Transcriptional Regulation of IL-5 Gene by Nontransformed Human T Cells Through the Proximal Promoter Element

Akio Mori, Osamu Kaminuma*, Koji Ogawa*, Hirokazu Okudaira** and Kazuo Akiyama

Abstract

Objective IL-5 is strongly involved in the eosinophilic inflammation in bronchial asthma and atopic dermatitis. We have previously reported that IL-5 synthesis in atopic and nonatopic asthmatics is significantly enhanced compared to control subjects. T cell IL-5 synthesis is regulated through several transcriptional elements, one of which is the proximal human IL-5 promoter (−62 to −46). The present study was undertaken to delineate the transcriptional regulation through this element using nontransformed human T cells.

Methods Con A blast lymphocytes which tolerate electroporation were derived from peripheral blood lymphocytes. Luciferase reporter analysis and gel shift analysis were performed.

Results The proximal promoter element is the overlapping binding site for the constitutive binding factor, Oct-1, and the inducible one, AP-1. The transcriptional induction was ascribed to the inducible binding, while the constitutive binding was rather inhibitory. A mutant element which lost the constitutive binding but retained the inducible binding exerted 3 times more transcriptional activity compared to the wild type element. In contrast, another mutant element which lost the inducible binding and retained the constitutive binding exhibited no transcriptional induction. Gel shift analysis clarified that the inducible binding was more prominent and the constitutive binding was less in IL-5-producing T cells derived from asthma patients compared to IL-5-nonproducing cells derived from control subjects.

Conclusions The ratio of the inducible/constitutive binding to the proximal promoter element may determine the capacity of human Th cells to transcribe IL-5 gene, and its regulation may control eosinophilic inflammation.

(Key words: gene transcription, NF-AT, bronchial asthma, allergy, eosinophilic inflammation)

Introduction

Bronchial asthma is characterized by persistent eosinophilic inflammation of the bronchial mucosa (1, 2). T cell cytokines including interleukin-5 (IL-5) are closely involved in the local infiltration and activation of eosinophils (2, 3). IL-5 is a potent selective growth factor, differentiation factor, activating factor and chemotactic factor for human eosinophils (4, 5). The number of CD4+ T cells expressing IL-5 mRNA is increased in the bronchial mucosa of symptomatic asthmatic patients (6), is correlated with the number of activated eosinophils, and is further increased upon allergen inhalation challenge (7, 8). Bronchoalveolar lavage (BAL) fluid obtained from atopic and non-atopic asthmatics showed an increased concentration of IL-5 (9). IL-5 is the predominant eosinophil-active cytokine present in the BAL fluid obtained from asthmatic patients (10). Serum IL-5 concentration was elevated in symptomatic asthmatics and decreased after oral prednisolone therapy (11). The intensity of IL-5 mRNA expression correlated well with that of eosinophilic infiltration, whereas that of IL-3 and GM-CSF did not (12). We have reported that IL-5 production by CD4+ T cells of asthmatic patients is significantly enhanced compared to that of healthy controls (13). Several experimental asthma models revealed that administration of anti-IL-5 neutralizing antibody inhibited the recruitment of eosinophils into the lung and abrogated the late phase bronchoconstriction (14–17), clearly indicating the essential role of IL-5 in the late phase asthmatic response. T cells producing IL-3, GM-CSF, and IL-5 were also demonstrated in the late phase cutaneous reaction of atopic dermatitis patients upon antigen challenge (18). Accumulating evidence including the above-mentioned studies has suggested that IL-5 is the key cytokine involved in the allergic disorders associated with eosinophilic inflammation. The regulation of T cell IL-5 synthesis may be an effective management for eosinophilic disorders.

IL-2 and IL-4 synthesis by helper T (Th) cells is mainly controlled by transcriptional regulation (19–21). A variety of transcription factors and elements have also been reported to control IL-5 gene (22), although most investigations have ana-
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Materials and Methods

Subjects

Adult atopic asthma patients referred to the Allergy Clinic at National Sagamihara Hospital were enrolled in this study. All patients were non-smokers and fulfilled the criteria of the International Consensus Report on Diagnosis and Management of Asthma (34), and all demonstrated at least 20% improvement of their FEV₁₀ after β₂-agonist inhalation. Atopy was defined as the detection of one or more positive skin prick tests to a range of 20 common airborne allergens in the presence of a positive histamine control and a negative vehicle control. Patients receiving systemic or inhaled corticosteroids were excluded from the study. Treatment with β₂-stimulants, anti-cholinergics, and theophylline was stopped at least 12 hours before blood sampling. The control subjects were healthy age- and sex-matched individuals with normal IgE levels, negative skin prick tests, no history of allergy or asthma, and no medications. All subjects gave written informed consent to the protocol as approved by the Institution’s Ethics Committee.

