Research article

Mast cells modulate transport of CD23/IgE/antigen complex across human intestinal epithelial barrier

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Background: Food allergy and chronic intestinal inflammation are common in western countries. The complex of antigen/IgE is taken up into the body from the gut lumen with the aid of epithelial cell-derived CD23 (low affinity IgE receptor II) that plays an important role in the pathogenesis of intestinal allergy. This study aimed to elucidate the role of mast cell on modulation of antigen/IgE complex transport across intestinal epithelial barrier. **Methods**: Human intestinal epithelial cell line HT29 cell monolayer was used as a study platform. Transepithelial electric resistance (TER) and permeability to ovalbumin (OVA) were used as the markers of intestinal epithelial barrier function that were recorded in response to the stimulation of mast cell-derived chemical mediators. **Results**: Conditioned media from naïve mast cell line HMC-1 cells or monocyte cell line THP-1 cells significantly upregulated the expression of CD23 and increased the antigen transport across the epithelium. Treatment with stem cell factor (SCF), nerve growth factor (NGF), retinoic acid (RA) or dimethyl sulphoxide (DMSO) enhanced CD23 expression in HT29 cells. Conditioned media from SCF, NGF or RA-treated HMC-1 cells, and SCF, NGF, DMSO or RA-treated THP-1 cells enhanced immune complex transport via enhancing the expression of the CD23 in HT29 cells and the release of inflammatory mediator TNF-α. Nuclear factor kappa B inhibitor, tryptase and TNF-α inhibited the increase in CD23 in HT29 cells and prevents the enhancement of epithelial barrier permeability. **Conclusions**: Mast cells play an important role in modulating the intestinal CD23 expression and the transport of antigen/IgE/CD23 complex across epithelial barrier. (Tu YH, Oluwole C, Struiksma S, Perdue MH, Yang PC. Mast cells modulate transport of CD23/IgE/antigen complex across human intestinal epithelial barrier. **North Am J Med Sci** 2009; 1: 16-24).

Key words: Intestine; Epithelium; Barrier function; Mast cells; Allergy.

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Introduction

Our previous studies [1-3] indicated that intestinal epithelial cell express the low affinity IgE receptor (FcεRII or CD23). We recent found that the function of epithelial cell-derived CD23 forming complex with IgE that facilitates the specific antigen transport across intestinal epithelial barrier. In a mouse model of food allergy and in a human intestinal epithelial cell culture system, IgE receptor expression was shown to be upregulated by the Th2 cytokine IL-4 [3-6], thereby facilitating IgE and IgE-antigen immune complexes to be transported across intestinal epithelial barrier. Transport of intact antigen into intestinal mucosa has the potential in resulting in the immediate hypersensitivity reaction or/and leads to systemic anaphylaxis. However, the modulating factors on antigen/IgE transport across intestinal epithelial barrier are to be further understood.

In the human fetus and naïve adult rodents, there is little or no expression of CD23 protein in intestinal epithelial cells. However, in adult human, sensitized rodents, and human fetal intestine stimulated with IL-4, intestinal epithelial cells express CD23 [3, 7-8]. The expression of CD23 in epithelial cells is upregulated in the intestine of the patients with Crohn's disease, ulcerative colitis with cow's milk allergy [9]. Patients with Crohn's disease have increased antigen uptake into the intestine [10]. These findings suggest that hypersensitivity and inflammation may affect intestinal CD23 expression and its function with respect to transepithelial antigen transport.

Mast cell is a major effector cell in allergic reactions. Mast cells also play an important role in both acute and chronic inflammation [11, 12]. In addition, in chronic inflammatory and allergic diseases, various types of inflammatory cells infiltrate in inflammatory sites. Interactions between inflammatory cells and intestinal epithelial cells may result in cytokine expression and/or direct injury to the epithelium and thus compromise the epithelial barrier function.

Under normal conditions, mast cells are distributed throughout connective tissues and beneath epithelium. Mast cells originated from bone marrow progenitor cells that migrate into the circulation as morphologically indistinct precursors. After being recruited to different tissues they complete their differentiation under the influence of stem cell

factor (SCF) and other locally produced cytokines [13-14]. The c-kit receptor for SCF and nerve growth factor (NGF) receptors are expressed by human mast cell line HMC-1 cells [15-16]. SCF is a potent growth factor involved in the early stages of haematopoiesis, SCF can induce mast cell degranulation both *in vitro* [17-19] and *in vivo* [20-21], and greatly enhances the antigen-induced degranulation of human lung-derived mast cells in vitro [22-23]. NGF is a neurotropic factor, with various effects on inflammatory and immune cells [24-25].

