Selective Inhibition of Spontaneous IgE and IgG4 Production by Interleukin-8 in Atopic Patients

By H. Kimata, I. Lindley, and K. Furusho

The effects of interleukin (IL)-8 on spontaneous IgE and IgG4 production in atopic patients were studied. IL-8 inhibited IgE and IgG4 production by purified surface (s) IgE+ and slgG4+ B cells, respectively, while it had no effect on IgG1, IgG2, IgG3, IgM, IgA1, and IgA2 production by corresponding slg+ B cells. The IL-8-induced inhibition was counteracted by IL-6 and tumor necrosis factor-α (TNF-α) and was blocked by anti-IL-8 monoclonal antibody (MoAb). Conversely, the addition of anti-IL-6 MoAb and anti-TNF-α MoAb, in the absence of IL-8, inhibited IgE and IgG4 production by slg+ and slgG4+ B cells, respectively. Purified slgE+ and slgG4+ B cells expressed IL-6 receptors (R), TNF-αR, and IL-8R, and they produced IL-6 and TNF-α, but not IL-8. IL-8 had no effect on IL-6R or TNF-αR, while it abrogated IL-8 and TNF-α production in these cells. In contrast, slgG1+, slgG2+, slgG3+, slgM+, slgA1+, and slgA2+ B cells expressed IL-6R and TNF-αR but not IL-8R, and they produced IL-6 and TNF-α. IL-8 had no effect on IL-6R and TNF-αR, or on TNF-α and IL-6 production in these cells. These results indicate that IL-8 inhibits spontaneous IgE and IgG4 production in slgE+ and slgG4+ B cells, respectively, by inhibiting the endogenous production of IL-6 and TNF-α.

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Submitted October 10, 1994; accepted January 17, 1995.

Supported by a grant from the Ministry of Health and Welfare of Japan and a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, and Culture, Japan.

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MATERIALS AND METHODS

Reagents. Human recombinant IL-4 and IL-5 were provided by Ono Pharmaceutical Company (Osaka, Japan) and Suntory Research Center (Osaka, Japan), respectively. Human recombinant IL-8 and mouse IgG1 anti–IL-8 monoclonal antibody (MoAb; 4G9/AS/A7) were obtained from Sandoz Research Institute (Vienna, Austria). The following human recombinant cytokines and antibodies were purchased from the indicated companies: TGF-β and rabbit anti-TGF-β antibodies (Genzyme, Boston, MA); IL-9 and IL-10 (Funakoshi, Ltd, Tokyo, Japan); IFN-α, IFN-γ, anti-CD40 MoAb, mouse IgG1 anti–IFN-α MoAb, and anti-IFN-γ MoAb (Cosmo Bio Co Ltd, Tokyo, Japan); IL-1β, IL-2, IL-3, IL-6, mouse IgG1 anti–IL-6 MoAb (MAB206), IL-9, IL-10, rabbit anti–IL-12 antibody, and mouse IgG1 anti–TNF-α MoAb (MAB210) (R & D Systems, Minneapolis, MN); and IL-13 ( Pepro Tech Inc. Rocky Hill, NJ).

Cells. Tonsillar mononuclear cells were obtained at tonsillectomy for chronic tonsillitis from atopic patients with atopic dermatitis with or without bronchial asthma (n = 10; aged 14 to 36 years; serum IgE level, 3,246 to 12,156 U/mL) and nonatopic donors (n = 5; aged 15 to 32 years; serum IgE level, less than 300 U/mL) after they had given their informed consent. Atopic patients had clinical features of moderate to severe atopic dermatitis by Hanifin and Rajika’s grading and by our skin scoring system. None of the atopic patients or nonatopic donors were receiving medications at the time of tonsillectomy. Highly purified B cells were obtained by sheep red blood cell rosetting, followed by L-leucine methyl ester incubation, as described previously. The purified B-cell fractions contained less than 1% CD3+ T cells, less than 1% CD14+ monocytes, less than 1% CD16+ natural killer cells, and greater than 98% CD20+ B cells. B cells from atopic patients were further fractionated into large activated B cells by Percoll density centrifugation, and then slgE+ B cells, including slgE+ and slgG4+ B cells, were enriched by repeated panning, as reported earlier. Purified large slgE+ B-cell fractions each contained greater than 98% corresponding slgE+ B cells. On the other hand, slgE+ and slgG4+ B cells could not be enriched in nonatopic donors because of the paucity of these cells. Therefore, B cells were stimulated with IL-4 (1,000 U/mL) + anti-CD40 MoAb (0.1 μg/mL) for 5 days, and in vitro-generated slgE+ and slgG4+ B cells were enriched by panning.

