Biochemical and Biophysical Research Communications 456 (2015) 700–705

Contents lists available at ScienceDirect

Biochemical and Biophysical Research Communications

journal homepage: www.elsevier.com/locate/ybbrc

Treatment of murine mast cells with IgEκ and protein L enhances apoptotic cell death induced by IL-3 withdrawal

Satoshi Nunomura [a,b,*], Yoshimichi Okayama [b], Tadashi Terui [a], Chisei Ra [b,c,d]

[a] Department of Dermatology, Nihon University School of Medicine, Tokyo, Japan
[b] Allergy and Immunology Group, Research Institute of Medical Science, Nihon University School of Medicine, Tokyo, Japan
[c] Department of Microbiology, Nihon University School of Medicine, Tokyo, Japan
[d] Asahi Hospital, Chiba, Japan

ARTICLE INFO

Article history:
Received 14 November 2014
Available online 15 December 2014

Keywords:
Cell death
IgE receptor
Mast cells
Protein L
Superantigen

ABSTRACT

Engagement of the high-affinity IgE receptor (FcεRI) can be either protective or non-protective against apoptotic cell death (ACD) in bone marrow-derived murine mast cells (BMMCs) after IL-3 withdrawal, depending on the avidity between IgE and its antigen. We recently reported that protein L (PpL), a bacterial Igκ-binding soluble protein, is able to stimulate intracellular signaling to induce activation of BMMCs by interacting with the IgEκ–FcεRI complex. However, it is unclear if cross-linking of FcεRI with IgEκ and PpL prevents or enhances IL-3-dependent ACD in BMMCs. In the present study, we found that IL-3-dependent ACD of BMMCs is accelerated by loading soluble PpL in the presence of IgEκ-occupied FcεRIα. For this purpose, soluble PpL was incorporated into the BMMCs. Unlike soluble PpL, immobilized PpL failed to enhance ACD, although both forms of PpL induced IL-6 production equally in BMMCs. In addition, we observed that DNS_5-BSA protected anti-DNS IgE-sensitized BMMCs from IL-3 depletion-mediated ACD by inducing the production of autocrine IL-3. In contrast, DNS_5-PpL enhanced IL-3 withdrawal-induced ACD of anti-DNS IgE-sensitized BMMCs and reduced the production of autocrine IL-3. These findings suggest that PpL increases IL-3 withdrawal-induced ACD of IgEκ-sensitized BMMCs by incorporating PpL into the BMMCs and that this internalized PpL may interfere with survival signals via FcεRI.

© 2014 Elsevier Inc. All rights reserved.

1. Introduction

Mast cells (MCs) express the high-affinity IgE receptor (FcεRI) on their cell surface. FcεRI is engaged by IgE and its specific multivalent antigens, triggering FcεRI-dependent intracellular signals that lead to MC activation and associated cellular processes, such as the degranulation response, cytokine production, and cell survival [1]. However, the diverse responses of MCs to FcεRI activation depend on the quality of FcεRI cross-linking. The interaction of a low-affinity antigen with the IgE–FcεRI complex or the engagement of small numbers of FcεRIs promotes cell survival and cytokine production without inducing a strong degranulation response [2,3]. By contrast, a high-affinity antigen or large numbers of aggregated FcεRIs evokes a robust degranulation response without cell survival or cytokine production [4,5].

Finegoldia magna is one of the opportunistic pathogens present in the oral cavity and in the intestinal and urogenital tracts [6,7]. These bacteria express a B cell superantigen, protein L (PpL), with multiple (four or five) Igκ binding regions [8–10]. Interestingly, stimulating FcεRI with a murine IgEκ mAb and PpL elicits cytokine production but fails to induce a robust degranulation response [11]. This finding potentially indicates that the avidity between murine IgEκ and PpL is as low as the avidity between IgE and a low-affinity antigen and that the engagement of FcεRI with IgEκ and PpL leads to cell survival in murine MCs.

To address this possibility, we investigated the effects of cross-linking FcεRI with murine IgEκ and PpL during IL-3 depletion-induced apoptotic cell death (ACD) in bone marrow-derived murine MCs (BMMCs). Here, we report that stimulation of FcεRI with murine IgEκ and PpL enhanced the ACD induced by IL-3 withdrawal. Furthermore, we investigated how PpL increases IL-3-dependent ACD in BMMCs.

Abbreviations: ACD, apoptotic cell death; BMMCs, bone marrow-derived murine mast cells; FcεRI, high-affinity IgE receptor; FITC, fluorescein isothiocyanate; PpL, protein L; RBL, rat basophilic leukemia.

* Corresponding author at: Department of Dermatology, Nihon University School of Medicine, 30-1 Oyaguchikami-cho, Itabashi-ku, Tokyo 173-8610, Japan.
E-mail address: nunomura.satoshi@nihon-u.ac.jp (S. Nunomura).

http://dx.doi.org/10.1016/j.bbrc.2014.12.045
0006-291X/© 2014 Elsevier Inc. All rights reserved.

