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Identification of the minimal region of peptide derived from ADP-ribosylation factor1 (ARF1) that inhibits IgE-mediated mast cell activation

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ABSTRACT

Mast cells play a pivotal role in allergic reactions and inflammations. Aggregation of the high affinity IgE receptor (FcεRI) eventually leads to the release of granule components such as histamine, as well as the *de novo* synthesis of inflammatory cytokines and lipid mediators. These substances are involved in the development of allergy and inflammation. Therefore, efficient inhibitors of mast cell activation would be therapeutically beneficial. We previously demonstrated that the synthetic peptide derived from the NH_2-terminal region (2–17: GNIFANLFKGLFGKKE) of a small GTPase ARF1 (ADP-ribosylation factor1) inhibited FcεRI-induced mast cell degranulation. However, detailed structure-activity relationship study of NH_2-terminal portion of ARF1 peptide has not been done. In addition, it is still unclear whether the NH_2-terminal peptide of ARF1 suppresses FcεRI-induced production of cytokines and lipid mediators such as leukotriene C4 (LTC_4) from mast cells.

Here we show that amino acid residues K^{10}-K^{16} are necessary for ARF1 peptide to efficiently inhibit FcεRI-induced activation of bone marrow-derived mast cells (BMMCs), indicated by decreased mast cell degranulation, cytokine secretion and leukotriene release. Furthermore, we show that ARF1 peptide inhibits IgE-mediated passive cutaneous anaphylaxis reaction. Our results suggest that the peptide derived from ARF1 could be developed into a novel anti-allergic agent for therapeutic intervention in allergy and mast cell-related pathologies.

1. Introduction

Mast cells participate in a variety of immune responses such as type I hypersensitivity reactions (Galli and Tsai, 2012; Kawakami et al., 2009). Engagement of the high affinity receptors for IgE (FcεRI) on mast cells initiates signaling cascades leading to the secretion of chemical mediators and various cytokines (Gilfillan and Rivera, 2009). These released molecules play pivotal roles in the inflammatory reactions observed in patients with allergic diseases. Currently, several anti-allergy drugs including antihistamines and antileukotrienes are clinically used. However, each of these receptor antagonists is effective against only one chemical mediator without affecting the others. Inhibition of mast cell activation by targeting upstream regulators of FcεRI-mediated signaling can therefore be an effective strategy for controlling allergic diseases.

The ADP-ribosylation factors (ARFs) are members of the Ras superfamily of small monomeric G proteins which consist of six isoforms (Moss and Vaughan, 1995; Roth, 1999). Their GTPase cycle is regulated by both guanine nucleotide exchange factors (GEFs) that activate ARFs and GTPase-activating proteins (GAPs) that deactivate them (Moss and Vaughan, 1998; Randazzo and Hirsch, 2004; Wright et al., 2014). ARF1-GTP is myristoylated at the NH_2-terminal Gly residue, and this lipid modification leads to the translocation of ARF1-GTP to the membrane. ARF1-GTP can then recruit various effector molecules such

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as COPI/II, phospholipase D, AKT and Rac1 on the membrane (Nie et al., 2003; Spang, 2002; Donaldson, 2009; Haines et al., 2015; Lewis-Saravalli et al., 2013).

We previously showed that FcεRI-induced ARF1 activation regulates mast cell degranulation (Nishida et al., 2011). Our report suggested that a small GTPase ARF1 is involved in the FcεRI-mediated signal transduction. In addition, we have shown that MTM-ARF1(2–17), a cell-permeable fusion peptide consisting of a membrane-translocating motif (MTM) (Hawiger, 1999) and the NH_2-terminal portion of ARF1 corresponding to residues 2–17, efficiently inhibited the FcεRI-induced ARF1 activation and mast cell degranulation (Nishida et al., 2011). In this study, we investigated the detailed structure-activity relationship of ARF1 NH_2-terminal residue for mast cell activation in terms of degranulation, cytokine production and lipid mediator secretion.

2. Materials and methods

2.1. Peptide synthesis

Peptides were synthesized and purified by reverse phase or countercurrent distribution chromatography by Toray Research Center (Kanagawa, Japan).

2.2. Mice

C57BL/6J and BALB/c mice were obtained from Japan SLC. The mice were maintained under specific pathogen-free conditions and were analyzed between 8 and 12 weeks of age for all studies performed. We obtained approval from the animal research committee at Suzuka University of Medical Science for all animal experiments performed.