Monocytes are another important type of the inflammatory cells. After activation, the cells are transformed into macrophages. Infiltration of immature macrophages is a common phenomenon in allergic inflammation [26-28]. The human monocyte cell line (THP-1) synthesizes NGF endogenously [29]. THP-1 cells also express the c-kit receptor (phenotype CD117) [30] and are capable of expressing CD23 [3].

Nuclear factor-kappaB (NF-κB) is a transcription factor that regulates the expression of multiple inflammatory genes. NF-κB is activated in the colonic mucosa from patients with ulcerative colitis [31]. The signal transduction pathway of CD23 triggered NF-κB activation, which targeted IκB kinase [32-33]. NF-κB plays a pivotal role in the regulation of immune response, apoptosis, and inflammation [34]. BAY11-7082 is a potent NF-κB inhibitor. It inhibits NF-κB p65-DNA binding activity and IκB kinase (IKK-α) protein expression [35]. Inhibition of p38 MAP kinase and NF-κB-signaling suppresses the inflammatory bowel disease [36].

TNF-α and tryptase are critical factors in affecting and regulating intestinal epithelial barrier function. Addition of TNF-α decreases the transepithelial electrical resistance (TER) via altering structure and function of tight junction [37]. The intestine highly expresses proteinase-activated receptor-2 (PAR-2). Trypsin and mast cell-derived tryptase are the agonists of PAR2. Administration of PAR2 agonist activated PAR-2 receptors in the epithelium, and increased epithelial barrier permeability [38]. Therefore, we hypothesized that mast cell-derived mediators might affect intestinal epithelial barrier function by modulating the expression of CD23 and the specific antigen transport across intestinal epithelial barrier. In this study, we used an in vitro cell system and found that mast cells did have the capacity in modulating the expression of intestinal epithelial CD23 and transepithelial transport of antigen.

Materials and Methods

Reagents: CD23 antibody (clone Tu1. NovoCastra Laboratories Ltd, Newcastle upon Tyne, UK). Anti-tryptase antibody (DAKO Diagnostics Canada, Mississauga, ON, Canada). Chimeric human IgE raised against 4-hydroxy-3-nitrophenylacetyl (NP) (Serotec Inc. Oxford, UK). NP (16)-OVA (Biosearch Technologies Inc. Novato, CA). SCF, NGF and IL-6 (Leinco Technologies. St. Louis, Missouri, US). cocktail of protease inhibitors, anti-human beta-actin and all-trans retinoic acid (Sigma-Aldrich. St. Louis, MO). BAY 11-7082 (Bay 11) (Calbiochem-Novabiochem; San Diego, USA). Bio-Rad protein assay kit (Bio-Rad Laboratories, Mississauga, ON, Canada). TNF-α specific ELISA kit (R&D systems Inc., Minneapolis, US). Histamine ELISA kit (IBL Immuno Biological Laboratories, Hamburg, Germany).

Experimental Design: Monolayers of human epithelial cell line, HT29 cells, were incubated with supernatants from HMC-1 cells or THP-1 monocytes after treatment with inflammatory agents or vehicle. Expression of CD23 was detected in epithelial cells by Western blotting. The transport of IgE-antigen immune complexes across HT29 monolayers were determined before and after the addition of conditioned supernatants. Inflammatory agents using in the experiments included tryptase, histamine and TNF-α. Inhibitor of NF-κB, Bay 11, was also employed.

Cell Culture: HT29-Cl 19A human intestinal epithelial cells were cultured in McCoy's 5A modified medium without glucose, supplemented with 5% FBS, 0.0375 % sodium bicarbonate, 0.2 mM L-glutamine, and penicillin/streptomycin. The cells were split every five days; culture media were changed every two or three days. 8×10^5 cells were seeded onto a transwell filter (Corning Inc., Corning, New York). The cells were cultured in a 50 ml conical tube with 25 ml media for 7 days in an atmosphere of 5% CO_2 at 37ºC. The filter was returned to the Transwell compartment when the transepithelial resistance was at least 400 Ω/cm^2 measured by an Ohm meter with chopstick electrodes (Millicell-RES; Millipore, Bedford, MA). Under these conditions, the cells formed differentiated monolayer as viewed by electron microscopy (data not shown).