Reagents

Phorbol 12-myristate 13-acetate (PMA) was purchased from Sigma (St. Louis, MO), and ionomycin (IOM) was purchased from Calbiochem (La Jolla, CA). Concanavalin A (Con A) was from Pharmacia Biotech (Uppsala, Sweden). Recombinant human IL-2 (rIL-2) was provided by Shionogi Pharmaceutical Co. (Osaka). AIM-V medium and RPMI 1640 medium (Gibco BRL, Gaithersburg, MD) were used for culturing T cells.

Con A blast lymphocytes

Peripheral blood mononuclear cells (PBMC) were prepared by Ficoll-Paque density gradient centrifugation as described previously (13). Cells (2×10⁶/ml) were cultured with Con A (3 µg/ml) in RPMI 1,640 medium containing 10% fetal calf serum (FCS) for 3 days. Non-adherent cells increased in number by three to five fold. Cells were subsequently maintained in fresh AIM-V medium containing 10% FCS and 10 U/ml IL-2 for 6–7 days. Then, Con A blast lymphocytes were harvested, washed twice, and resuspended in fresh medium. The resulting preparation usually consisted of more than 95% CD3-positive cells, as determined by flow cytometry.
**Cell Separation**

CD4- or CD8-positive cells were depleted from the Con A blast lymphocytes using anti-CD4 or anti-CD8-coupled magnetic beads (Dynal, Great Neck, NY), respectively, according to the manufacturer’s directions. The efficiency of the depletion was determined by FACS analysis. Less than 5% positive cells remained after each depletion procedure.

**Quantitation of cytokines in culture supernatants**

IL-5 was measured by a sandwich enzyme-linked immunosorbent assay (ELISA) using monoclonal anti-human IL-5 (D138) as the capture antibody and biotinylated purified rabbit anti-human IL-5 as the second antibody, as described previously (13).

**Plasmid constructs**

pIL-5(-511)Luc, a human IL-5 promoter/enhancer (~511 to +4 relative to the transcription initiation site)-luciferase gene construct, was prepared as described previously (35). The reporter constructs (3xCLE0-tk-Luc, 3xCLE0mt6-tk-Luc, and 3xCLE0mt7-tk-Luc) were generated by cloning three copies of the corresponding oligonucleotides as direct repeats into the Xho I and Hind III sites of the pGL3-tk vector, which carries the truncated thymidine kinase (tk) promoter connected to the luciferase reporter gene. Identity of the promoter/enhancer sequence was confirmed by chain termination sequencing using Sequenase 2.0 (Strategene). pCMV-β-gal control vector (Riken DNA Bank, Tokyo) was used as a transfection control.

**Transient transfection, luciferase assay, and β-galactosidase assay**

Con A blast lymphocytes (10^7 cells) were suspended in 500 μl cRPMI 1,640 medium containing 10 U/ml rIL-2 in a 0.4 cm electroporation cuvette, incubated with 50 μg luciferase reporter plasmids and 10 μg pCMV-β-gal, and then transfected by electroporation using a Gene Pulser (Bio-Rad, Richmond, CA) at 300 V, 960 μF with a mean time constant of 20 msec. Transfected cells were pooled and 4×10^6 cells per well were cultured in 24-well culture plates with or without stimulation for 24 hours. Protein extracts were then prepared and luciferase activity was assayed using the Luciferase Assay System (Promega). β-Galactosidase activity was assayed using chlorophenol red-β-D-galactopyranoside (CPRG) as the substrate, as described previously (35).

