Dexamethasone Induces FcγRIIb Expression in RBL-2H3 Cells

Prashanta Silwal1, Mi-Nam Lee2, Choong-Jae Lee2, Jang-Hee Hong2, Uk Namgung2, Zee-Won Lee1, Jinhyun Kim2, Kyu Lim1, Gi Ryang Kweon1, Jong IL Park1, and Seung Kiel Park1

1Research Institute for Medical Sciences and Department of Biochemistry, 2Department of Pharmacology, College of Medicine, Chungnam National University, Daejeon 301-747, 3Department of Oriental Medicine, Chungnam University, Daejeon 301-721, 4Division of Life Science, Korea Basic Science Institute, Daejeon 300-716, 5Department of Internal Medicine, Chungnam National University Hospital, Daejeon 305-806, Korea

Mast cells are involved in allergic responses, protection against pathogens and autoimmune diseases. Dexamethasone (Dex) and other glucocorticoids suppress FcεRI-mediated release of inflammatory mediators from mast cells. The inhibition mechanisms were mainly investigated on the downstream signaling of Fc receptor activations. Here, we addressed the effects of Dex on Fc receptor expressions in rat mast cell line RBL-2H3. We measured mRNA levels of Fc receptors by real-time PCR. As expected, Dex decreased the mRNA levels of activating Fc receptor for IgE (FcεRI) and increased the mRNA levels of the inhibitory Fc receptor for IgG FcγRIIb. Interestingly, Dex stimulated transcriptions of other activating receptors such as Fc receptors for IgG (FcγRI and FcγRIII). To investigate the mechanisms underlying transcriptional regulation, we employed a transcription inhibitor actinomycin D and a translation inhibitor cycloheximide. The inhibition of protein synthesis without Dex treatment affected. Next, we examined expressions of the Fc receptors on cell surfaces by the flow cytometric method. Only FcγRIIb protein expression was significantly enhanced by Dex treatment, while FcγRI, FcγRIII and FcεRI expression levels were marginally changed. Our data showed, for the first time, that Dex regulates Fc receptor expressions resulting in augmentation of the inhibitory receptor FcγRIIb.

Key Words: Degranulation, Fc receptor, Glucocorticoid, Mast cells, Transcription

INTRODUCTION

Mast cells are hematopoietic origin cells that take part in allergic reactions and autoimmune diseases [1-4]. Stimulation of mast cells elicits inflammatory responses, such as degranulation, production of lipid-mediated inflammatory mediators, and cytokine production. Granules of mast cells contain histamine, proteases, β-hexosaminidase and many inflammatory molecules. Mast and other immune cells express receptors for Fc region of IgG (FcγRI). Mast and other immune cells express receptors for Fc region inflammatory molecules. They result in the activation of protein kinase C (PKC) and produce diacylglycerols and inositol 1,4,5-trisphosphates. PLC hydrolyzes phosphatidylinositol 4,5-bisphosphate to diacylglycerol and inositol 1,4,5-triphosphate. They produce diacylglycerol and inositol 1,4,5-trisphosphates. They result in the activation of cellular elements. discozyglycerol and inositol 1,4,5-trisphosphates. They result in the activation of protein kinase C (PKC) and calcium ion mobilization required for degranulation. Grb2 recruits Ras GTPase and activates extracellular receptor.
activated kinase (ERK) that is involved with phospholipase A2 activation and cytokine gene expression. Fyn phospho-
rylates Gab2 and phosphorylated Gab2 recruits phosphati-
dylinositol 3-kinase (PI3-kinase) which is essential for the phosphor-
ylation of the survival factor Akt by the phosphoi-
nositide-dependent kinase (PDK). In contrast, the inhibitory 
receptor FcγRIIb has an immunoreceptor tyrosine-based 
inhibition motif (ITIM) that is phosphorylated by Src family 
kinas [6]. Phosphorylated ITIM recruits SH2 domain con-
taining phosphatase (SHP) and phosphatidylinositol 5'-pho-
sphatase (SHP). They remove phosphate groups in activat-
ing signaling molecules and, thereby, downregulate activa-
tion signals. The balance between activating and inhibitory 
receptors maintains homeostasis in immune cells.