2. Materials and methods

2.1. Reagents

Two commercially available anti-TNP IgEκ (15.3.2 and C48-2) and anti-DNS IgEκ (27.72) mAbs were purchased from BD Biosciences (CA, USA). The recombinant PpL and anti-DNP IgE (SPE-7) were obtained from Sigma (MO, USA). DNS_5-PpL (5 mol DNS per mol of BSA), DNS_5-BSA (5 mol DNS per mol of BSA), and PpL–fluorescein isothiocyanate (FITC) were prepared in our laboratory, and the recombinant murine (rm) IL-3 was purchased from PeproTech (NJ, USA).

2.2. Preparation of BMMCs

C57BL6/J mice were obtained from Charles River Laboratories in Japan (Kanagawa, Japan). For some experiments, thighbones from FcεRIα$^{-/-}$ and FcεRIα$^{+/+}$ mice were provided by Dr. Toshiaki Kawakami (La Jolla Institute of Allergy and Immunology). After obtaining animal care committee approval, all experiments were performed in accordance with the Nihon University guidelines for the care and use of laboratory animals. BMMCs were prepared from the femurs of C57BL/6J mice as previously described. Rat basophilic leukemia (RBL)-2H3 cells were cultured in DMEM supplemented with 10% (v/v) FBS (Invitrogen/Gibco, CA, USA).

2.3. Evaluation of cell death

ACD was evaluated by double staining with FITC-conjugated annexin V and propidium iodide (PI) as previously described [12]. BMMCs (1×10^6) were or were not sensitized with each 0.5 μg/ml IgEκ mAb overnight. The IgEκ-sensitized or unsensitized BMMCs (1×10^5) were stimulated with soluble PpL in the presence or absence of 5 ng/ml rmIL-3 for 30 h. Alternatively, the IgEκ-sensitized BMMCs (1×10^5) were stimulated with immobilized PpL for 30 h. After stimulation, the BMMCs were labeled with annexin V and PI and then analyzed using a FACSCalibur flow cytometer (BD Biosciences, CA, USA). The following cell populations were identified: annexin V$^+$/PI$^-$ (early apoptotic cells), annexin V$^+$/PI$^+$ (late apoptotic cells), and annexin V$^-$/PI$^-$ (living cells).

2.4. Degranulation and cytokine production assays

BMMCs (1×10^6) were sensitized with 0.5 μg/ml IgEκ mAb overnight. In some experiments, unsensitized BMMCs were also analyzed. The IgE-sensitized and unsensitized BMMCs (2×10^5) were washed with PBS and then stimulated or not stimulated with at the indicated concentrations for 0.5 h (for degranulation) or 6 h (for cytokine production). In some experiments, the IgEκ-sensitized BMMCs were stimulated with immobilized PpL for 6 h. In addition to PpL, antigens (DNS_5-BSA and DNS_5-PpL), anti-DNP IgE (SPE7), and A23187 were used as stimuli in this study. Degranulation was detected according to β-hexosaminidase release as described previously [13]. The percentage of β-hexosaminidase released was calculated as follows: (supernatant optical density of cells)/(total cell lysate optical density of cells) × 100. IL-3 and IL-6 production was analyzed using specific ELISA kits (Affymetrix eBioscience, CA, USA).

2.5. Analysis of DNA fragmentation and caspase-3 activation

After stimulation with PpL for 18 h, the BMMCs were harvested and washed twice with PBS. DNA was prepared from the cells using an Apoptosis Ladder Detection Kit (Wako Chemical, Tokyo, Japan). Fragmented DNA was resolved on a 1% agarose gel and visualized with ethidium bromide. Activated caspase-3 was assayed using a Caspase-3 Detection Kit (FITC-DEVD-FMK) (Merck Millipore, MA, USA) according to the manufacturer's protocol. Stained cells were evaluated using a FACSCalibur flow cytometer.

2.6. Confocal microscopy

RBL-2H3 cells (2×10^5) were sensitized with 0.5 μg/ml 15.3.2 or C48-2 in a cover-glass culture overnight. The cells were stimulated with PpL for 0.5 h, washed twice with PBS, fixed with 4% paraformaldehyde for 0.5 h, and permeabilized in PBS containing 0.1% Triton-X100 for 15 min at room temperature. The cells were washed twice with 1 ml of PBS and stained with FITC-conjugated PpL (1:1000) for 1 h in the dark. The cover glasses were washed with PBS and then mounted. Confocal microscopy was performed using the FV1000 system and the FLUOVIEW software (OLYMPUS CORPORATION, Tokyo, Japan).

2.7. FcεRI internalization assay

Receptor internalization was detected by changes in the cell surface FcεRI expression after PpL stimulation. Briefly, RBL-2H3 cells (2×10^5) were sensitized or not sensitized with 0.5 μg/ml 15.3.2 or C48-2 overnight. The sensitized cells were washed with PBS and stimulated or not stimulated with 30 nM PpL for the indicated times. The cells were labeled with 0.1 μg/ml anti-mouse IgE mAb-FITC for 15 min on ice. The labeled cells were analyzed with a FACSCalibur flow cytometer.

