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Cationic liposomes suppress intracellular calcium ion concentration increase via inhibition of PI3 kinase pathway in mast cells

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ABSTRACT

Cationic liposomes are commonly used as vectors to effectively introduce foreign genes (antisense DNA, plasmid DNA, siRNA, etc.) into target cells. Cationic liposomes are also known to affect cellular immunocompetences such as the mast cell function in allergic reactions. In particular, we previously showed that the cationic liposomes bound to the mast cell surface suppress the degranulation induced by cross-linking of high affinity IgE receptors in a time- and dose-dependent manner. This suppression is mediated by impairment of the sustained level of intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) via inhibition of store-operated Ca^{2+} entry (SOCE). Here we study the mechanism underlying an impaired $[Ca^{2+}]_i$ increase by cationic liposomes in mast cells. We show that cationic liposomes inhibit the phosphorylation of Akt and PI3 kinases but not Syk and LAT. As a consequence, SOCE is suppressed but Ca^{2+} release from endoplasmic reticulum (ER) is not. Cationic liposomes inhibit the formation of STIM1 puncta, which is essential to SOCE by interacting with Orai1 following the Ca^{2+} concentration decrease in the ER. These data suggest that cationic liposomes suppress SOCE by inhibiting the phosphorylation of PI3 and Akt kinases in mast cells.

1. Introduction

Several studies have shown that cationic liposomes exert immunomodulatory effects associated with low immunogenicity and toxicity and offer advantages such as easy preparation and targeting [1–4]. Cationic liposomes not only transport DNA to immune cells but also enhance the function of antigen-presenting cells such as dendritic cells and macrophages [5–7]. Previously, we investigated the effect of a particular cationic liposome on the mast cell function during allergic reactions and found that the cationic liposomes suppressed degranulation induced by cross-linking of high affinity IgE receptors (FcεRI) in a time- and dose-dependent manner [8]. The suppression of degranulation is mediated by the impairment of a sustained level of intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) derived from the inhibition of store-operated Ca^{2+} entry (SOCE). Furthermore, cationic liposomes suppress vascular permeability elevation induced by mast cell activation in mice.

Mast cells play important roles in innate and adaptive immune responses [9]. Cross-linking of FcεRI on mast cells by multivalent antigens induces two pathways activated by src-family protein tyrosine kinases, Lyn and Fyn [10]. Lyn phosphorylates the tyrosine residues in the immunoreceptor tyrosine-based activation motif (ITAM) of FcεRI β- and γ-chains. Phosphorylated ITAMs of the γ-chain create binding sites for the Src homology 2 (SH2) domains of the tyrosine kinase Syk, which is then activated by phosphorylation. The activated Syk subsequently phosphorylates linker for activation of T cells (LAT), leading to the organization of a complex with phospholipase C (PLC) γ [11]. Activation of PLCγ in this complex causes the hydrolysis of phosphatidylinositol 4,5-bisphosphate (PIP_2) into inositol-1,4,5-triphosphate (IP_3) and diacylglycerol (DAG), increasing the $[Ca^{2+}]_i$ through Ca^{2+} release from endoplasmic reticulum (ER) [12]. This pathway is known as the Lyn–Syk–LAT pathway. The LAT-activating pathway is the main contributor to Ca^{2+} depletion in the ER because LAT organizes the complexes comprising PLCγ, SLP76, and other adaptor proteins.

In addition to Syk, the second src-family protein tyrosine kinase Fyn also phosphorylates Grb-associated binder 2 (Gab2), an adapter protein essential for phosphatidylinositol-3 kinase–Akt activation (PI3K–Akt pathway) [13–15]. The activation of this pathway leads to extracellular Ca^{2+} influx, an indispensable step for mast cell degranulation. To regulate SOCE following a Ca^{2+} decrease in ER, the ER protein stromal interaction molecule 1 (STIM1) forms oligomers, translocates to the plasma membrane region (ER-PM junctions), and interacts with Orai1 [16,17]. Indeed, ER-PM junctions are often visualized as the formation of STIM1 puncta [18,19].

