Involvement of Syntaxin 7 in Human Gastric Epithelial Cell Vacuolation Induced by the *Helicobacter pylori*-produced Cytotoxin VacA*

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The *Helicobacter pylori*-produced cytotoxin VacA induces intracellular vacuolation. The formed vacuole is assumed to be a hybrid of late endosome and lysosome. To elucidate the molecular mechanism of VacA-induced vacuolation, we examined the participation of syntaxin 7 in the human gastric epithelial cell line AGS. Immunocytochemistry revealed that endogenous syntaxin 7 was localized to vacuoles induced by VacA. Northern and Western blotting demonstrated that VacA intoxication increased syntaxin 7 mRNA and protein expression, respectively, in a time-dependent manner. Transient transfection of dominant-negative mutant syntaxin 7, which lacks a carboxyl-terminal transmembrane domain, inhibited VacA-induced vacuolation. In contrast, transient transfection of wild-type syntaxin 7, dominant-negative mutant syntaxin 1a, or dominant-negative mutant syntaxin 4 did not alter VacA-induced vacuolation. Furthermore, under VacA treatment, neutral red dye uptake, a parameter of VacA-induced vacuolation, was inhibited in cells stably transfected with mutant syntaxin 7 but not in cells stably transfected with wild-type syntaxin 7, mutant syntaxin 1a, or mutant syntaxin 4. Sequential immunocytochemical observation confirmed that expression of mutant syntaxin 7 did not affect VacA attachment to or internalization into AGS cells. We suggest that syntaxin 7 is involved in the intracellular vacuolation induced by VacA.

*H. pylori*-related diseases. Previous studies reported that intragastric administration of VacA to mice induced erosion of gastric epithelium (1). In *vitro*, VacA induces cytoplasmic vacuolation. The intracellular vacuolation is assumed to represent an early pathophysiological event leading to cell suffrance and eventually to necrosis. These vacuoles induced by VacA contain both a late endosomal marker, rab7, and a lysosomal marker, lgp110, suggesting that they are hybrids of late endosomes and lysosomes (2, 3). Papini et al. (4) reported recently that rab7, a small molecular weight GTP-binding protein that regulates late endosomal trafficking, plays an essential role in VacA-induced vacuolation. More recently, we reported that dynamin, a large molecular weight GTP-binding protein functioning as a mechanochemical enzyme in vesicle formation, is involved in VacA-induced vacuolation (5). In addition, we revealed that VacA cytopathic effect on intoxicated cells was also attenuated by inhibiting the dynamin function (5). These results suggest that VacA-induced vacuolation is a result of a toxin-induced alteration of intracellular vesicle trafficking and that VacA cytopathic effect can be prevented by inhibiting VacA-induced vacuolation. Thus, the elucidation of the molecular mechanism of VacA-induced vacuolation will contribute to the development of novel therapeutic strategy for *H. pylori*-related diseases. However, the molecular mechanism of the final and key step of the VacA-induced vacuolation, that is fusion of late endosome and lysosome resulting in vacuolation, is still unknown.

Recently, the SNARE hypothesis has provided a model for fusion events of intracellular trafficking (6). SNARE proteins are present on cellular membranous organelles including transport vesicles and function to bridge two membranes about to undergo membrane fusion (7). They form cytoplasmic coiled-coil bundles with other SNARE proteins using their cytoplasmic amphipathic helices and mediate docking and fusion of two membranous organella (7). SNARE proteins are classified into Q- and R-SNARE, according whether they contain a glutamine or an arginine, respectively, in the central region of their helical bundles (7). Of these, syntaxin protein family is a representative of Q-SNARE proteins. A number of syntaxin proteins have been identified with their specific localization and function. Syntaxin 1, 2, 3, and 4 are localized to the plasma membrane and play their roles in synaptic vesicle exocytosis, platelet-release factor attachment protein receptors; GFP, green fluorescent protein.

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‡‡ The abbreviations used are: SNARE, soluble N-ethylmaleimide-sensitive factor attachment protein receptors; GFP, green fluorescent protein.
VacA and Syntaxin 7

MATERIALS AND METHODS

Cell Culture, Purification, and Activation of VacA and Intoxication of Cells—AGS cells, a human gastric adenocarcinoma cell line, were provided by Dr. Hiroyuki Matoh (Jichi Medical School, Tochigi, Japan) and were cultured in Dulbecco’s modified Eagle’s medium supplemented with 10% fetal calf serum and 100 units/ml penicillin in a 5% CO2 atmosphere at 37 °C. VacA cytotoxin was purified from the toxin-producing strain H. pylori ATCC49503 (American Type Culture Collection, Manassas, VA), according to the reported procedures (14), and then it was activated with acidic pH treatment as described (15). For VacA intoxication, cells were treated with 1 µg/ml activated VacA at 37 °C. Temporarily transfected cells were treated with VacA 24 h after transfection. Vaccination was examined 18 h after VacA intoxication.