Glucocorticoids are extremely potent immune-suppressive 
agents that must be carefully used when treating immune 
diseases because of their undesirable side effects [8]. The 
molecular action mechanism of glucocorticoids is complex 
and still an important topic of study [9]. Glucocorticoids in-
teract with intracellular glucocorticoid receptors (GR) and 
bind as dimers to glucocorticoid response elements (GRE), 
namely GGCTACAnnTGTYCTK and variants thereof on 
genes. This binding stimulates gene transcription, a process 
referred to as transactivation [10]. In contrast, glucocorti-
coids suppress cytokine gene transcriptions. They interact 
with GRs and then with transcription factors or co-activa-
tors to suppress cytokine gene transcriptions by a process 
referred to as transrepression. In addition to these negative 
or positive regulations of gene transcriptions, glucocorti-
coids regulate mRNA stabilities of target genes [11,12]. 
Furthermore, glucocorticoids exhibit rapid effects by non-
genomic actions [13,14]. In mast cells, inhibitory mecha-
nisms of glucocorticoids on FcεRI-mediated mast cell acti-
vation are mainly investigated in downstream signaling 
molecules of the receptor such as upregulating downstream 
of tyrosine kinase (Dok)-1 [15], DUSP1 [16,17] and Src-like 
adaptor protein (SLAP) [17,18].

Here, we addressed regulation of Fc receptors by a gluco-
corticoid Dex in rat RBL-2H3 mast cells. Using actinomycin 
D and cycloheximide as inhibitors for transcription or 
translation, respectively, we demonstrated that Dex in-
creased mRNA levels of FcγRI, FcγRIIb and FcγRIII but 
decreased FcεRI transcript level. Although protein ex-
pressions of FcεRI, FcγRIIb and FcγRIII on cell surfaces 
were slightly changed, the expression of inhibitory receptor 
FcγRIIb increased significantly. Our data suggests that 
Dex suppresses Fc receptor-mediated mast cell activations 
by shifting Fc receptor expression toward the inhibitory re-
ceptor FcγRIIb on their cell surfaces.

METHODS

Cell culture and transient transfection of siRNAs

RBL-2H3 cells were maintained in minimal essential me-
dium (MEM) supplemented with 15% fetal calf serum, 2 
mM glutamine, and an antibiotic-antimycotic solution. For 
transfection with siRNAs, cells were detached with tryp-
sin-EDTA solution, and 2×10^6 cells were pelleted and sus-
pended in 100 μl of Nucleofector Solution R (Amaxa). 
The suspension was mixed with siRNA against FcγRIIb 
(Invitrogen) at the concentration of 50 nM and transfection 
by electroporation program X-001 (Amaxa). The transfected 
cells were transferred to complete medium containing 100 
g/ml DNP-specific IgE and were cultured in 24 well plate 
(0.1×10^5 cells/1 ml/well).

Measurement of mRNAs

RBL-2H3 cells were plated in 6-well (0.25×10^6 cells/2.5 
ml/well) plates for measurement of mRNA. Cells were in-
cubated for 24 h and treated with 100 nM Dex for the in-
dicated time. Actinomycin D or/and cycloheximide were 
added before Dex treatment at 200 ng/ml or/and 1 μg/ml, 
respectively. They were washed twice with PBS and then 
lysed with 1 ml Easy blue (iNTRON). Total RNAs were pu-
rified from cells, and 1 μg of total RNAs was used for syn-
thesis of cDNA in accordance to manufacturer’s protocol 
(ELPis). Transcript levels of β-actin (an internal control 
to calculate fold induction) and target genes were assayed 
by real-time PCR (Applied Biosystems) with following pri-
mers: β-actin, TCTGTTGTGATTGTGGTGCCT TA, CTGCT 
TGCTGTACCACTATGC; FcεRI, GGACGACGGATCGTC; 
AAGATTC, TGGTACGTGCGACTGTCA; FcγRIIb, CTGGAC 
ATGGGCAAGGACCAT; TCCGACCTGAATGATCCA 
CCA, ACCTTAAATACAGGCGTGTTTC. The fold changes 
in transcript levels were calculated using the 2^-ΔΔCt meth-
od [ΔΔCt=ΔC(target gene−ΔC-β-actin) Experimental groups−(ΔC-target 
gene −ΔC-β-actin)Control].