The aim of this study was to examine the mechanism of impaired

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$[Ca^{2+}]_i$ increase by the treatment with cationic liposomes in RBL-2H3 cells. In this paper, we report that cationic liposomes suppress SOCE through the inhibition of PI3K and Akt activation. Our results might contribute to the clinical development of cationic liposomes as a useful therapeutic tool for allergic diseases mediated by mast cell activation.

2. Materials and methods

2.1. Materials

The synthesis of the cationic cholesterol derivative containing a hydrophilic amino head group, cholesteryl-3β-carboxyamidoethylene-*N*-hydroxyethylamine (OH-Chol) was described in a previous study [20] and 1,2-dioleoyl-*sn*-glycero-3-phosphatidylethanolamine (DOPE) was purchased from Sigma-Aldrich (St. Louis, MO, USA). Mouse anti-dinitrophenyl (DNP)-IgE was provided by Prof. T. Kishimoto (Osaka University). DNP-conjugated bovine serum albumin (DNP-BSA) was prepared using previously described methods [21]. In the present experiments, six DNP groups, on average, were conjugated with a single BSA molecule. Thapsigargin was purchased from Wako Pure Chemical Industries (Osaka, Japan). PhosphoBLOCKER™, rabbit anti-phospho-Syk(Y323) antibody, rabbit anti-phospho-LAT(Y191) antibody, rabbit anti-phospho-PI3K p85(Y458)/p55(Y199) antibody, rabbit anti-phospho-Akt(T308) antibody, horse radish peroxidase (HRP)-labeled goat anti-rabbit IgG, HRP-labeled goat anti-mouse IgG, and rabbit anti-STIM1 antibodies were purchased from Cell Signaling Technology (Danvers, MA, USA). Rabbit anti-Orai1 antibody was purchased from Proteintech (Rosemont, IL, USA). Mouse anti-β-actin antibody was purchased from Sigma-Aldrich. Alexa Fluor 555-labeled goat anti-rabbit IgG antibody was obtained from Molecular Probes (Cambridge Cambridgeshire, UK).

2.2. Preparation of liposomes

The cationic liposomes were prepared by ultrasonication methods according to our previously described procedures [22–24]. In brief, DOPE (20 nmol) and OH-Chol (30 nmol) were mixed and dried with N_2 gas under reduced pressure to remove the chloroform solvent. The lipid film was hydrated with 400 μl of phosphate buffered saline (PBS) for 1 h. Samples were sonicated in a bath-type sonicator (Branson model B 1200) to generate small unilamellar vesicles. We measured the average size of cationic liposome by dynamic light scattering using zetasizer Nano ZS90 (Malvern Instruments, Worcestershire, UK) with a scattering angle of 90°. The size of cationic liposome was 453.2 ± 83.2 nm. We confirmed that the size peak of liposome and lipoplexes was so sharp and polydispersity index was low.

2.3. Cell culture

The rat mast cell line RBL-2H3, which is the most widely used, as a model for mast cells, was cultured in minimum essential medium (Nissui, Tokyo, Japan) supplemented with 10% fetal calf serum (Roche, Mannheim, Germany).

