A Tea Catechin Suppresses the Expression of the High-Affinity IgE Receptor FcεRI in Human Basophilic KU812 Cells

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Human basophilic KU812 cells express the high-affinity IgE receptor FcεRI, which plays a central role in the IgE-mediated allergic response. The effect of several major tea catechins, (+)-catechin, (−)-epicatechin, (−)-epigallocatechin, (−)-epicatechin gallate, and (−)-epigallocatechin gallate (EGCg), on the cell surface expression of FcεRI in KU812 cells was studied. Flow cytometric analysis showed that only EGCg was able to decrease the cell surface expression of FcεRI after a 24 h treatment in a dose-dependent manner. Moreover, immunoblot analysis revealed that the total cellular expression of the FcεRI α chain decreased upon treatment with EGCg. FcεRI is a tetrameric structure comprising one α chain, one β chain, and two γ chains. The level of mRNA production of each subunit in KU812 cells was investigated. KU812 cells treated with EGCg expressed lower levels of FcεRI α and γ mRNA than nontreated cells. These results suggest that EGCg has an ability to down-regulate FcεRI expression, and this suppressive effect may be due to the down-regulation of FcεRI α and γ mRNA levels.

Keywords: *Tea catechin; basophil; KU812; FcεRI*

INTRODUCTION

The cross-linking of the allergen-specific IgE bound to the high-affinity IgE receptor FcεRI, which is expressed on the cell surface of mast cells and basophils, with multivalent allergens results in the release of both preformed and newly generated mediators such as histamine, proteases, chemotactic factors, and arachidoic metabolites and in the manifestation of allergic symptoms (*1*−*3*). Therefore, FcεRI is the key molecule in triggering the IgE-mediated allergic reaction such as in atopic dermatitis, bronchial asthma, allergic rhitis, and food allergy. It has been reported that the FcεRI is expressed not only on mast cells and basophils but also on dermal Langerhans cells, monocytes, eosinophils, and dendritic cells (*4*−*8*). IgE-binding and signal-transducing functions for the FcεRI molecule are performed separately by distinct subunits (*1*, *9*). FcεRI is a tetrameric receptor consisting of one α chain, one β chain, and two disulfide-linked γ chains. In humans, the tetrameric structure is not obligatory. An alternative form is present comprising an $\alpha\gamma_2$ trimer. The FcεRI α chain mostly extends out to the extracellular region of the FcεRI and binds to the Fc portion of IgE with high affinity. Analysis of FcεRI α chain deficient mice demonstrated that IgE cannot bind to the cell surface of mast cells, thereby degranulation through IgE-binding was not induced (*10*). Thus, it is expected that the down-regulation of FcεRI expression in mast cells and basophils leads to the attenuation of the IgE-mediated allergic symptoms. However, studies to elucidate the molecular mechanism for FcεRI expression have been rarely reported.

Screening of anti- or proallergic factors in foodstuffs has been performed. It has been reported that antioxidants in foodstuffs, such as tea polyphenols and flavonoids, can modify allergic reactions by inhibiting histamine release (*11*−*14*). It has been shown that an unsaturated fatty acid may inhibit the production and release of leukotriene (*15*). However, an evaluation of antiallergic activity of foodstuffs based on the suppression of FcεRI expression has not been reported yet. Here, we investigated the effect of major tea catechins on FcεRI expression in the human basophilic cell line KU812 and found that one particular tea catechin has the ability to down-regulate FcεRI expression.

MATERIALS AND METHODS

Reagents. Protein A Sepharose beads were purchased from Amersham Pharmacia Biotech. Mouse anti-human FcεRI α chain monoclonal antibody CRA-1 was obtained from Kyokuto Seiyaku (Tokyo, Japan). Mouse IgG2b antibody and fluorescein isothiocyanate (FITC)-conjugated mouse IgG1 antibody used for negative control were bought from Dako. (+)-Catechin (C), (−)-epicatechin (EC), (−)-epigallocatechin (EGC), (−)-epicatechin gallate (ECg), and (−)-epigallocatechin gallate (EGCg) were purchased from Kurita Water Industries Ltd. (Tokyo, Japan). The chemical structures of these catechins are shown in Figure 1.