2.8. Statistical analysis

The data shown are means ± SE or SD. The statistical analyses were performed using Student's *t*-test. *p*-Values less than 0.05 were considered to indicate statistically significant differences.

3. Results

3.1. Engagement of FcεRI with IgEκ mAb (15.3.2) and soluble PpL augments MC death induced by IL-3 withdrawal

We first confirmed whether the engagement of FcεRI with IgE and a low-affinity antigen is protective against MC death induced by IL-3 depletion. For this purpose, BMMCs were sensitized with anti-DNS IgE (27.74) and then stimulated with 30 nM DNS_5-BSA in the absence of IL-3. Fig. 1A shows that 27.74-sensitized BMMCs were protected from MC death after IL-3 withdrawal in the presence of DNS_5-BSA but not BSA. The 27.74 antibody is an IgEκ mAb that cannot bind PpL [11]. As shown in Fig. 1B, PpL loading did not affect survival during IL-3-dependent cell death in 27.74-sensitized BMMCs. Unlike 27.74, the 15.3.2 antibody is a PpL-binding IgEκ mAb [11]. We observed that PpL loading enhanced IL-3-dependent cell death in BMMCs sensitized with 15.3.2 in a concentration-dependent manner (Fig. 1B). Fig. 1C and D show that unsensitized WT and 15.3.2-sensitized FcεRIα$^{-/-}$ BMMCs were resistant to PpL-induced cell death. In addition, the enhanced cell death in MCs stimulated with 15.3.2 and PpL was not rescued by lactose, which inhibits the interaction between IgE and alternative IgE binding proteins, such as those of the galectin family [14–16] (Fig. 1E). These results clearly indicate that FcεRIα, the IgE binding subunit of FcεRI, is responsible for the PpL-dependent augmentation of cell death induced by IL-3 deprivation.