2.4. Western blot analysis

Cultured RBL-2H3 cells were seeded in 60 mm plates at a density of 5×10^5 cells/well 24 h before introduction of the cationic liposomes. Cells were incubated with 23.3 μg/ml of cationic liposomes for 3 h and washed in HEPES buffer [10 mM HEPES (pH 7.2), 140 mM NaCl, 5 mM KCl, 0.6 mM $MgCl_2$, 1 mM $CaCl_2$, 0.1% glucose, 0.1% BSA, and 0.01% sulfinpyrazone]. After sensitizing the RBL-2H3 cells with anti-DNP IgE for 30 min at 37 °C, the cells were washed twice with HEPES buffer. Thereafter, cells were lysed with cold lysis buffer [20 mM HEPES (pH 7.9), 0.1% NP-40, 50 mM NaCl, 1 mM EDTA, 1 mM dithiothreitol, 10 mM Na_3VO_4, 10 μg/ml phenylmethylsulfonyl fluoride, 10 μg/ml leupeptin, and 10% glycerol]. The lysates were kept on ice for 30 min, followed by centrifugation at 15,000 rpm for 20 min at 0 °C. The resulting supernatants were solubilized by treatment with Laemmli buffer at 100 °C for 3 min. Subsequently, proteins were separated using 10% SDS-polyacrylamide gel electrophoresis. The separated proteins were transferred to a PVDF membrane with an electroblotter. After blocking with 5% PhosphoBLOCKER™, the membranes were probed with rabbit anti-phospho-Syk (Y323) (1:1000), rabbit anti-phospho-LAT (Y191) (1:1000), rabbit anti-phospho-PI3K p85 (Y458)/p55(Y199) (1:1000), rabbit anti-phospho-Akt (T308) (1:1000), rabbit anti-STIM1 (1:1000), mouse anti-Orai1 (1:1000), or mouse anti-β-actin (1:40,000) antibody at 4 °C overnight. Subsequently, treatment with HRP-labeled goat anti-rabbit IgG (1:2000) or HRP-labeled goat anti-mouse IgG (1:2000) was performed. Immunoreactivity was detected using enhanced chemiluminescence (ECL; GE Healthcare, Buckinghamshire, UK) with a LAS-3000mini (Fujifilm, Tokyo, Japan) and analyzed using Image Gauge (Fujifilm).

2.5. Confocal laser scanning microscopy (CLSM)

RBL-2H3 cells were incubated with 23.3 μg/ml cationic liposomes for 3 h and washed in HEPES buffer. After sensitizing the RBL-2H3 cells with anti-DNP IgE at 37 °C, cells were washed twice with HEPES buffer and then immediately fixed with ice-cold paraformaldehyde in PBS overnight. The next day, cells were incubated with rabbit anti-STIM1 (1:800) at 4 °C overnight. Subsequently, treatment with Alexa Fluoro 555-labeled goat anti-rabbit IgG antibody (1:400) was performed. The distribution of STIM1 was analyzed in an observation chamber (Elecon, Chiba, Japan) by CLSM (LSM 510-META; Zeiss, Oberkochen, Germany). The Alexa Fluor 555-labeled goat anti-rabbit IgG antibody was excited by a He–Ne laser (543 nm), and fluorescence was detected through a band-pass filter at 560–580 nm.

2.6. Measurement of $[Ca^{2+}]_i$

RBL-2H3 cells (5×10^5 cells) were loaded with 1 μM Fura 2-AM (Molecular Probes, Eugene, OR, USA.), sensitized with anti-DNP IgE for 30 min at 37 °C, and then washed twice with HEPES buffer or Ca^{2+}-free HEPES buffer. Fluorescence intensities at 500 nm using excitation wavelengths of 340 and 360 nm (F340 and F360, respectively) were measured at 37 °C, and the F340/F360 ratio was calculated using a spectrofluorometer connected to a personal computer (RF-5300PC; Shimadzu, Kyoto, Japan). Ratios were converted to Ca^{2+} concentrations by a previously described procedure [25].

3. Results

3.1. Effects of cationic liposomes on Ca^{2+} release from ER and SOCE

Initially, to check the effects of cationic liposomes on Ca^{2+} release from ER, we measured the $[Ca^{2+}]_i$ in RBL-2H3 cells in the absence of extracellular Ca^{2+} following antigen stimulation. We found that there was no significant difference in the $[Ca^{2+}]_i$ increase in RBL-2H3 cells with and without treatment with cationic liposomes (22.3 μg/ml) for 3 h (Fig. 1), indicating that cationic liposomes do not affect the amount of Ca^{2+} release from ER. On the contrary, the pretreatment with cationic liposomes significantly suppressed the $[Ca^{2+}]_i$ increase in the presence of extracellular Ca^{2+} (3 mM) (Fig. 1). This result indicates that cationic liposomes inhibit SOCE but not Ca^{2+} release from ER in RBL-2H3 cells stimulated by antigen.

