 3 days postinfection, the mean bacterial load was \( 2 \times 10^4 \) cfu/eye in the control group and only \( 1 \times 10^2 \) cfu/eye in Pam3Cys-pretreated eyes. Thus, Pam3Cys pretreatment greatly enhanced bacterial clearance.

**Pam3Cys induces cytokine and antimicrobial peptide expression in the retina.** Having shown that Pam3Cys pretreatment prevented the development of \( S. aureus \) endophthalmitis and enhanced bacterial clearance in C57BL/6 mice eyes, we next investigated the effect of Pam3Cys on the innate response in vivo by assessing the expression of proinflammatory cytokines and the antimicrobial peptide, CRAMP. In the PBS-injected eyes, there was slight increase in the levels of both MIP-2 and IL-1\( \beta \), probably attributable to needle injury (Figure 5A). In Pam3Cys-treated eyes, there were moderate increases for these 2 cytokines, compared with the PBS-treated eyes, at 6 and 12 h post-treatment. However, by 24 h, the levels of IL-1\( \beta \) in the Pam3Cys-treated eyes were similar to that of the control and PBS-injected eyes, whereas the levels of MIP2 were slightly higher (Figure 5A). Interestingly, although PBS injection resulted in the induction of CRAMP expression at low- to moderate levels, intravitreal injection of Pam3Cys induced abundant CRAMP expression as early as 6 h post-treatment. Remarkably, at 24 h, CRAMP levels remained elevated or even higher in Pam3Cys-pretreated eyes, whereas cytokine levels returned to basal levels, as observed in untreated, normal eyes (Figure 5B and 5C).

**Pam3Cys induces the activation of retinal microglia and production of CRAMP.** We reasoned that microglial cells, like neural macrophages, might be activated by Pam3Cys pretreatment and used microglia ramification as readout to assess their activation in vivo. Figure 6 shows representative retinal whole-mount immunostained with Iba1, a marker for microglial cells. In the control and PBS-injected eyes, retinal microglial cells exhibited more ramified morphology, and in the Pam3Cys-treated retina, microglial cells appeared less ramified and started assuming an amoeboid morphology (activated). The number of microglial cells in the Pam3Cs-treated retina also appeared to be increased, compared with that in the control and PBS-injected eyes (Figure 6A). Moreover, we assessed the levels of Iba-1 expression in the retina by Western blot. The eye treated with Pam3Cys had much higher Iba-1 protein level, compared with that in PBS and untreated controls (Figure 6B and 6C), suggesting that Pam3Cys induces the activation/proliferation of retinal microglia.
Figure 5. Pam3Cys induces the expression of proinflammatory cytokines and cathelicidin-related antimicrobial peptide (CRAMP) in the mouse retina. C57BL/6 mice were given intravitreal injection of sterile phosphate-buffered saline (PBS) or Pam3cys (0.1 μg/eye). At indicated time points, the eyes (3 per group) were enucleated, and the retinal protein lysate was used for MIP-2 and IL-1β detection by enzyme-linked immunosorbent assay (A) and Western blot analysis of CRAMP expression (B). The band intensity of Western blot was quantitated by densitometric analysis and normalized with ERK, which was used as a protein loading control (C).

We next sought to determine whether microglia is a source of Pam3Cys-induced expression of CRAMP and proinflammatory cytokines. BV-2 cells were challenged with Pam3Cys for 24 h, and we found that Pam3Cys markedly increased the production and secretion of CRAMP as detected by Western blot (Figure 6D) and dot-blot (Figure 6E), respectively. ELISA analysis of cultured media revealed that Pam3Cys significantly increased the secretion of TNF-α (Figure 6F). To assess the biological function of induced CRAMP expression, we performed an antibacterial assay against S. aureus. The conditioned media derived from Pam3Cys-challenged microglia inhibited the growth of S. aureus by ~40% (1 μg Pam3) and 55% (10 μg Pam3), compared with untreated control cells (Figure 6G). Taken together, our data suggest that microglia contributes to Pam3Cys-induced expression of CRAMP and antibacterial defense in the retina.

DISCUSSION

In the present study, we showed that the retina and retinal cells express TLR2, and that signaling via this TLR results in the further induction of its expression. With use of a well-characterized mouse model of S. aureus endophthalmitis [25, 28], we demonstrated a novel protective mechanism(s) induced by TLR2 activation against bacterial infection in the retina. We showed that intravitreal injection of Pam3Cys prior to bacterial inoculation significantly attenuated the pathology of S. aureus.
endophthalmitis, greatly reduced the bacterial load in the retina, and preserved the visual function in C57BL/6 mice.

Activation of the innate immune response is the first line of defense after tissue injury and infection [29, 30]. When an infectious agent enters the retina through surgery or injection site, it is critically important for this inflammation-sensitive tissue to have a rapid response system to eliminate invading pathogens, thus minimizing tissue damage to the nonregenerating retina [24]. Recent studies have demonstrated that the innate immune system composed of TLRs is a primary rapid response system to infection [15, 18]. Studies investigating the role of TLRs in retinal innate immunity were initiated recently [24], and TLRs have been linked to viral retinitis, uveitis [31, 32], and geographic atrophy in age-related macular degeneration [33, 34]. To understand the innate response of the retina to infection, we showed that TLR2 is expressed in the retina, suggesting that this neural tissue possesses the ability to recognize gram-positive bacteria. Because the cells in the retina are in a sterile environment, one might expect that TLRs are expressed at the basal level in the resting state, and that recognition of the pathogen or activation of the TLR will result in up-regulation of the same or different TLRs in the retina. Indeed, we showed that exposure of the retina to TLR2 agonist resulted in the up-regulation of TLR2, whereas <i>S. aureus</i> down-regulated its expression. Although the reason for the opposite effects of Pam3Cys and <i>S. aureus</i> on TLR2 expression remains elusive, the observed effect of <i>S. aureus</i> is similar to evaded recognition by innate receptors in patients with bacterial sepsis [35]. Thus, we suggest that exposure of the retina to TLR ligands may serve as a danger signal to alert the retinal innate immune system, including the up-regulation of TLRs, and this alerted retina is better prepared to combat invading pathogens.

