

Specific inhibition of TH2-type cytokine production from human peripheral T cells by terfenadine *in vitro*

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Summary

Background Cytokine imbalance is thought to be one of the causes for allergic diseases. The effect of anti-allergic drugs on cytokine production from T cells should be examined in a convenient way.

Objectives To study the *in vitro* effect of terfenadine, a prototype non-sedating H1 receptor antagonist, on cytokine production from activated T cells.

Methods T cells were cultured in the presence of terfenadine on anti-CD3 mAb and anti-CD26 mAb-coated wells, anti-CD3 mAb and anti-CD28 mAb-coated wells, and anti-CD3 mAb wells with PMA. T-cell proliferation, along with the concentrations of interleukin (IL) -2, interferon (IFN) - γ , IL-4, and IL-5 were measured.

Results Terfenadine inhibited T-cell proliferation and IL-4 and IL-5 production under each costimulatory condition tested, whereas it had no effect on IL-2 and IFN- γ production.

Conclusions These results indicate that terfenadine has a specific inhibitory effect on TH2-type cytokine production induced by several ways of costimulatory activation.

Keywords: terfenadine, CD26, CD28, CD3, costimulation, interferon-gamma, interleukin-2, interleukin-4, interleukin-5, T cell

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Introduction

Terfenadine is a prototype non-sedating H1 receptor antagonist used for the treatment of allergic diseases [1]. Although it was removed from the USA market because of unexpected side-effect of dysrhythmia under the co-administration of certain antibiotics [2], terfenadine itself is still evaluated as an effective allergic medicine in other countries in Europe and Asia. Its effect has been believed to be brought on by its antagonistic reaction against histamine receptors. On the other hand, recent studies have suggested that it may possess additional properties unrelated to the blockage of histamine at its receptor level [3–5]. Therefore, it is anticipated that other mechanisms by which terfenadine is effective for the treatment of allergic diseases may be present.

In a hypersensitive reaction, many kinds of inflammatory

cells contribute to maintaining this reaction, through producing soluble factors, such as cytokines, or cell–cell interactions. Helper T (TH) cells are specifically regarded to be the effector cells and play an important role in regulating the hypersensitive reaction. Based on the cytokine production profile, two subtypes of TH cells have been identified [6,7]. The first is the TH1-type cell, which releases interleukin (IL) -2 and interferon-gamma (IFN- γ) [6,7]. The second is the TH2-type cell, which releases IL-4 and IL-5 [6,7]. In some allergic diseases, TH2 cells are reported to accumulate predominantly at the site of inflammation, and these cells trigger the hypersensitive reaction [8–10]. Thus, specific inhibition of TH2 cell functions may lead to the successful treatment of allergic diseases, or hypersensitivity.

In the initial stage of a hypersensitive reaction, a certain allergen would be engaged by the TcR, followed by allergic cytokine release. However, this process alone is not sufficient for induction of all events that accompany T-cell activation. Accumulating evidence has suggested the presence

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of so-called costimulatory signals that occur through additional T-cell surface molecules, which are independent of the TcR [11]. These costimulatory signals are indispensable for full activation of T cells, which is characterized by T-cell proliferation and cytokine production. Therefore, the triggering of costimulatory signals plays an important role in the generation of a hypersensitive immune reaction. The costimulatory signals can be provided by a number of accessory molecules such as CD28/CTLA-4 [12–14]. Furthermore, we have recently established the identity of a novel costimulatory molecule, CD26, which is preferentially expressed on CD4⁺ memory T cells [15–17], and is speculated to be involved in effector T cells which migrate to the focus of inflammation in some diseases [18,19].

To further determine the mechanism of action of terfenadine on inhibiting an allergic reaction, we attempted to determine the effect of terfenadine on T-cell proliferation and cytokine production through different costimulatory signalling pathways. The results revealed that terfenadine inhibited T-cell proliferation in a dose-dependent manner under the costimulatory conditions. More interestingly, terfenadine clearly inhibited IL-4 and IL-5 production, whereas it did not affect TH1-associated IL-2 and IFN- γ production. Our findings indicate that terfenadine specifically inhibits TH2-type cytokine production from human peripheral T cells *in vitro*, suggesting yet another mechanism of the effectiveness of this drug for allergic diseases.

Materials and methods

General remarks

The data shown in this article are representatives from a single individual among seven independent healthy donors. The results from each individual represented the same tendency as the results presented in this article (data not shown).