HMC-1 and THP-1 cells were cultivated in RPMI 1640 medium, supplemented with 10 % fetal calf serum, 2.25 mM L-glutamine, 27 mM HEPES and penicillin/streptomycin. The cells were treated with SCF (50 ng/ml), NGF (20 ng/ml), retinoic acid (1μM) or IL-6 (2 ng/ml) or DMSO (1 %) for 7 days. The concentrations of the inflammatory reagents were referred to published data [39, 40, 15, 16] or determined by our preliminary experiments.

Measurements of CD23 and Tryptase by Western Blot: After treatment, cells were washed twice with cold PBS (pH 7.2), containing a cocktail of protease inhibitors. Cells were harvested by scraping in 500 μl ice-cold lyses buffer (100 mM NaCl, 10 mM Tris•HCl, 2 mM EDTA, 1.8 % triton X-100 and protease inhibitors) at pH 7.8 [3, 41]. Protein in the lysates was measured by Bio-Rad protein assay kit. 80 μg of protein for each sample was separated on a 10% acrylamide gel. The proteins were transferred electrophoretically onto a nitrocellulose membrane, and incubated with anti-human CD23 antibody (1:500) for 48h or anti-human mast cell tryptase overnight at 4˚C. After washing with 0.01 M PBS, the membrane was incubated with horseradish peroxidase (HRP) conjugated

secondary antibody for 1 h at room temperature. The target protein was detected by the enhanced chemiluminescence (ECL) detection system and recorded by X ray film. The integrated intensity of the blots was quantified by scanning densitometry.

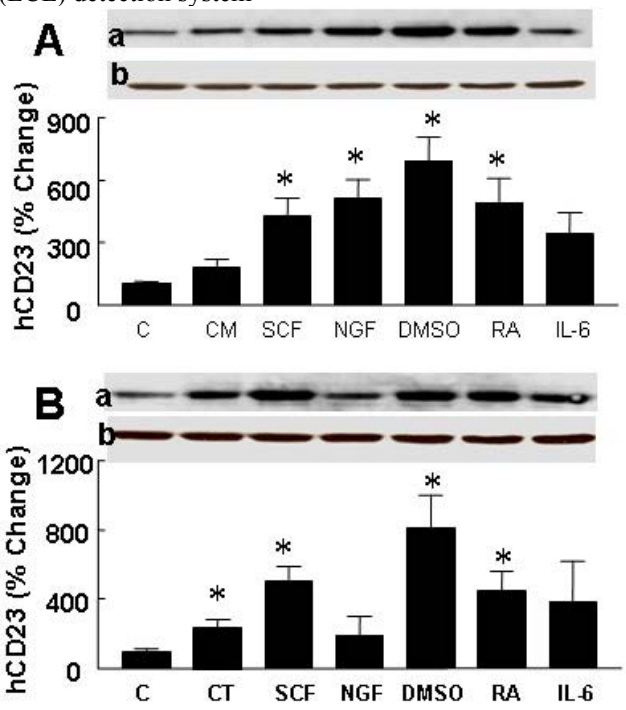

Fig.1. Alteration of the epithelial CD23 expression. Supernatants from HMC-1 (A) or THP-1 (B) were collected. The Western blot bands show the expression of CD23. * p<0.05, compared to controls (C). Gel a: CD23; gel b: beta actin.

Measurement of TNF-α and Histamine by enzyme-linked immunosorbent assay (ELISA):

10^6 of either HMC-1 mast cells or THP-1 cells were seeded into a flask with 5 ml culture media. The cells were treated with inflammatory reagents and cultured for 7 days. TNF-α and histamine in the supernatant was measured by ELISA.