The foregoing conclusion suggests that activation of TLR2 may induce protective mechanisms in a sterile environment such as the retina. We chose Pam3Cys because it is a known activator of TLR2 [27] and is a synthetic compound with less cytotoxicity than other bacterial components [36]. Previous studies have shown a protective role of Pam3Cys pretreatment in mouse models of bacterial sepsis [37] and colitis [38]. Interestingly, a recent study showed that intravitreal injection of Pam3Cys has a neuroprotective role in a rat model of optic nerve injury [39]. In this study, we observed that at high dosages (1 μg/eye or higher) Pam3Cys caused noticeable inflammation. However, at lower dosages (0.1–0.5 μg/eye), Pam3Cys induced transient and low-level inflammation that disappeared rapidly. More importantly, we showed that Pam3Cys pretreatment attenuated the development of <i>S. aureus</i> endophthalmitis and preserved intact retinal architecture and normal electroreti-
nogram response. Hence, postsurgical application of Pam3Cys or other TLR2 ligands might be used as an adjuvant therapy to antibiotics for prophylactic treatment of ocular surgeries. We recently found that intravitreal injection of Pam3Cys, alone or with antibiotics (vancomycin and ceftazidime), 24 h after *S. aureus* infection significantly improved the outcome of endophthalmitis in C57BL/6 mice (A.K., unpublished data). However, further studies are warranted to delineate the underlying mechanisms of use of Pam3Cys for prophylactic and therapeutic actions in the retina.

How might Pam3Cys pretreatment reduce or prevent endophthalmitis? One major factor is the rapid elimination of the invading pathogens in the pretreated retina. We showed that Pam3Cys pretreatment reduced the bacterial load in the retina, indicating that bacterial growth was inhibited in an environment where rapidly proliferating bacterial population was expected. Hence, the exposure of the retina to TLR ligands results in the induction of a strong, endogenous protective mechanism. The increased bacterial clearance, especially at the early stage of the infection, is a key factor for the eradication of invaded bacteria and marked reduction of inflammation and tissue damage. This, in turn, allows functional recovery of the retina, which we detected in Pam3Cys-pretreated eyes after *S. aureus* infection.

One major group of innate defense molecules induced on TLR activation is the antimicrobial peptides, including defensins and cathelicidin [40–42]. Although the TLR-mediated expression of cathelicidin in non-neuronal tissues is well documented [40, 41], its expression and regulation in neural systems are less clear. Here, we showed that Pam3Cys induced an abundant and persistent (tested at 24 h) expression of CRAMP. Presence of high levels of CRAMP and/or other antimicrobial peptides within the retina or secreted into the vitreous in response to TLR activation may result in greatly enhanced bacterial killing on contact with pathogens. We speculated that retinal residential cells could be the source of CRAMP; thus, we focused our attention on retinal microglia, which are blood-derived resident immune cells of the retina and play an important role in host defense against invading microorganisms, initiation of inflammatory processes, and tissue repair [43]. We hypothesized that Pam3Cys pretreatment should activate microglial cells expressing TLR2 at cell surface [44, 45] and that activated microglia may contribute to innate killing of the invading pathogens. Consistent with this, we showed that Pam3Cys induces activation/proliferation of retinal microglia. Interestingly, human LL-37 was found in the cerebrospinal fluid of patients with bacterial meningitis but not in healthy control individuals [46]. In an animal model of bacterial meningitis, rat CRAMP was localized in the glia, choroid plexus, and ependymal cells [46]. Our in vitro studies, which used a mouse microglia cell line, revealed that Pam3Cys induced the expression of CRAMP in BV-2 cells and that the culture media of Pam3Cys-stimulated cells inhibited *S. aureus* growth. Thus, we conclude that Pam3Cys-challenged microglial cells contribute to increased expression of CRAMP in the retina. A recent study showed TLR2 activation increases the phagocytotic activity of microglia against bacteria [47], suggesting another potential mechanism of microglia to kill invading pathogens.

In summary, we demonstrate that intravitreal injection of Pam3Cys was efficient in inducing retinal innate immunity in a mouse model of staphylococcal endophthalmitis. We suggest that local delivery of TLR ligands can be explored as a prophylactic/therapeutic strategy to prevent the development of endophthalmitis in patients undergoing ocular surgeries.

Acknowledgments

We thank Dr David Thomas (VA medical center, Wayne State University) for providing BV-2 cell line, Dr Robert Galo (University of California San Francisco) for anti-CRAMP antibody, Dr Vijay Sarthy (Northwestern University) for rMC-1 cell line, and Dr Jamin Brown (Kresge Eye Institute) for his help in clinical examination of mice. We also thank the lab members for the inspiration and insightful discussion during the study.

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