3.2. Effects of cationic liposomes on phosphorylation of signaling proteins

In mast cells, when FcεRI are crosslinked by multivalent antigens, two pathways are activated via src-kinase Lyn and Fyn. Although both Lyn and Fyn phosphorylate Syk, Lyn and Fyn subsequently activate LAT

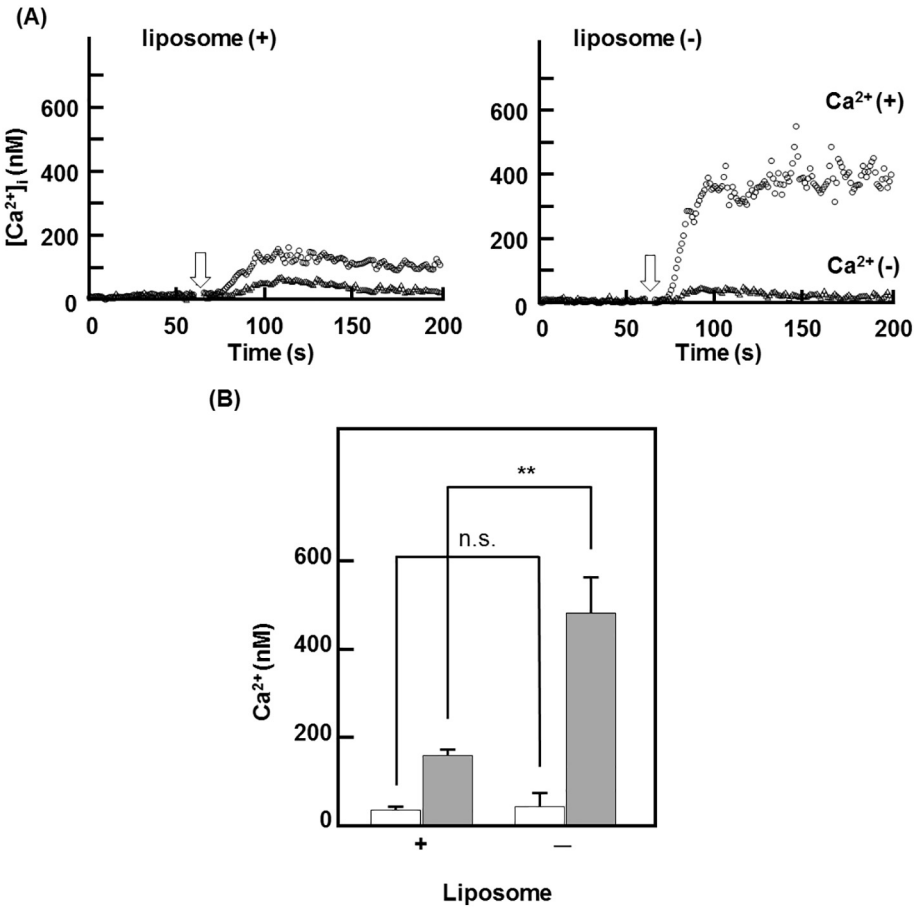

Fig. 1. Release of Ca^{2+} from ER in RBL-2H3 cells after antigen stimulation.
Cells incubated with anti-DNP IgE and Fura 2-AM for 30 min were stimulated with antigen (DNP-BSA; 50 ng/ml) at the time indicated by arrows (60 s). (A) A typical time-course of $[Ca^{2+}]_i$ in RBL-2H3 cells pretreated with and without cationic liposomes (22.3 μg/ml) for 3 h in the presence (circles) and absence (triangles) of extracellular Ca^{2+}. (B) The averaged $[Ca^{2+}]_i$ at 140 s after addition of antigen in RBL-2H3 cells pretreated with and without cationic liposomes (22.3 μg/ml) for 3 h in the presence (grey bars) and absence (white bars) of extracellular Ca^{2+}. Data are the mean ± SE (n = 4–5) $^{**}P < 0.01$ by *t*-test.

and PI3K, respectively. Fyn and Syk phosphorylate the adapters such as Gab2, which are essential for PI3K activation, followed by Akt phosphorylation (PI3K–Akt pathway) [11]. PI3K activation is essential for SOCE and optimal degranulation in mast cells [26–30].