Assessment of transport of IgE-antigen Immune Complex: An immune complex of IgE anti NP and NP-OVA was made by incubation of the IgE anti NP (0.2 μM) and NP-OVA (0.5 μM) in the IgE binding buffer (in mM: 10 Tris•HCl (pH 7.35), 140 NaCl, 2 $CaCl_2$, and 1 $MgCl_2$, with 1.8 g/l glucose) for 1 hour. The complex was added to the apical or basal compartment of transwell system. After incubation at 37ºC, 5% CO_2 atmosphere, media in the basal or apical compartment of the monolayer were collected and analyzed by western blotting assay. A secondary antibody to OVA (1:20,000) was employed to detect the NP-OVA [41].

Statistical Analysis: Data were presented as means ± SE. Differences of means were analyzed by two-tail student *t* test between two groups or ANOVA if more than two groups. $p < 0.05$ was considered to be significant.

Results

Upregulation of intestinal epithelial CD23 protein by conditioned media from HMC-1 mast cells, THP-1 monocytes, but not EBV-transformed B lymphocytes

Incubation of the HT29 monolayer with the vehicle or conditioned medium from 7 days upregulated the expression of CD23 protein by intestinal epithelial cells by 80% as compared with those HT29 cells incubated with normal medium (vehicle). The CD23 protein expression in HT29 cells was further enhanced by the conditioned media from SCF, NGF, DMSO and RA-treated HMC-1 cell culture, but not by the supernatant from IL-6-treated HMC-1 cell culture (figure 1A).

Using as a comparison, we also observed that incubation of the HT29 cells with the supernatant from THP-1 cell culture with or without the stimulation of inflammatory agents. The expression of CD23 by HT29 cells was increased by 120% (figure 1B).

Alteration of tryptase and histamine production by HMC-1 cells by exposure to inflammatory agents

Tryptase and histamine are the major chemical mediators of mast cells that can be released into the vicinity of cells and induce inflammatory reactions. To elucidate the underlying mechanism by which supernatant of HMC-1 cells induced CD23 expression in HT29 cells, we evaluated the levels of tryptase and histamine in culture media of HMC-1 cells in the presence or absence of inflammatory agents. As shown by ELISA data, SCF and NGF did not, while DMSO and retinoic acid markedly increased the released of tryptase into culture media. (figure 2A).

In observation of histamine release from HMC-1 cells in response to exposure to inflammatory agents, different results were noted as compared with that from tryptase release. SCF and DMSO had powerful effect on histamine release from HMC-1 cells while retinoic acid had less effect, NGF had no effect on histamine release (figure 2B).

Alteration of TNF-α in the culture media of HMC-1 and THP-1 cells after treatment

TNF-α is an important proinflammatory mediator that is involved in a broad array of inflammatory disorders. Mast cells have a unique feature that can synthesize TNF-α and

store it in cellular granules to be released upon activation. To elucidate if other inflammatory agents had any effects on

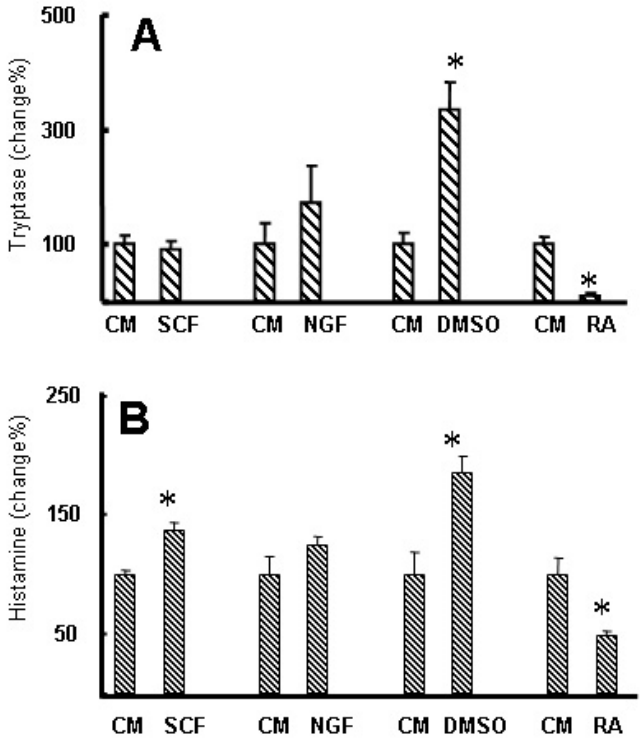

Fig.2. Release of tryptase and histamine from HMC-1 mast cells HMC-1 cells were cultured in the presence of inflammatory agents for 7 days. Bars indicate the levels of tryptase (A) and histamine (B) in culture media that were determined by ELISA. *, $p<0.05$, compared with controls (CM). Data were presented as mean ± SE from 3-5 separate experiments.