DNA and Plasmid Constructions—Full-length human syntaxin 7 cDNA and dominant-negative mutant cDNAs of human syntaxin 4 (3–273 amino acids) and syntaxin 7 (2–234 amino acids), lacking their carboxyl-terminal hydrophobic regions, were amplified by PCR from human liver and brain cDNA libraries (provided by Dr. Yukio Horikawa, Gunma University, Gunma, Japan). Dominant-negative mutant cDNA of human syntaxin 1a (2–260 amino acids) was amplified by PCR using full-length human syntaxin 1a cDNA (a gift of Dr. Tetsuro Iwum, University of Gunma) as a template. PCR was performed with the following primers: syntaxin 1a mutant, 5′-GGGTTCTAGAAG-ACCAGAACCCAG-GAGCTCCGC-3′ (sense) and 5′-CTATCTTGCTTCTTG-TCTG-TACTTGAGGCTTCCTC-3′ (antisense); syntaxin 4 mutant, 5′-GAC-GAGGCCCAGGCTGAGACA-3′ (sense) and 5′-CTATCTTGCTTCTTG-TCTG-TACTTGAGGCTTCCTC-3′ (antisense); syntaxin 7 mutant, 5′-TCTAGATTTACCTCAGGAGGTTGG-3′ (sense) and 5′-CTATCTTGCTTCTTG-TCTG-TACTTGAGGCTTCCTC-3′ (antisense); full-length syntaxin 7, 5′-TCTAGATTTACCTCAGGAGGTTGG-3′ (sense) and 5′-TCTATCTGTTAGGACTCCATAGGT-3′ (antisense). Amplified cDNAs were verified by sequencing and subcloned into the pcDNA3.1(−)/GFP(1−) vector (Invitrogen) and expressed as GFP fusion proteins. We used a pcDNA3.1(−)/GFP vector (Invitrogen) as a control plasmid for mock transfection.

Transfection—Transfection procedures were performed using LipofectAMINE PLUS Reagent (Invitrogen), according to the manufacturer’s instruction. AGS cells were seeded at a density of 104/cm2 and transfected with constructed plasmids described above. For selecting stably transfected cell lines, gene-specific resistant clones were screened and then their potential to express transfected GFP-tagged proteins was confirmed by observing the GFP signals by fluorescence microscopy.

Antibodies—Anti-syntaxin 7 rabbit polyclonal antibody and anti-VacA rabbit polyclonal antibody were prepared as described (12, 15). Cy3-conjugated donkey anti-rabbit IgG and horseradish peroxidase-conjugated donkey anti-rabbit IgG were purchased from Jackson ImmunoResearch Laboratories, Inc. (West Grove, PA).

Immunofluorescence Microscopy—Cells were fixed with 2% formaldehyde in phosphate-buffered saline, treated with Triton X-100 in phosphate-buffered saline for 5 min, and incubated sequentially with Blocking Ace (Snow Brand Milk Products, Tokyo, Japan), first antibodies, and secondary antibodies. Samples were examined under a Nikon E-600 fluorescence microscope (Nikon, Tokyo, Japan). Images were captured and digitized using a Spot charged coupled device camera (Diagnostic Instruments, Sterling Heights, MI) and then edited using Adobe Photoshop 5.0 software (Adobe Systems Inc., Mountain View, CA).

Western Blotting—For electrophoresis, 20 µg of protein from each sample per lane was loaded onto 12.5% SDS-PAGE gels and run at 200 V. Proteins were then transferred to nitrocellulose membranes at 30 V for 3 h. Western blotting was done as described previously (16), using the enhanced chemiluminescence reagent to visualize the secondary antibody.

Northern Blotting—Northern blotting was performed as described previously (17). Briefly, 20-µg total RNA extracted from the cells was denatured and blotted onto Hybond-N+ nylon membrane (Amersham Biosciences). The blot was hybridized with 32P-labeled cDNA probe and washed at a final stringency of 0.1× standard saline citrate and 0.1% SDS at 60 °C for 30 min before exposure to x-ray film.