Cell cultures. The slgE+ B cells (2 × 10^4/0.2 mL per well) were cultured in 96-well U-bottomed microtiter plates (Costar, Cambridge, MA) for 5 days in RPMI 1640 medium (M.A. Bioproducts, Walkersville, MD) containing 10% fetal calf serum (Irvine Scientific, US Biological, Nutley, NJ).
Irvine, CA), 2 mmol/L L-glutamine, 50 U/mL penicillin, 50 μg/mL streptomycin, and 50 μg/mL transferrin; various factors were added, as described in Results. Control cultures for the evaluation of preformed Ig were performed in the presence of cycloheximide (100 μg/mL). The amounts of IgE, IgG subclasses, IgM, and IgA subclasses in the supernatants were determined by enzyme-linked immunosorbent assay (ELISA).7,12 For the measurement of proliferation, sIgE+ B cells were cultured as above for 2 days, pulsed with 1 μCi ³H-thymidine, and harvested after 16 hours; thymidine uptake was then determined. In some experiments, the binding of IL-6, TNF-α, and IL-8 to sIgE+ B cells was studied using biotinylated IL-6, TNF-α, and IL-8 (R & D Systems, Minneapolis, MN). Briefly, various sIgE+ B cells (2 × 10⁵/0.2 mL per well) were cultured with medium or with IL-8 (100 ng/mL) for 2 days, washed with an acidic buffer, and incubated for 3 hours at 4°C in the presence of 5 mmol/L of biotinylated cytokines. They were then stained with streptavidin-phycoerythrin (PE) and analyzed with a FACScan (Becton Dickinson, Mountain View, CA). The mean fluorescence intensity (MFI) value of biotinylated cytokine-specific binding, determined after the subtraction of nonspecific binding in the presence of a 100-fold excess of unlabeled cytokines, was expressed as ∆MFI, as previously described.11,13 In some experiments, coexpression of IL-8R and sIgE or sIgG4 on B cells was studied by double-staining. Various sIgE+ B cells were also cultured (2 × 10⁵/0.2 mL per well) with medium alone for 2 days, and the production of IL-6, TNF-α, and IL-8 was determined by ELISA.11,14 Statistical analysis was performed with the two-tailed Student's t test.

RESULTS

Effect of IL-8 on spontaneous Ig production and thymidine uptake by sIgE+ B cells. We have previously reported that, in atopic patients, purified sIgE+ B cells produced IgE up to 50 ng/mL in vitro, while sIgG4+ B cells produced IgG4 up to 100 ng/mL.11,12 As shown in Fig 1A and B, IL-8 inhibited the IgE and IgG4 production by sIgE+ and sIgG4+ B cells, respectively, in a dose-dependent fashion without affecting thymidine uptake. IL-8 also did not affect thymidine uptake or days 4 and 5 (data not shown). In contrast, IL-8 had no inhibitory effect on the spontaneous production of IgG1, IgM, IgG2, IgA, IgG3, and IgA2, or on thymidine uptake in the corresponding sIgG+ B cells (Fig 1C and D). In five experiments, the percent inhibition of IgE and IgG4 production by IL-8 (100 ng/mL) was 84% ± 12% and 82% ± 9%, respectively, while the percent inhibition of the production of other Ig by IL-8 was less than 15%.

