BPB Reports

Regular Article

Candidalysin Induces Inflammatory Responses in the Human Microglial Cell Line HMC3 through Autophagy-Dependent Activation of Nuclear Factor-KappaB Signaling

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Received November 23, 2025; Accepted December 4, 2025

Neuroinflammation induced by microglial activation has recently attracted attention as a cause of neurodegenerative diseases, such as Alzheimer's disease (AD). *Candida albicans* is a prevalent fungal species in human microbiota, and suspected of causing AD through neuroinflammation, as *C. albicans* has been detected in the brain tissue of AD patients, and the intravenous injection of *C. albicans* induced mild memory impairment, accompanied by *C. albicans* invasion of the brain and neuroinflammation in mice. However, the detailed mechanism by which *C. albicans* induces neuroinflammation remains unclear. In this study, we showed that candidalysin, a cytolytic peptide toxin secreted by *C. albicans*, induces the production of the inflammatory cytokine IL-6 accompanied by nuclear translocation of nuclear factor-kappaB (NF-κB) through the degradation of inhibitor of κBα (IκBα) in the human microglial cell line HMC3. We also found that candidalysin induced autophagy, and that an autophagy inhibitor suppressed candidalysin-induced IκBα degradation, nuclear translocation of NF-κB, and IL-6 mRNA expression. These findings suggest that candidalysin triggers autophagy, which induces inflammatory responses via NF-κB in human microglia. Thus, the present study may have uncovered an important pathway for neuroinflammation via microglia when *C. albicans* invades the brain.

Key words candidalysin, microglia, autophagy, nuclear factor-kappaB, neuroinflammation

INTRODUCTION

Neuroinflammation induced by the production of inflammatory cytokines by microglia leads to neuronal death. Therefore, neuroinflammation has recently been recognized as an important contributor to the onset or progression of neurodegenerative diseases, such as Alzheimer's disease (AD) and Parkinson's disease.[1,2] Given this relationship, it is important to elucidate the causes and mechanisms of neuroinflammation in order to prevent these diseases.

One cause of neuroinflammation is invasion of microbes into the brain. *Candida albicans* is suspected to cause AD through neuroinflammation because *C. albicans* has been detected in the brain tissue of AD patients.[3] *C. albicans* is among the most prevalent fungal species in the human microbiota and asymptomatically colonizes healthy individuals.[4] However, it often causes serious opportunistic mucosal and blood-borne infections, particularly in the context of immune deficiency.[5,6] *C. albicans* can invade the brain because it secretes aspartic proteinases that disrupt the tight junction proteins of the blood-brain barrier.[7] In fact, intravenous injection of *C. albicans* has been reported to induce mild memory impairment associated with fungal invasion, activated microglia, and increased inflammatory cytokine production in mouse brains.[8] However, the detailed mechanism by which *C. albicans* induces neuroinflammation remains unclear.

Candidalysin is a cytolytic peptide toxin secreted by the hyphal form of *C. albicans*.[9] It has been shown to induce the production of inflammatory cytokines in BV2 cells, a mouse microglial cell line.[7] Therefore, we focused on candidalysin and investigated the mechanisms of candidalysin-induced inflammatory responses in human embryonic microglial clone 3 (HMC3) cells.

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MATERIALS AND METHODS

Cell Culture HMC3 (CRL-3304) cell lines (ATCC, Manassas, VA, USA) were maintained at 37°C in Dulbecco's modified Eagle's medium (DMEM) containing 10% (v/v) heat-inactivated fetal bovine serum (FBS), 2 mg/mL glucose, 2 mM glutamine, 100 units/mL penicillin, and 100 μg/mL streptomycin.

Quantitative Reverse Transcription Polymerase Chain Reaction (RT-qPCR) HMC3 cells were cultured in a 24-well plate at a density of 1×10^5 cells/well overnight and, then incubated with DMEM containing dimethyl sulfoxide (DMSO [a solvent of candidalysin]) or 1 μM synthetic candidalysin (Peptide Institute, Inc., Osaka, Japan) at 37°C for 1.5 or 3 h. In some experiments, HMC3 cells were pre-incubated with 10 mM 3-methyladenine (3-MA; Santa Cruz Biotechnology, Dallas, TX, USA) for 24 h before incubation with candidalysin.