2.3. Cell culture

Bone marrow–derived mast cells (BMMC) were prepared as described previously (Nishida et al., 2002). Briefly, 8-week-old C57BL6J mice were sacrificed and their bone-marrow cells were cultured in RPMI 1640 supplemented with 10% heat-inactivated FBS, 10 mU/mL penicillin, 0.1 mg/mL streptomycin, and IL-3 in a 5% CO_2 and 95% humidified atmosphere at 37 °C. After culturing for 4–5 weeks, cell-surface expression of FcεRI and c-Kit was confirmed and cells were harvested for experiments (< 95% mast cells).

2.4. BMMC degranulation assay

Cells were sensitized with 0.5 μg/mL IgE for 12 h at 37 °C. After sensitization, the cells were washed twice with Tyrode's buffer (10 mM HEPES pH 7.4, 130 mM NaCl, 5 mM KCl, 1.4 mM $CaCl_2$, 1 mM $MgCl_2$, 5.6 mM glucose), then suspended in the same buffer and stimulated with polyvalent dinitrophenyl-human serum albumin (DNP-HSA, BIOSEARCH TECHNOLOGIES) for 30 min. For the β-hexosaminidase reaction, 50 μL of supernatant or cell lysate and 100 μL of 1.3 mg/mL p-nitrophenyl-*N*-acetyl-D-glucosamide (in 0.1 M citrate, pH 4.5) were added to each well of a 96-well plate, and the color was developed for 50 min at 37 °C. The enzyme reaction was then stopped by adding 150 μL of 0.2 M glycine-NaOH, pH 10.2, and the absorbance at 405 nm was measured in a microplate reader (Bio-Rad). Cells were lysed with Tyrode's buffer containing 1% Triton X-100 and the β- hexosaminidase activity was measured. The secretion rate of β-hexosaminidase was calculated using the following formula: secretion (%) = supernatant / (supernatant + cell lysate) x 100.

2.5. Measurement of cytokines and chemical mediators

Cells were activated as described above, and IL-6 in the cell culture supernatants were measured with an ELISA kit (BD) and IL-13 supernatants were measured with ELISA kit (eBioscience). The level of leukotrienes was determined using an ELISA kit (Cayman Chemical) following the manufacturer's instructions.

2.6. Real-time PCR analysis

Cells were homogenized with Sepasol RNAI (Nacalai Tesque), and total RNA was isolated following the manufacturer's instructions. For standard RT-PCR, cDNA was synthesized from 1 μg of total RNA with reverse transcriptase (ReverTra Ace; Toyobo) and 500 ng of oligo (dT) primer (Invitrogen) for 30 min at 42 °C A portion of the cDNA was used for real-time PCR. *Il-6* gene expression relative to the reference gene *g3pdh* was measured using the SYBR® Green system (TaKaRa). The primers used in these experiments were purchased from Invitrogen, and the sequences were as follows: IL-6: forward primer, 5′- GAGGATACC ACTCCCAACAGACC-3′ and reverse primer, 5′- AAGTGCATCATCGTTG TTCATACA-3′; IL-13: forward primer, 5′- TGGGTCCTGTAGATGGCA TTG-3′ and reverse primer, 5′- AGACCA GACTCCCCTGTGCA-3′; G3PDH: forward primer, 5′- TTCACCACCATGGAGAAGGCCG-3′ and reverse primer, 5′- GGCATGGACTGTGGTCATGA-3′.

2.7. Passive cutaneous anaphylaxis and histology of the ears

Balb/c mice were sensitized for 12 h or overnight with 0.5 μg of IgE subcutaneously injected into both ears. They were then injected intraperitoneally with vehicle or MTM-ARF1(8–16) peptide at the indicated concentrations. After 30 min, 250 μg of multivalent dinitrophenyl-bovine serum albumin (DNP-BSA) (Cosmo Bio Co., LTD) and 5 μg/mL Evans blue dye (Sigma-Aldrich) in saline was administered subcutaneously. Extravasation of Evans blue in the ear was monitored for 30 min, then the mice were sacrificed, both ears were dissected, and the blue dye was extracted in 700 μL of formamide at 63°C overnight. The absorbance of Evans blue-extracted formamide was measured at 620 nm.

2.8. Lactate Dehydrogenase (LDH) assay

Quantification of cell toxicity was performed by measuring LDH release into the medium. LDH activity was measured using a Cytotoxicity LDH Assay Kit-WST (Dojindo Laboratories) according to the manufacturer's protocol. Mast cells were seeded at a density of 1×10^6 cells/mL and cultured in the presence or absence of MTM-ARF1(8–16) peptide. The leakage of LDH was expressed as the amount of LDH released into the medium after a 0.5 or 3 h exposure to MTM-ARF1(8–16) peptide. Aliquots of the cultured medium were transferred to 96-well microplates, to which working solution was then added. The microplate was protected from the light and incubated at room temperature for 30 min. The microplate reader (SpectraMax M5, Molecular Devices) was used to measure the absorbance at 490 nm.