Measurement of FcεRI, FcγRI, FcγRII and FcγRIII on cell surface

RBL-2H3 cells were detached from culture plates by re-
petted pipetting and then washed with Dulbecco’s PBS con-
taining 0.1% sodium azide (FACS buffer). For flow cyto-
metric analysis, 1×10^6 cells in 100 
μl FACS buffer were added before Dex treatment at 200 ng/ml or/and 1 μg/ml, 
respectively. They were washed twice with PBS and then 
lysed with 1 ml Easy blue (iNTRON). Total RNAs were pu-
rified from cells, and 1 μg of total RNAs was used for syn-
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(ELPis). Transcript levels of β-actin (an internal control 
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mers: β-actin, TCTGTTGTGATTGTGGTGCCT TA, CTGCT 
TGCTGTACCACTATGC; FcεRI, GGACGACGGATCGTC; 
AAGATTC, TGGTACGTGCGACTGTCA; FcγRIIb, CTGGAC 
ATGGGCAAGGACCAT; TCCGACCTGAATGATCCA 
CCA, ACCTTAAATACAGGCGTGTTTC. The fold changes 
in transcript levels were calculated using the 2^-ΔΔCt meth-
od [ΔΔCt=ΔC(target gene−ΔC-β-actin) Experimental groups−(ΔC-target 
gene −ΔC-β-actin)Control].

Measurement of degranulation

The degree of mast cell degranulation was assessed via 
measurement of granule enzyme β-hexosaminidase. RBL-
2H3 cells were plated in 24-well (0.1×10^5 cells/1 ml/well). 
Cells were incubated for 24 h at 37°C in culture medium 
containing 100 ng/ml anti-DNP-IgE and treated with 100 
μl of the indicated time. The cultures were washed 
twice with glucose saline/PIPES buffer (119 mM NaCl, 5 
mM KCl, 5.6 mM glucose, 0.4 mM MgCl₂, 25 mM PIPES 
pH 7.2, 1 mM CaCl₂, 1% bovine serum albumin) and simul-
ated with 100 ng/ml DNP-HSA in saline/PIPES buffer for 
20 min for assay of the β-hexosaminidase in medium and 
cells [19]. Data were expressed as a percent of cellular 
β-hexosaminidase that was released into the medium with 
the equation; % of release= stimulated release/release+re-
tained in the cells)×100.

Statistical analyses

All data were expressed as the mean±SD, and all differ-
Dexamethasone Regulates Fc Receptors

RESULTS

Dexamethasone inhibits antigen induced degranulation

To examine the inhibitory effects of Dex on FcεRI-mediated activation, we treated Dex to RBL-2H3 cells 6 h and 18 h before stimulation of FcεRI. We measured the extent of β-hexosaminidase release into the medium by degranulation process. Antigen stimulation produced 38% degranulation efficiency. Pretreatment of Dex for 6 h or 18 h inhibited 58% or 79% of degranulation, respectively (Fig. 1) in agreement with previous reports [18,20]. The inhibition mechanisms of glucocorticoids were described mainly on the regulation of downstream signaling molecules of Fc receptors [15-18]. Therefore, we addressed the regulation of Fc receptors by Dex.