**Preparation of nuclear extracts and Electrophoretic mobility shift assay (EMSA)**

Crude nuclear and cytoplasmic extracts were prepared from unstimulated or stimulated cells as described by Schreiber et al (36) with modifications. Pairs of synthetic HPLC-purified oligonucleotides (Sawady Technology, Tokyo) containing complementary sequences were annealed by boiling equimolar concentrations of each strand for 10 minutes and the mixture was allowed to slowly cool in a water bath to room temperature. EMSA was performed using 32P end-labeled oligonucleotides as described previously (37, 38). In competition experiments, a 50 molar excess of unlabeled oligonucleotides, relative to the probe, was added to the binding reaction. A GATA binding element oligonucleotide (Santa Cruz Biotechnology, Inc., Santa Cruz, CA) was used as a negative control. For supershift experiments, antibodies at a final concentration of 10 μg/ml were added to the designated reactions. After 1 hour incubation, the resulting complexes were resolved on 4% polyacrylamide gels by electrophoresis at 100 V in 0.5x TBE buffer (1x TBE: 89 mM Tris-HCl, pH 8.0, 89 mM boric acid and 2 mM EDTA) at room temperature. The gel was subsequently dried and exposed to RX film (Fuji Photo Film, Tokyo) at −70°C. The intensity of each binding complex was quantified by scanning densitometry.

**Protein assay**

Protein concentrations were determined using bichoronicin acid (BCA) protein assay reagent (Pierce, Rockford, IL), according to the manufacturer’s directions.

**Statistical analysis**

Statistical analysis was performed using Student’s t-test. A value of p<0.05 was considered statistically significant. Responses are presented as the mean±standard error of the mean (SEM).

**Results**

**Transcriptional induction through the proximal promoter element by the inducible binding factor**

The first experiment was performed to determine the role of the proximal promoter element in the transcriptional induction of IL-5 gene by nontransformed human T cells. As the resting peripheral lymphocytes were not sufficiently efficient for transfection experiments, Con A blast lymphocytes were derived from peripheral blood mononuclear cells, and tested for the transcriptional activity. Con A blast lymphocytes derived from asthmatic donors produced a significant amount of IL-5 and transcribed PIL-5(-511)Luc upon stimulation with PMA (20 nM) plus ionomycin (1 μM), whereas the cells derived from healthy controls scarcely produced IL-5 nor transcribed pIL-5(-511)Luc (39). Those cells that produced more than 100 pg/ml, 10 to 100 pg/ml, and less than 10 pg/ml of IL-5 were designated as IL-5 high-, low-, and non-producing cells, respectively. Cell depletion experiment using magnetic beads coated with anti-CD4 or CD8 antibodies revealed that CD4+ T (Th) cells were solely responsible for IL-5 production, as IL-5 production was totally abrogated by the depletion of CD4 T cells but not CD8 T cells (Table 1). Transcriptional activity mediated by this element was analyzed by transfecting the Con A blast lymphocytes with 3xCLE0-tk-Luc. As shown in Table 2, 3xCLE0-tk-Luc was clearly induced upon activation by IL-5 high-producing ConA blast lymphocytes derived from asthmatic donors, but not by the cells derived from control donors which produced no detectable IL-5, indicating a differential regulation of this promoter among IL-5 high-, low-, and non-producing T cells. The transfection efficiency was determined...
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Table 1. IL-5 Production and Transcriptional Activity of Con A Blast Lymphocytes Derived from Asthmatic Donors and Control Subjects

<table>
<thead>
<tr>
<th>Con A blasts</th>
<th>IL-5 production (pg/ml)</th>
<th>Luciferase activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. Type Donor</td>
<td>Control</td>
<td>CD4-depleted</td>
</tr>
<tr>
<td>1 H A</td>
<td>441.4±23.1</td>
<td>1.6±0.1</td>
</tr>
<tr>
<td>2 H A</td>
<td>398.1±21.9</td>
<td>0.9±0.0</td>
</tr>
<tr>
<td>3 L A</td>
<td>22.9±3.2</td>
<td>0.4±0.1</td>
</tr>
<tr>
<td>4 N C</td>
<td>0.2±0.0</td>
<td>0.0±0.0</td>
</tr>
</tbody>
</table>

*aCon A blast lymphocytes were derived from the peripheral blood mononuclear cells obtained from asthmatic patients and healthy control subjects. †H: IL-5 high-producing (>100 pg/ml), L: low-producing (10 to 100 pg/ml), N: non-producing (<10 pg/ml). ‡A: asthmatic donors, C: healthy control donors. §Con A blast lymphocytes were incubated with magnetic beads coated with either control IgG, anti-CD4, or anti-CD8 antibody. Unbound cell fractions (10⁶/well) were cultured in triplicate in 96-well round bottom culture plates with PMA (20 nM) plus ionomycin (1 µM) or left unstimulated. The supernatants were collected after 24 hours and assayed for IL-5 with a specific ELISA. Data are presented as the mean of triplicate cultures ± SEM. IL-5 production of the cultures without stimulation was below the detection limit of the ELISA (1 pg/ml).

by the cotransfection with CMV-β-gal, and did not differ significantly among these cell preparations (data not shown).