Effects of various factors on IL-8–induced IgE and IgG4 production. We and others have reported that various cytokines modulate IL-4–induced IgE and IgG4 production.15,16 Therefore, we studied the effects of these cytokines on the IL-8–induced inhibition of IgE and IgG4 production. As shown in Fig 2A, IL-5, IL-6, and TNF-α enhanced IgE production by sIgE+ B cells without affecting thymidine uptake (data not shown), while IL-4, IL-13, and neutralizing amounts of anti–IL-8 MoAb, anti–IL-12 antibody, anti–TGF-β antibody, anti–IFN-γ MoAb, and anti–IFN-γ MoAb had no effect. IL-6 and TNF-α, but not IL-5, each partially counteracted the IL-8–induced inhibition of IgE production, while the anti–IL-8 MoAb completely blocked inhibition. Other cytokines (ie, IL-1α, up to 200 U/mL; IL-2, up to 300 U/mL; IL-3, up to 200 ng/mL; IL-9, up to 200 ng/mL; IL-10, up to 200 ng/mL; IFN-α, up to 2,000 U/mL; IFN-γ, up to 2,000 U/mL; and TGF-β, up to 20 ng/mL) had no effect on the production of IgE and IgG4 in cultures with medium or with IL-8 (data not shown). Identical results were observed for IgG4 production by sIgG4+ B cells (Fig 2B).

Specificity of the effects of IL-6 and TNF-α on IL-8–induced inhibition. The specificity of the counteracting effects of IL-6 and TNF-α is shown in Fig 3. The addition of anti–IL-6 MoAb or anti–TNF-α MoAb inhibited spontaneous IgE production (Fig 3A), whereas thymidine uptake was not inhibited (data not shown). Moreover, the simultaneous addition of anti–IL-6 MoAb and anti–TNF-α MoAb further inhibited IgE production. In contrast, anti–IL-6 MoAb or anti–TNF-α, either alone or together, did not augment the IL-8–induced inhibition. Conversely, IL-6 and TNF-α each partially counteracted the IL-8–induced inhibition. Moreover, the simultaneous addition of IL-6 and TNF-α completely counteracted the inhibition, and this counteractive effect was blocked by anti–IL-6 MoAb plus anti–TNF-α MoAb, but not by control IgG1. Identical results were observed for IgG4 production (Fig 3B).

Effects of IL-6 and TNF-α on IL-8–induced inhibition of IgE and IgG4 production in nonatopic donors. We next studied whether IL-6 or TNF-α could counteract IL-8–induced inhibition of IgE and IgG4 production in nonatopic donors. As sIgE+ and sIgG4+ B cells could not be enriched in nonatopic donors because of the paucity of these cells,8

we stimulated B cells with IL-4 plus anti-CD40 MoAb. Thereafter, in vitro-generated slgE' and slgG4' B cells were purified. As shown in Table 1, IL-6 enhanced control IgE production by slgE' B cells and partially counteracted IL-8–induced inhibition of IgE production. In contrast, TNF-α neither enhanced control IgE production nor counteracted IL-8–induced inhibition. Identical results were observed for IgG4 production (Table 1).

**Effects of IL-8 on binding and production of cytokines in atopic patients.** These results indicate that endogenous IL-6 and TNF-α play a role in enhancing IgE and IgG4 production. It is possible that IL-8 inhibits IgE and IgG4 production either by downregulating IL-6 and TNF-α receptors, or by decreasing the endogenous production of IL-6 and TNF-α. We also attempted to determine the mechanisms responsible for the lack of inhibition of the production of other Ig by IL-8 in slgG1', slgG2', slgG3', slgM', slgA1', and slgA2' B cells. For this purpose, we cultured various slg' B cells with medium or with IL-8 and determined the binding of IL-6, TNF-α, and IL-8 and the production of IL-6 and TNF-α in these cells. As shown in Fig 4, slgE' and slgG4' B cells significantly bound IL-6, TNF-α, and IL-8, and produced IL-6 and TNF-α. IL-8 had no effect on the binding of IL-6 and TNF-α, while it slightly downregulated IL-8 binding. However, IL-8 abrogated the production of IL-6 and TNF-α in slgE' and slgG4' B cells. In contrast, slgG1', slgM', and slgA1' B cells bound IL-6 and TNF-α, but not IL-8, and produced IL-6 and TNF-α. IL-8 had no effect on binding of IL-6 and TNF-α or on the production of IL-6 and TNF-α. Similar results were observed for slgG1', slgG3', and slgA2' B cells (data not shown). None of the slg' B cells produced IL-8 (less than 20 pg/mL). As shown in Fig 5, coexpression of IL-8 receptor (R) and slgE or slgG4, but not slgG1 or slgM, on B cells was directly demonstrated by double-staining. In addition, no IL-8R was detected on slgG2', slgG3', or slgA2' B cells by double-staining (data not shown). IL-8 inhibited the production of IL-6 and TNF-α in slgE' and slgG4' B cells in a dose-dependent fashion but did not inhibit this production in slgG1', slgG2', slgG3', slgM', slgA1', and slgA2' B cells (Fig 6).
inhibition of IL-6 and TNF-α production was blocked by the anti-IL-8 MoAb (Fig 5A and B), but not by control IgG1 (data not shown).