Dexamethasone regulates transcript levels for Fc receptors

Although anti-inflammatory effects of glucocorticoids have been attributed, in part, to upregulation of the expressions of inhibitory molecules of Fc receptor signaling, the effect of glucocorticoids on Fc receptor itself has not been studied. To examine if Dex regulates Fc receptor expressions in mast cells, we assessed the kinetics of induction of Fc receptor mRNAs by Dex in RBL-2H3 cells. The real time RT-PCR analysis of RBL-2H3 cells indicated 50% decrease in mRNA levels for FcεRI 6 h after the addition of Dex. The amount of FcεRI mRNAs reached near minimal levels by 18 h and remained at decreased levels for at least 24 h (Fig. 2A). Next, the effects of Dex on mRNA levels of activating Fcγ receptors FcγRI and FcγRIII were investigated. Unexpectedly, transcript levels of these activating receptors increased in the presence of immune suppressive agent Dex. The amount of FcγRI mRNAs rapidly reached the highest level 3 h after the treatment of Dex by 17-fold, then declined relatively rapidly and reached basal levels (Fig. 2B). The mRNA level of FcγRIII increased gradually and showed maximal level 18 h after Dex treatment by 3-fold more (Fig. 2D). We then investigated transcript regulation of the inhibitory receptor FcγRIIb by Dex. The mRNA level gradually increased as expected and was maximal 18 h after treatment of Dex and remained constant for up to 24 h (Fig. 2C). The expression profiles of those Fc receptors indicated that Dex regulates their expressions differentially.
Dexamethasone regulates Fc receptor expressions by different mechanisms in RBL-2H3 cells

To examine mechanisms underlying regulation mechanisms of Fc receptor expressions by Dex, we investigated the effect of actinomycin D on Fc receptor expressions by Dex (Fig. 3). The inductions of FcεRI, FcγRIIb and FcγRIII transcripts by Dex were blocked by actinomycin D pretreatment. These results indicated that Dex induced transcriptions of these genes through the process of transactivation. In contrast, the amount of FcεRI transcripts was reduced by Dex. This means that transrepression mechanism of Dex inhibited the transcription of FcεRI gene. We employed a protein synthesis inhibitor cycloheximide to determine if proteins involved in mRNA stabilities regulate the transcript levels. Cycloheximide augmented FcεRI and FcγRII mRNA levels by 5- and 8-fold, respectively (Fig. 3B and D). These results suggest that their mRNAs are constitutively produced without stimulation by Dex and that mRNA destabilizing proteins degrade their mRNAs. Meanwhile, Dex can stimulate their transcriptions (Fig. 2). Therefore, co-treatment of Dex and cycloheximide which results in the induction of transcriptions by Dex and reduction of mRNA destabilizing protein synthesis enhanced transcript levels maximally and in an additive manner. However, transcripts of FcεRI and FcγRIIb were not affected by cycloheximide treatment (Fig. 3A and C). These results suggest that mRNA levels of FcεRI and FcγRIIb are regulated mainly by transrepression and transactivation mechanisms of Dex, respectively, while mRNA levels of FcγRI and FcγRIII are controlled through the transactivation mechanism by Dex and mRNA destabilizing proteins.

Organization of FcγRIIb gene

The effects of Dex on production of Fc receptor transcripts raise the possibility that these genes are regulated, at least in part, through GRE. The MULAN program [21] was used to search for predicted GREs that are evolutionarily conserved in the Fc receptor genes of mouse and rat. Predicted GRE sites were present only in FcγRIIb gene. Two GREs were in reverse directions to the consensus GRE. One was upstream of the transcription start site and the other was within the fifth intron (Fig. 4A). The first putative GRE was CAGAAGTGATTATGTA and the second was CAGAACAGAGTTAAAA. These GREs are notable because of their location in the chromosome. The FcγRIIb gene is close to FcγRIII genes (Fig. 4B). Therefore, these GREs are candidate regulators for both genes since FcγRIII is also upregulated by Dex in RBL-2H3 cells (Fig. 2C).