Total RNA was extracted using TRIzol reagent (Thermo Fisher Scientific, Waltham, MA, USA) and extracted RNA (2 μg) was subjected to cDNA synthesis with ReverTra Ace (TOYOBO, Osaka, Japan). After a 1 min denaturation step at 95°C, IL-6 and glyceraldehyde-3-phosphate dehydrogenase (GAPDH) cDNAs were amplified by 45 cycles of denaturation at 95 °C for 15 s, annealing at 52°C (IL-6) or 55°C (GAPDH) for 15 s, and extension at 72°C for 32 s (IL-6) or 21 s (GAPDH). The cDNA was amplified in triplicate with Thunderbird next SYBR qPCR mix (TOYOBO) and a Real-Time PCR System TP990 (TaKaRa-bio, Shiga, Japan). The primer sequences were as follows: IL-6, 5′- GAACTCCTTCTCCACAAGCG-3′ and 5′-TTTTCTGCCAGTGAATCTTT-3′; GAPDH, 5′-CTCCTCTGACTTCAACAGCG-3′ and 5′-CCACCCTGTTGCTGTAGCC-3′. For data normalization, an internal control (GAPDH) was used as cDNA input, and the relative units were calculated using a calibration curve method.

Immunoblotting Analyses HMC3 cells were cultured in a 6-cm dish at a density of 1×10^6 cells/dish overnight and, then incubated with DMEM containing DMSO or 1 μM candidalysin at 37°C for the indicated times in the figure legends. In some experiments, HMC3 cells were preincubated with 10 mM 3-MA for 24 h before incubation with candidalysin. The cells were then lysed with RIPA buffer (10 mM Tris-HCl, pH 7.5, 1% [v/v] NP-40, 0.1% [w/v] sodium deoxycholate, 0.1% [w/v] sodium dodecyl sulfate [SDS], 150 mM NaCl, 1 mM ethylenediaminetetraacetic acid [EDTA], protease inhibitor), and cell lysates were electrophoresed using 10% or 15% (w/v) SDS-polyacrylamide gels.

The proteins on the gel were transferred to a nitrocellulose membrane and blocked with Blocking One (Nacalai Tesque, Kyoto, Japan). After blocking, the membrane was incubated overnight at 4°C with rabbit anti-IL-6 antibody (1:1,000; Proteintech, Rosemont, IL, USA), rabbit anti-inhibitor of κBα (IκBα) antibody (1:1,000; Abcam, Cambridge, UK), rabbit anti-microtubule-associated protein light chain 3B (LC3B) antibody (1:1,000; Cell Signaling, Danvers, MA, USA), or rabbit anti-GAPDH antibody (1:1,000; Proteintech). After washing, the membranes were incubated for 1 h at room temperature with horseradish peroxidase (HRP)-labelled anti-rabbit IgG antibodies (1:1,000; GE Healthcare, Chicago, IL, USA). Membrane-bound HRP-labelled antibodies were detected with the Amersham ECL Western blotting Detection Reagent (Cytiva, Tokyo, Japan) and an imaging analyzer (LAS-4000; Fujifilm, Tokyo, Japan). Signal intensities were measured using the Image Lab 6.0.1 software program (Bio-Rad, Hercules, CA, USA).

Immunofluorescent Staining HMC3 cells were cultured in a Nunc™ Lab-Tek™ II Chamber Slide™ System (Thermo Fisher Scientific) at a density of 1×10^4 cells/well overnight and then incubated with DMEM containing DMSO or 1 μM candidalysin at 37°C for 60 min. In some experiments, HMC3 cells were preincubated with 10 mM 3-MA for 24 h before incubation with candidalysin. After incubation, cells were fixed with 4% (w/v) paraformaldehyde for 15 min and then permeabilized with 0.2% (v/v) Triton X-100 in phosphate buffered saline (PBS). After washing with PBS, the cells were blocked with 3% (w/v) bovine serum albumin (BSA) in PBS and then incubated overnight with rabbit anti-nuclear factor κB (NF-κB) p65 antibody (1:500; Abcam) followed by incubation with anti-rabbit IgG-Alexa555 antibody (1:500; Abcam) for 45 min. Nuclei were detected with Hoechst 33342 (1:10,000; Thermo Fisher Scientific). Fluorescence and differential interference contrast (DIC) images were acquired using a confocal microscope (FV1000; Olympus, Tokyo, Japan). Line plots were constructed using the ImageJ Fiji software program (Wayne Rasband [NIH], Bethesda, MD, USA).