When we checked the phosphorylation levels of Syk and LAT, both Syk and LAT were found to be phosphorylated in similar levels after addition of antigen in RBL-2H3 cells pretreated and non-treated with cationic liposomes (Fig. 2). This indicates that cationic liposomes do not affect phosphorylation of Syk and LAT, considering to be consistent with effect on Ca^{2+} release from ER (Fig. 1). Next, we examined the phosphorylation levels of Akt and PI3K. Interestingly, the phosphorylation of Akt and PI3K induced by antigen stimulation was significantly suppressed by the pretreatment with cationic liposomes (Fig. 3). From these results, we considered that inhibition of Akt-PI3K pathway caused the suppression of SOCE by cationic liposomes.

3.3. Effects of cationic liposomes on the expression of STIM1 and Orai1, and the formation of STIM1 puncta in activated in RBL-2H3 cells

Previous reports have shown that STIM1 is intimately involved in

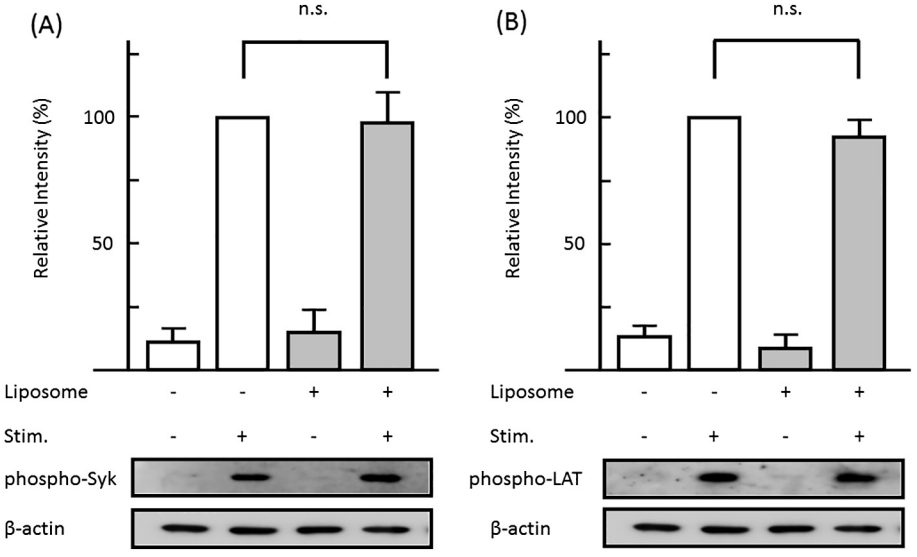

Fig. 2. Effect of cationic liposomes on Syk and LAT phosphorylation.
RBL-2H3 cells pretreated with and without cationic liposomes (22.3 μg/ml) for 3 h were stimulated with DNP-BSA for 30 min. The phosphorylation levels of (A) Syk and (B) LAT were analyzed by western blotting, respectively. Lower panels show typical western blotting data. Upper panels show relative intensity of phosphorylated proteins normalized by β-actin. Data represent the intensity of lane of liposome (−) and stimulation (+) as 100%. Data are the mean ± SE (n = 8–10) $^{**}P < 0.01$ by t-test.