Fc receptor expressions on RBL-2H3 cell surfaces

Surface expressions of Fc receptors by Dex were examined by flow cytometric analysis. Dex treatment did not alter FcεRI protein levels until 18 h (Fig. 5A), although Dex decreased its transcripts (Fig. 2A). While mRNA levels of

![Fig. 4. Organization of FcγRIIb genes. (A) Exons and introns are indicated by the numbered boxes and solid lines, respectively. Dashed lines indicate non-transcribed regions. (B) Genes surrounding the FcγRIIb gene.](image)

![Fig. 5. Effects of Dex treatment on cell surface expressions of FcεRI, FcγRI, FcγRIIb and FcγRIII. Cultured RBL-2H3 cells were treated with Dex (100 nM) for 18 h, and cells were stained with antibodies specific to FcεRI (A), FcγRI (B), FcγRIIb (C) and FcγRIII (D). The surface expressions of Fc receptors were verified by cell fluorescence analysis. Dex treatment or control is represented with filled or empty area, respectively. Data is a representative from three separate experiments.](image)

![Fig. 6. Effects of downregulation of FcγRIIb by transfection of anti-FcγRIIb siRNA. The effects of transfection with siRNA against FcγRIIb on its transcript level (A) and degranulation efficiency by the cross-linking of FcεRI (B). Cells were incubated 24 h after transfection with the siRNA. After cells were incubated for 18 h in the presence or absence of 100 nM Dex, degranulation efficiency was determined by β-hexosaminidase assay, and cell surface expression was evaluated by flow cytometric analysis. Data are expressed as mean±SD, n=3. Flow cytometric data is a representative from three separate experiments.](image)
Fcγ RI and Fcγ RIII increased significantly in the presence of Dex (Fig. 2B and D), changes of their surface expressions were rather marginal (Fig. 5B and D). In contrast, Fcγ RIIB surface levels significantly increased 1.8-fold by Dex (Fig. 5C) pertaining to its transcript regulation (Fig. 2C). The augmentation of Fc receptor transcripts did not always result in their protein expression. These data suggest that Dex stimulates expression of an inhibitory Fc receptor Fcε RIIB on the cell surface without increases in protein expressions of activating receptors Fcε RI, Fcγ RI and Fcγ RIII.

**The effects of downregulation of Fcγ RIIB by siRNA transfection on mast cell activation**

Transfection of siRNA against Fcγ RIIB mRNA decreased its transcript level and attenuated Dex-mediated enhancement of Fcγ RIIB transcripts by 50% (Fig. 6A). Accordingly, cell surface expression of Fcγ RIIB was reduced in the presence of Dex or in the absence of Dex by 50% (Fig. 6A). We measured degranulation efficiency by cross-linking of Fcε RI in these conditions. Interestingly, downregulation did not affect degranulation efficiency (Fig. 6B).

**DISCUSSION**

We showed that a glucocorticoid Dex regulated Fc receptor transcripts and enhanced the protein expression of an inhibitory receptor, Fcγ RIIB, on cell surfaces of RBL-2H3 mast cells. Glucocorticoids regulate transcript expression directly or indirectly. Ligand-bound glucocorticoid receptors interact with AP1 and NF-κB which are transcription factors that promote inflammatory cytokine production [10]. These interactions inhibit transcriptional activities of AP1 or NF-κB and result in the suppression of inflammatory cytokine production. Dex repressed Fcε RI transcription and enhanced transcriptions of IgG receptors Fcγ RI, Fcγ RIIB and Fcγ RIII (Fig. 2). We assumed that the transcription mechanism may be involved in regulating Fcε RI gene expression. Although the transcript level of Fcε RI decreased by Dex, cell surface expression of Fcε RI protein did not change (Fig. 5A). Longer exposure to Dex would decrease Fcε RI proteins level. In mouse mast cells, Dex downregulated cell surface expression of Fcε RI [20,22] in the same exposure time to Dex with our experimental conditions. Fcε RI proteins of a rat mast cell RBL-2H3 may be more stable than proteins of mouse origin cells.