TNF-α release from mast cells, HMC-1 cells were cultured for 7 days in the presence or absence of the inflammatory agents as aforementioned. As shown by ELISA data, treatment of HMC-1 with SCF or NGF for 7 days, no significant change of TNF-α was detected in supernatant of HMC-1. However, treatment of the HMC-1 with DMSO, or retinoic acid for 7 days, markedly decrease in TNF-α was noted in culture media. The results indicate that DMSO and retinoic acid have the ability to inhibit the release of the TNF-α into the culture media (figure 3A).

We also observed the release of TNF-α in THP-1 cells upon the stimulation of the inflammatory agents. Treatment of THP-1 monocytes with SCF or NGF significantly increased the release of TNF-α in the supernatant whereas treatment with either DMSO or retinoic acid showed inhibitory effect on the release of TNF-α (figure 3B). Treatment with fresh culture medium, no TNF-α was detected.

Effects of conditioned media on specific antigen transport across monolayer epithelial barrier

Conditioned media were collected from cell culture supernatant of HMC-1 or THP-1 cells after exposure to inflammatory agents. The transport of complex of NP-specific IgE/NP-OVA across HT29 monolayer after exposure

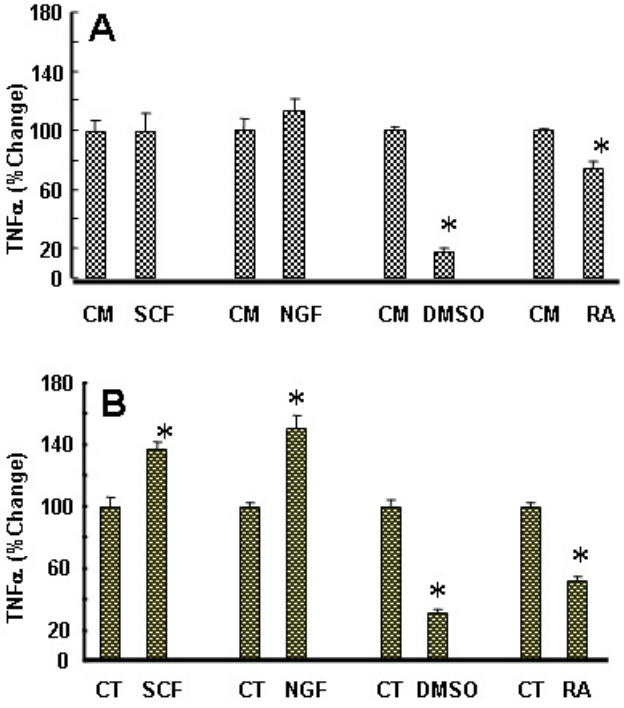

Fig.3. Release of TNF-α from HMC-1 or THP-1 cells. Supernatants of the reagent-treated HMC-1 or THP-1 cells were subjected to ELISA for determining levels of TNF-α. Bars indicate the levels of TNF-α. *, $p<0.05$, compared with controls (CM or CT). Data were presented as mean ± SE from four separate experiments.

to the conditioned media was observed. The results showed that SCF-, NGF-, DMSO- and RA-conditioned media increased the complex transport across HT29 monolayer at 30, 20, 1 and 27 folds respectively (Figure 4A). All conditioned media did not change the TER of HT29 monolayer (figure 4B). The results indicate that these conditioned media do not influence the paracellular pathway of HT29 monolayer, but increase the rate of intracellular transport.

As shown by Figure 5, conditioned media made from THP-1 cells also had similar results on the transport of complex of NP-specific IgE/NP-OVA across HT29 monolayer. SCF-, NGF-, DMSO- and RA-conditioned THP-1 cell culture media increased the transport by 47, 26, 39 or 34 folds respectively.