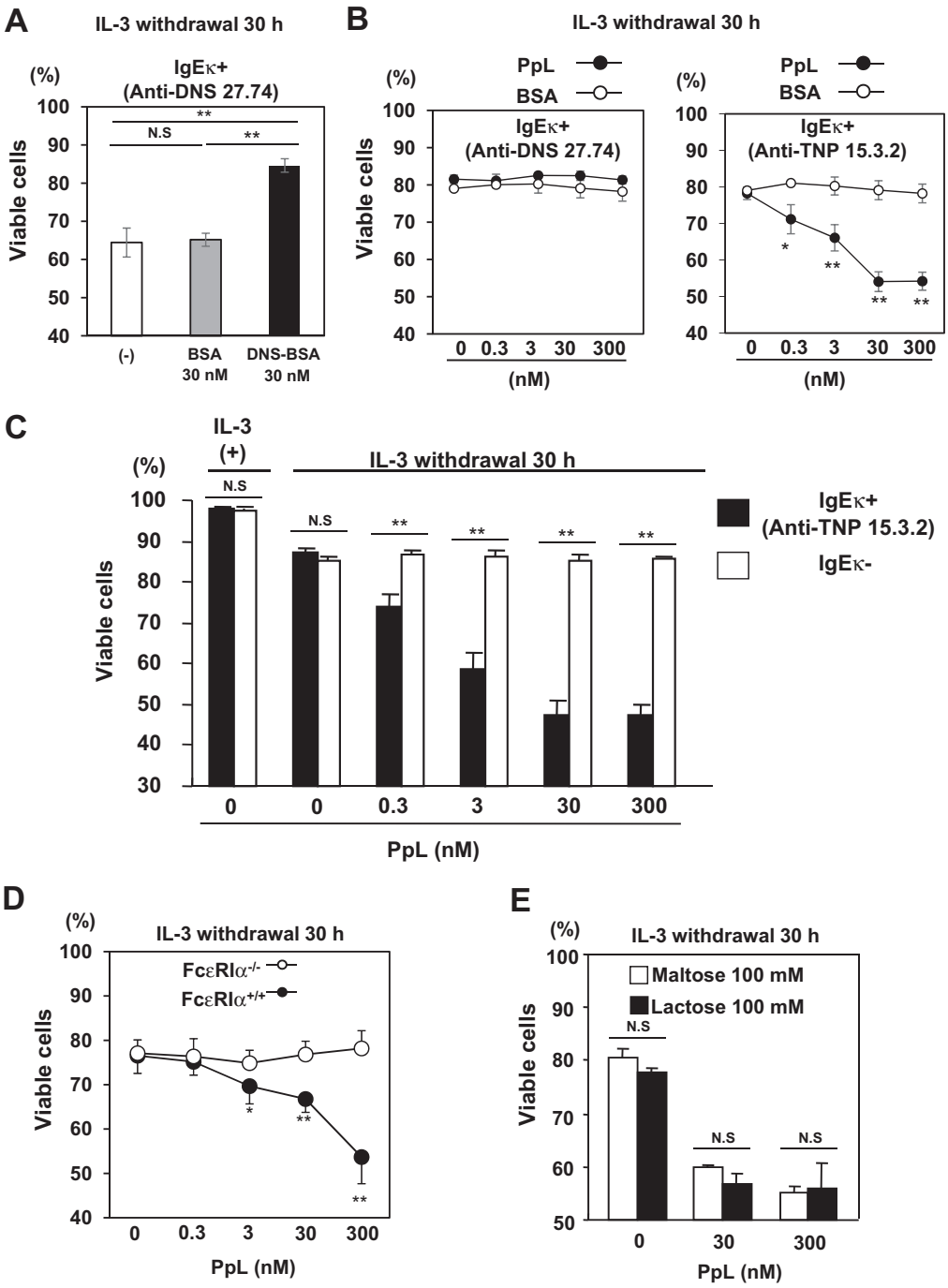

Fig. 1. FcεRIα and IgEκ mAb (15.3.2) are required for amplification of IL-3 withdrawal-induced MC death upon PpL loading. BMMCs were sensitized with 27.72 (A) or 15.3.2 (B)–(E). The sensitized or unsensitized MCs were incubated with BSA, DNS-BSA, protein L (PpL) or medium for 30 h in the presence or absence of IL-3. The cells were labeled with annexin V-FITC and PI as described in Section 2. Viable cells were defined as annexin V^-/PI^- cells. (A) Cell survival of 27.72-sensitized MCs induced by DNS-BSA. (B) Enhancement of cell death in 15.3.2-sensitized MCs induced by PpL. Requirement of 15.3.2 sensitization (C) and FcεRIα expression (D) for the PpL-mediated pro-apoptotic effects. (E) Insignificant effects of 100 mM lactose on the PpL-mediated augmentation of ACD. In (A)–(E), the data are expressed as the mean ± SE of four separate experiments. Statistical analysis was performed using Student's *t*-test. $^*p < 0.05$; $^{**}p < 0.01$.

3.2. Enhancement of ACD is not mediated by soluble factors from BMMCs stimulated with 15.3.2 and soluble PpL

To further characterize the observed cell death enhancement, we examined whether PpL loading increased typical apoptotic features, such as DNA fragmentation and caspase-3 activation. Fig. 2A and B show that DNA fragmentation and caspase-3 activation were also increased in PpL-treated cells. Together, these data suggest that the stimulation of MCs with 15.3.2 and PpL further amplifies the ACD induced by IL-3 deprivation. Next, we examined whether 15.3.2 and PpL-induced amplification of ACD is mediated by soluble factors from activated BMMCs. For this purpose, we performed a trans-well assay with upper and lower chambers separated by a permeable membrane; 15.3.2-sensitized BMMCs were cultured with PpL in the lower chamber, and unsensitized BMMCs were cultured with PpL in the upper chamber in the absence of IL-3. As