Cell Culture and Stimulation. KU812 cells were obtained from the Japanese Cancer Research Resources Bank (Tokyo, Japan) and were maintained in RPMI-1640 (Nissui, Tokyo, Japan) supplemented with 10% fetal bovine serum (Intergen, Purchase, NY), 100 units/mL penicillin G, 100 mg/mL streptomycin, and 10 mM HEPES buffer. KU812 cells were cultured at 37 °C in a humidified atmosphere with 5% CO_2. For stimulation with tea catechins, KU812 cells were first centrifuged and washed with RPMI-1640 medium. Then the cells were cultured in serum-free RPMI-1640 medium with or without tea catechins.

Flow Cytometric Analysis of the Cell Surface Expression of FcεRI. The cell surface expression of FcεRI was assessed by flow cytometry. In brief, cells were incubated with the anti-FcεRI α chain antibody CRA-1 for 60 min at 4 °C.

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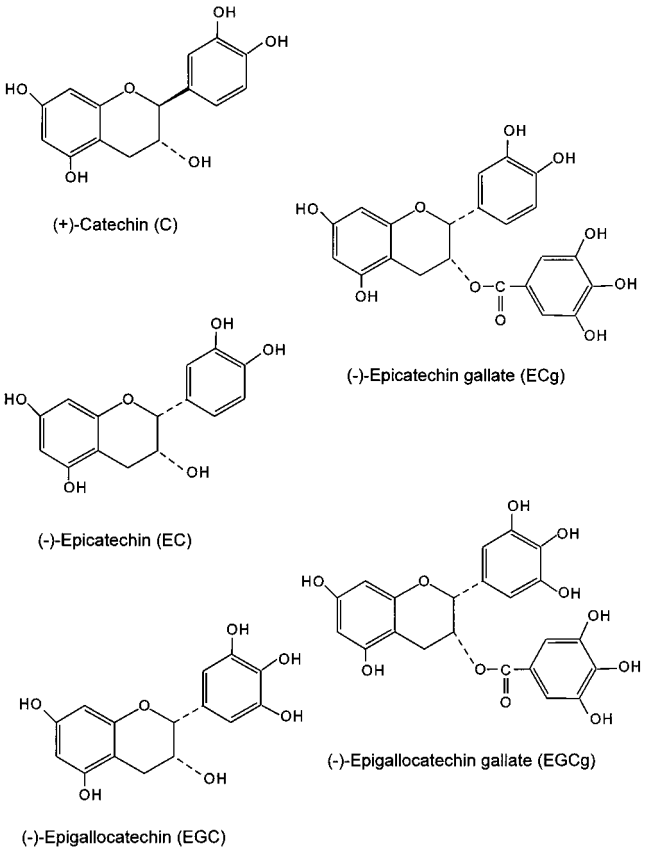

Figure 1. Chemical structures of the major tea catechins.

Then the cells were washed twice in phosphate-buffered saline (PBS; pH 7.5) and exposed to the FITC-conjugated $F(ab')_2$ goat anti-mouse IgG for 60 min at 4 °C. The cells were washed twice in PBS and subjected to flow cytometry (FACSCalibur; Becton Dickinson, Sunnyvale, CA). As a negative control, mouse subclass-matched polyclonal IgG2b antibody was used. The extent of FcεRI expression is represented as the mean fluorescence intensity of CRA-1, and the value is indicated in each panel of Figures 2−4. The vertical line in the figure indicates the peak point for CRA-1 in the nontreated cells. A representative example from three independent experiments is shown.

Immunoprecipitation and Immunoblot Analysis of Total Cellular FcεRI α Chain. KU812 cells were cultured with 50 μM EGCg for 24 h under serum-free conditions; 2×10^7 cells were lysed in cell lysis buffer containing 0.01 M Tris-HCl, pH 8.0, 0.14 M NaCl, 10% Triton X-100, 0.025% NaN_3, 1.0 mM phenylmethanesulfonyl fluoride (PMSF), and 2.0 μg/mL aprotinin. Whole cell lysates were incubated with protein A Sepharose beads overnight at 4 °C. After centrifugation, cell lysates were incubated with protein A Sepharose beads bound with the anti-FcεRI α chain antibody CAR-1 for 4 h at 4 °C. The beads were washed three times with lysis buffer and then resuspended in sodium dodecyl sulfate−polyacrylamide gel electrophoresis (SDS-PAGE) sample buffer containing 0.057 M Tris-HCl, pH 6.8, 9.1% glycerol, 1.8% SDS, 0.02% bromophenol blue, and 0.65 M 2-mercaptoethanol and boiled for 5 min. The beads were removed by centrifugation, and supernatants were subjected to Western blot analysis. The immunoprecipitates were loaded onto 12% SDS-PAGE gel, and electrophoresis was done under reducing conditions. The samples were then electrotransferred onto a nitrocellulose membrane. The blotted nitrocellulose was probed for FcεRI α chain using the anti-FcεRI α chain antibody CRA-1. The secondary antibody was horseradish peroxidase (HRP)-conjugated anti-mouse IgG, and detection was done using the ECL kit (Amersham Pharmacia Biotech). The relative density of FcεRI α chain was calculated using the NIH image program.