**DISCUSSION**

We have shown that IL-8 selectively inhibited spontaneous IgE and IgG4 production, without affecting thymidine uptake, in sIgE⁺ and sIgG4⁺ B cells, respectively, obtained from atopic patients. The inhibition was direct and specific, as IL-8 inhibited the production of IgE and IgG4 by purified sIgE⁺ and sIgG4⁺ B cells, respectively, and the inhibition was specifically blocked by the anti-IL-8 MoAb. Of the various cytokines examined, IL-6 and TNF-α counteracted the IL-8⁻induced inhibition, while the other cytokines (IL-4, IL-5, IL-9, IL-10, and IL-13) and the anti-IL-12 antibody, anti-IFN-α MoAb, anti-IFN-γ MoAb, or anti-TGF-β antibody did not. The simultaneous addition of IL-6 and TNF-α synergistically counteracted IL-8⁻induced inhibition, and this counteractive effect was blocked by anti-IL-6 MoAb and anti-TNF-α MoAb, but not by control IgG1. Moreover, in the absence of IL-8, anti-IL-6 MoAb and anti-TNF-α MoAb each inhibited IgE and IgG4 production by sIgE⁺ and sIgG4⁺ B cells, respectively. However, these MoAbs did not augment the IL-8⁻induced inhibition. Subsequent study showed that sIgE⁺ and sIgG4⁺ B cells expressed IL-6R, TNF-αR, and IL-8R, and that they produced IL-6 and TNF-α, but not IL-8. The addition of IL-8 decreased IL-6 and TNF-α production without affecting IL-6R and TNF-αR, although IL-8R was downregulated, a result that is in accordance with previous reports. Collectively, these results indicate that IL-8 may inhibit IgE and IgG4 production by sIgE⁺ and sIgG4⁺ B cells, respectively, via the inhibition of endogenous production of IL-6 and TNF-α. Studies are currently in progress to obtain direct evidence for the mechanisms of the inhibition.

It has been reported that IL-6 and TNF-α were spontaneously produced in vitro by B cells that were activated in
Table 1. Effects of IL-6 and TNF-α on IL-8–Induced Inhibition of IgE and IgG4 Production in Nonatopic Donors

<table>
<thead>
<tr>
<th>B Cells</th>
<th>Factors</th>
<th>Exp 1</th>
<th>Exp 2</th>
<th>Exp 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>slgE+</td>
<td>Medium</td>
<td>5.2 ± 0.7</td>
<td>10.3 ± 2.5</td>
<td>15.7 ± 1.8</td>
</tr>
<tr>
<td>slgG4+</td>
<td>Medium</td>
<td>8.5 ± 0.3</td>
<td>19.2 ± 2.1</td>
<td>30.2 ± 4.6</td>
</tr>
</tbody>
</table>

In vitro-generated slgE+ and slgG4+ B cells from nonatopic donors were cultured with medium or IL-8 in the presence or absence of the indicated factors. On day 10 of culture, IgE and IgG4 production were determined. IL-8 was used at 100 ng/mL, IL-6 at 200 ng/mL, and TNF-α at 50 ng/mL. Values are means ± 1 SD.