Unexpectedly, an immune suppressive agent, Dex, stimulated transcriptions of the activating receptors Fcγ RI and Fcγ RIII (Fig. 2B and D). The inhibition of protein synthesis alone strongly increased mRNA levels as much as Dex did and augmented the Dex-induced mRNA levels of Fcγ RI and Fcγ RIII (Fig. 3). Proteins involved in mRNA degradation, such as tristetraproline [23], may degrade Fcγ RI and Fcγ RIII transcripts. Their mRNAs may be constitutively produced and degraded by mRNA destabilizing proteins that are expressed in a Dex-independent manner. Although enhancement of activating receptors by the immune suppressive agent, Dex, seems to be absurd, this can be explained by the fact that the expression ratio of activating and inhibitory Ig receptors determines the outcome of immune responses [6]. The experiment performed with monocytes from immune thrombocytopenia patients showed that Dex induces both activating and inhibitory receptors, with Fcγ RIIB at higher amplitudes. Also, Fcγ RIII expression in human neutrophils is sometimes increased slightly by Dex [24]. Accordingly, our data suggest that Dex shifted mast cell Fc receptor balance toward inhibitory Fcγ RIIB (Fig. 5). Alternatively, increased Fc receptors having ITAM motifs by Dex may act as negative immune regulators. Recent studies showed that ITAMs of activating receptors recruit negative signaling molecules such as SHP-1 in some conditions and then inhibit other activating receptor signals [25,26]. Dex treatment might make favorable cell conditions for ITAM of Fcγ RIII to act as an inhibitory ITAM.

Dex treatment suppressed Fcε RI-mediated degranulation efficiency (Fig. 1). However, reduction of Fcε RI protein expression on cell surfaces was not observed (Fig. 5). The shifting Fc receptor expression toward inhibitory receptor Fcγ RIIB by Dex would contribute to the reduction of degranulation efficiency in addition to induction of inhibitory molecules in the downstream signaling of FcεRII activation [17,18]. However, downregulation of Fcγ RIIB expression by transfection with Fcγ RIIB siRNA did not show any significant effect on degranulation efficiency (Fig. 6A). These data suggest that binding affinity of IgE to Fcγ RIIB in vitro may not be enough to inhibit Fcε RI-mediated activation signals even though the IgE-mediated degranulation is augmented in Fcγ RIIB-deficient mice in vivo [27]. Another possibility is that 50% reduction of Fcγ RIIB expression by the siRNA transfection (Fig. 6) was not enough to inhibit Fcε RI-mediated degranulation. The complete downregulation of Fcγ RIIB transcripts in Fcγ RIIB-deficient mice may contribute to the decrease in degranulation efficiency.

Fcγ RI, Fcγ RIII and Fcγ RIIB genes are clustered at chromosome 13 in rats and chromosome 1 in mice (Fig. 4). In humans, Fcγ RIII and Fcγ RIIB are also close. The predicted transcription factor binding sites in evolutionarily conserved regions between species give more valuable idea. We found two evolutionary conserved GREs in Fcγ RIIB gene region between a rat and a mouse, but not between human and murine. These conserved elements may regulate murine Fcγ RI, Fcγ RIIB and Fcγ RIII genes coordinately in response to Dex as shown in this investigation (Fig. 2B and D). These receptor expression mechanisms in response to Dex would be different from human and murine.

Fcγ RIIB is the only inhibitory Fc receptor that is expressed on mast cells and other immune cells such as granulocytes, myeloid cells and lymphoid cells, missing only from T and NK cells. It acts as a key negative regulator to maintain immune balance from activating Fc receptor signals. Mast cells express IgE receptors and also IgG receptors (Fcγ RI, Fcγ RIIB, Fcγ RIII). Mast cells elicit IgG-mediated immune responses supported by the observation that IgG cross-linking of mast cells, basophils, and macrophages resulted in Fyn- and Lyn-regulated mediator release in vitro [28]. Up-regulation of Fcγ RIIB by Dex in mast cells may contribute to Dex effects as an immune suppressive agent in the Arthus reaction where Fcγ RIII on mast cells is necessary for this inflammatory response [29]. Recent reports suggest that mast cells are involved in the developments of immune diseases such as multiple sclerosis, inflammatory arthritis, atherosclerosis and diet-induced obesity and diabetes [1-4] where autoimmunity is possibly involved. Fcγ RIIB deficiency makes normally resistant mouse strains to be susceptible to several antibody- or immune complex-dependent models of autoimmunity [6]. Our finding that Dex enhanced Fcγ RIIB expression on mast cells may give a rationale for use of Dex in the treatment
of autoimmune diseases where mast cells are involved.

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