2.9. Statistical analysis

All data were statistically analyzed using Students' two-tailed *t*-test. Data were considered statistically significant when the *P* value was less than 0.05.

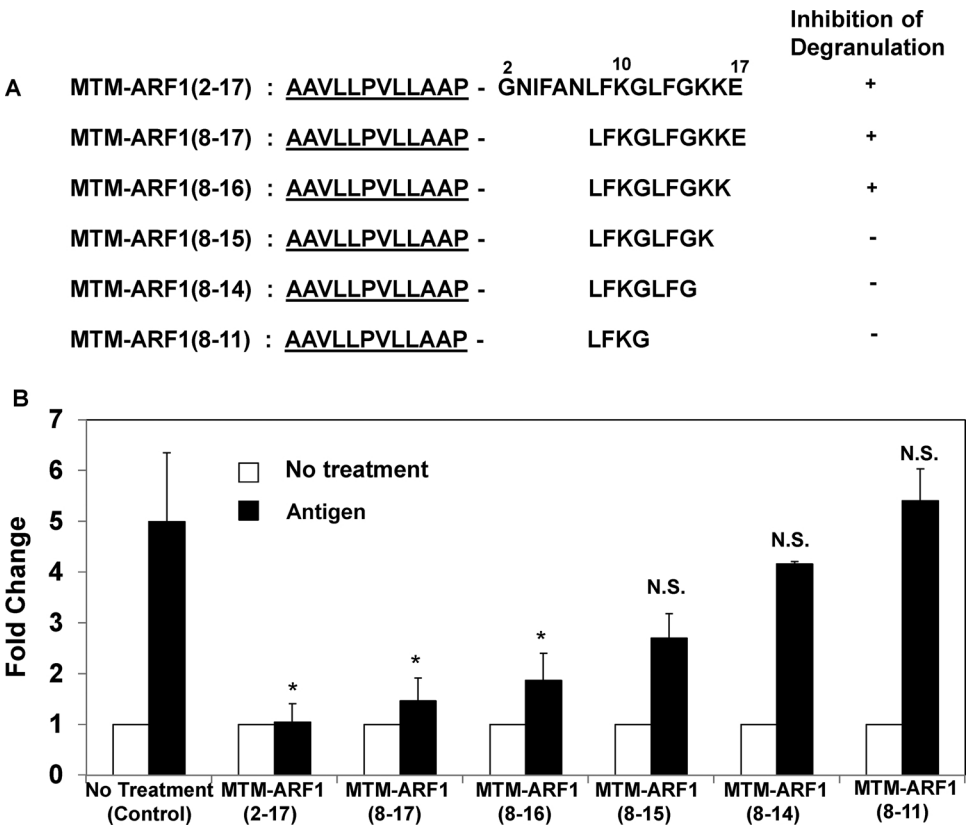

Fig. 1. Effects of deletions in the COOH-terminal regions of MTM-ARF1 on mast cell degranulation.
(A) Structure-activity relationships of synthetic peptides representing the COOH-terminal region of MTM-ARF1. The inhibitory effect of these peptides on mast cell degranulation was examined by measuring β-hexosaminidase activity. Inhibition was considered statistically significant (marked with "+") when the *P* value was less than 0.05. (B) Effect of MTM-ARF1 variants on mast cell degranulation. Mast cells were treated with or without 15 μM of each peptide variants for 5 min followed by 30-minute stimulation of FcεRI with antigen. Mast cell degranulation was then examined by measuring β-hexosaminidase activity. Values represent the mean ± standard deviation (SD). Statistical analysis was performed using Student's two-tailed t-test. N.S., not significant, *, $P < 0.05$.