Neutral Red Dye Uptake Assay—AGS cells were seeded into 96-well plates and cultured for 24 h. Cells were then treated with VacA and incubated for a further 18 h. After the incubation, the vacuolation rate induced by VacA was examined by the method described (15), in which uptake of neutral red dye into intracellular acidic compartments was determined by measuring the absorbance at 540 nm. The potential differences in cell numbers of each preparation were corrected by measuring the protein concentration of each sample. Neutral red uptake into VacA-induced vacuoles was expressed as a percentage of neutral red accumulation into VacA-induced vacuoles in GFP mock-transfected cells.

Statistical Analysis—Statistical analysis was performed using analysis of variance. p < 0.05 was considered significant.

RESULTS

Localization of Endogenous Syntaxin 7 in VacA-induced Vacuoles in AGS Cells—In the first attempt to investigate whether syntaxin 7 participates in the VacA-induced vacuolation in AGS cells, we examined the localization of endogenous syntaxin 7 in VacA-treated and untreated AGS cells by immunocytochemistry. As shown in Fig. 1, endogenous syntaxin 7 was localized to the perinuclear region of the untreated cells, consistent with the previous observation that syntaxin 7 is present on late endosomes and lysosomes (12, 13). In VacA-treated AGS cells, in contrast, endogenous syntaxin 7 was localized to vacuoles induced by VacA. These data suggest the involvement of syntaxin 7 in VacA-induced vacuolization in AGS cells.

VacA Increased the Expression of Syntaxin 7 mRNA and Protein in AGS Cells—Next we examined the expression of endogenous syntaxin 7 in VacA-treated AGS cells by both Northern and Western blotting. As shown in Fig. 2A, VacA intoxication increased the expression of syntaxin 7 mRNA in AGS cells in a time-dependent manner. Moreover, Western blotting revealed that the amount of syntaxin 7 protein in AGS cells was also increased by VacA (Fig. 2B). At 12 to 24 h after

**FIG. 1. Immunocytochemical localization of endogenous syntaxin 7 to VacA-induced vacuoles in AGS cells.** Naïve AGS cells (A) and VacA-treated AGS cells (B–D) were fixed, stained with anti-syntaxin 7 antibody, and visualized with Cy3-conjugated anti-rabbit IgG antibody. A, perinuclear distribution of endogenous syntaxin 7 in naïve AGS cells. B–D, localization of endogenous syntaxin 7 on VacA-induced vacuoles in intoxicated AGS cells. Bars, 50 µm.
VacA intoxication, the expression of both syntaxin 7 mRNA and protein reached the maximum. Because VacA-induced vacuolation is also accomplished at the same time point (data not shown), the increase of syntaxin 7 by VacA was well accompanied with that of intracellular vacuolation. These results, as well as its subcellular localization (Fig. 1), suggest that syntaxin 7 participates in the VacA-induced vacuolation in AGS cells.

**Transient Transfection of Dominant-negative Mutant Syntaxin 7 Inhibits the VacA-induced Vacuolation in AGS Cells**—We next investigated participation of syntaxin 7 in VacA-induced vacuolation by a different approach. We generated AGS cells transiently overexpressing either GFP-tagged wild-type syntaxin 7 or dominant-negative mutant syntaxin 7. The cytosolic part of syntaxin 7 protein interacts with its counterpart to form a SNARE complex. The SNARE complex mediates the docking and fusion of the two compartments by functioning as a linker. However, mutant syntaxin 7, which lacks the carboxyl-terminal hydrophobic region, is expected to compete with endogenous syntaxin 7 in binding with other SNARE proteins. Thus, mutant syntaxin 7 acts as a dominant-negative syntaxin 7 as shown in previous studies (12, 13). As shown in Fig. 3, overexpressed GFP-tagged wild-type syntaxin 7 changed its intracellular localization from the perinuclear region (panels A and E) to the vacuoles after VacA intoxication (panels B and F). This is consistent with the localization of endogenous syntaxin 7 to VacA-induced vacuoles (Fig. 1). In contrast, most overexpressed GFP-tagged mutant syntaxin 7 was localized to cytoplasm uniformly in both VacA-treated (panel D) and untreated cells (panel C). The mutant syntaxin 7 inhibited the VacA-induced vacuolation in VacA-treated AGS cells (panels D and H, arrowheads), whereas overexpressed wild-type syntaxin 7 did not affect the VacA-induced vacuolation in AGS cells (panels B and F, arrows). For quantitative estimations, we compared the numbers of vacuolated cells under each experimental condition. To investigate the specific inhibitory effect of mutant syntaxin 7 on VacA-induced vacuolation, we utilized GFP-tagged dominant-negative mutant syntaxin 1α and syntaxin 4 as controls. When expressed in AGS cells, these control mutant syntaxins were localized to cytoplasm in the similar manner to that of mutant syntaxin 7 (data not shown). As depicted in Fig. 4, the inhibitory effect of mutant syntaxin 7 on VacA-induced vacuolation was statistically significant. In contrast, either mutant syntaxin 1α or mutant syntaxin 4 did not inhibit VacA-induced vacuolation. These data indicate that mutant syntaxin 7 specifically inhibited VacA-induced vacuolation, suggesting the syntaxin 7 involvement in the molecular machinery of VacA-induced vacuolation.