Cells and reagents

Human peripheral blood mononuclear cells were isolated from healthy volunteer donors by Ficoll-Hypaque (Pharmacia Biotech Inc., Piscataway, NJ, USA) density gradient centrifugation [15]. Unfractionated mononuclear cells were separated into an E rosette-positive (E⁺) population and were used as resting T cells. Monocytes were depleted by adherence to plastic plates for 4 h at 37 °C followed by incubation with 5 mmol/L L-leucine methyl ester HCl (Sigma, St Louis, MO, USA) for 1 h. Monoclonal antibodies reactive with the T-cell surface antigens CD3 (OKT3) and CD26 (1F7) had been previously described [15]. Anti-CD28 monoclonal antibody, 4B10, was developed in our laboratory by standard techniques after immunization of a mouse with human PBL-PHA

blasts [20]. Terfenadine was purchased from Sigma (St Louis, MO, USA).

T-cell proliferation assays

One hundred microlitres of phosphate-buffered saline (PBS) containing 0.05 μ g/mL of OKT3, or with 1 μ g/mL of 1F7, or with 2 μ g/mL of 4B10 mAb was coated in 96-well flat-bottomed plates (Coster, Cambridge, MA, USA) in triplicate and incubated overnight at 4 °C, as described previously [16]. Before use, these plates were washed once with 200 μ L of PBS. Highly purified T cells were resuspended at 1×10^5 in 200 μ L of RPMI medium, consisting of 10% human AB serum, along with three different concentrations of terfenadine (0, 16, and 64 μ mol/L). To assess PMA stimulation, the cell suspension with 5 ng/mL of PMA was applied into OKT3-coated wells. Cells were incubated at 37 °C in 5% CO₂-humidified atmosphere for 3 days. Cells were pulsed with 1 mCi/well of [³H]thymidine (ICN Radiochemicals, Irvine, CA, USA) 8 h prior to harvesting onto a glass-fibre filter (Wallac, Turku, Finland), and the incorporated radioactivity was quantified by a liquid scintillation counter (Wallac).

Cytokine production assays

Antibody-coated plates and purified T cells were prepared in the same way as above with the exception of OKT3 concentration, 0.5 μ g/mL. Cytokine production by T cells was assayed in triplicate wells in 96-well, flat-bottomed plates as described above for the T-cell proliferation assay. After 24 h of incubation, culture supernatants were subjected to ELISA (IL-2, and IL-4: Biosource International, Camarillo, CA, USA; IFN- γ , and IL-5: R & D Systems, Minneapolis, MN, USA) for measuring the amount of IL-2, IFN- γ , IL-4 and IL-5. Since the amount of IL-4 was sometimes small for the detection by ELISA system described above, we measured it again by high sensitivity ELISA system (R & D Systems), in such cases. Sensitivity of each ELISA kit is, IL-2: <9 pg/mL, IL-4: <2 pg/mL (Biosource International), IFN- γ : <2 pg/mL, IL-5: <3 pg/mL, IL-4: <0.09 pg/mL (R & D Systems).

Cell viability

The trypan blue exclusion test was used to assess cell viability. In all experiments, the viability was found to be over 90% at each point measured. Moreover, T-cell proliferation assay was done on both T cells exposed to 64 μ mol/L of terfenadine for 24 h and T cells without exposing to terfenadine. No significant difference was observed between these two (data not shown).

Results

Effect of terfenadine on T-cell proliferation through different activation pathways

To test the different regulatory effects of terfenadine on T-cell activation, we chose three different costimulatory pathways. The first was PMA with stimulation of anti-CD3. The second was stimulation to one of the representative T-cell costimulatory molecules, CD28, with stimulation of anti-CD3. The third was stimulation to CD26, which is preferentially expressed on CD4⁺ memory T cells, with stimulation of anti-CD3. For this purpose, purified T cells were stimulated with immobilized anti-CD3 alone, anti-CD3 and anti-CD26, anti-CD3 and anti-CD28, or anti-CD3 with PMA in the presence of various concentrations of terfenadine. As shown in Fig. 1a, the stimulus to CD3 alone did not induce T-cell proliferation. T-cell proliferation was observed when stimulus to CD3 was combined with additional second stimulus, such as anti-CD26, anti-CD28, or PMA. Under these conditions, terfenadine clearly inhibited T-cell proliferation in a dose-dependent manner. Terfenadine at 16 $\mu\text{mol/L}$ and 64 $\mu\text{mol/L}$ provided almost 10–20% and 50% inhibition of T-cell proliferation, respectively, under

each of the costimulatory conditions (Fig. 1b). It should be noted that this inhibitory effect was not due to terfenadine's cytotoxic adverse effects, since over 95% T cells were viable at the time of assay. There were no apparent differences in the inhibition of T-cell proliferation induced by the above costimulatory pathways.