Analysis of FcεRI α, β, and γ mRNA Expression. Total cellular RNA was isolated using TRIZOL reagent (GIBCO BRL, Gaithersburg, MD) according to the manufacturer's instructions. For cDNA synthesis, 10 μg of total RNA was denatured at 70 °C for 10 min, quickly chilled on ice for 10 min, and reverse-transcribed in the reaction volume of 20 μL containing 0.5 μg of oligo dT20, 20 units of Moloney mouse leukemia virus (MMLV)-reverse transcriptase (Amersham Pharmacia Biotech), 1.0 mM dNTP, and 0.1 unit of RNase inhibitor (Takara, Shiga, Japan) in reaction buffer, incubated at 37 °C for 60 min. Reactions were terminated by heating at 95 °C for 5 min. The resultant cDNA samples were subjected to 11 cycles of PCR amplification in the presence of specific sense and antisense primers for the FcεRI α, β, and γ chains, respectively (1.0 μM), 200 μM dNTP, 0.05 unit/μL Taq DNA polymerase (Fermentas), and PCR buffer containing 1.5 mM $MgCl_2$, 50 mM KCl, 10 mM Tris-HCl, pH 8.8, and 0.08% Nonidet P40. Human glyceraldehyde-3-phosphoryl dehydrogenase (G3PDH) cDNA was amplified as an internal control, and distilled water substituting template cDNA was used as a negative control. Temperatures were 94 °C for denaturation, 60 °C (FcεRI α, γ chain and G3PDH) or 58 °C (FcεRI β chain) for annealing, and 72 °C for polymerizations. Sequences of PCR primers and sizes of expected products were as follows: for the FcεRI α chain, sense 5′-CTTAGGATGTGGGTTCAGAAGT-3′ and antisense 5′-GACAGTGGAGAATACAAATGTCA-3′ (495 bp); for the FcεRI β chain, sense 5′-TAATTCTTCATAAAGAC-GATCATC (A, G, C, or T) GG-3′ and antisense 5′-ATATGC-CTTTGTTTTGGAACAATGGTGTG-3′ (457 bp); for the FcεRI γ chain, sense 5′-TAGGGCCAGCTGGTGTTAATGGCA-3′ and antisense 5′-GATGATTCCAGCAGTGGTCTTGCT-3′ (364 bp); and for G3PDH, sense 5′-GCTCAGACACCATGGGGAAGGT-3′ and antisense 5′-GTGGTGCAGGAGGCATTGCTGA-3′ (404 bp). The amplified PCR products were subjected to electrophoresis on 1.5% agarose gel, transferred to a Hybond-N^+ membrane (Amersham Pharmacia Biotech), and hybridized with probes specific for the FcεRI α, β, and γ chains and G3PDH, respectively. The hybridized probe was detected using the Gene Images detection kit (Amersham Pharmacia Biotech).

RESULTS

Effect of Major Tea Catechins on the Cell Surface Expression of FcεRI in KU812 Cells. To examine whether the expression of FcεRI on the cell surface of KU812 cells was affected by the major tea catechins (C, EC, EGC, ECg, and EGCg), the cells were treated with each catechin at a concentration of 50 μM for 24 h under serum-free conditions. Because the expression of the FcεRI α chain is limited to FcεRI-expressing cells and the FcεRI α chain mostly extends out to the extracellular region of FcεRI, the cell surface expression of FcεRI was measured by flow cytometric analysis using the anti-FcεRI α chain antibody CRA-1. As shown in Figure 2, among the tea catechins tested, a decrease of the cell surface expression of FcεRI was observed only in EGCg-treated cells, whereas there was no decrease in the level of FcεRI expression upon treatment with the other catechins. In the dose-dependent experiment, the suppressive effect of EGCg on FcεRI expression was observed when more than 25 μM was used (Figure 3). At time point 0 h, treatment with EGCg did not suppress the expression level of FcεRI (Figure 4). The suppression of FcεRI expression was detected at 12 h after EGCg addition and was sustained for a period of at least 24 h. These results suggest that the suppression of FcεRI expression by EGCg requires at least a 12 h stimulation.