**Effect of Stable Transfection of Mutant Syntaxin 7 on Neutral Red Dye Uptake into VacA-treated AGS Cells**—For another quantitative estimation of the inhibitory effect of mutant syntaxin 7 on VacA-induced vacuolation, we constructed AGS cell lines stably transfected with mutant syntaxin 7, wild-type syntaxin 7, mutant syntaxin 1α, mutant syntaxin 4, or GFP alone. Using these cell lines, we examined the neutral red dye uptake...
under VacA-exposure condition. Because neutral red dye is predominantly taken up by acidic lumen of the vacuoles, it has been used as a quantitative marker for VacA-induced vacuolation (5, 15). We established clones that expressed GFP-tagged mutant syntaxin 7, wild-type syntaxin 7, mutant syntaxin 1a, or mutant syntaxin 4 proteins (Fig. 5A). In stably transfected cells, GFP-tagged mutant syntaxin proteins were localized to cytoplasm (Fig. 5A, panels a–c), whereas GFP-tagged wild-type syntaxin 7 was localized to perinuclear region (Fig. 5A, panel d). Their intracellular localizations were consistent with those in transiently transfected cells (Fig. 3). As shown in Fig. 5B, mutant syntaxin 7 inhibited neutral red dye uptake into VacA-treated cells compared with that into cells with GFP mock transfection, whereas wild-type syntaxin 7, mutant syntaxin 1a or mutant syntaxin 4 did not alter neutral red dye uptake under VacA-exposed condition. These data indicate again that mutant syntaxin 7 specifically inhibited VacA-induced vacuolation, suggesting the direct involvement of syntaxin 7 in the VacA-induced vacuolation mechanism.

**Mutant Syntaxin 7 Does Not Affect the VacA Internalization into AGS Cells**—Syntaxin 7 functions physiologically in endocytotic pathways. Although our observation with transfection approaches strongly suggest direct involvement of syntaxin 7 in VacA-induced vacuolation, the possibility still remained that the inhibitory effect of mutant syntaxin 7 on VacA-induced vacuolation might be a result from a block of VacA internalization into AGS cells. To exclude this possibility, we examined the effect of mutant syntaxin 7 on the VacA internalization into AGS cells. AGS cells were transiently transfected with mutant syntaxin 7, and the time course of VacA internalization was analyzed by immunocytochemistry. As shown in Fig. 6, signals of VacA toxin staining were observed at the plasma membranes in both transfected and non-transfected cells after 1 h of incubation with VacA. This indicates that mutant syntaxin 7 did not affect VacA binding to AGS cells. After 3 h of incubation with VacA, intracellular signals of VacA staining were detected in cytoplasm of both mutant syntaxin 7-expressing and non-expressing cells. We followed VacA localization until 6 h after incubation and found that intracellular signals of VacA staining were localized to the perinuclear region in both GFP-tagged mutant syntaxin 7-transfected and non-transfected cells. These data indicate that dominant-negative mutant syntaxin 7 does not affect binding or internalization of VacA to AGS cells and that syntaxin 7 is directly involved in molecular mechanism of VacA-induced vacuole formation.

**DISCUSSION**

In the present study, we have demonstrated the participation of syntaxin 7 in the VacA-induced vacuolation in AGS cells. We showed that both endogenous and overexpressed wild-type syntaxin 7 localized to the vacuoles induced by VacA. Moreover, VacA increased the expression of both syntaxin 7 mRNA and protein. Mutant syntaxin 7 inhibited the VacA-induced vacuolation in both transiently and stably transfected AGS cells, without affecting VacA internalization. From these lines of evidence, we concluded that syntaxin 7 directly participates in VacA-induced vacuolation in AGS cells.