Effect of terfenadine on TH1-type cytokine production through different costimulatory pathways

To examine whether the inhibitory effect of terfenadine is also observed in cytokine production induced by the above stimuli, we measured the amount of IL-2 and IFN- γ in the culture supernatant stimulated by various costimulatory signals. As shown in Fig. 2, terfenadine did not inhibit IL-2 production under all costimulatory conditions we used, even at 64 $\mu\text{mol/L}$ of terfenadine. The amounts of IL-2 induced by anti-CD3 with PMA were 406, 485 and 535 pg/mL under 0, 16, and 64 $\mu\text{mol/L}$ of terfenadine, respectively. The amounts of IL-2 induced by anti-CD3 with anti-CD26, were 522, 726, and 536 pg/mL under 0, 16, and 64 $\mu\text{mol/L}$ of terfenadine, respectively. The amounts of IL-2 induced by anti-CD3 with anti-CD28 were 815, 831, and

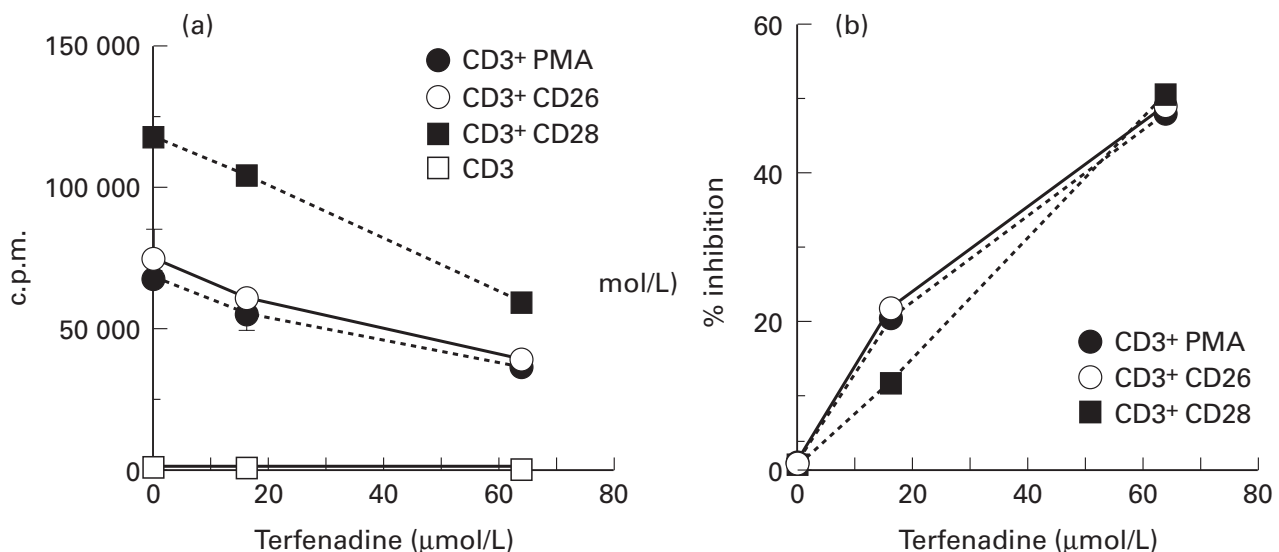


Fig. 1. Effect of terfenadine on T-cell proliferation with different stimuli. Proliferation assays were performed as described in Materials and methods. Data shown above are representative of three separate experiments. (a) The counts per minute in the presence of 0, 16 and 64 $\mu\text{mol/L}$ terfenadine were $68\,325 \pm 4170$, $54\,636 \pm 5144$, and $20\,842 \pm 306$ for anti-CD3 plus PMA stimulation; $75\,629 \pm 9820$, $59\,652 \pm 2155$, and $26\,508 \pm 1442$ for anti-CD3 plus anti-CD26 stimulation; $117\,712 \pm 3380$, $103\,813 \pm 2222$, and $58\,830 \pm 3248$ for anti-CD3 plus anti-CD28 stimulation, respectively. The [^3H]-incorporation under anti-CD3 stimulation alone in the presence of 0, 16 and 64 $\mu\text{mol/L}$ were 2190 ± 375 , 2072 ± 295 , and 1080 ± 89 , respectively. (b) Inhibition ratios were presented calculated from the data described above, regarding the count without terfenadine as a hundred percentage in each costimulatory condition. The inhibition ratios in the presence of 16 and 64 $\mu\text{mol/L}$ of terfenadine were 20 and 47 for anti-CD3 plus PMA stimulation; 21 and 49 for anti-CD3 plus anti-CD26 stimulation; 11 and 50 for anti-CD3 plus anti-CD28 stimulation, respectively. The data is the representative of seven independent experiments from different donors.