Effect of EGCg on the Total Cellular FcεRI α Chain Protein Level. To examine whether suppression of the cell surface expression of the FcεRI α chain by EGCg is due to the decrease in the amount of total

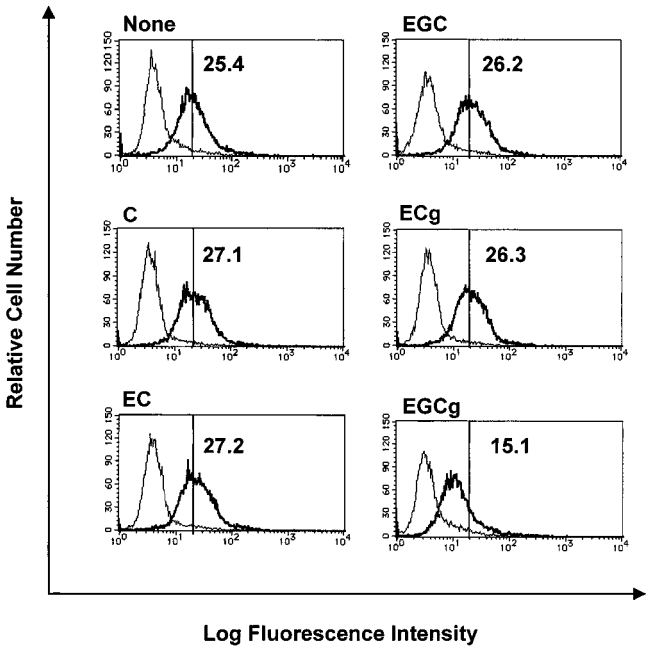

Figure 2. Effect of major tea catechins on the cell surface expression of FcεRI. KU812 cells were stimulated with each tea catechin for 24 h under serum-free conditions. Cells were incubated with CRA-1 (heavy line) followed by staining with the FITC-conjugated goat anti-mouse IgG. Mouse IgG2b (thin line) was used as the isotype-matched negative control. The fluorescence intensity was determined using the FACSCalibur. Three independent trials were performed, and the histograms shown are from a representative experiment.

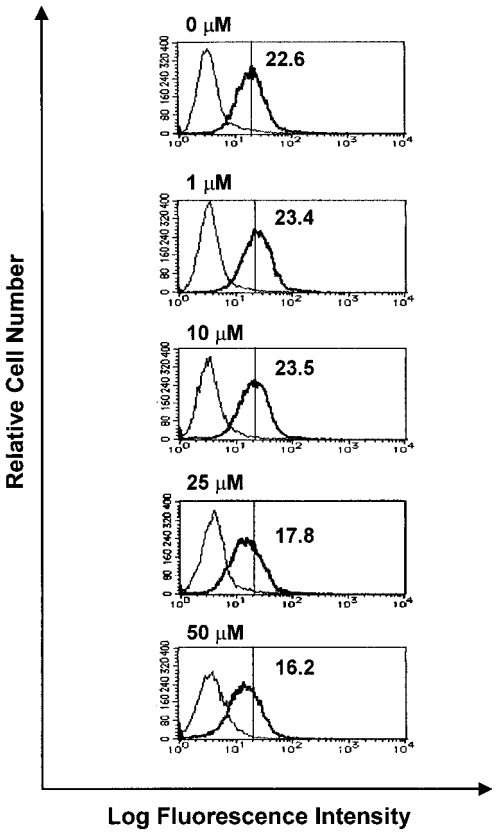

Figure 3. Dose-dependent effect of EGCg on the cell surface expression of FcεRI. KU812 cells were cultured in the presence of different concentrations of EGCg (0, 1.0, 10, 25, and 50 μM) for 24 h. Then, cells were incubated with CRA-1 (heavy line) followed by staining with the FITC-conjugated goat anti-mouse IgG. Mouse IgG2b (thin line) was used as the isotype-matched negative control. Three independent trials were performed, and the histograms shown are from a representative experiment.

cellular FcεRI α chain level, we performed an immunoblot analysis. After a 50 μM EGCg treatment for 24 h, the cells were lysed and immunoprecipitated with CRA-1, followed by immunoblot analysis. As shown in Figure 5, the amount of total cellular FcεRI α chain level decreased upon treatment with EGCg. This result indicates that the EGCg-induced decrease in the amount of cellular FcεRI α chain level may be associated with the suppression of the cell surface expression.