3. Results

3.1. Effects of deletions in the COOH-terminal regions of ARF1 peptide on mast cell degranulation

To identify the minimal region of MTM-ARF1(2–17) necessary for inhibition of mast cell degranulation, peptides derived from NH_2-terminal ARF1 were synthesized as shown in Fig. 1A. As MTM sequence is incorporated to increase cell permeability, amino acid residues in this sequence were not changed in this study. The inhibitory activity of these peptides on mast cell degranulation was examined by measuring β-hexosaminidase activity in the supernatant from FcεRI-stimulated mast cells. Consistent with our previous observation (Nishida et al., 2011), MTM-ARF1(2–17) exhibited a strong inhibition of FcεRI-induced mast cell degranulation (Fig. 1B). In addition, no significant change in the amount of LDH released was observed after 0.5 or 3 h exposure to MTM-ARF1 peptide (Supplementary Fig. 1). These data suggested that inhibition of mast cell degranulation induced by antigenic stimulation is not due to cytotoxic effect of MTM-ARF1 peptide. The truncated peptide MTM-ARF1(8–17), which lacks G^2-N^7 residues of MTM-ARF1(2–17) retained the inhibitory activity of mast cell degranulation (Fig. 1B). When E^{17} at the COOH-terminal of MTM-ARF1(8–17) was removed, the inhibitory activity was also retained (Fig. 1B). However, deleting the COOH-terminal residues such as E^{17} and K^{16} or E^{17}, K^{16} and K^{15} weakened the inhibitory effect, and there was no significant difference between these variants and the control (Fig. 1B). The inhibitory effect was completely lost in MTM-ARF1(8–11) (Fig. 1B). These data indicated that K^{16} and K^{15} residues of MTM-ARF1(2–17) are required for the inhibition of mast cell degranulation.

3.2. Effects of deletions in the NH_2-terminal regions of ARF1 peptide on the mast cell degranulation

To study the effects of the NH_2-terminal region of ARF1 peptide, several peptides representing stepwise deletion from the NH_2-terminal of ARF1(7–16) were synthesized (Fig. 2A). MTM-ARF1(7–16) completely inhibited FcεRI-induced mast cell degranulation (Fig. 2B). When N^7 or N^7 and L^6 or N^7, L^6 and F^5 at the NH_2-terminal residues of MTM-ARF1(7–16) were deleted, mast cell degranulation was also significantly inhibited (Fig. 2A). However, MTM-ARF1(11–16), in which K^{10} on MTM-ARF1(10–16) was deleted, did not show the inhibitory activity (Fig. 2B). Based on these results, we considered that K^{10}-K^{16} including three K residues are necessary to exert effective inhibitory activity in mast cell degranulation.

3.3. Effects of the MTM-ARF1 peptide on cytokine production in mast cells

To investigate the effect of MTM-ARF1(8–16) on cytokine production in mast cells, RNA and protein expression of IL-6 and IL-13 induced by FcεRI stimulation was examined by ELISA and real-time PCR analysis. As shown in Figs. 3A and B, IL-6 and IL-13 protein levels were significantly reduced in mast cells treated with MTM-ARF1(8–16), but not in cells treated with MTM-ARF1(11–16). Furthermore, MTM-ARF1(8–16) peptide also inhibited FcεRI-induced IL-6 and IL-13 gene expression (Fig. 3C and D). These results indicated that MTM-ARF1(8–16) peptide disturbed IL-6 and IL-13 production at the transcription level.