Detection of Autolysosomes HMC3 cells were cultured in a Nunc™ Lab-Tek™ II Chamber Slide™ System (Thermo Fisher Scientific) at a density of 1.5×10^4 cells/well overnight and then incubated with DMEM containing 1 μM DALGreen (Dojindo, Kumamoto, Japan) at 37°C for 30 min. After washing the cells with DMEM twice, they were incubated with DMEM containing DMSO or 1 μM candidalysin at 37°C for 60 min. Immediately after incubation with candidalysin, the cells were observed without fixation, and fluorescence and DIC images were acquired using a confocal microscope (FV1000).

Data Processing and Statistical Analyses Data are shown as the mean ± standard error. Statistical analyses, including Student's *t*-test and a one-way ANOVA, were performed using the Graph Pad Prism 8 software program (Graph Pad Software Inc., San Diego, CA, USA). $p < 0.05$ was considered to indicate a statistically significant difference.

RESULTS AND DISCUSSION

Induction of Inflammatory Responses in the Human Microglia Cell Line HMC3 by Candidalysin We first investigated whether candidalysin induces the production of inflammatory cytokines in HMC3 cells, a human microglial cell line. RT-qPCR showed that the mean mRNA level of IL-6 was significantly increased in HMC3 cells after incubation with candidalysin for 1.5 and 3 h (Fig. 1A). Western blotting confirmed that the mean protein level of IL-6 was also significantly increased in HMC3 cells after 1.5 h of incubation with candidalysin (Fig. 1B). These results indicate that candidalysin induces inflammatory responses in HMC3 cells. Therefore, HMC3 cells provide a useful model for studying the mechanism underlying candidalysin-induced neuroinflammation.

Activation of the NF-κB Pathway through IκBα Degradation in HMC3 Cells after Incubation with Candidalysin We next examined NF-κB activation in HMC3 microglia during exposure to candidalysin, as NF-κB is known as a transcription factor of many inflammatory cytokines, including IL-6,[10] and plays an important role in microglial inflamma-

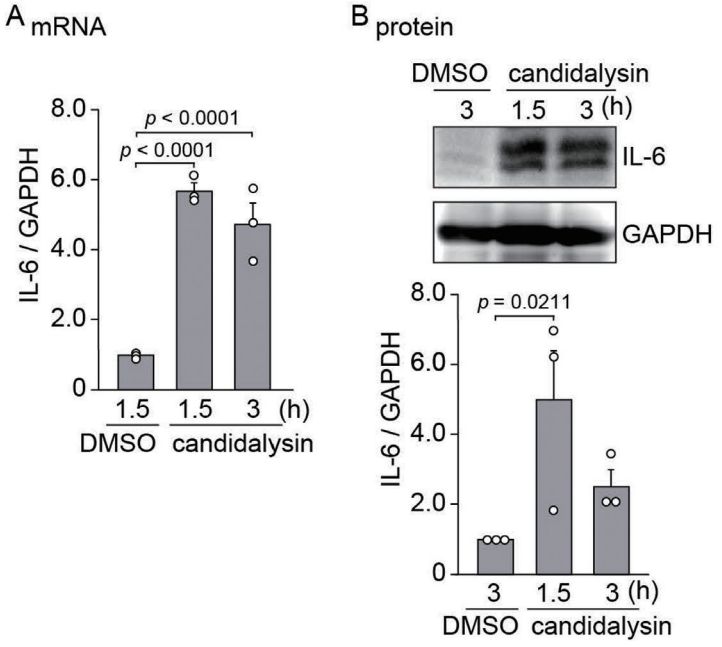

Fig. 1. The Increase in the IL-6 mRNA and Protein Level in HMC3 Microglia after Incubation with Candidalysin

