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CagA, a major virulence factor of Helicobacter pylori, promotes the production and underglycosylation of IgA1 in DAKIKI cells

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ABSTRACT

While *Helicobacter pylori* (Hp) infection is closely associated with IgA nephropathy (IgAN), the underlying molecular mechanisms remain to be elucidated. This study was to investigate the effect of cytotoxin associated gene A protein (CagA), a major virulence factor of Hp, on the production and underglycosylation of IgA1 in the B cell *line DAKIKI cells*. Cells were cultured and treated with recombinant CagA protein. We found that CagA stimulated cell proliferation and the production of IgA1 in a dose-dependent and time-dependent manner. Moreover, CagA promoted the underglycosylation of IgA1, which at least partly attributed to the downregulation of β1,3-galactosyltransferase (C1GALT1) and its chaperone Cosmc. In conclusion, we demonstrated that Hp infection, at least via CagA, may participate in the pathogenesis of IgAN by influencing the production and glycosylation of IgA1 in B cells.

1. Introduction

IgA nephropathy (IgAN) is the most common primary glomerulonephritis worldwide, which is characterized by mesangial deposition of IgA1-containing immune complexes [1]. After renal transplantation, IgAN tends to recur in the renal allograft in at least 50% of IgAN patients. Conversely, in patients with different kidney diseases, IgA1 deposits disappear from renal allografts taken from donors with subclinical IgAN [2]. Therefore, extrarenal abnormalities in IgA immune system, rather than intrinsic renal abnormalities, may play a more important role in the pathogenesis of IgAN.

Renal biopsy in IgAN has shown that IgA1 in renal deposits is present predominantly in polymeric form, which is also the characteristic of mucosal-type IgA1 [1]. Consistently, IgAN often aggravates or relapses during an upper respiratory infection especially tonsillitis. However, Tonsillectomy may have a favorable effect on the prognosis of IgAN [3]. All above suggest that mucosal infection may be the initial event in IgAN and antigens of microbial origin may participate in the pathogenesis of IgAN.

Helicobacter pylori (Hp), a gram-negative bacterium, has been implicated in the pathogenesis of a number of gastrointestinal diseases such as chronic gastritis and peptic ulcers [4]. The protein cytotoxin associated gene A (CagA) has been shown to be the key virulence factor for Hp-inducing inflammation [5]. In two recent Japanese studies, it is reported that Hp exists in coccoid form in palatine tonsil in all studied IgAN patients, moreover, CagA is positive in 78.6% of these IgAN patients, which suggesting that tonsillar Hp may be a causative pathogen of IgAN [6,7].

The production of underglycosylated IgA1, which resulted from abnormal expression or activities of multiple glycosyltransferases in B lymphocytes, plays a central role in the pathogenesis of IgAN [1]. It is found that gene expression of β1,3-galactosyltransferase (C1GALT1), an important enzyme in the glycosylation process of IgA1, and its chaperone Cosmc are significantly downregulated in tonsillar B lymphocytes from IgAN patients and closely associated with clinical manifestation [8]. Our previous study on peripheral B lymphocytes from IgAN patients also showed the similar results [9]. On the other hand, it has been reported that mucosal Hp infection stimulates the production of polymeric and underglycosylated anti-Hp IgA1 antibody in IgAN patients [10,11]. However, the molecular mechanisms by which Hp participates in the pathogenesis of IgAN have not been fully elucidated.

The aim of the present study was to investigate the effect of CagA, the key virulence factor of Hp, on the production and underglycosylation of IgA1 as well as the corresponding mechanisms in DAKIKI cells, the surface IgA1-positive human B lymphoma cell line which is widely used for the studies of IgAN [12,13].

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2. Materials and methods

2.1. Cell culture and experimental protocol

DAKIKI cell line was purchased from ATCC (Manassas, VA) and cultured in RPMI 1640 medium containing 10% (v/v) heat-inactivated fetal calf serum, 100 U/ml penicillin and 100 μg/ml streptomycin in a humidified atmosphere at 37 °C with 5% CO_2. Recombinant CagA protein was purchased from Shanghai Linc-Bio Science Co. Ltd (Shanghai, China).