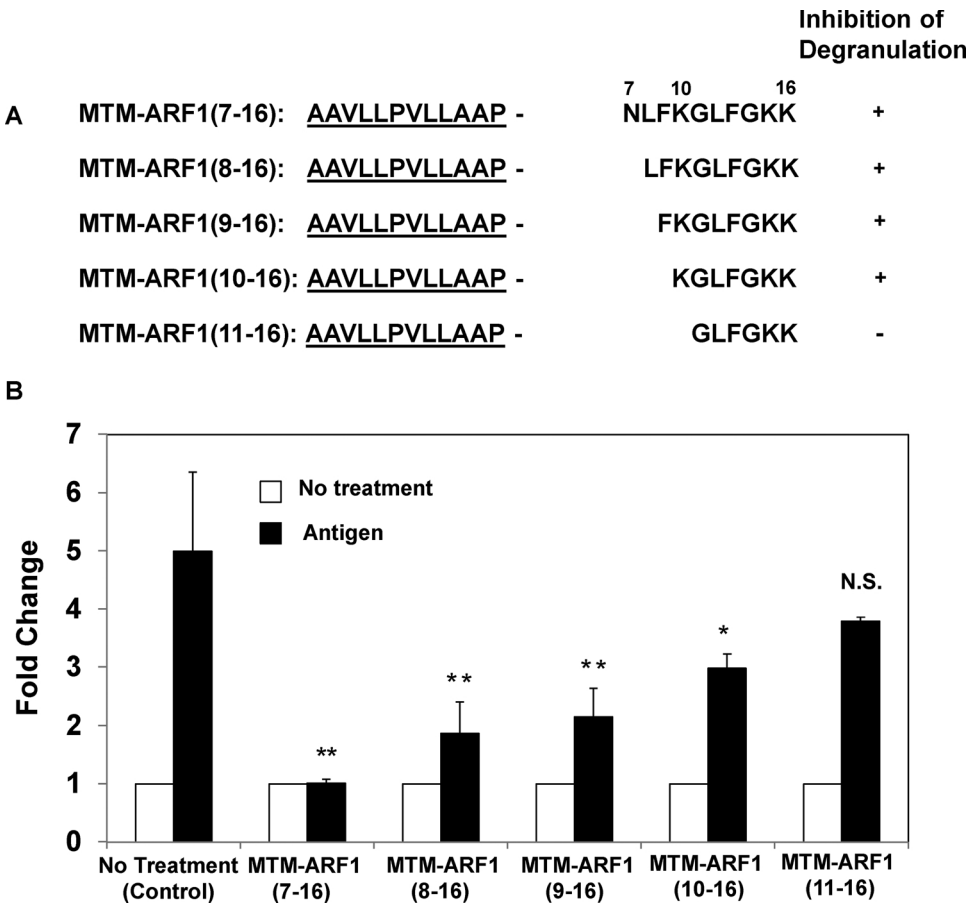

Fig. 2. Effects of deletions in the NH_2-terminal regions of MTM-ARF1 on mast cell degranulation.
(A) Structure-activity relationships of synthetic peptides representing the NH_2-terminal region of MTM-ARF1. The inhibitory effect of these peptides on mast cell degranulation was examined by measuring β-hexosaminidase activity. Inhibition was considered statistically significant (marked with "+") when $P < 0.05$. (B) Effect of MTM-ARF1 variants on mast cell degranulation. Mast cells were treated with or without 15 μM of each peptide variant for 5 min followed by 30-minute stimulation of FcεRI with antigen. Mast cell degranulation was then examined by measuring β-hexosaminidase activity. Values represent the mean ± standard deviation (SD). Statistical analysis was performed using Student's two-tailed t-test. N.S., not significant, *, $P < 0.05$, **, $P < 0.01$.

3.4. Effects of the MTM-ARF1 peptide on lipid mediator secretion from mast cells

FcεRI stimulation can induce the secretion of lipid mediators such as leukotriene C_4 (LTC_4) (Boyce, 2007). To investigate whether MTM-ARF1(8–16) inhibits FcεRI-induced LTC_4 secretion, LTC_4 level was measured by ELISA. FcεRI stimulation of mast cells lead to an increase in LTC_4 level. However, LTC_4 secretion was significantly decreased in MTM-ARF1(8–16)-treated mast cells (Fig. 4).

3.5. MTM-ARF1 peptide inhibits antigen-dependent passive cutaneous anaphylaxis

To study the potential role of MTM-ARF1(8–16) in mast cell degranulation *in vivo*, we assessed its efficacy in allergic reactions using a mouse passive cutaneous anaphylaxis (PCA) model, to which antigen-specific IgE was injected into the ear. Pretreatment of mice by intraperitoneal administration of MTM-ARF1(8–16) significantly inhibited the IgE-dependent PCA reactions (Fig. 5). These result clearly showed that MTM-ARF1(8–16) effectively inhibited antigen-dependent mast cell degranulation *in vivo*.

4. Discussion

Along with the progress of research in the field of immunology and molecular biology, our understanding of the mechanism for suppressing allergic inflammation by anti-allergy drugs has been improving. However, allergic diseases have yet to be completely conquered and it is necessary to develop new allergy medications in the future.

In this study, we analyzed the structure-activity relationship of the ARF1 peptide that exerts an inhibitory effect on mast cell degranulation. We identified the peptide MTM-ARF1(8–16) as a novel pharmacological inhibitor of mast cell activation and showed that this peptide requires three lysine residues (K^{10}, K^{15}, K^{16}) to efficiently inhibit FcεRI-induced mast cell degranulation (*i.e.*, β-hexosaminidase release). Furthermore, MTM-ARF1(8–16) inhibited FcεRI-mediated cytokine production and leukotriene release. Thus, the ARF peptide can potentially be a unique anti-allergic agent that controls various chemical mediators and cytokines.

How might the NH_2-terminal peptide of ARF1 exert its inhibitory effect?

ARF1 protein is associated with many molecules such as proteins, lipid membrane components, and guanine nucleotides during biochemical events (D'Souza-Schorey and Chavrier, 2006). As one of the structural features, ARF1 protein has a myristoyl group at G^2 and NH_2-terminal amphiphilic α-helix region (G^2-F^{13}), which are thought to facilitate membrane interaction by anchoring (Liu et al., 2009, 2010). Additionally, ARF1 have positively charged sites, composed of K^{10}, K^{15}, K^{16}, K^{59}, K^{181} and R^{178}, for PIP_2 (phosphatidylinositol 4,5-bisphosphate) binding on the membrane surface. Among them, residues K^{15}, K^{16}, K^{181}, and R^{178} were reported to be involved in its interaction with PIP_2 (Randazzo, 1997; Seidel et al., 2004). Our present study has clearly shown that deletion of K^{10}, K^{15}, and K^{16} within the NH_2-terminal ARF1 sequence peptides decreased inhibitory activity in mast cell degranulation, suggesting the importance of these positively charged amino acid residues. The hypothetical mechanism is that MTM-ARF1(8–16) containing three lysine residues competitively inhibit ARF1-membrane association, especially ARF1-PIP_2 interaction on the membrane surface. MTM-ARF1(8–16) peptide may interfere with this step, leading to the inhibition of mast cell degranulation, cytokine production and lipid mediator secretion. It is known that the translocation of ARF1 protein to the membrane is important in the activation