NF-κB plays a critical role in TNF-α release from THP-1 cells

TNF-α is an important proinflammatory cytokine that is involved in many inflammatory disorders such as inflammatory bowel disease. Monocytes are one of the major sources of TNF-α that can be released to the vicinity in response to noxious stimuli. To understand the mechanism by which conditioned media from THP-1 cells on modulating complex of IgE/antigen transport across intestinal epithelial barrier, we treated THP-1 monocytes with BAY 11-7082 (a NF-κB inhibitor) followed by addition of SCF, NGF, DMSO, or retinoic acid into the culture respectively. As expected, the amount of TNF-α in the supernatant of the THP-1 was dramatically decreased in all the treatment (Figure 6). The

result indicates that NF-κB is a critical molecule in mediating the inflammatory agent-induced intestinal epithelial barrier dysfunction.

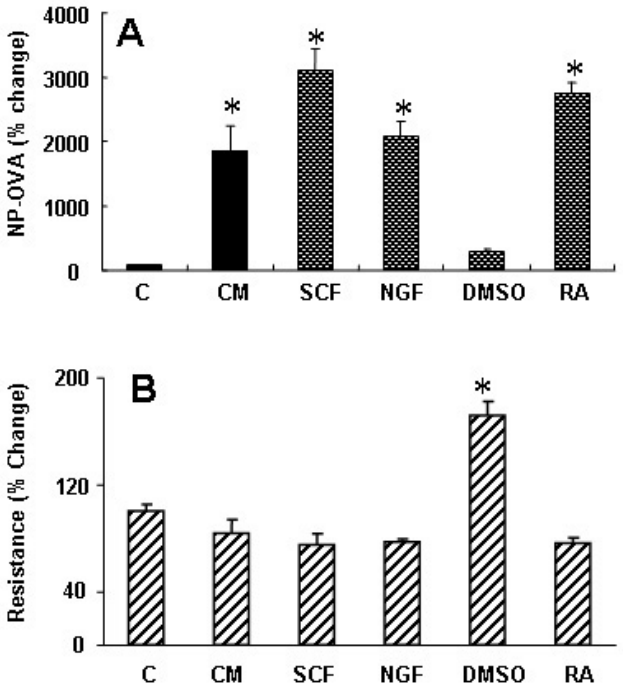

Fig.4. Conditioned media increases transport of IgE-antigen complex across intestinal epithelial barrier. Complex of IgE/antigen was added to the upper chamber of transwells. Samples collected from the basal chambers were subjected to analysis of the transport rate of complex. Bars indicate the rate of recovered complex in basal chambers. *, p<0.05, compared with controls (CM). Data were presented as mean ± SE from four separate experiments.

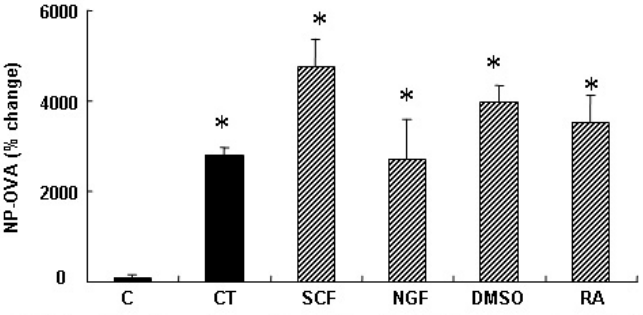

Fig.5. Specific antigen transport in THP-1 cells. THP-1 cells were treated with the procedures in Fig.4. Bars indicate the rate of recovered complex in basal chambers. *, p<0.05, compared with controls (CT). Data were presented as mean ± SE from four separate experiments.

Inhibition of tryptase release from HMC-1 mast cells by BAY 11-7082

Tryptase is one of the major chemical mediators in mast cells that is also involved in many inflammatory reactions. Based on the obtained results, we realized that NF-κB might mediate the release of tryptase from mast cells in response to inflammatory agent stimuli. Indeed, pretreatment with NF-κB inhibitor dramatically decreased the tryptase release from HMC-1 cells as compared with controls (figure 7).