For dose-dependent experiments, cells were cultured with different concentration (0, 0.2, 0.4, 0.8, 1.6 and 3.2 μg/ml) of recombinant CagA protein for 48 h; for time-dependent experiments, cells were cultured with the optimal concentration of recombinant CagA protein for 24, 48 and 72 h. Then cell proliferation was assessed by cell counting manually using a hemocytometer or cell counting kit-8 (CCK8) assay (Sigma–Aldrich, St. Louis, MO) according to the manufacturer's protocol; the production and underglycosylation of IgA1 in the supernatants were determined by sandwich enzyme-linked immunosorbent assay (ELISA) and helix aspersa lectin (HAA; Sigma–Aldrich, St. Louis, MO) binding assay, respectively.

To study the mechanisms of underglycosylation of IgA1, cells were stimulated with 1.6 μg/ml of recombinant CagA protein or 12.5 μg/ml of lipopolysaccharide (LPS; Sigma–Aldrich, St. Louis, MO) for 48 h, then the expression of C1GALT1 and Cosmc were measured by real time RT-PCR and Western blotting. LPS is a marker of gram-negative bacteria infection. In previous studies, we and other groups have already demonstrated that LPS can suppress the expression of C1GALT1 and its chaperone Cosmc [14,15]. Therefore, in the present study, LPS was used as positive control.

2.2. Enzyme-linked immunosorbent assay

The production of IgA1 in the supernatant from each culture was determined by ELISA. As described previously, 96-well plates were coated with goat anti-human IgA antibody (Southern Biotechnology Associates, Birmingham, AL) overnight at 4 °C [9]. After plates were blocked, samples were added in duplicate. The plates were incubated overnight at 4 °C, and then incubated with horseradish peroxidase-conjugated goat anti-human IgA antibody (Southern Biotechnology Associates, Birmingham, AL) for 2 h at 37 °C. The color was developed using tetramethyl benzidine dilution (TMB) and detected with Bio-Rad 550 at 450 nm.

2.3. Helix aspersa lectin binding assay

The underglycosylation of IgA1 in the supernatant from each culture was measured by helix aspersa lectin (HAA) binding assay as previously reported [13]. Briefly, 96-well plates were coated with goat anti-human IgA antibody and blocked as described above. Samples were added to the plates in duplicate and incubated overnight at 4 °C. The captured IgA1 was subsequently desialylated by treatment with neuraminidase from *Vibrio cholerae* (Roche, Penzberg, Germany) for 3 h at 37 °C. Then the plates were incubated with biotinylated HAA lectin for 3 h at 37 °C. The lectin binding was detected with avidin-horseradish peroxidase conjugate (ExtrAvidin; Sigma–Aldrich, St. Louis, MO). The color was developed and measured as above.

2.4. Real time RT-PCR

Total RNA was extracted from cells using Trizol reagent (Invitrogen, Carlsbad, CA). cDNA was synthesized from total RNA using the RevertAid First Strand cDNA Synthesis Kit (Thermo Scientific Fermentas, Vilnius, Lithuania). Resulting cDNA (1 μg) was amplified in real time, with a 20 μl reaction mixture containing SYBR Green PCR Master Mix (Applied Biosystems, Foster City, CA), appropriate primer pairs and water in a Bio-Rad/MJ Chromo4 real-time PCR machine (Bio-Rad, Hercules, CA). The samples were incubated at 95 °C for 3 min, followed by 40 cycles with 30 s denaturation at 94 °C, 30 s annealing at 60 °C and 30 s extension at 72 °C. The expression of target gene was normalized to the reference gene β-actin measured in the same cDNA sample. Sequences of primers used in this study were as follows: C1GALT1: forward, 5′-AAGGTTGACACCCAGCCTAA-3′, reverse, 5′-CTTTGA-CGTGTTT GGCCTTT-3′; Cosmc: forward, 5′-GCTCCTTTTTGAAGGGTGTG-3′, reverse, 5′-TACTGCAGCCCAAAGACTCA-3′; β-actin: forward, 5′-TCACCCACACTGTGCCC-ATCTACGA-3′, reverse, 5′-CAGCGGAACCG CTCATTGCCAATGG-3′. All reactions were carried out in triplicate and the results were analyzed by a $2^{-\Delta\Delta CT}$ method.