To elucidate the role of two complexes binding to the proximal promoter element of human IL-5 gene, 3xCLE0-tk-Luc, 3xCLE0mt6-tk-Luc, and 3xCLE0mt7-tk-Luc constructs were transfected into the IL-5 high-producing Con A blast lymphocytes, and the resultant transcriptional induction was analyzed. As previously reported, CLE0mt6 oligonucleotide retains the inducible binding (AP-1) and loses the constitutive binding (Oct-1), whereas CLEmt7 oligonucleotide loses the inducible binding and retains the constitutive binding (33). A representative result of three independent experiments is shown in Fig. 1. 3xCLE0mt6-tk-Luc was induced more vigorously than the wild type gene construct, whereas 3xCLE0mt7-tk-Luc exhibited no transcriptional induction, suggesting that the inducible binding factor is responsible for the transcriptional activation through this element, and the constitutive binding factor functions as a negative regulator. Significant induction of luciferase activity was not detected by transfecting IL-5 low- and non-producing Con A blast lymphocytes with these three constructs (data not shown), consistent with the lower transcriptional induction of pIL-5(-511)Luc compared with IL-5 high-producing Con A blast lymphocytes (Table 2). The results are consistent with our previous findings obtained using human T cell hybridomas that transcribe IL-5 gene upon activation (33), and further extend that the transcriptional regulation through the proximal promoter element is essential for the nontransformed human T cells which might work in asthmatic patients in vivo.

Table 2. IL-5 Production and Transcriptional Activity of Con A Blast Lymphocytes Derived from Asthmatic Donors and Control Subjects

<table>
<thead>
<tr>
<th>Con A blasts</th>
<th>IL-5 production (pg/ml)</th>
<th>Luciferase activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. Type Donor</td>
<td>Control</td>
<td>CD4-depleted</td>
</tr>
<tr>
<td>1 H A</td>
<td>554.6±36.5</td>
<td>19.3±1.1</td>
</tr>
<tr>
<td>2 H A</td>
<td>745.2±58.1</td>
<td>21.8±2.1</td>
</tr>
<tr>
<td>3 L A</td>
<td>34.5±7.2</td>
<td>20.4±1.7</td>
</tr>
<tr>
<td>4 L A</td>
<td>25.3±8.1</td>
<td>20.3±2.2</td>
</tr>
<tr>
<td>5 N C</td>
<td>0.4±0.2</td>
<td>18.3±1.9</td>
</tr>
<tr>
<td>6 N C</td>
<td>0.2±0.0</td>
<td>17.3±1.7</td>
</tr>
</tbody>
</table>

*aCon A blast lymphocytes were derived from the peripheral blood mononuclear cells obtained from asthmatic patients and healthy control subjects. †H: IL-5 high-producing (>100 pg/ml), L: low-producing (10 to 100 pg/ml), N: non-producing (<10 pg/ml). ‡A: asthmatic donors, C: healthy control donors. §Con A blast lymphocytes (10⁶/well) were cultured in triplicate in 96-well round bottom culture plates with PMA (20 nM) plus ionomycin (1 µM) left unstimulated. The supernatants were collected after 24 hours and assayed for IL-5 with a specific ELISA. Data are presented as the mean of triplicate cultures ± SEM. IL-5 production of the cultures without stimulation was below the detection limit of the ELISA (1 pg/ml). §Con A blast lymphocytes were transiently transfected with 3xCLE0-tk-Luc (50 µg) + pCMV-β-gal (10 µg) by electroporation (300 V, 960 µF) using a 0.4 cm cuvette. Cells were either stimulated with PMA (20 nM) plus ionomycin (1 µM) or left unstimulated in 24-well culture plates. After 24 hours, cell lysates were prepared and tested for luciferase activity using Luciferase Assay System (Promega) and β-galactosidase activity using chlorophenol red-β-D-galactopyranoside (CPRG) as a substrate. Data are presented as the mean of triplicate cultures.