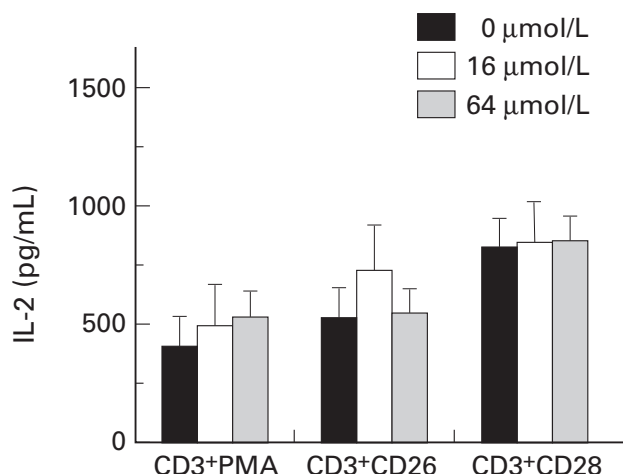


Fig. 2. Effect of terfenadine on IL-2 production with different stimuli. Highly purified T cells were stimulated by solid-phase immobilized anti-CD3 with PMA, anti-CD3 with CD26, and anti-CD3 with anti-CD28, as described in Materials and methods. After 24 h, culture supernatants were harvested and assayed for IL-2 content by ELISA. The data is the representative of seven independent experiments from different donors.

842 under 0, 16, and 64 $\mu\text{mol/L}$ of terfenadine, respectively. In addition to IL-2, terfenadine did not display any apparent effects on the production of IFN- γ (Fig. 3). The amounts of IFN- γ induced by anti-CD3 with PMA were 1716, 1656, and 1564 pg/mL under 0, 16, and 64 $\mu\text{mol/L}$ of terfenadine, respectively. The amounts of IFN- γ induced by anti-CD3

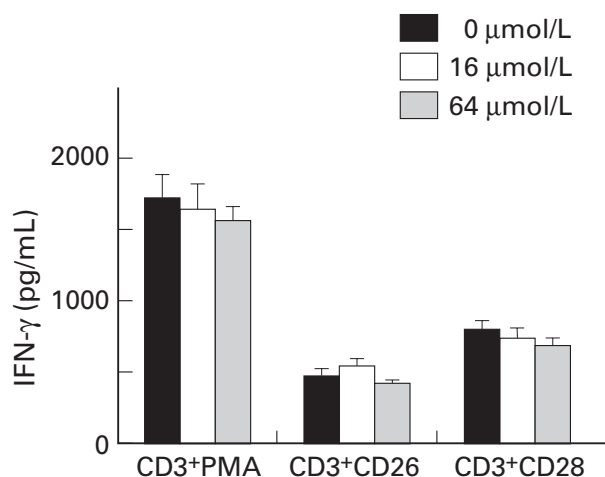


Fig. 3. Effect of terfenadine on IFN- γ production with different stimuli. Highly purified T cells were stimulated by solid-phase immobilized anti-CD3 with PMA, anti-CD3 with PMA, anti-CD3 with CD26, and anti-CD3 with anti-CD28, as described in Materials and methods. After 24 h, culture supernatants were harvested and assayed for IFN- γ content by ELISA. The data is the representative of seven independent experiments from different donors.

with anti-CD26 were 474, 548, and 423 pg/mL under 0, 16, and 64 $\mu\text{mol/L}$ of terfenadine, respectively. The amounts of IFN- γ induced by anti-CD3 with anti-CD28 were 793, 742, and 704 pg/mL under 0, 16, and 64 $\mu\text{mol/L}$ of terfenadine, respectively.