Effect of EGCg on FcεRI α, β, and γ mRNA Expression. We also examined if this FcεRI α chain expression decrease by EGCg is due to the suppression of the mRNA expression of the FcεRI α chain gene. KU812 cells were cultured for 24 h with or without 50 μM EGCg, and total RNA was isolated from the cells. The mRNA levels of the α chain as well as the β and γ chains were measured by RT-PCR followed by Southern blotting (Figure 6). The FcεRI α mRNAand γ mRNA of nontreated cells were clearly detected, and the corresponding mRNA levels in the EGCg-stimulated cells were shown to be significantly reduced. The FcεRI β mRNA was not detected in either condition. Thus, it was suggested that the suppressive effect of EGCg on the cell surface expression of FcεRI was at least related to the down-regulation of the expression of the FcεRI α and γ mRNA.

DISCUSSION

Green tea is consumed daily in Asian countries, and this tea has been suggested to prevent cancer in many animal studies and several epidemiological studies (*16*, *17*). Tea polyphenols are the most abundant components in green tea leaves and have been shown to have antioxidative, antitumor, antibacterial, and antifungal activities (*18*−*20*, *33*). Among the tea polyphenols, EGCg is the most abundant component, followed by EGC, ECg, EC, and C (*21*). In the present study, of all the tea catechins tested, only EGCg was able to decrease the expression of the FcεRI in KU812 cells. EGC, having a triphenol structure the same as EGCg but not containing the galloyl group, did not show an ability to suppress FcεRI expression. ECg, which contains the galloyl group but unlike EGCg has a diphenol structure, also could not suppress the expression. These results indicated that the combination of a triphenol structure and a galloyl group may be responsible for the exertion of the decrease of FcεRI expression by EGCg. Our findings show that EGCg may have the novel activity to attenuate the IgE-mediated allergic reaction.

After the mRNA of FcεRI subunits was analyzed, the mRNA level of the FcεRI α chain was shown to be down-regulated by EGCg. On the protein level, EGCg suppressed not only the cell surface expression of FcεRI α chain but also total cellular expression, suggesting that the decrease of the cell surface expression may be due to the decrease in the amount of total cellular FcεRI α chain produed. Moreover, the mRNA level of FcεRI γ chain also decreased upon EGCg stimulation. It is known that the γ chain is an essential molecule for the FcεRI α chain to be expressed on the cell surface and plays a critical role in signal transduction (*1*, *3*). The γ chain is a common component of other Fc receptors and T cell receptor complexes (*3*, *22*−*26*). Unlike the expres-

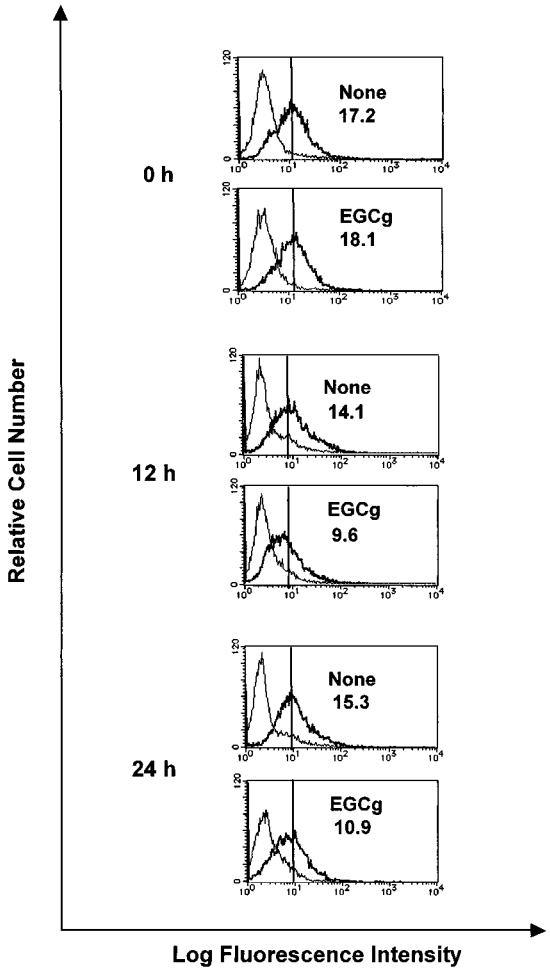

Figure 4. Time course analysis of the cell surface expression of FcεRI in KU812 cells treated with EGCg. KU812 cells were cultured with or without 50 μM EGCg for 0, 12, or 24 h. Then, cells were incubated with CRA-1 (heavy line) followed by staining with the FITC-conjugated goat anti-mouse IgG. Mouse IgG2b (thin line) was used as the isotype-matched negative control. Three independent trials were performed, and the histograms shown are from a representative experiment.