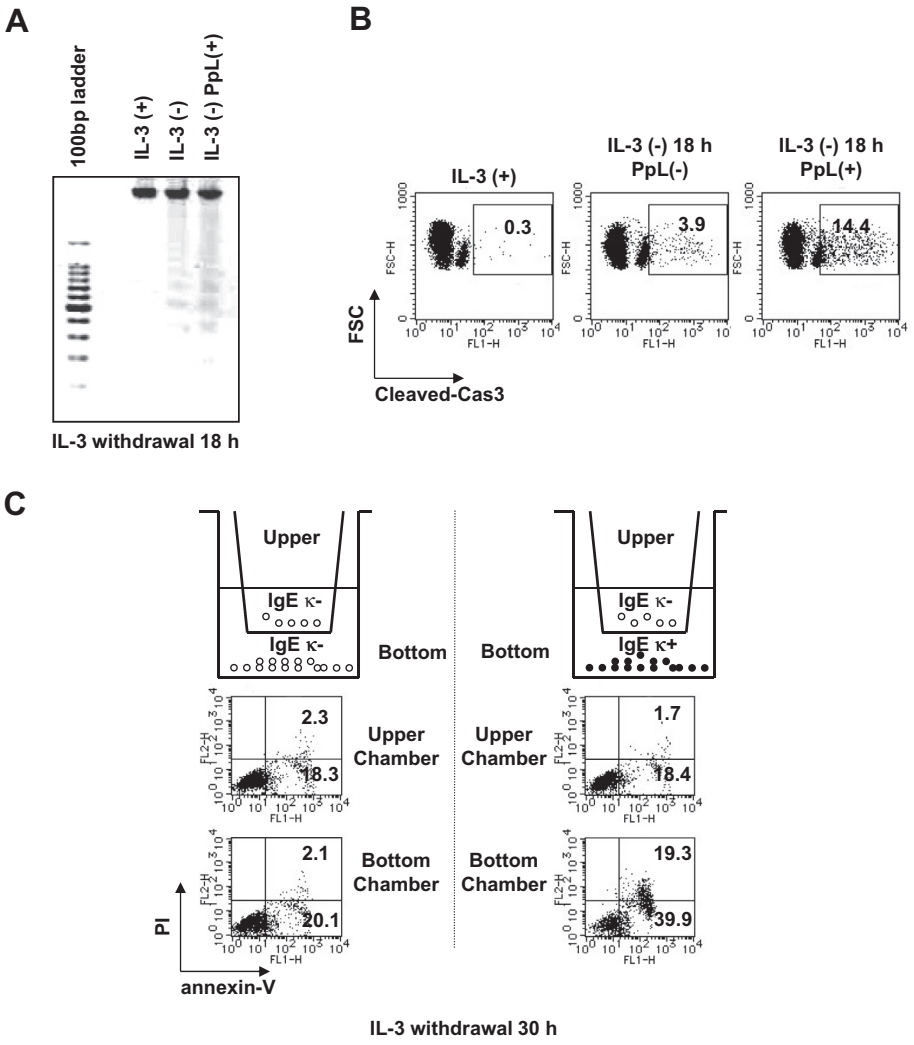

Fig. 2. Soluble factors do not mediate enhancement of ACD in BMMCs. 15.3.2-sensitized BMMCs were stimulated or not stimulated with PpL for 18 h in the presence or absence of IL-3. DNA fragmentation (A) and caspase-3 activation (B) in BMMCs were determined according to the manufacturer's protocols. (C) Trans-well assays were performed as described in Section 2. The data are representative of three independent experiments with similar results.

shown in Fig. 2C, enhanced ACD was observed only in the 15.3.2-sensitized BMMCs in the lower chamber, indicating that soluble factors are not involved in the enhancement of ACD in BMMCs.

3.3. Enhancement of ACD is not induced in BMMCs stimulated with 15.3.2 and immobilized PpL

The cross-linked IgE–FcεRI–antigen complex is immediately internalized into endosomes/lysosomes and then degraded by lysosomal proteases [17]. As shown in Fig. 3A, internalization of the 15.3.2–FcεRI–PpL complex was induced upon PpL loading. We observed that PpL–FITC is localized to endosome/lysosome-like vesicles. Because dysregulation of the lysosomal protein degradation system is associated with cell death [18], we examined the effects of an inhibitor of lysosomal proteases (pepstatin A) on the enhanced ACD of BMMCs. Fig. 3C shows that pepstatin A further increased the enhancement of ACD in BMMCs stimulated with 15.3.2 and PpL. These data raise the possibility that internalization of the FcεRI complex, including PpL, plays an important role in the enhancement of MC death. To address this possibility, we immobilized PpL on the culture plate and examined whether the immobilized PpL was able to enhance IL-3 dependent ACD in BMMCs. Both immobilized PpL and non-immobilized PpL induced comparable production of IL-6 in 15.3.2-sensitized BMMCs; however, immobilized PpL prevented enhanced ACD in BMMCs without increasing the production of autocrine IL-3 (Fig. 3D).

3.4. DNS_5-PpL enhances ACD in 27.74-sensitized MCs

As demonstrated in Fig. 1, cross-linking FcεRI with an anti-DNS IgEκ mAb (27.74) and DNS_5-BSA protected BMMCs against IL-3 withdrawal-induced ACD. When BSA was replaced with PpL, however, DNS_5-PpL enhanced ACD in 27.74-sensitized BMMCs (Fig. 4A). Fig. 4B and C show that both DNS_5-BSA and DNS_5-PpL induced a weak degranulation response and robust IL-6 production in 27.74-sensitized BMMCs at similar levels. Stimulation of FcεRI with 27.74 and DNS_5-BSA robustly promoted the production of autocrine IL-3. Compared to the engagement of FcεRI by 27.74 and DNS_5-BSA, cross-linking FcεRI with 27.74 and DNS_5-PpL reduced the production of autocrine IL-3 in BMMCs (Fig. 4D).

4. Discussion

In this study, we demonstrated for the first time the amplifying effect of IgEκ mAb (15.3.2) and soluble PpL on IL-3 depletion-induced ACD in murine MCs. In addition to FcεRI, murine BMMCs