Effect of terfenadine on TH2-type cytokine production through different activation pathways

Next we examined the effect of terfenadine on the TH2-type cytokine, IL-4 and IL-5 production. As shown in Fig. 4, terfenadine markedly inhibited IL-4 production under each of the costimulatory conditions in a dose-dependent manner. Although the production level was not high, the same tendency was observed in other donors. In the presence of 0, 16, and 64 $\mu\text{mol/L}$ terfenadine, the amounts of IL-4 were 2.2, 0.8, and 0.5 pg/mL for anti-CD3 plus PMA stimulation, 3.6, 2.5, and 1.2 pg/mL for anti-CD3 plus anti-CD26 stimulation, 2.2, 0.4, and 0.4 pg/mL for anti-CD3 plus anti-CD28 stimulation, respectively. We next examined the effect of terfenadine on IL-5 production as shown in Fig. 5. We also observed the clear inhibition of IL-5 production by terfenadine in a dose-dependent manner under all costimulatory conditions tested. In the presence of 0, 16, and 64 $\mu\text{mol/L}$ terfenadine, the amounts of IL-5 were 128, 57, and 14 pg/mL for anti-CD3 plus PMA stimulation, 103, 73 and 15 pg/mL for anti-CD3 plus anti-CD26 stimulation, 84, 31 and 14 pg/mL for anti-CD3 plus anti-CD28 stimulation, respectively. These results clearly indicate that terfenadine has a specific

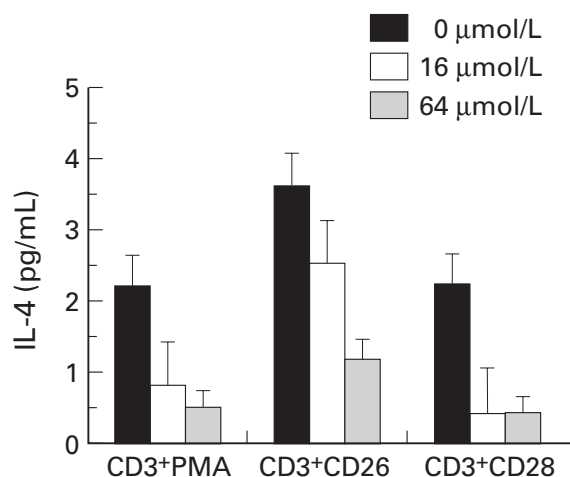


Fig. 4. Effect of terfenadine on IL-4 production with different stimuli. Highly purified T cells were stimulated by solid-phase immobilized anti-CD3 with PMA, anti-CD3 with PMA, anti-CD3 with CD26, and anti-CD3 with anti-CD28, as described in Materials and methods. After 24 h, culture supernatants were harvested and assayed for IL-4 content by ELISA. The data is the representative of seven independent experiments from different donors.

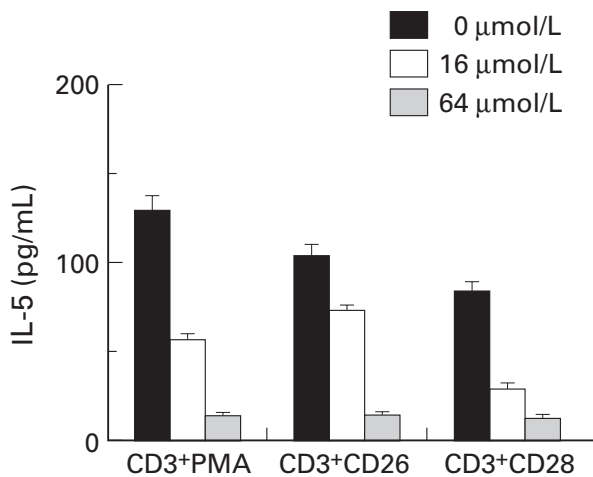


Fig. 5. Effect of terfenadine on IL-5 production with different stimuli. Highly purified T cells were stimulated by solid-phase immobilized anti-CD3 with PMA, anti-CD3 with PMA, anti-CD3 with CD26, and anti-CD3 with anti-CD28, as described in Materials and methods. After 24 h, culture supernatants were harvested and assayed for IL-5 content by ELISA. The data is the representative of seven independent experiments from different donors.

inhibitory effect on TH2-type cytokine production such as IL-4 and IL-5 induced by several ways of costimulatory activation.

Discussion

In the present study, we demonstrated that terfenadine clearly inhibited the TH2-type cytokine, IL-4, and IL-5 production, whereas it virtually did not affect TH1-type cytokine, such as IL-2 and IFN- γ , production.