2.5. Western blotting

Western blotting analyses were performed as described previously [16]. The primary antibodies were anti-C1GALT1 antibody (1:200; Santa Cruz Biotechnology, Santa Cruz, CA), anti-Cosmc antibody (1:200; Santa Cruz Biotechnology, Santa Cruz, CA), and anti-β-actin antibody (1:200; Santa Cruz Biotechnology, Santa Cruz, CA). The relative protein levels of C1GALT1 and Cosmc were normalized to β-actin, then the ratio was compared with that of control group.

2.6. Statistical analysis

All the experiments were performed at least three times. All data were presented as mean ± standard deviation (SD). Statistical differences between groups were evaluated by independent Student's *t*-test using SPSS software (version 16.0; SPSS, Chicago, IL, USA). A *P*-value of <0.05 was considered significant.

3. Results

3.1. Cell proliferation in DAKIKI cells treated with CagA

To investigate the effect of CagA on cell proliferation in DAKIKI cells, dose-dependent and time-dependent experiments were performed. In dose-dependent experiments, 1.6 μg/ml of CagA stimulated cell proliferation while 3.2 μg/ml of CagA inhibited cell proliferation as assessed by cell counting manually (Fig. 1A) and CCK8 assay (Fig. 1B). Moreover, within the range of 0.4–1.6 μg/ml, CagA stimulated cell proliferation in a dose-dependent manner as examined by cell counting manually (Fig. 1A). Accordingly, 1.6 μg/ml was chosen as the optimal concentration of CagA for further study. In time-dependent experiments, 1.6 μg/ml of CagA stimulated cell proliferation in a time-dependent manner as evaluated by cell counting manually (Fig. 1C).

3.2. Production and underglycosylation of IgA1 in DAKIKI cells treated with CagA

Within the range of 0.2–3.2 μg/ml, CagA stimulated the production of IgA1, with 1.6 μg/ml of CagA had the strongest effect on the production of IgA1 (Fig. 2A). On the other hand, 1.6 μg/ml of CagA stimulated the production of IgA1 in a time-dependent manner at 24, 48 and 72 h (Fig. 2B).

As for the effect of CagA on the underglycosylation of IgA1 in DAKIKI cells, the results showed that within the range of 1.6–3.2 μg/ml, CagA stimulated the underglycosylation of IgA1. Although inhibiting cell proliferation, 3.2 μg/ml of CagA had much stronger effect on underglycosylation of IgA1 than that of 1.6 μg/