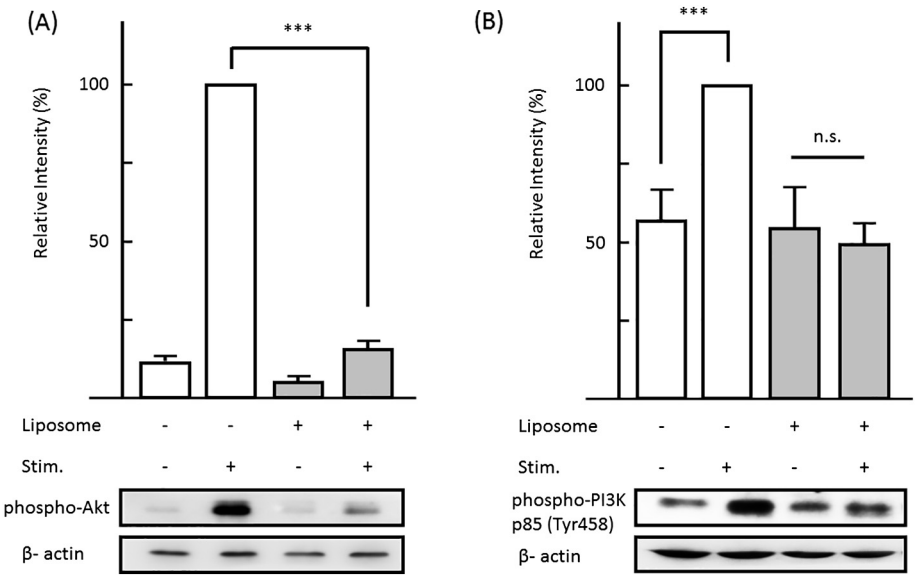

Fig. 3. Inhibition of Akt and PI3K phosphorylation by the cationic liposomes.
RBL-2H3 cells pretreated with and without cationic liposomes (22.3 μg/ml) for 3 h were stimulated with DNP-BSA for 30 min. The phosphorylation levels of (A) Akt and (B) PI3K were analyzed by Western blotting, respectively. Lower panels show typical data by Western blotting. Upper panels show relative intensity of phosphorylated proteins normalized by β-actin. Data represent the lane intensity of liposome (−) and stimulation (+) as 100%. Data are the mean ± SE (n = 6–8) $^{**}P < 0.01$ by t-test.

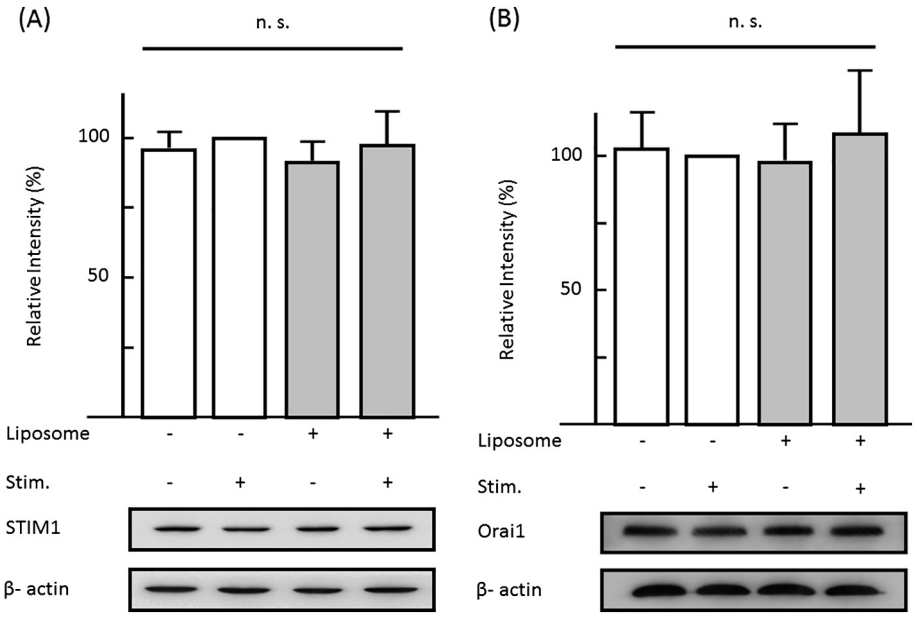

Fig. 4. Expression of STIM1and Orai1 in RBL-2H3 cells.
RBL-2H3 cells pretreated with and without cationic liposomes (22.3 μg/ml) for 3 h were stimulated with DNP-BSA for 30 min. Expression levels of (A) STIM1and (B) Orai1 were analyzed by Western blotting. Data represent the lane intensity of liposome (−) and stimulation (+) as 100%. Data are the mean ± SE (n = 6–8) $^{**}P < 0.01$ by t-test.

SOCE. After depletion of Ca^{2+} in ER, STIM1 forms oligomer, translocate to ER-PM junction, and localizes to the PM. These phenomena can be observed as the formation of STIM1 puncta [18,19]. Though cationic liposomes had no effects of the expression of STIM1 and Orai1 in RBL-2H3 cells (Fig. 4A, B), cationic liposomes inhibited the translocation of STIM1 into puncta after antigen stimulation, as shown in Fig. 5 middle panels. Next, we observed the STIM1 puncta in RBL-2H3 cells after stimulation with thapsigargin, which is often used to mimic antigen stimulation without cross-linking of FcεRI because thapsigargin induces Ca^{2+} leakage from the ER by inhibition of the sarcoplasmic/endoplasmic reticulum Ca^{2+}-ATPase. As we expected, STIM1 translocation of puncta was observed by thapsigargin stimulation in untreated RBL-2H3 cells (Fig. 5 lower panels). In RBL-2H3 cells pretreated by cationic liposomes, thapsigargin-induced STIM1 translocation into puncta was inhibited (Fig. 5 lower panels).