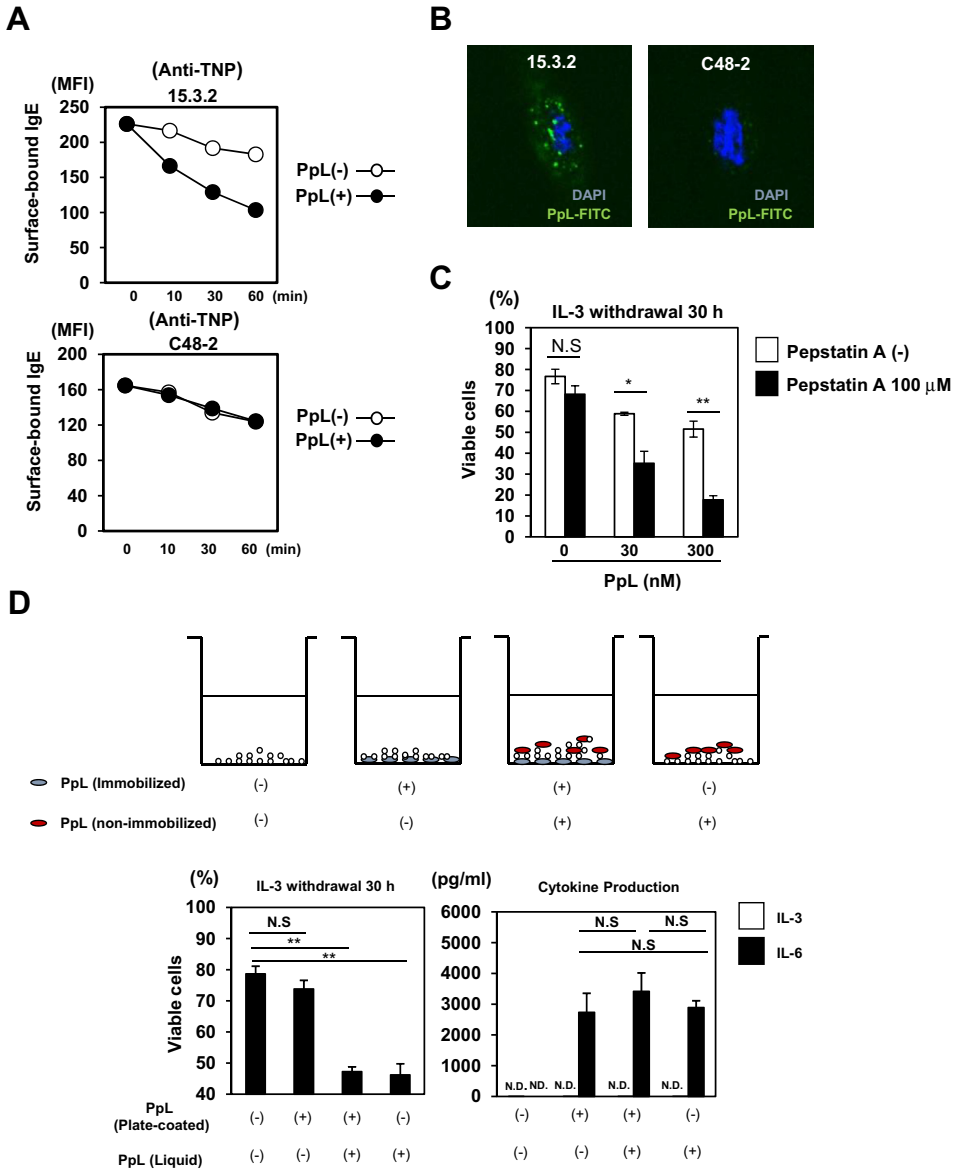

Fig. 3. Stimulation of FcεRI with 15.3.2 and immobilized PpL fails to enhance IL-3 deprivation-induced ACD in BMMCs. RBL-2H3 cells were sensitized with 15.3.2 or C48.2. C48.2 was used as an anti-TNP IgEκ control mAb that cannot bind PpL. The cells were stimulated with PpL (A) or PpL–FITC (B) for 0.5 h. (A) The changes in cell-surface FcεRI expression in 15.3.2- or C48.2-sensitized RBL-2H3 cells upon PpL loading. (B) Confocal microscopic analyses of the localization of PpL–FITC in RBL-2H3 cells sensitized with 15.3.2 or C48.2. The data are representative of three independent experiments with similar results. (C) Effects of pepstatin A on BMMC apoptosis enhanced by 15.3.2 and PpL. (D) Loss of enhanced ACD in BMMCs stimulated with 15.3.2 and immobilized PpL. In (C) and (D), the data are the mean ± SE of three independent experiments. Statistical analysis was performed using Student's *t*-test. $^{*}p < 0.05$; $^{**}p < 0.01$.

express galectin-3 on their cell surface as an alternative IgE binding protein [15]. However, we exclude the possibility that galectin-3 mediates the pro-apoptotic effect of 15.3.2 and soluble PpL on BMMCs in the absence of IL-3 for the following reasons: (i) FcεRIα was required for the enhancement of ACD in BMMCs stimulated with 15.3.2 and soluble PpL and (ii) pretreatment of BMMCs with lactose did not protect against the enhanced ACD in BMMCs in response to stimulation with 15.3.2 and soluble PpL.

In peripheral murine B cells expressing membrane-associated Igκ, soluble PpL acts as a superantigen that can trigger activation-induced ACD by interacting with membrane-associated Igκ [9]. However, FcεRI stimulation does not induce ACD in activated BMMCs, at least not in the presence of IL-3 [19–21]. In accordance with previous reports, stimulation of FcεRI with 15.3.2 and soluble PpL failed to induce apoptosis in BMMCs cultured in medium containing IL-3 (data not shown). Together, these findings suggest that IL-3 acts as a potent survival factor in murine MCs. Kohno et al. reported that, upon stimulation of FcεRI with highly cytokinergic IgEs, BMMC-derived IL-3 protects cells from IL-3 withdrawal-induced ACD [22]. Because (i) immobilized PpL failed to enhance IL-3 withdrawal-induced ACD of 15.3.2-sensitized BMMCs and (ii) neither non-immobilized nor immobilized PpL induced significant production of IL-3 from 15.3.2-sensitized BMMCs, we conclude that the inability of immobilized PpL to enhance ACD occurs independently of autocrine IL-3 production. Currently, we speculate that PpL incorporated via FcεRI internalization is involved in the mechanism of ACD amplification. Interestingly, replacing DNS_5-BSA with DNS_5-PpL significantly affected cell survival and autocrine IL-3 production induced by the interaction between the anti-DNS IgEκ mAb (27.73) and multivalent DNS (Fig. 4). Although the underlying mechanisms remain unclear, we believe that reduced IL-3 production may be involved in the PpL-dependent loss of FcεRI-mediated cell survival.