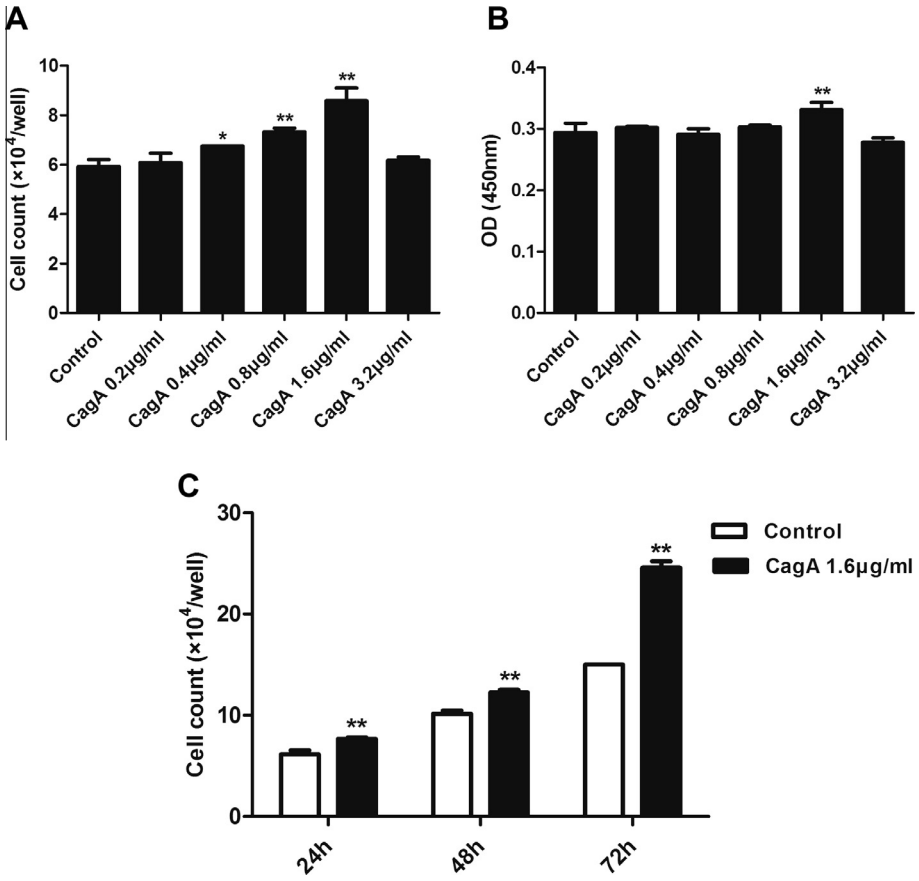

Fig. 1. Effect of CagA on cell proliferation in DAKIKI cells. (A) In dose-dependent experiments, CagA within the range of 0.4–1.6 μg/ml dose-dependently stimulated cell proliferation of DAKIKI cells. However, 3.2 μg/ml of CagA inhibited cell proliferation of DAKIKI cells as measured by cell counting manually. (B) 1.6 μg/ml of CagA significantly stimulated cell proliferation of DAKIKI cells in CCK8 assay. (C) 1.6 μg/ml of CagA time-dependently stimulated cell proliferation of DAKIKI cells as examined by cell counting manually. $^{*}p < 0.05$, compared with control; $^{**}p < 0.01$, compared with control.

ml of CagA (Fig. 2C). In time-dependent experiments, 1.6 μg/ml of CagA stimulated the underglycosylation of IgA1 at 24, 48 and 72 h in a time-dependent manner (Fig. 2D).

3.3. Effect of CagA on mRNA expression of C1GALT1 and Cosmc in DAKIKI cells

Real-time RT-PCR was performed to examine the mRNA expression levels of C1GALT1 and its chaperone Cosmc in DAKIKI cells treated with CagA. Compared with negative control, the mRNA expression of C1GALT1 was significantly downregulated under the stimulation of 1.6 μg/ml of CagA, although 12.5 μg/ml of LPS, which served as a positive control, had more significant effect in downregulating the expression of C1GALT1 (Fig. 3A). Similar results were obtained for the mRNA expression of chaperone Cosmc (Fig. 3B).

3.4. Effect of CagA on protein expression of C1GALT1 and Cosmc in DAKIKI cells

Western blotting were doned to assess the protein expression levels of C1GALT1 and its chaperone Cosmc in DAKIKI cells treated with CagA. Compared with negative control, the protein expression of C1GALT1 was significantly decreased under the stimulation of 1.6 μg/ml of CagA, although 12.5 μg/ml of LPS, which served as a positive control, decreased the expression of C1GALT1 more significantly (Fig. 4A and B). Similar results were observed for the protein expression of chaperone Cosmc (Fig. 4A and C).

4. Discussion

The present study showed that CagA, a key virulence factor of Hp, stimulated the cell proliferation, production and underglycosylation of IgA1 in the B cell line DAKIKI cells. The molecular mechanisms for the underglycosylation of IgA1, at least partly, attributed to the downregulation of C1GALT1 and its chaperone Cosmc.

CagA-positive Hp infection is closely associated with the initiation and progression of gastric mucosa-associated lymphoid tissue (MALT) B-cell lymphomas while eradication of Hp infection can lead to complete remission of these tumors [17]. Further studies have shown that CagA is the major factor responsible for Hp-induced MALT B-cell lymphomas [17,18]. By directly translocating into B cell and subsequently upregulating the expressions of anti-apoptotic proteins Bcl-2 and Bcl-X_L, or phosphorylating the pro-apoptotic protein Bad and subsequently hampering Bad/Bcl-2 interactions, CagA can inhibit cell apoptosis and promote cell proliferation. In the present study, we also found that CagA stimulated cell proliferation in the B cell line DAKIKI cells. It has been reported that in gastric epithelial cells, biliary cells and B cells, the effect of Hp infection on cell growth depends on the extent of infection [19–21]. Mild Hp infection protects cell from apoptosis and promotes cell growth while severe Hp infection reduces cell survival. In the present study, we further revealed that the major virulence protein of Hp, CagA, at low concentration promoted while at high concentration inhibited cell proliferation.