Abbreviation: Exp, experiment.
*P < .01 compared with medium alone.
†P < .01 compared with IL-8 alone.

vivo; these B cells expressed IL-6R and TNF-αR and produced large amounts of IgG. In those B cells, TNF-α and IL-6 were essential for Ig production. For example, tonsil B cells from patients with chronic tonsillitis spontaneously produced 300 ng/mL of IgG, which was inhibited by anti–TNF-α MoAb (greater than 70% inhibition). B cells from patients with systemic lupus erythematosus spontaneously produced IgG and IgM, which was inhibited by anti–IL-6R MoAb (up to 80%). Collectively, these results indicate that spontaneous Ig production still depends on endogenous cytokines. Our findings that activated slgE+ and slgG4+ B cells produced IL-6 and TNF-α, which enhanced IgE and IgG4 production through IL-6R and TNF-αR, are in accordance with these reports. As IL-8 abrogated the production of IL-6 and TNF-α, complete inhibition of spontaneous IgE and IgG4 production by IL-8 in atopic patients is not surprising.

In addition, the IL-8–induced inhibition of spontaneous IgE and IgG4 production is not restricted to atopic patients. It has been reported that B cells from patients with hyper-IgE syndrome spontaneously produced IgE and IgG4. IL-8 (100 ng/mL) inhibited production of IgE (76% ± 13% inhibition) and IgG4 (72% ± 14% inhibition) in slgE+ and slgG4+ B cells, respectively, obtained from such patients, while IL-6 and TNF-α counteracted IL-8–induced inhibition. In those studies, although IL-8 inhibited IgE and IgG4 production by in vitro-generated slgE+ and slgG4+ B cells, respectively, only IL-6, but not TNF-α, counteracted IL-8–induced inhibition. It has been reported that anti–IL-6 antibody inhibited IgE and IgG4 production in a nonatopic donor’s B cells stimulated with IL-4 plus anti-CD40 MoAb, while anti–TNF-α MoAb did not do so. These results indicate that endogenous IL-6 and TNF-α are essential for IgE and IgG4 production in spontaneous IgE production in atopic patients, while IL-6, but not TNF-α, is essential for those responses in nonatopic donors. Collectively, TNF-α responses may be specific to atopic patients.

Purified slgE+ and slgG4+ B cells also expressed IL-8R. In contrast, slgG1+ sIgG2+, slgG3+, sIgM+, sIgA1+, and sIgA2+ B cells expressed IL-6R and TNF-αR, but not IL-8R, although they produced IL-6 and TNF-α. The lack of IL-8 effect on these sIgG+ B cells is most likely due to their lack of IL-8R. However, this lack of effect is not surprising. We have previously reported that IL-8 selectively inhibited IgE production by purified B cells stimulated with IL-4 plus anti-CD40 MoAb, indicating the presence of functional IL-8 receptors on slgE+ B cells. As slgE+ and slgG4+ B cells, but not other sIg+, B cells in atopic patients were selectively activated by IL-4 in vivo, it is possible that these slgE+ and slgG4+ B cells preferentially expressed IL-8R. Indeed, when slgE+ and slgG4+ B cells from nonatopic donors were stimulated with IL-4 plus anti-CD40 MoAb, some of them were differentiated into slgE+ and slgG4+ B cells, respectively. Enriched slgE+ and slgG4+ B cells expressed IL-8R, while
other sIg⁺ (sIgG1⁺, sIgG2⁺, sIgG3⁺, sIgM⁺, sIgA1⁺, and sIgA2⁺) B cells and sIgE⁺ and sIgG4⁺ B cells did not. The values for ΔMFI of IL-8R were 35 ± 6, 33 ± 7, 4 ± 4, 2 ± 3, and 3 ± 2, in sIgE⁺, sIgG4⁺, other sIg⁺, sIgE⁺, and sIgG4⁺ B cells, respectively. It has recently been reported that IL-8R were detected on neutrophils, basophils, monocytes, monoblast cell lines, T cells, a T cell line, and melanoma cell lines.15,16,23,26 For the first time, we have shown IL-8R on sIgE⁺ and sIgG4⁺ B cells. We are currently characterizing the IL-8R on sIgE⁺ and sIgG4⁺ B cells and the detailed mechanisms of the effects of IL-8 on these cells in atopic patients.