(**A**) The mean mRNA level of IL-6 in HMC3 cells was determined by RT-qPCR, and GAPDH mRNA served as the internal control for the normalization. HMC3 cells were incubated with 1 μM candidalysin for 1.5, 3 h or DMSO for 1.5 h. These are shown here compared to values in cells treated with DMSO for 1.5 h. (**B**) The representative immunoblot data show IL-6 in HMC3 cells after incubation with 1 μM candidalysin for 1.5, 3 h or DMSO for 3 h. GAPDH was the loading control. The bottom panel indicates the mean intensities of IL-6 detected by three immunoblot data, measured and normalized against those of GAPDH signals. These are shown here relative to values in cells treated with DMSO for 3 h. The data are presented as the mean ± SE of three (A, B [bottom]) independent experiments, and p values were calculated using a one-way ANOVA with a post-hoc Tukey's test. A value of $p < 0.05$ was considered to indicate statistical significance.

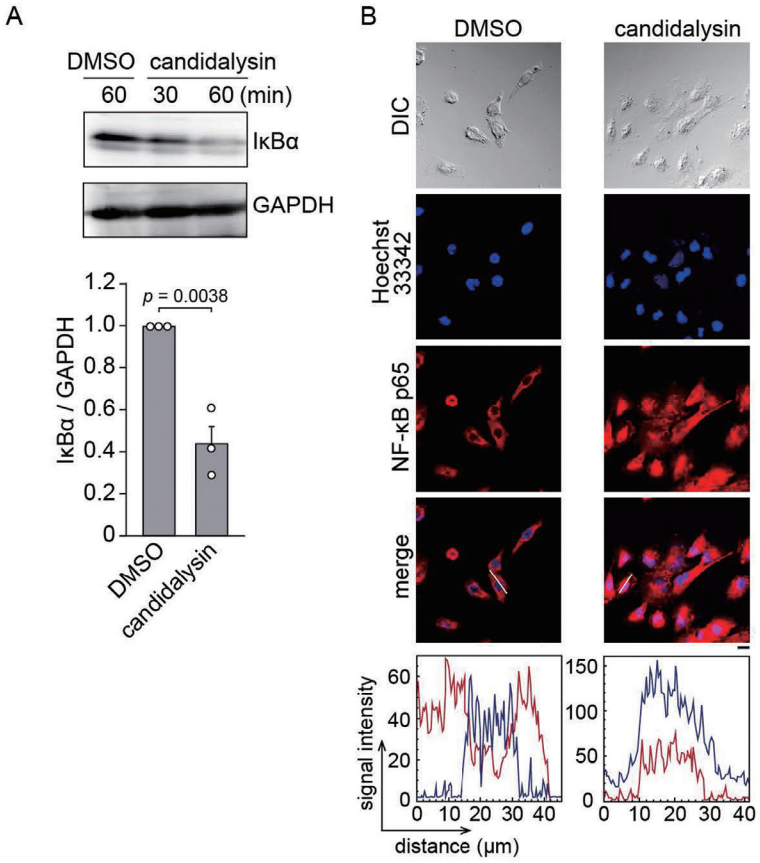

Fig. 2. The Activation of the NF-κB Pathway through IκBα Degradation in HMC3 Cells after Incubation with Candidalysin

(**A**) The representative immunoblot data show IκBα in HMC3 cells after incubation with 1 μM candidalysin for 30, 60 min or DMSO for 60 min. GAPDH was the loading control. The bottom panel indicates the mean intensities of IκBα detected by three immunoblot data in HMC3 cells after incubation with 1 μM candidalysin for 60 min, measured and normalized against those of GAPDH signals. These are shown here relative to values in cells treated with DMSO for 60 min. (**B**) Immunofluorescence images indicating the nuclear translocation of NF-κB p65 (red) in HMC3 cells with Hoechst-stained nuclei (blue) at 60 min after incubation with 1 μM candidalysin or DMSO. Scale bar: 20 μm. The bottom panel shows line plot profile of the typical cells. The signal intensities were measured from the left side on the white line shown in the upper panel. Red and blue plots indicate signal intensities of NF-κB p65 and Hoechst 33342, respectively. The data are presented as the mean ± SE of three independent experiments (A [bottom]), and p value was calculated using Student's t-test. A value of $p < 0.05$ was considered to indicate statistical significance.