IgA1 protease is a proteolytic enzyme specific for human IgA1 [22]. In gastritis induced by Hp infection, the pathogenic Hp strains

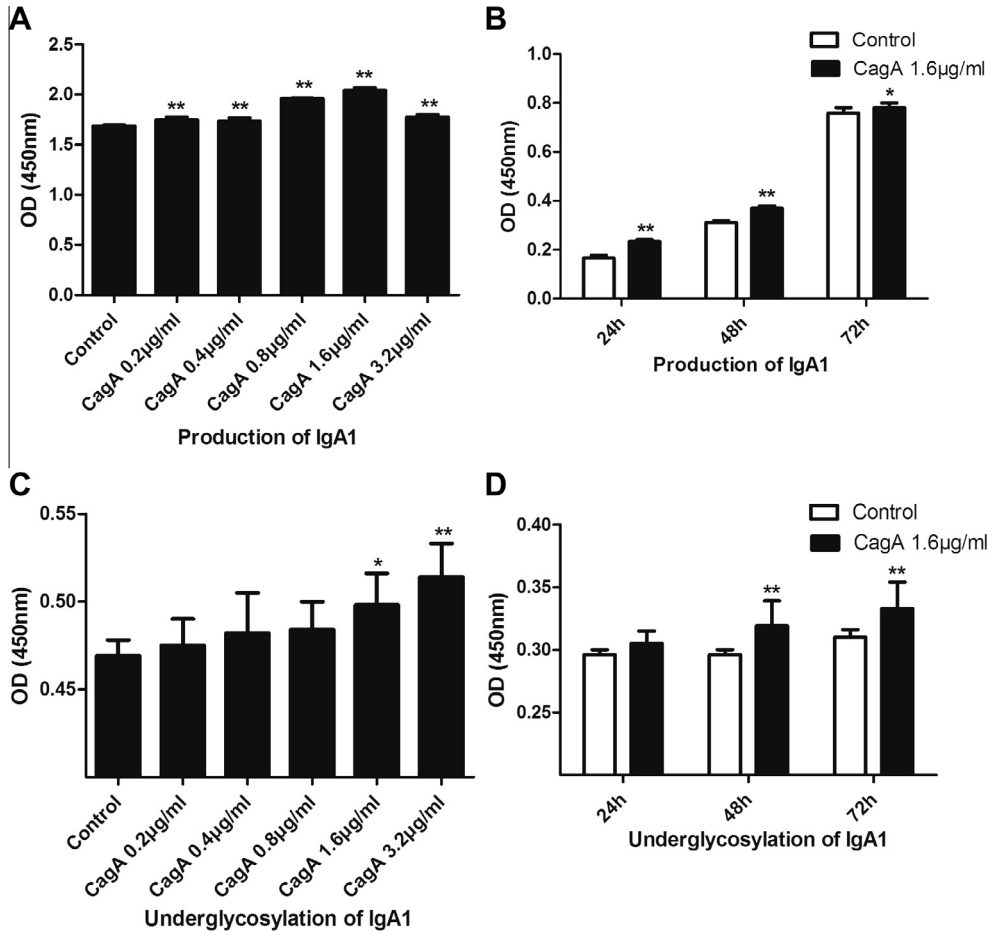

Fig. 2. Effect of CagA on production and underglycosylation of IgA1 in DAKIKI cells. (A) CagA within the range of 0.2–1.6 μg/ml dose-dependently stimulated the production of IgA1 in DAKIKI cells. 3.2 μg/ml of CagA still had the similar effect, although the amount of produced IgA1 was lower than stimulated with 1.6 μg/ml of CagA. (B) 1.6 μg/ml of CagA time-dependently stimulated the production of IgA1 in DAKIKI cells at 24, 48 and 72 h. (C) CagA within the range of 1.6–3.2 μg/ml dose-dependently stimulated the underglycosylation of IgA1 in DAKIKI cells. (D) 1.6 μg/ml of CagA time-dependently stimulated the underglycosylation of IgA1 in DAKIKI cells at 24, 48 and 72 h. $^{*}p < 0.05$, compared with control; $^{**}p < 0.01$, compared with control.