**Difference in the proximal promoter binding complexes between IL-5-producing and nonproducing human Con A blast lymphocytes**

IL-5 high-producing Con A blast lymphocytes were stimulated with 20 nM PMA and 1 µM IOM for 2 hours, and then nuclear extracts were prepared for EMSA. As shown in Fig. 2A, a constitutive binding complex was observed using nuclear extract obtained from the unstimulated cells (lane 1). Upon stimulation, the inducible band with a faster mobility became detectable (lane 2). The CLEmt6 oligonucleotide competed out the faster migrating complex (lane 4), whereas the CLEmt7 oligonucleotide competed out the slower migrating complex (lane 6), thus confirming these mutagenesis effects previously reported by us (33). The proximal promoter binding complexes were next characterized among IL-5 high-, low-, and non-producing Con A blast lymphocytes. IL-5 high- and low-producing Con A blast lymphocytes were derived from asthma patients, while IL-5 non-producing Con A blast lymphocytes were derived from control subjects. As shown in Fig. 2B, the inducible binding complex was prominent in IL-5 high-producing cells, but scarcely detectable in the IL-5 low- and non-produc-
Figure 1. Transcriptional induction of mutant and wild type proximal promoter elements. A) DNA sequences of the wild type and mutant elements are shown. Lower case letters represent the mutated nucleotides. B) Con A blast lymphocytes (10^7 cells in 500 μl cRPMI1640 medium) were transiently transfected with 3×CLE0-tk-Luc, 3×CLE0mt6-tk-Luc, or 3×CLE0mt7-tk-Luc (50 μg) by electroporation (300 V, 960 μF) using 0.4 cm cuvette, and cultured in triplicate with PMA (20 nM) plus ionomycin (1 μM) or kept unstimulated for 24 hours. Cell lysates were prepared and tested for the luciferase and β-galactosidase activities. Protein concentrations were determined with bicinchoninic acid (BCA) protein assay reagent. The data are expressed as the mean of triplicate cultures ± SEM. C) The structural implication as to the proximal promoter sequence spanning -67 to -40 is shown. The bases indicated by * and # were mutated for mt6 and mt7 mutants, respectively.

Discussion

The present findings clearly indicate that the proximal promoter element regulates the transcriptional induction of IL-5 gene in nontransformed human Th cells. The ratio of the inducible factor/the constitutive factor might determine the on/off of the IL-5 gene transcription of Th cells, which is enhanced in eosinophilic disorders.

As IL-5 is a potent growth factor and activating factor for human eosinophils (4, 5), great attention has been paid to the relationship between IL-5 production and the eosinophilic inflammation. Uregulation of protein and mRNA expression of IL-5 was demonstrated in the bronchial mucosa of atopic and nonatopic asthma patients, which well correlated with the intensity of the infiltration and activation status of eosinophils (6, 40, 41). We reported that mice adoptively transferred IL-5-producing Th clones developed airway eosinophilic inflammation and bronchial hyperresponsiveness upon inhalation of the relevant antigen, clearly indicating the importance of Th cells as the source of IL-5 (42). IL-5 production by CD4+ T cells of asthmatic patients is significantly enhanced compared to that of healthy controls (13). In addition, glucocorticoids and FK506 not only suppress IL-5 synthesis in vitro, but also reduce IL-5 production by peripheral Th cells in parallel with the clinical improvement (13, 43). It is, thus, suggested that enhanced IL-5 production by Th cells is characteristic of allergic diseases associated with eosinophilic inflammation, and its correction is an effective therapeutic target. Elucidation of the regulatory mechanisms involved in the selectively enhanced gene transcription of IL-5 seems to be essential to understand the molecular basis of the allergic inflammatory diseases such as bronchial asthma, atopic dermatitis, and allergic granulomatous angitis.