VacA-induced vacuole has been assumed to be a hybrid of late endosome and lysosome, because both late endosomal marker rab7 and lysosomal marker lgp110 are colocalized (2, 3). However, it is still unclear whether the vacuole is formed as a result of the fusion of late endosome and lysosome. rab7 is physiologically localized to late endosome and regulates intracellular transport around late endosomes (18). However, rab7 is not an integral membrane protein of late endosome membrane but is cycling between late endosome membranes and cytosol. Thus, rab7 localization to VacA-induced vacuoles might not result from late endosome fusion but might be the aberrant targeting caused by VacA-intoxication. By contrast, lgp110 is an integral membrane protein of lysosome, and its existence on VacA-induced vacuole indicates that the vacuole is, at least partly, consisting of lysosome. Although lgp110 has been shown to play a role in the fusion of lysosome and autophagosome (19), its participation in lysosome and late endosome fusion has not been described. Syntaxin 7 is also an integral membrane protein present on both late endosome and lysosome and functions in their heterotypic fusion as a compartment of SNARE complex with other SNARE proteins. Thus, our observations that both endogenous and overexpressed syntaxin 7 are localized to VacA-induced vacuoles re-inforce that the vacuole results from the fusion of late endosome and lysosome.

The phenomenon that expression of both syntaxin 7 mRNA and protein in AGS cell was enhanced by the exposure to VacA strongly suggests that syntaxin 7 is involved in the VacA-induced vacuolation. It was reported that syntaxin 7 is widely expressed in tissues and regulates a membrane transport with late endosomes and lysosomes of mammalian cells (20). However, the expression level of syntaxin 7 varied with tissues and cell lines. In B16 melanoma cells, syntaxin 7 was shown to function in melanogenesis. Syntaxin 7 in B16 melanoma cells was present at about 10-fold higher than in other tissues and cell lines, and it was up-regulated upon the induction of melanogenesis (21). Thus, it was suggested that elevated expression level of syntaxin 7 facilitated melanogenesis that is, in part, related to lysosomal biogenesis. In the analogy of melanogenesis, our current observation suggests that VacA induces the
up-regulation of syntaxin 7 expression to facilitate the intracellular vacuolation.

Recent studies have reported that VacA-induced vacuolation did not depend on late endosomal SNAREs. Using a procedure of microinjection of anti-syntaxin 7 antibodies into cells, they revealed that anti-syntaxin 7 antibodies did not affect VacA-induced vacuolation and concluded that syntaxin 7 did not participate in the VacA-induced vacuolation. In our study, however, the localization and the elevated expression of syntaxin 7 strongly suggest its involvement in the VacA-induced vacuolation. Moreover, the direct participation of syntaxin 7 in VacA-induced vacuolation was ascertained by showing the inhibitory effects of dominant-negative mutant syntaxin 7 in two different experiments, counting vacuolated cell numbers among transiently transfected cells and determining neutral red uptake in stably transfected cells. The obvious discrepancy between de Bernard et al.'s group and ours may be ascribed to the difference of procedures used in the studies. It is noteworthy to point out that we used AGS cells originated from human gastric epithelial cells, a relevant target of VacA cytotoxin, whereas de Bernard et al. (22) used HeLa cells that originated from human uterine epithelial cells. As described above, the endogenous level of syntaxin 7 varied with tissues and cell lines (20, 21). Therefore, the difference of the cell lines used in the studies may also resulted in the discrepancy of the findings.

Our immunocytochemistry data that VacA cytotoxin is internalized even into cells expressing mutant syntaxin 7 are important. They reinforce that the dominant-negative syntaxin 7 mutant inhibited VacA-induced vacuolation by blocking endogenous syntaxin 7 but not by perturbing VacA internalization into cells. Various cytotoxins enter target cells through a vesicular endocytosis-dependent or -independent pathway or both. Although the mechanism of VacA internalization into target cells has been still unclear (23), we reported recently (5) that VacA internalization into cells is independent of early endocytotic pathway. Moreover, we showed in the current study that VacA internalization into cells was not blocked by mutant syntaxin 7, suggesting that VacA internalization is independent of late endocytotic pathway. Thus, it is reasonable to conclude that VacA is internalized, at least in part, by a mechanism distinct from the early and late endocytotic machinery.

In conclusion, we have shown that syntaxin 7 is involved in the molecular machinery of VacA-induced vacuolation. These observations provide new insights related to the molecular pathogenesis of gastroduodenal disease by the H. pylori bacterium.
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