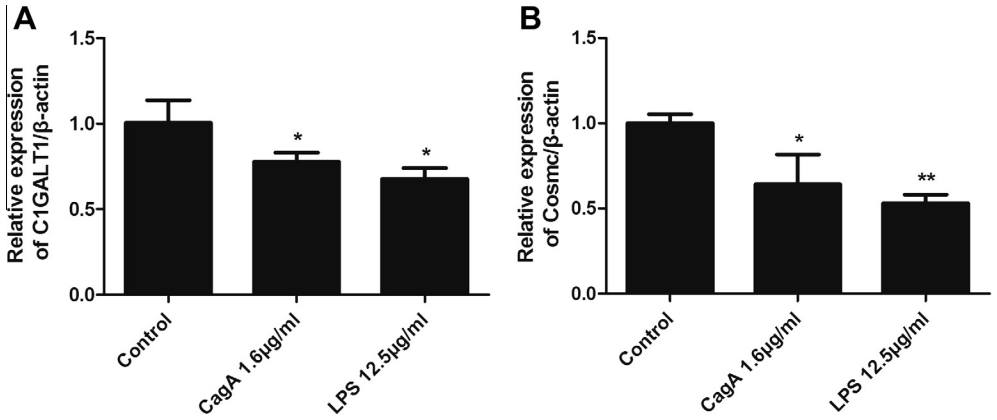

Fig. 3. CagA downregulated the mRNA expression of C1GALT1 and Cosmc in DAKIKI cells. Cells were stimulated with 1.6 μg/ml of CagA, while stimulated with 12.5 μg/ml of LPS served as a positive control. (A) Compared with negative control, CagA significantly downregulated the mRNA expression of C1GALT1, although the effect was a little weaker than that of LPS. (B) Compared with negative control, CagA obviously downregulated the mRNA expression of Cosmc, although the effect was much weaker than that of LPS.$^{*}p < 0.05$, compared with control; $^{**}p < 0.01$, compared with control.

have no IgA1 protease activity [23]. Moreover, although the expression of J chain, a marker of mucosal-type IgA1, is reduced in IgA-producing cells, the number of IgA-producing cells has a 4- to 12-fold increase. Consequently, the production of mucosal-type IgA1 appears to be elevated [23]. In IgAN patients, it is also reported that mucosal Hp infection causes increased mucosal-type IgA1 antibody against Hp in the serum [10]. Furthermore, it has been shown that the presence of IgA antibodies against Hp is closely associated with CagA-positive Hp infection [24]. In the present study, we demonstrated that CagA, the key virulence protein of Hp,