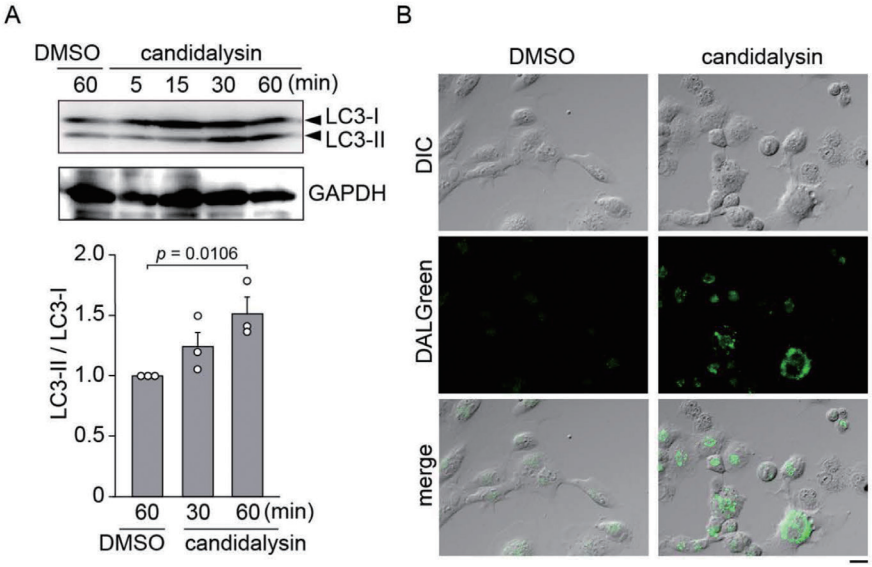

Fig. 3. The Induction of Autophagy in HMC3 Cells after Incubation with Candidalysin

(**A**) The representative immunoblot data show LC3 in HMC3 cells after incubation with 1 μM candidalysin for 5–60 min or DMSO for 60 min. GAPDH was the loading control. The bottom panel indicates the mean ratio of LC3-II to LC3-I which were detected by three immunoblot data in HMC3 cells after incubation with 1 μM candidalysin for 30 or 60 min. These are shown here relative to values in cells treated with DMSO for 60 min. (**B**) The confocal microscopy images of HMC3 cells after treatment with 1 μM candidalysin for 60 min. Autolysosome were detected using DALGreen (green), and fluorescence images were merged with DIC images. Scale bar: 20 μm. The data are presented as the mean ± SE of three (A [bottom]) independent experiments, and p value was calculated using a one-way ANOVA with a post-hoc Tukey's test. A value of $p < 0.05$ was considered to indicate statistical significance.

tory responses.[11] In resting cells, the nuclear translocation of NF-κB dimers containing p65 and p50 is inhibited by the binding of inhibitor of κBα (IκBα). When a stimulus is applied, IκBα is degraded by the proteasome and the free NF-κB dimer translocates into the nucleus and initiates the transcription of target genes.[12] We found that the mean protein level of IκBα was significantly decreased in HMC3 cells after 60 min of incubation with candidalysin (Fig. 2A). In addition, the nuclear translocation of NF-κB was also increased in HMC3 cells after incubation for 60 min. (Fig. 2B). These results indicate that candidalysin activates NF-κB through IκBα degradation in HMC3 cells.

Induction of Autophagy in HMC3 Cells after Incubation with Candidalysin and Requirement of Autophagy Induction for NF-κB Activation via IκBα Degradation and IL-6 Gene Expression Next, we investigated the upstream mechanism of IκBα degradation in candidalysin-induced inflammatory responses in HMC3 cells. Autophagy activates NF-κB through IκBα degradation.[13] In addition, *C. albicans* induces autophagy in the human epithelial cell lines HeLa, HCT116 and RAW-Blue.[14,15] Therefore, we hypothesized that candidalysin induces autophagy, leading to NF-κB activation through IκBα degradation and ultimately triggering an inflammatory response in HMC3 cells.