The finding that IL-8 decreases the production of IL-6 and TNF-α is interesting, as both IL-6 and TNF-α are potent inducers of IL-8.27,28 However, this decreasing effect is not surprising. It has been reported that TNF-α induced IL-6 production, while IL-6 decreased TNF-α production in human B cells, and IL-6 downregulated TNF-αR in human macrophages.27,28 It is possible that there may be such interaction between IL-8 versus IL-6 and TNF-α. Indeed, IL-6 downregulated TNF-αR in human macrophages and blocked neutrophil adhesion to TNF-α-activated endothelial cells.29,30 The effect of IL-8 on message transcription or translation remains to be elucidated. However, we measured cell-associated IL-6 and TNF-α by lysing sIgE⁺ and sIgG4⁺ B cells and found that IL-8 also decreased cell-associated IL-6 and TNF-α. In four experiments, cell-associated cytokines in sIgE⁺ B cells cultured with medium and IL-8 (100 ng/mL) were 0.63 ± 0.21 ng/mL and 0.09 ± 0.03 ng/mL of IL-6, respectively, and 0.51 ± 0.24 ng/mL and 0.08 ± 0.02 ng/mL of TNF-α, respectively. Similarly, those cytokines in sIgG4⁺ B cells cultured with medium and IL-8 were 0.64 ± 0.18 ng/mL and 0.07 ± 0.03 ng/mL of IL-6, respectively, and 0.61 ± 0.15 ng/mL and 0.05 ± 0.02 ng/mL of TNF-α, respectively. These results indicate that IL-8—induced inhibition of IL-6 and TNF-α production may not be simply due to inhibition of release of these cytokines from the cell membrane. Detailed molecular analysis is currently under investigation.

The precise in vivo role played by IL-8, IL-6, and TNF-α in atopic patients remains to be elucidated. It has been reported that IL-6 and TNF-α are produced by an allergen-induced nasal response, and TNF-α mRNA-positive cells have been found in bronchoalveolar lavage fluid and in the skin of the allergen-induced reaction in atopic patients.30,31 On the other hand, IL-6 protein and IL-8 mRNA have been found in the bronchial epithelial cells of asthmatic patients, but not in these cells obtained from nonasthmatic donors.32 Moreover, we and others have found high levels of IL-8 and TNF-α, but not IL-6, in the plasma of patients with atopic dermatitis, and it has also been found that spontaneous IgE production in vitro was correlated with plasma IL-8 levels in these patients.14,33 These results suggest that IL-8 and TNF-α responses in spontaneous IgE and IgG4 production may be exaggerated or specific to atopic patients. In contrast,
IL-6 may augment those responses in a nonspecific fashion; ie, IL-6 responses may be common to all IgE and IgG4 B cells. Further studies are needed to clarify this. We are currently studying which cytokines are exaggeratedly or specifically involved in IgE and IgG4 production in atopic patients. It is also possible that, on one hand, IL-8 exacerbates inflammation by activating neutrophils, basophils, and T cells, while, on the other hand, it counteracts the IgE- and IgG4-mediated allergic reaction by inhibiting IgE and IgG4 production. This dual action is not surprising, as the dual effects of cytokines are well known. For example, although IL-4 induces IgE and IgG4, which may exacerbate the allergic reaction, it also has potent antiinflammatory effects, due to its suppression of the inflammatory factors IL-1 and prostaglandin E2.

In conclusion, we found that IL-8 directly inhibited spontaneous IgE and IgG4 production in slgE+ and slgG4+ B cells, respectively, by interacting with IL-6 and TNF-α. To our knowledge, this is the first cytokine shown to directly inhibit Ig production in these cells. These findings may shed some light on the pathogenesis of atopy and may ultimately lead to efficient therapy in atopic patients.

ACKNOWLEDGMENT

We thank Dr P. Peichl and M. Česka, respectively, for the production and purification of the anti-IL-8 MoAb, and E. Wasterauer for the purification of IL-8.

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