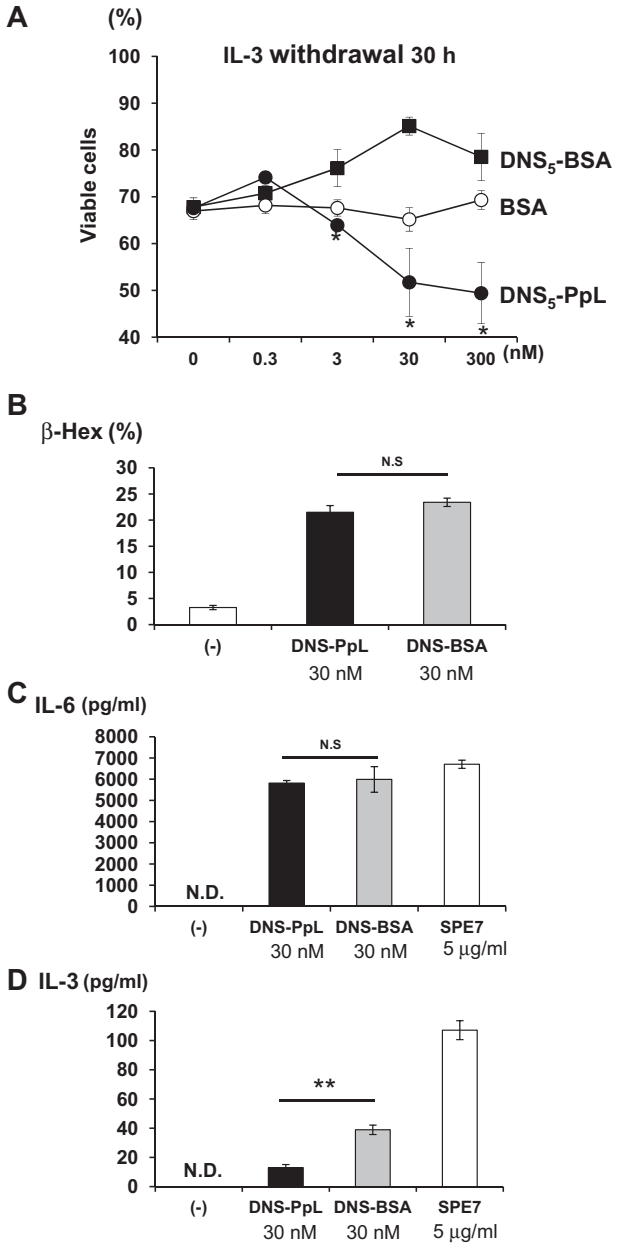

Fig. 4. PpL interferes with autocrine IL-3 production in BMMCs. BMMCs were sensitized with 27.72 and then stimulated with DNS_5-BSA or DNS_5-PpL for 0.5 h (B), 6 h (C and D), or 30 h (A) in the absence of IL-3. (A) Enhancement of BMMC apoptosis induced by 27.72 and DNS_5-PpL. (B) The degranulation response was evaluated as described in Section 2. Production of IL-6 (C) and IL-3 (D). In (C) and (D), SPE-7 was used as a positive control for the production of IL-6 and IL-3. In (A), the data are the mean ± SE of three separate experiments. In (B)–(D), the data shown are the mean ± SD of assays performed in quadruplicate. $^{*}p < 0.05$; $^{**}p < 0.01$. Similar data were obtained in three independent experiments.

MCs are found in numerous tissues, where they act as innate immune cells to protect their hosts from infection by opportunistic pathogens. Recently, Kambayashi et al. reported that ACD in antigen-captured MCs indirectly potentiates rapid antigen presentation in dendritic cells [21]. Therefore, our novel finding in the present study that increased ACD in MCs elicited by PpL loading requires both FcεRIα and PpL-binding IgEκ may provide valuable information for understanding the roles of IgEκ and MCs in the immune system response to *F. magna*.

Conflict of interest

The authors have declared no conflicting interests.

Acknowledgment

This work was supported in part by the Grants-in-Aid for private universities to C.R. from the Ministry of Education, Culture, Sports, Science, and Technology of Japan.