We first examined whether autophagy was induced in HMC3 cells following exposure to candidalysin. When autophagy is induced, double-membrane vesicles, termed autophagosomes, engulf the cytoplasmic components. Concomitantly, a cytosolic form of microtubule-associated protein light chain 3 (LC3-I) is conjugated to phosphatidylethanolamine to form an LC3-phosphatidylethanolamine conjugate (LC3-II), which is recruited to autophagosomal membranes. Finally, autophagosomes fuse with lysosomes to form autolysosomes, and intra-autophagosomal components are degraded by lysosomal hydrolases.[16] We therefore examined the conversion of LC3-I to LC3-II as a hallmark of autophagy induction. We found that the mean LC3-II/LC3-I ratio was significantly increased in HMC3 cells after 60 min of incubation with candidalysin (Fig. 3A), suggesting the induction of autophagy.

We next confirmed that candidalysin induces autophagy in HMC3 cells by using DALGreen. DALGreen is a dye incorporated into the autophagosome membrane when autophagy is induced. And, it increases fluorescence in the acidic compartment. Therefore, DALGreen is useful for detecting autolysosomes. As expected, DALGreen signals increased in HMC3 cells after 60 min of incubation with candidalysin (Fig. 3B), suggesting an increase in autolysosomes.

Finally, we investigated whether the induction of autophagy was involved in the microglial inflammatory response associated with NF-κB activation. We confirmed that 3-methyladenine (3-MA), an inhibitor of Class III PI3K that is required for autophagy induction, significantly inhibited the increase in the mean LC3-II/LC3-I ratio in HMC3 cells after 60 min of incubation with candidalysin (Fig. 4A), suggesting that 3-MA repressed candidalysin-induced autophagy. The same treatment with 3-MA as in Fig. 4A suppressed the degradation of IκBα (Fig. 4B) and nuclear translocation of NF-κB in HMC3 cells after 60 min of incubation with candidalysin (Fig. 4C). In addition, 3-MA partly inhibited candidalysin-induced expression of the IL-6 gene (Fig. 4D). These results indicate that candidalysin triggers autophagy, which induces inflammatory responses via NF-κB in HMC3 cells (Fig. 5). The incomplete suppression of candidalysin-induced IL-6 expression by 3-MA may result from its modest effect or from other pathways independent of autophagy. Autophagy is known to sequester and degrade A20, which inhibits NF-κB by regulating the activi-