Terfenadine, α -[4-(1,1-dimethylethyl) phenyl]-4-(hydroxydiphenylmethyl)-piperidinebutanol, the first non-sedating antihistamine compound [1], is clinically used for allergic diseases. Its effect was mainly described from the perspective of a histamine receptor antagonist that affected mast cells. Recent studies have revealed that terfenadine has effects on a variety of target cells such as T cells, basophils, and eosinophils [3–5]. In a hypersensitive response, helper T cells play a key role for triggering the inflammatory response. Namely, cytokine production caused by TH2-type cells is indispensable to initiating and maintaining the hypersensitive inflammatory response [21,22]. The predominance of TH2-type cells is speculated to induce allergic states. Therefore, specific inhibition of TH2-type cell function may be the essential therapeutic strategy for allergic diseases. Previous reports indicated that terfenadine had an inhibitory effect on mitogen-induced T-cell proliferation [3,23]. Lahti reported that terfenadine actually inhibited erythema and oedema of prick test reactions, but not for

nonimmunological contact urticaria, suggesting that terfenadine may affect antigen- (allergen) dependent inflammatory processes [24]. These findings have prompted us to examine its effect on T cells which are stimulated through CD3/TcR. As mentioned before, costimulatory signals are an absolute requirement for full activation of antigen-specific T cells. We developed a model of costimulation, and examined terfenadine's effect on T-cell proliferation and cytokine production induced by several ways of costimulatory activation. We showed that terfenadine inhibited T-cell proliferation induced by several costimulatory signals in a dose-dependent manner. Regarding cytokine production, terfenadine represented no apparent effect on TH1-type cytokine production, such as IL-2 and IFN- γ , whereas it inhibited TH2-type cytokine, IL-4 and IL-5 production. This result seems to conflict with the result reported by Konno *et al.* [23]. They reported that terfenadine inhibited Con A-induced T-cell proliferation as well as Con A-induced IL-2, IL-4, and IL-5 production, although inhibition was observed at a higher concentration of terfenadine in their system. However, in our case, although terfenadine inhibited T-cell proliferation induced by various costimulation signals, the inhibition of cytokine production displayed a relatively different pattern. Namely, terfenadine inhibited only the TH2-type cytokine, IL-4 and IL-5. The clinical dose of terfenadine in the blood stream of the patients is speculated as 0.64 $\mu\text{mol/L}$ according to the reference provided from the pharmaceutical company. The dose we tested was a hundred times more than the physiological dose. However, the *in vitro* effect of terfenadine could be observed from 10–100 times higher concentrations than the physiological concentration. Although our results along with that of Konno's were observed at 100 $\times$ higher concentration than the physiological one, it is worth evaluating the *in vitro* effect of terfenadine at a higher concentration. The precise reason for the difference between our results and the results of the system applied by Konno *et al.* is not clear at this moment. However, the discrepancy is possibly due to the differences in the methods of stimulation and the types of cells they used in the experimental procedure. Konno *et al.* used non-specific mitogen Con A, whereas we used costimulatory activation. Therefore, it should be emphasized here again that the costimulatory signal actually occurs at the allergen-presenting stage *in vivo*, and our system may better reflect the actual physiological condition of the hypersensitive immune reaction. It would be reasonable to evaluate the T-cell response in our costimulatory system. The TH1-type cytokine productions, such as IL-2 and IFN- γ , induced by the costimulatory conditions, are refractory to terfenadine. On the other hand, TH2-type cytokine, such as IL-4 and IL-5, production was clearly inhibited by terfenadine in a dose-dependent fashion. These data suggest that terfenadine specifically inhibits TH2-type cytokine production in

human peripheral T cells. There are several reports which describe differential regulation of IL-4 vs IL-2 [25–27]. IL-2 productions are regulated by intracellular cAMP levels, whereas IL-4 production is not influenced by cAMP. It suggests that IL-4 production may be regulated by factors other than cAMP in TH2-type T cells, and it is possible to speculate that terfenadine may have an effect on such factors. It is not clear at this moment, whether this effect originates from terfenadine's antagonistic effect against the H1 receptor. Further studies are in progress to clarify these points.

Terfenadine's specific effect on the inhibition of TH2-type cytokine production presented here supports the rationale to its clinical use for allergic diseases and may provide a clue to clarify the novel mechanism of action of H1 antagonistic compounds.

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