It is well known that synthesis of major T cell cytokines such as IL-2 and IL-4 is transcriptionally regulated (19-21, 44). To date, the information on human IL-5 gene transcription is still limited, while quite a few studies have been performed to analyze murine IL-5 gene (23-26, 45, 46). We have employed allergen-specific Th clones and hybridomas to study cytokine synthesis involved in allergic inflammation (47), and found that human T cell IL-5 synthesis is regulated at the level of gene transcription through the 515 bp gene segment 5’ upstream of the coding region, and unique transcriptional mechanisms distinct from those regulating IL-2 or IL-4 gene seemed to control IL-5 gene (37, 38, 48, 49). The present finding that transcriptional activity of IL-5 promoter by Con A blast lym-
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Figure 2. Constitutive and inducible binding proteins for CLE0 element. A) IL-5 high-producing Con A blast lymphocytes (4×10^6/well) were stimulated with PMA (20 nM) plus ionomycin (1 μM) for 2 hours. Then, cells were harvested and nuclear protein prepared. ^32P-labeled oligonucleotide containing the sequence from -62 to -42 of the human IL-5 gene (IL-5CLE0) was incubated with nuclear extracts. Unbound and protein-bound DNA were resolved by native gel electrophoresis (lane 2). A 50-fold molar excess of unlabeled CLE0mt7 (lane 6), CLE0 (lane 5), CLE0mt6 (lane 4), and unrelated GATA binding element (lane 3) oligonucleotides were included in the binding reaction. For lane 1, nuclear proteins extracted from the resting T cells were used. The bands indicated by the arrowheads were the specific binding determined by the addition of excess unlabeled probes in the preliminary experiments. B) Con A blast lymphocytes were derived from the peripheral blood mononuclear cells of asthmatic patients and control subjects. IL-5 high-, low-, and non-producing Con A blast lymphocytes (4×10^6/well) were stimulated with PMA (20 nM) plus ionomycin (1 μM) for 2 hours. Then, cells were harvested and nuclear protein prepared. ^32P-labeled oligonucleotide containing the sequence from -62 to -42 of the human IL-5 gene (IL-5CLE0) was incubated with nuclear extracts. Unbound and protein-bound DNA were resolved by native gel electrophoresis. The bands indicated by the arrowheads were the specific binding determined by the addition of excess unlabeled probes in the preliminary experiments. C) Relative levels of the inducible binding complexes were determined by densitometric scanning of the autoradiographic bands and normalized to the corresponding constitutive binding complex.

phocytes is correlated with the protein production further support the notion. Of note is that IL-5 high-producing Con A blast lymphocytes can be derived from asthmatic donors and not from control donors as we have reported (39).

Transcriptional regulation of human IL-5 gene through the proximal promoter element was previously studied employing T cell hybridomas (31). The present study clarified for the first time that the proximal promoter element is involved in the activation of IL-5 gene by Con A blast lymphocytes, non-transformed human T cells. An inducible binding complex which is comprised of AP-1 family proteins and a constitutive binding complex which was identified as Oct-1 molecule were also detected for Con A blast lymphocytes (Fig. 2). The essential role of the inducible binding was demonstrated employing the mt7 mutant element which lost inducible binding but retained constitutive binding capacity (Fig. 1). IL-5 high-producing cells exhibited a higher level of inducible binding, suggesting that the more abundant inducible binding complex (I) results in the transcriptional induction in the “allergic” T cells by more frequently replacing the constitutive binding complex (Fig. 3). The precise molecular nature of inducible binding complex warrants further clarification. Future elucidation of transcription factors involved in IL-5 gene transcription (NF-IL-5) would greatly improve the understanding of atopic diseases associated with eosinophilic inflammation, and facilitate the development of novel therapeutic interventions.

This work was supported in part by a grant to A. M. from the Mochida Memorial Foundation.

References

Figure 3. Schematic representation of CLE0 homologous element and its binding factors. The proximal promoter element is occupied by the constitutive binding factor (C) at the resting stage. Upon activation, the inducible factor (I) binds the element, which results in the transcriptional induction. The intensity of the inducible binding complex was higher in IL-5 high-producing T cells compared to IL-5 low- and non-producing cells. IL-5 synthesis seems to be controlled by the binding of the inducible factor (I) which is lacking in IL-5 non-producing Th cells, although other transcriptional elements and factors are also involved to achieve multi-regulated expression of IL-5 gene.


37) Mori A, Suko M, Kaminuma O, et al. IL-2-induced IL-5 synthesis, but
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