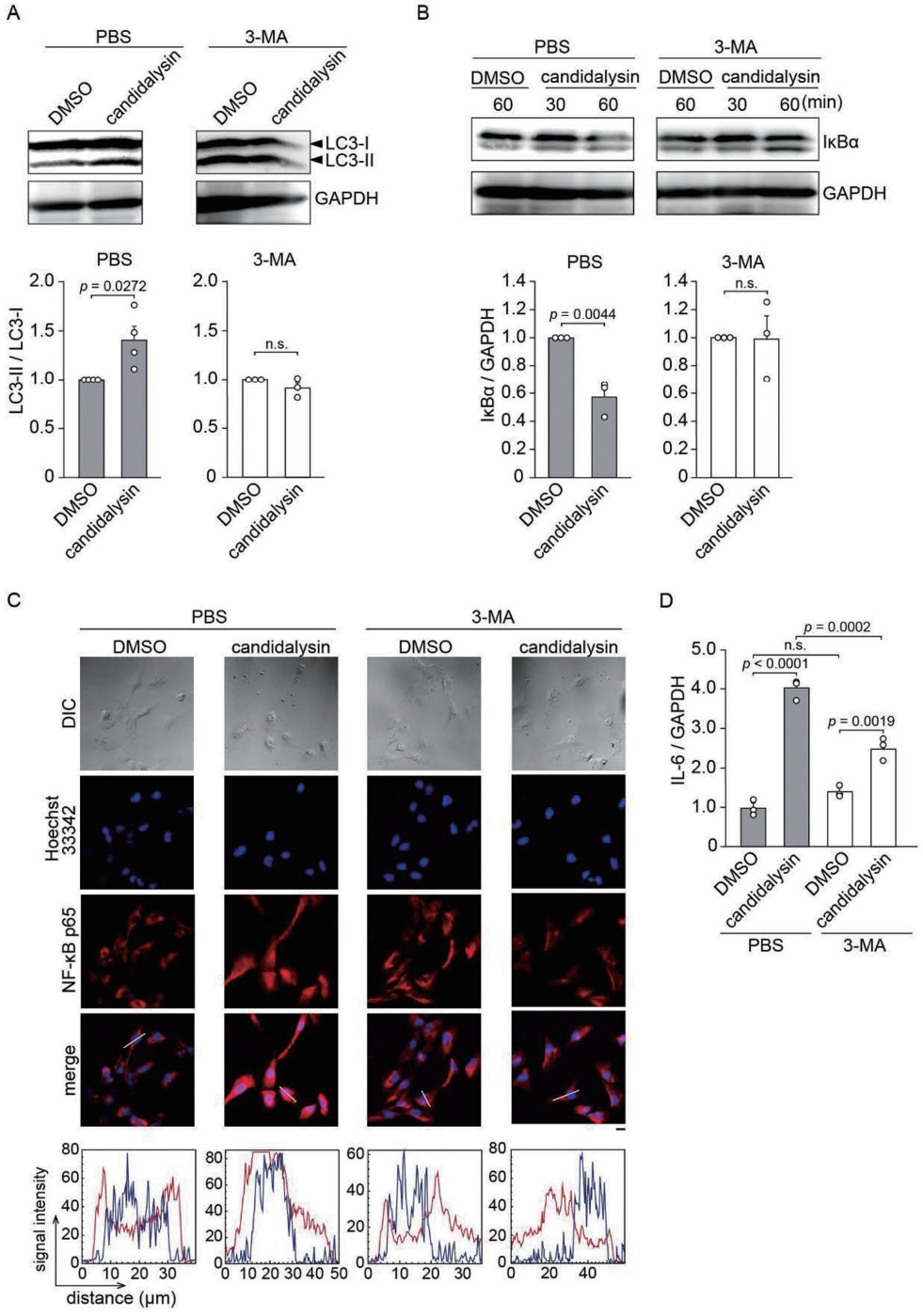

Fig. 4. The Requirement of Autophagy Induction for NF-κB Activation through IκBα Degradation and IL-6 Gene Expression in HMC3 Cells after Incubation with Candidalysin

(**A**) The representative immunoblot data show LC3 in HMC3 cells after incubation with 1 μM candidalysin or DMSO for 60 min in the presence of PBS or 10 mM 3-MA. PBS is a solvent of 3-MA. GAPDH was the loading control. The bottom panel indicates the mean ratio of LC3-II to LC3-I which were detected by three or four immunoblot data in HMC3 cells after incubation with 1 μM candidalysin for 60 min in the presence of PBS or 3-MA. They are shown here relative to the values in cells treated with DMSO for 60 min in the presence of PBS (left) or 3-MA (right). (**B**) The representative immunoblot data show IκBα in HMC3 cells after incubation with 1 μM candidalysin for 30, 60 min or DMSO for 60 min in the presence of PBS or 10 mM 3-MA. GAPDH was the loading control. The bottom panel indicates the mean intensities of IκBα detected by three immunoblot data in HMC3 cells after incubation with 1 μM candidalysin for 60 min in the presence of PBS or 3-MA, measured and normalized against those of GAPDH signals. They are shown here relative to the values in cells treated with DMSO for 60 min in the presence of PBS (left) or 3-MA (right). (**C**) Immunofluorescence images indicating the nuclear translocation of NF-κB p65 (red) in HMC3 cells with Hoechst-stained nuclei (blue) at 60 min after incubation with 1 μM candidalysin or DMSO in the presence of PBS or 10 mM 3-MA. Scale bar: 20 μm. The bottom panel shows the line plot profile of typical cells. The signal intensities were measured from the left side on the white line shown in the upper panel. Red and blue plots indicate signal intensities of NF-κB p65 and Hoechst 33342, respectively. (**D**) The mean mRNA level of IL-6 in HMC3 cells was determined by RT-qPCR, and GAPDH mRNA served as the internal control for the normalization. HMC3 cells were incubated with 1 μM candidalysin or DMSO for 1.5 h in the presence of PBS or 10 mM 3-MA. They are shown here relative to the values in DMSO-treated cells in the presence of PBS. The data are presented as the mean ± SE of three or four (A [bottom]), three (B [bottom], D) independent experiments. *p* values were calculated using Student's *t*-test (A, B) or a one-way ANOVA with a post-hoc Tukey's test (D). A value of $p < 0.05$ was considered to indicate statistical significance.