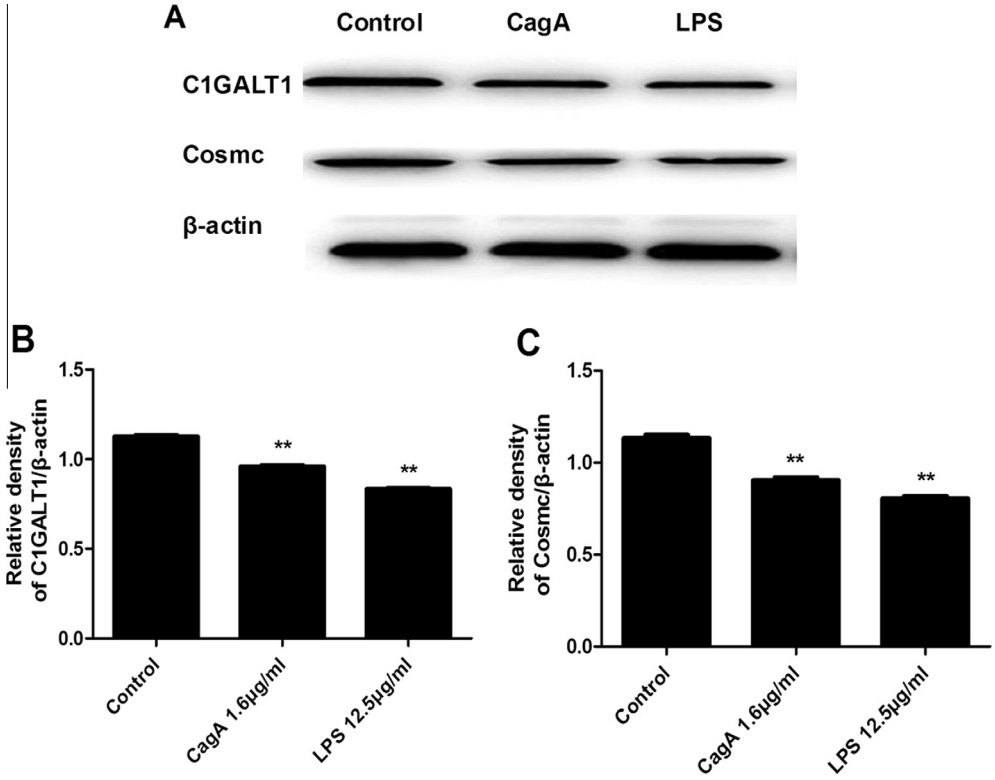

Fig. 4. CagA decreased the protein expression of C1GALT1 and Cosmc in DAKIKI cells. Cells were stimulated with 1.6 μg/ml of CagA, while stimulated with 12.5 μg/ml of LPS served as a positive control. (A) Western blotting analysis showed that compared with negative control, CagA significantly decreased the protein expression of C1GALT1 and its chaperone Cosmc, although the effect was a little weaker than that of LPS. (B and C) Quantitative analysis of relative protein level of C1GALT1 and Cosmc (normalized to β-actin). $^{**}p < 0.01$, compared with negative control.

promoted the production of IgA1 in the IgA1 producing cell line DAKIKI cells, which may be at least partly due to the increase in cell number resulted from cell proliferation.

Hp infection can influence protein glycosylation. Altered glycosylation of gastric mucins including MUC1 is found in Hp infected stomach [25]. In IgAN patients, it is also reported that mucosal Hp infection leads to underglycosylation of IgA1 [11]. A number of virulence factors including CagA have been identified from Hp [26]. However, among them which are responsible for altering protein glycosylation, remains unknown. In the present study, we demonstrated that CagA, a major virulence factor of Hp, promoted underglycosylation of IgA1, in addition to stimulating its production in DAKIKI cells.

C1GALT1 and its chaperone Cosmc play a key role in the process of protein glycosylation [1]. Abnormal expression or activity of C1GALT1 and Cosmc may result in aberrent protein glycosylation. In human gastric mucosa tissue, Hp infection inhibits the activity of galactosyltransferase [27]. In peripheral blood mononuclear cells (PBMC), tonsil tissue and tonsillar B cells from IgAN patients, the expression of C1GALT1 and Cosmc are significantly downregulated [13,15,28]. Moreover, the expression level of C1GALT1 in tonsillar B cells from IgAN patients is notably correlated with clinical characteristics such as estimated glomerular flow rate (GFR), proteinuria and histologic injury score [28]. While tonsillar Hp infection is closely associated with IgAN, whether Hp infection has an influence on the expression of C1GALT1 and Cosmc in tonsillar B cells, which remains elusive [6,7]. In the present study, we showed that CagA, the main virulence factor of Hp, decreased the expression of C1GALT1 and Cosmc in the B cell line DAKIKI cells, which may contribute to the underglycosylation of IgA1.

In conclusion, we demonstrated that CagA, a key virulence factor of Hp, stimulated cell proliferation and the production of IgA1 in DAKIKI cells. Moreover, CagA promoted underglycosylation of IgA1, at least partly by downregulating the expression of C1GALT1 and Cosmc. Therefore, tonsillar Hp infection, at least via CagA, may participate in the pathogenesis of IgAN by influencing the production and glycosylation of IgA1 in B cells. Anti-Hp or anti-CagA therapy may be helpful for the treatment of IgAN associated with Hp infection in the future.

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