4. Discussion

Cationic liposomes are commonly used as vectors for the effective introduction of foreign plasmid DNA, antisense DNA, siRNA, and proteins into target cells [31–34]. While studying the effects of cationic liposomes on cell biology, we previously found that cationic liposomes composed of DOPE and OH-Chol have the ability to suppress mast cell degranulation by impaired $[Ca^{2+}]_i$ increase in vitro and to diminish the induced vascular permeability in vivo [8]. To develop cationic liposomes as a new therapy for mast cells based allergic disorders, discovering the molecular mechanism underlying the degranulation suppression by cationic liposomes is essential.

Cross-linking FcεRI by multivalent antigens induces the phosphorylation of several protein tyrosine kinases in mast cells. The signaling cascade initiated by the interaction of FcεRI with Lyn and Fyn is followed by the phosphorylation of downstream tyrosine kinase proteins [35]. Phosphorylation of Syk by Lyn leads to the phosphorylation of LAT. The LAT-activating pathway is the main contributor to Ca^{2+} depletion in ER, because LAT organizes the complexes composed of PLCγ, SLP76, and other adaptor proteins. When we checked the phosphorylation status of Syk and LAT in this study, we observed that cationic liposomes did not suppress their phosphorylation (Fig. 2). When we measured the effects of cationic liposomes on Ca^{2+} release from ER after antigen stimulation, we confirmed that cationic liposomes did not