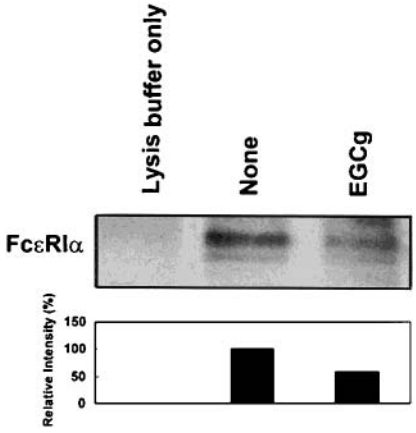

Figure 5. Immunoblot analysis of the expression of the cellular FcεRI α chain protein in KU812 cells treated with EGCg. Cells were treated with 50 μM EGCg under serum-free conditions for 24 h. Immunoblot analysis was performed on whole cell lysates, and the anti-FcεRI α chain antibody CRA-1 was employed.

sion of α chain, which is limited to the cells expressing FcεRI, the γ chain is found in various kinds of cells. We found here that EGCg suppresses the cell surface

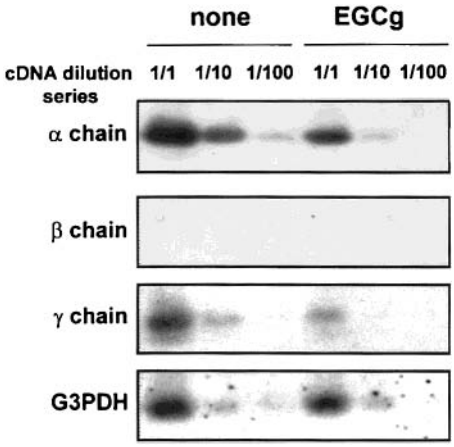

Figure 6. Analysis of the mRNA level for FcεRI α, β, and γ in KU812 cells treated with EGCg. After treatment with 50 μM EGCg for 24 h under serum-free conditions, total RNA was isolated from the cells. FcεRI α, β, and γ and G3PDH mRNA were analyzed by RT-PCR. Southern blotting using a specific probe for FcεRI α, β, and γ and G3PDH was performed to assess the PCR products.

expression of the α chain by down-regulating the α chain expression at protein or mRNA levels as well as the γ chain gene expression. As shown in Figure 2, the FcεRI β chain was not expressed in KU812 cells. In human cells, the $\alpha\gamma_2$ trimer has been previously demonstrated as an alternative form of FcεRI, and the β chain is shown to be unnecessary for the expression of functional human FcεRI on the cell surface (*27*). Therefore, the β chain may not be involved in the suppression of FcεRI expression by EGCg.

The α chain expression is regulated by two transcription factors, GATA-1 and Elf-1, in rodents or other mammals as well as humans (*28*). The expression of FcεRI has been shown to be up-regulated by interleukin-4 (*29*−*32*, *34*), which was known to transfer a signal to the signal transducers and activators of transcription (STAT) molecule STAT6 motif. For understanding of the suppressive mechanism of FcεRI expression, especially the down-regulation of the α chain by EGCg, it is necessary to examine the involvement of these transcription factors.

ABBREVIATIONS USED

FcεRI, high-affinity IgE receptor; PBS, phosphate-bufferd saline; RT-PCR, reverse transcriptase−Polymerase Chain Reaction; FITC, fluorescein isothiocyanate; HRP, horseradish peroxidase; SDS-PAGE, sodium dodecyl sulfate−polyacrylamide gel electrophoresis; G3PDH, glyceraldehyde-3-phosphoryl dehydrogenase; MMLV, Moloney mouse leukemia virus; PMSF, phenylmethanesulfonyl fluoride; C, (+)-catechin; EC, (−)-epicatechin; EGC, (−)-epigallocatechin; ECg, (−)-epicatechin gallate; EGCg, (−)-epigallocatechin gallate; STAT, signal transducers and activators of transcription.

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