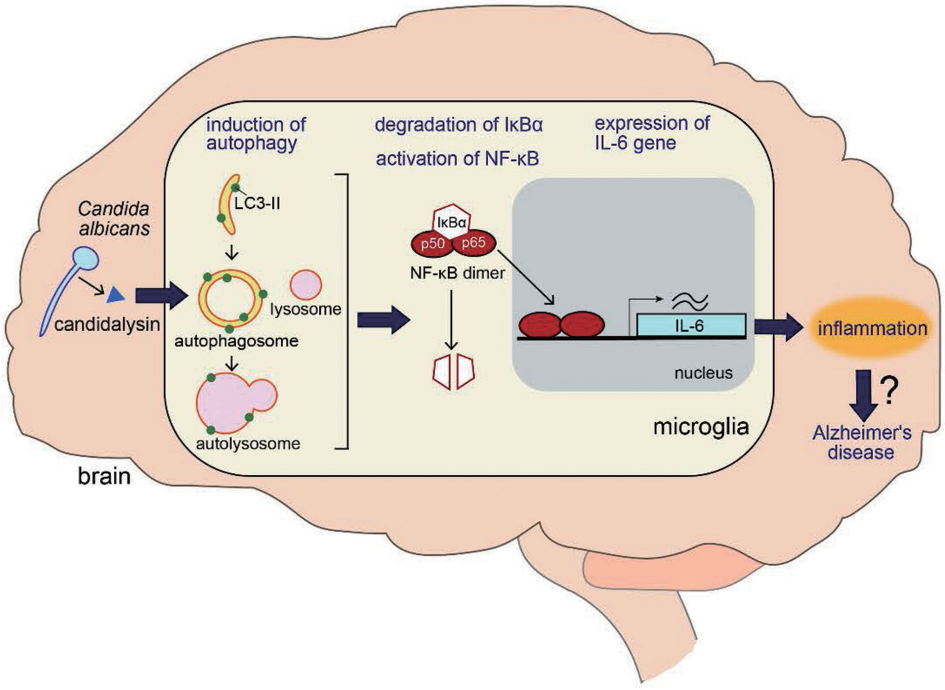

Fig. 5. A schematic Illustration Showing the Neuroinflammation Pathway Induced through Microglia Activation by Candidalysin

Candidalysin, a secreted toxin from *Candida albicans*, triggers autophagy in microglia, which induces NF-κB activation via IκBα degradation and the expression of IL-6 gene, resulting in neuroinflammation.

ty of IκBα kinase gamma in mouse peritoneal macrophages.[15] Therefore, candidalysin-induced autophagy may activate the NF-κB pathway through A20 degradation.

In addition, the mechanism by which candidalysin induces autophagy remains unclear, although membrane damage is a well-known trigger of autophagy.[17] Candidalysin is known as a cytolytic peptide toxin that damages cell membranes.[18] Therefore, it is likely that candidalysin-induced cell membrane damage triggers autophagy. This requires further investigation.

In conclusion, the pathway identified in this study is thought to induce microglial activation and subsequent neuroinflammation upon *C. albicans* invasion of the brain. Neuroinflammation after the invasion of microbes or their virulence factors in the brain has recently attracted attention as a contributor to the progression of neurodegenerative diseases.[8, 19–21] Low-grade Candidemia induces the accumulation of activated microglia and mild memory impairment accompanied by the invasion of *C. albicans*, and the production of inflammatory cytokines in the mouse brain.[8] Furthermore, *C. albicans* has been reported to be detected in brain lesions in patients with Alzheimer's disease (AD).[3,22] Thus, the present study may have identified an important pathway contributing to the development or aggravation of AD caused by *C. albicans* infection in the brain. The relationship between this pathway and AD remains to be elucidated in future studies.

Acknowledgments This work was supported by the Japan Society for the Promotion of Science KAKENHI [grant number JP24K09808 to S.N., JP21K06383 to H.N.]. And, we thank Japan Medical Communication for English language review.

Conflict of interest The authors declare no conflict of interest.

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