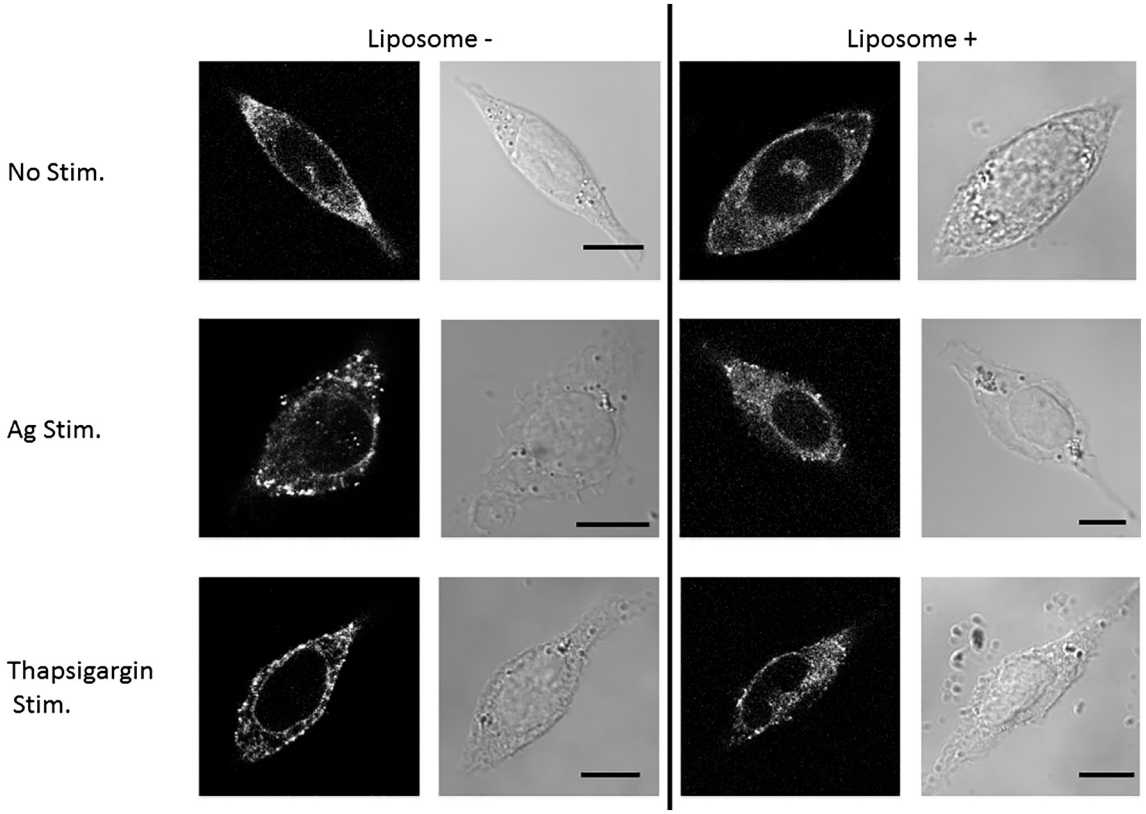

Fig. 5. Images of STIM1 puncta in RBL-2H3 cells.
Typical fluorescence images of STIM1 distribution in RBL-2H3 cells pretreated with or without cationic liposomes. These panels show absence of stimulation (upper panels), antigen addition (DNP-BSA; 50 ng/ml) (middle panels), and thapsigargin addition (20 nM) (lower panels) for 5 min. Scale bars mean 10 μm.

influence Ca^{2+} release (Fig. 1), suggesting that they do not suppress the upstream signaling of PLCγ activation. Moreover, cationic liposomes did not inhibit the phosphorylation of PLCγ (data not shown). Taken together, cationic liposomes were not involved in the signaling pathway inducing $[Ca^{2+}]_i$ increase and degranulation via activation of Lyn, Syk, and LAT.

Next, we focused on the PI3K-Akt signaling pathway, which is also essential for the regulation of FcεRI-mediated mast cell activation [26–30]. Specifically, we checked PI3K activation by assessing the phosphorylation levels of PI3K and Akt. After antigen stimulation, the phosphorylation of Akt and PI3K was suppressed by the pretreatment with cationic liposomes.

We observed STIM1 puncta after antigen stimulation, and showed that cationic liposomes inhibited the formation of STIM1 puncta without affecting STIM1 and Orai1 expression (Fig. 4A, B). The mechanism of translocation of STIM1 into the PM is not established yet. One model suggests that STIM1 interacts with Orai1 directly [36], while the other proposes that STIM1 directly binds, via its polybasic domains, phosphoinositides such as PIP_2 and phosphatidylinositol 3,4,5-triphosphate [16,37]. However, puncta are visualized only when i) STIM1 translocates into ER-PM junction, ii) STIM1 interacts with Orai1. PI3K inhibitors, wortmannin and LY294002, have been reported to inhibit antigen-mediated degranulation and Ca^{2+} influx [26–30] as well as STIM1 puncta formation. These data suggest that the pathway contributes to the regulation of Ca^{2+} influx through the recruitment of STIM1 to the PM following ER store depletion. In our study, we show that cationic liposomes suppress the formation of the STIM1 puncta via suppression of PI3K and Akt activation while they do not inhibit Ca^{2+} release from the ER. Furthermore, cationic liposomes inhibited SOCE (Fig. 1) and the formation of STIM1 puncta (Fig. 5), even after stimulation by thapsigargin. Taken together, cationic liposomes might inhibit store-operated Ca^{2+} channel formation by suppressing STIM1 translocation into ER-PM junction and/or STIM1 interaction with Orai1 via the PI3K-Akt pathway, without any effects on IP_3 and DAG, blocking the Ca^{2+} influx from extracellular medium and subsequently degranulation.

In summary, this study shows that cationic liposomes suppress the phosphorylation of Fyn-PI3K-Akt but not Lyn, Syk, and LAT. Thus, cationic liposomes do not inhibit the Ca^{2+} depletion of ER, but the STIM1-Orai1 interaction, leading to blockage of the Ca^{2+} influx from extracellular medium. Although the detailed mechanism remains to be clarified, this study proves the potential of cationic liposomes as anti-allergic drug carriers. The cationic liposomes with their anti-allergic action can lead to the development of innovative treatments for allergic diseases as their added features include targeting, easy preparation, and low toxicity.

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