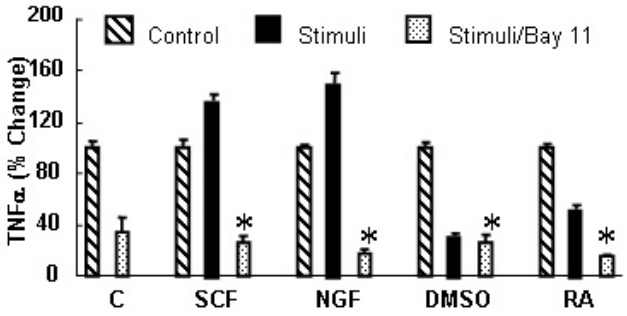

Fig.6. Inhibition of TNF-α release from THP-1 cells by BAY 11-7082. THP-1 cells were cultured with the same condition as in Fig.5. Some cells were pretreated with Bay11-7082. Bars indicate the levels of TNF-α in culture media that were determined by ELISA. *, p<0.05, compared with controls (C). Data were shown as mean ± SE from four separate experiments.

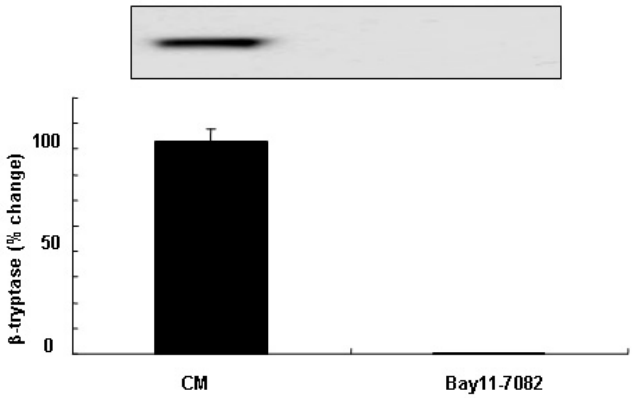

Fig.7. Inhibition of tryptase release by BAY 11-7082. HMC-1 cells were cultured with the same condition as in Fig.4. Some cells were pretreated with Bay11-7082. Bars indicate the levels of tryptase in culture media that were determined by ELISA. Data were presented as mean ± SE from four separate experiments.

NF-κB is a critical mediator in inflammatory agent-enhanced CD23 expression and specific antigen transport across intestinal epithelial barrier

The results above implicate that NF-κB is involved in inflammatory agent-induced increase in CD23 expression in intestinal epithelial cells and IgE/antigen transport across intestinal epithelial barrier. To test the speculation, we pretreated HT29 monolayers with NF-κB inhibitor BAY 11-7082, then exposed the monolayer to conditioned media. Indeed, both increases in CD23 expression in HT29 cells and IgE/antigen transport across HT29 monolayer were inhibited (Fig.8).

Discussion

The relevance between inflammatory cells and the intestinal epithelial cells during food allergy and inflammatory diseases has identified in many *in vivo* studies, which provides a crucial image in understanding the mechanism by which inflammatory factors affects intestinal homeostasis and initiates inflammatory disorders. The present study provides further evidence that several inflammatory agents are directly involved in compromising the intestinal epithelial barrier function by facilitating the expression of CD23 molecule in epithelial cells and promoting the IgE/antigen complex transport across intestinal epithelial barrier.