References

[1] U. Blank, J. Rivera, The ins and outs of IgE-dependent mast-cell exocytosis, Trends Immunol. 25 (2004) 266–273.
[2] A. Grodzki, K. Moon, E. Berenstein, R. Siraganian, FcepsilonRI-induced activation by low antigen concentrations results in nuclear signals in the absence of degranulation, Mol. Immunol. 46 (2009) 2539–2547.
[3] C. Gonzalez-Espinosa, S. Odom, A. Olivera, J. Hobson, M. Martinez, A. Oliveira-Dos-Santos, L. Barra, S. Spiegel, J. Penninger, J. Rivera, Preferential signaling and induction of allergy-promoting lymphokines upon weak stimulation of the high affinity IgE receptor on mast cells, J. Exp. Med. 197 (2003) 1453–1465.
[4] T. Kawakami, J. Kitaura, Mast cell survival and activation by IgE in the absence of antigen: a consideration of the biologic mechanisms and relevance, J. Immunol. 175 (2005) 4167–4173.
[5] J. Kitaura, J. Song, M. Tsai, K. Asai, M. Maeda-Yamamoto, A. Mocsai, Y. Kawakami, F. Liu, C. Lowell, B. Barisas, S. Galli, T. Kawakami, Evidence that IgE molecules mediate a spectrum of effects on mast cell survival and activation via aggregation of the FcepsilonRI, Proc. Natl. Acad. Sci. USA 100 (2003) 12911–12916.
[6] W. Kastern, E. Holst, E. Nielsen, U. Sjöbring, L. Björck, Protein L, a bacterial immunoglobulin-binding protein and possible virulence determinant, Infect. Immun. 58 (1990) 1217–1222.
[7] D.A. Murdoch, Gram-positive anaerobic cocci, Clin. Microbiol. Rev. 11 (1998) 81–120.
[8] L. Björck, Protein L. A novel bacterial cell wall protein with affinity for Ig L chains, J. Immunol. 140 (1988) 1194–1197.
[9] C.S. Goodyear, M. Narita, G.J. Silverman, In vivo VL-targeted activation-induced apoptotic supraclonal deletion by a microbial B cell toxin, J. Immunol. 172 (2004) 2870–2877.
[10] G.J. Silverman, C.S. Goodyear, Confounding B-cell defences: lessons from a staphylococcal superantigen, Nat. Rev. Immunol. 6 (2006) 465–475.
[11] S. Nunomura, Y. Kawakami, T. Kawakami, C. Ra, The FcR beta- and gamma-ITAMs play crucial but distinct roles in the full activation of mast cells induced by IgE kappa and protein L, J. Immunol. 188 (2012) 4052–4064.
[12] M. Fukunaga, S. Nunomura, S. Nishida, K. Endo, Y. Gon, S. Hashimoto, Y. Hashimoto, Y. Okayama, M. Makishima, C. Ra, Mast cell death induced by 24(S),25-epoxycholesterol, Exp. Cell Res. 316 (2010) 3272–3281.
[13] S. Nunomura, Y. Gon, T. Yoshimaru, J. Kashiwakura, T. Kawakami, C. Ra, FcepsilonRI beta-chain ITAM amplifies PI3K-signaling to ensure synergistic degranulation response via FcepsilonRI and adenosine receptors, Eur. J. Immunol. 40 (2010) 1205–1217.
[14] L.G. Frigeri, F.T. Liu, Surface expression of functional IgE binding protein, an endogenous lectin, on mast cells and macrophages, J. Immunol. 148 (1992) 861–867.
[15] Y. Suzuki, T. Inoue, T. Yoshimaru, C.S. Ra, Galectin-3 but not galectin-1 induces mast cell death by oxidative stress and mitochondrial permeability transition, Biochim. Biophys. Acta Mol. Cell Res. 1783 (2008) 924–934.
[16] T. Niki, S. Tsutsui, S. Hirose, S. Aradono, Y. Sugimoto, K. Takeshita, N. Nishi, M. Hirashima, Galectin-9 is a high affinity IgE-binding lectin with anti-allergic effect by blocking IgE–antigen complex formation, J. Biol. Chem. 284 (2009) 32344–32352.
[17] R. Molfetta, L. Quatrini, F. Gasparrini, B. Zitti, A. Santoni, R. Paolini, Regulation of fc receptor endocytic trafficking by ubiquitination, Front. Immunol. 5 (2014) 449.
[18] S. Aits, M. Jäättelä, Lysosomal cell death at a glance, J. Cell Sci. 126 (2013) 1905–1912.
[19] T. Inoue, Y. Suzuki, T. Yoshimaru, C. Ra, Nitric oxide protects mast cells from activation-induced cell death: the role of the phosphatidylinositol-3 kinase-Akt endothelial nitric oxide synthase pathway, J. Leukoc. Biol. 83 (2008) 1218–1229.
[20] Y. Suzuki, T. Yoshimaru, T. Inoue, C. Ra, Ca v 1.2 L-type Ca2+ channel protects mast cells against activation-induced cell death by preventing mitochondrial integrity disruption, Mol. Immunol. 46 (2009) 2370–2380.
[21] T. Kambayashi, J.D. Baranski, R.G. Baker, T. Zou, E.J. Allenspach, J.E. Shoag, P.L. Jones, G.A. Koretzky, Indirect involvement of allergen-captured mast cells in antigen presentation, Blood 111 (2008) 1489–1496.
[22] M. Kohno, S. Yamasaki, V.L. Tybulewicz, T. Saito, Rapid and large amount of autocrine IL-3 production is responsible for mast cell survival by IgE in the absence of antigen, Blood 105 (2005) 2059–2065.