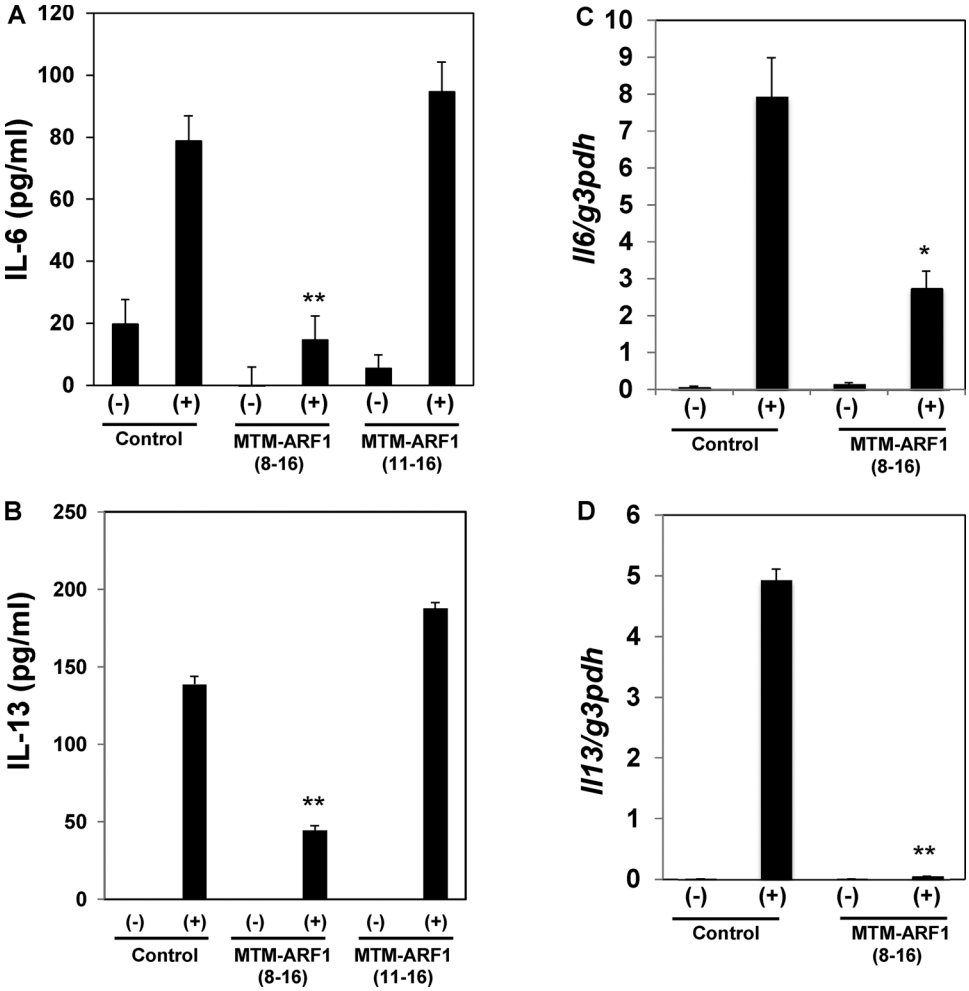

Fig. 3. Effects of MTM-ARF1(8–16) on cytokine production in mast cells.
(A) and (B) The level of IL-6 and Il-13 released into the culture supernatant from mast cells after 3 h of FcεRI stimulation (+). Cells were treated with or without 15 μM of synthetic peptide MTM-ARF1(8–16) or MTM-ARF1(11–16), and were stimulated for 3 h. IL-6 and Il-13 levels were then measured by ELISA. Values represent the mean ± SD. Statistical analysis was performed using Student's two-tailed t-test. **, $P < 0.01$. **(C) and (D)** FcεRI-mediated induction of *Il6* and *il13* transcription. Mast cells were treated with 15 μM of MTM-ARF1(8–16) peptide for 5 min, and *Il6* and *il13* mRNA were extracted 30 min after antigen stimulation (+). The expression level of *Il6* and *il13* were measured by real-time PCR. Values represent the mean ± SD. Statistical analysis was performed using Student's two-tailed t-test. *, $P < 0.05$, **, $P < 0.01$.