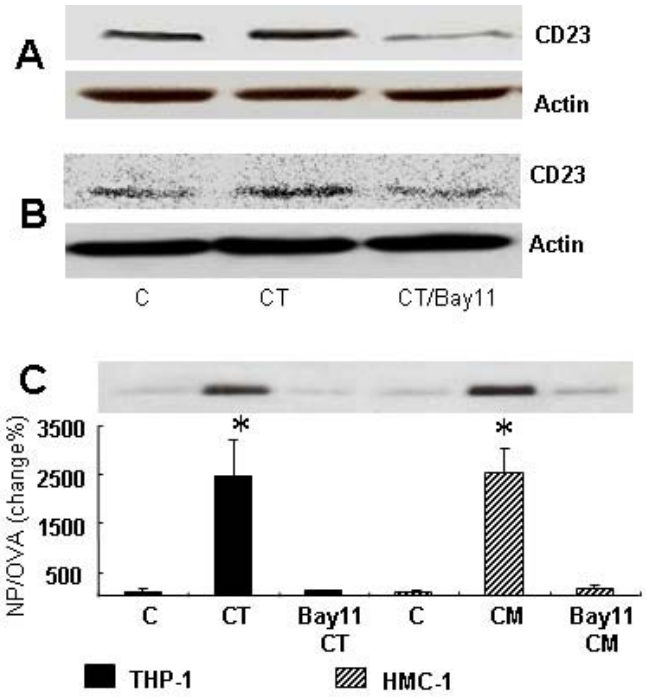

Fig.8. Inhibition of CD23 and antigen transport by BAY 11 -7082. HMC-1 or THP-1 cells were prepared as described in Fig4-7. CD23 protein and antigen transport were determined by Western blotting and ELISA. A and B, immune blots show CD23 protein from HMC-1 cells (A) and THP-1 cells (B). C, antigen transport was depicted by western blotting gel and bar graph. *, $p<0.05$, compared with controls (C). Data were presented as mean ± SE from four separate experiments.

CD23 molecules have been identified as a critical factor in the enhancement of antigen transport across epithelial barrier of sensitized rodents [42, 8]. The increased antigen transport across the intestinal epithelial barrier is specifically via binding to complex of CD23/IgE. The transepithelial antigen transport could be up regulated by Th2 cytokine IL-4. CD23 expression in human intestinal epithelial cells is mediated through the p38 MAPK pathway; inhibition of p38 MAPK abrogates the transport of IgE/antigen immune complexes across intestinal epithelial barrier [41]. During the onset of the Crohn's disease, ulcerative colitis, and cow's milk allergy [9], epithelial CD23 expression is upregulated in the intestine of patients. Interestingly, patients with Crohn's disease have increased antigen uptake into the intestine [10]. These findings suggest that hypersensitivity and inflammation may affect intestinal CD23 expression and its function with respect to transepithelial antigen transport. The present study provides further evidence that in addition to IL-4, inflammatory cells and their mediators also affect the intestinal epithelial CD23 expression and CD23/IgE complex-dependent specific antigen transport across epithelial barrier, which is in consistence with the phenomenon observed in the intestinal allergic diseases, indicating the importance of the CD23 in the pathogenesis of allergic disorders and manipulation of CD23 expression has a therapeutic potential for allergic diseases.

It has been shown that inflammatory cells, particularly mast cells and eosinophils, present in local tissue even if it is in asymptomatic periods such as in out-season [43]. Recruitment of the inflammatory cells to allergic sites may promote the local synthesis of IgE antibodies, production of pro-inflammatory factors TNF-α and some others, such as low affinity receptor for IgE (CD23). Tryptase is another harmful mediator from mast cells that is related to compromising the intestinal barrier function [38]. The present study shows that, in control media, there has little IgE-antigen complex being transported across HT29 monolayer. After exposure to conditioned media, the expression of CD23 was significantly increased [44]. The basic level of tryptase in media could influence expression of epithelial CD23 to facilitate specific antigen transport across intestinal epithelial barrier. In the Crohn's disease, the TNF-α expression upregulated, and caused an increase of the barrier permeability [10]. It is possible that increased TNF-α in the intestine up regulates the expression of CD23 in intestinal epithelial cells; CD23 then forms immune complexes with specific antigens to increase the specific antigen transport across intestinal epithelial barrier.

PAR-2 activation also increased paracellular permeability of the colon after exposure to its agonist, e.g., mast cell-derived tryptase. Disruption of the integrity of the intestinal barrier leads to high volume of uptake intact antigen, bacterial products and other noxious substance from the intestinal lumen [38]. This notion is supported by the present data.

BAY 11-7082 is a potent inhibitor for NF-κB activation that inhibits NF-κB DNA-binding activity, IκB kinase (IKK-α) protein phosphorylation, and the release of inflammatory mediators such as IL-6, IL-8 and TNF-α. In the present study, pretreatment with BAY 11-7082 inhibited the release of TNF-α from HMC-1 or THP-1 cells that further inhibited the expression of CD23 in intestinal epithelial cells, reduced TER and permeability to IgE/antigen complexes. The fact indicates that NF-κB is a critical molecule in inflammatory agents

induced CD23 expression and intestinal epithelial barrier dysfunction.

In summary, the present study revealed that inflammatory agents drove mast cells and monocytes to release inflammatory cytokine TNF-α; the latter increased the expression of CD23 in intestinal epithelial cells, compromise intestinal epithelial barrier function and facilitated the transport of antigen/IgE/CD23 across intestinal epithelial barrier.

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