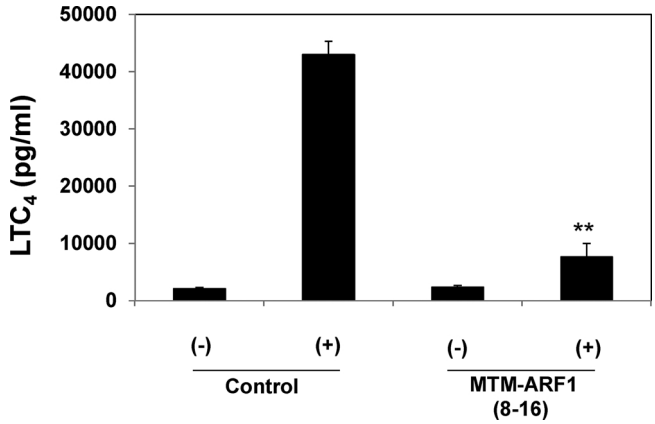

Fig. 4. Effects of MTM-ARF1(8–16) on lipid mediator secretion from mast cells. The level of leukotriene C_4 released into the culture supernatant after 30 min of FcεRI stimulation (+). Cells were treated with or without 15 μM of synthetic peptide MTM-ARF1(8–16) for 5 min, and were then stimulated for 30 min. The LTC_4 level was measured by ELISA. Values represent the mean ± SD. Statistical analysis was performed using Student's two-tailed t-test. **, $P < 0.01$.

step of ARF1. Activated ARF1 then recruits its effector molecules to the membrane, which inhibit ARF1-mediated biological events (Nie et al., 2003). AKT, which has been reported to regulate the FcεRI-mediated cytokine production in mast cells (Kitaura et al., 2000), is one of the potential effector molecules that interact with ARF1. Considering that the inhibition of ARF reduces cytokine production, we speculate that MTM-ARF1(8–16) peptide interferes with the ARF1-AKT signaling pathway, resulting in the inhibition of cytokine production.

In this study, we identified that MTM-ARF1(8–16) peptide can be a new anti-allergic agent. We showed that MTM-ARF1(8–16) peptide inhibited the FcεRI-dependent passive cutaneous anaphylaxis. Consistent with this *in vivo* effect, the MTM-ARF1(8–16) peptide strongly inhibited the FcεRI-induced mast cell degranulation. There is a possibility MTM-ARF1(8–16) peptide inhibits ARF activation. We have already shown that MTM-ARF1(2–17) suppressed FcεRI-induced ARF1 activation (Nishida et al., 2011). In addition, the ARF protein is ubiquitously expressed and plays a central role in the ER-Golgi transport system (D'Souza-Schorey and Chavrier, 2006). Therefore, potential side effects should be considered in order to develop the ARF peptide for therapeutic use, though no obvious adverse reaction was observed in mice administered with MTM-ARF1(8–16) in this study. For example, chemical modifications can improve the specificity of the peptide

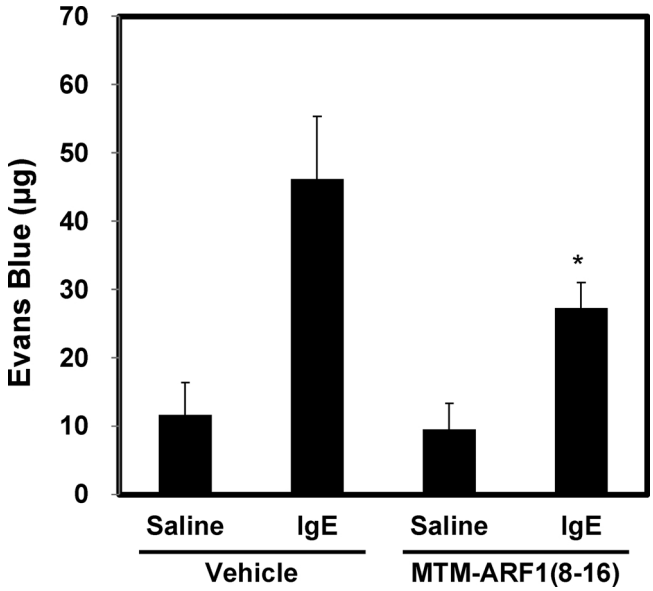

Fig. 5. MTM-ARF1(8–16) peptide administration into mice inhibits antigen-dependent passive cutaneous anaphylaxis.
The effect of MTM-ARF1(8–16) peptide *in vivo* was tested using a mouse model of passive cutaneous anaphylaxis (PCA). Mice were sensitized with IgE injected into the ear and then challenged with antigen (DNP-BSA) and Evans blue administered intravenously for 30 min. Prior to antigen challenge, mice were intravenously injected with MTM-ARF1(8–16) peptide. The amount of extravasated Evans blue dye in both ears was determined by extracting the dye and measuring the OD of the extract at 620 nm. Data are expressed as the mean + SD (n = 3 mice per group). Statistical analysis was performed using Student's two-tailed t-test. *, $P < 0.05$.

toward allergy-related tissues such as the lungs and the skin, and such ARF peptides can be effective therapeutic agents for bronchial asthma and atopic dermatitis.

In summary, our findings suggest that the MTM-ARF1(8–16) peptide could be developed into a new type of anti-allergic agent that acts differently from existing single-target drugs such as histamine receptor antagonists. Further investigation of the FcεRI-mediated signaling pathway may lead to the identification of key molecules that interacts with the MTM-ARF1 peptide. These would pave the way for developing new anti-allergic treatments.

Conflict-of-interest disclosure

The authors declare no competing financial interests.

Author contributions

R.U., T. E., and Y. F performed the experiments; R.U., T. E., Y.F., H.T., and K.N. designed the research and analyzed the data; Y.F., and K.N. wrote the manuscript; K.F., and S.T. contributed to the experiments for revision; and all authors reviewed and edited the manuscript.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.molimm.2018.11.002.

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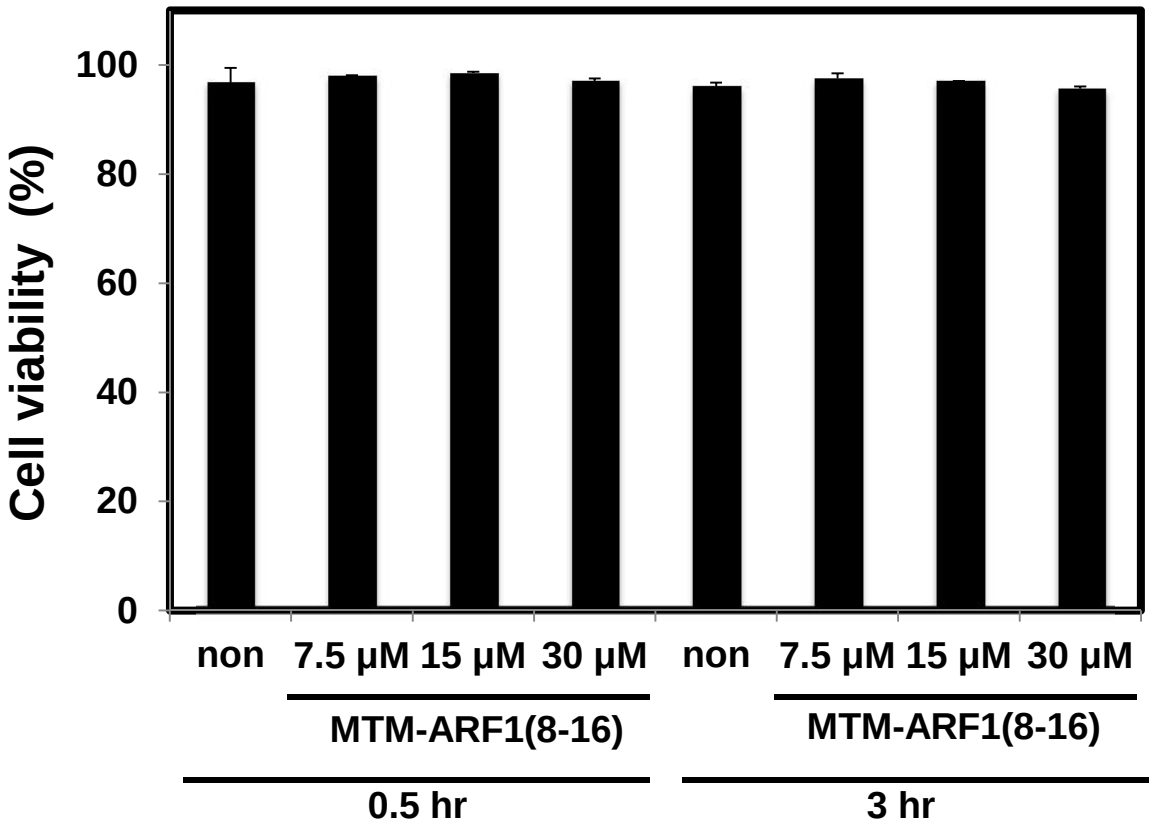
Supplementary figure 1