

## Growth Hormone and Insulin-like Growth Factor I Induce Immunoglobulin (Ig)E and IgG4 Production by Human B Cells

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### Summary

We studied the effects of growth hormone (GH), insulin-like growth factor I (IGF-I), IGF-II, and insulin on human immunoglobulin E (IgE) and IgG4 production. GH and IGF-I induced IgE and IgG4 production by normal donors' mononuclear cells (MNC) depleted of sIgE<sup>+</sup> and sIgG4<sup>+</sup> B cells without affecting IgM, IgG1, IgG2, IgG3, IgA1, or IgA2 production, whereas IGF-II and insulin failed to do so. GH-induced IgE and IgG4 production was specific, and was not mediated by IGF-I, interleukin 4 (IL-4), or IL-13, since it was blocked by anti-GH antibody (Ab), but not by anti-IGF-I Ab, anti-IL-4 Ab, or anti-IL-13 Ab. Conversely, IGF-I-induced IgE and IgG4 production was blocked by anti-IGF-I Ab, but not by anti-GH Ab, anti-IL-4 Ab, or anti-IL-13 Ab. Moreover, interferon  $\alpha$  (IFN- $\alpha$ ) or IFN- $\gamma$ , which counteracted IL-4- and IL-13-induced IgE and IgG4 production, had no effect on induction by GH or IGF-I. In contrast to MNC, GH or IGF-I failed to induce IgE and IgG4 production by purified sIgE<sup>-</sup>, sIgG4<sup>-</sup> B cells. However, in the presence of anti-CD40 monoclonal antibody (mAb), GH or IGF-I induced IgE and IgG4 production by these cells. Purified sIgE<sup>+</sup>, but not sIgE<sup>-</sup>, B cells from atopic patients spontaneously produced IgE. GH or IGF-I with anti-CD40 mAb failed to enhance IgE production by sIgE<sup>+</sup> B cells, whereas they induced IgE production by sIgE<sup>-</sup> B cells. Similarly, whereas GH or IGF-I with anti-CD40 mAb failed to enhance IgG4 production by sIgG4<sup>+</sup> B cells from atopic patients, they induced IgG4 production by sIgG4<sup>-</sup> B cells. Again, neither IgE nor IgG4 induction was blocked by anti-IL-4 Ab or anti-IL-13 Ab. These results indicate that GH and IGF-I induce IgE and IgG4 production by class switching in an IL-4- and IL-13-independent mechanism.

In mononuclear cells (MNC), IL-4 induces IgE and IgG4 production, which can be inhibited by IFN- $\alpha$  or IFN- $\gamma$  (1-3). In contrast, IL-4 alone cannot induce IgE and IgG4 production by purified B cells. However, IL-4 plus anti-CD40 mAb induces IgE and IgG4 production which is not inhibited by IFN- $\alpha$  or IFN- $\gamma$  (3-6). We and others (7, 8) have reported that T cells from patients with hyper IgE syndrome or atopy secrete IgE-enhancing activity that was not IL-4. We also found that IgE and IgG4 production was modulated by erythropoietin and neuropeptides in an IL-4-, IFN- $\alpha$ -, and IFN- $\gamma$ -independent fashion (9, 10). These results indicate that there may be another IgE- and IgG4-inducing cytokine(s). Indeed, IL-13 has been shown to induce IgE and IgG4 production in IL-4-independent mechanisms although there are commonalities between the IL-4 and IL-13 receptor, and it is still possible that other factors may be involved in induction of IgE and IgG4 production (11, 12).

We have recently reported that growth hormone (GH) and insulin-like growth factor I (IGF-I) enhanced IgE and IgG4 production by human plasma cell line and plasma cells, whereas IGF-II or insulin failed to do so (13). We therefore studied

whether GH and IGF-I would induce IgE and IgG4 production by normal B cells. Because hormones in serum modulated the GH-induced response, we compared the effects of peptides in serum- and hormone-free medium, DME/F-12 (13, 14). We show that GH and IGF-I, but not IGF-II or insulin, induce IgE and IgG4 production by tonsillar sIgE<sup>-</sup>, sIgG4<sup>-</sup> B cells in an IL-4- and IL-13-independent fashion.

### Materials and Methods

**Reagents.** The following recombinant human cytokines and Abs were kindly provided by companies described previously (2, 3): IL-4 and rabbit anti-IL-4 Ab (Ono Pharmaceutical Company, Osaka, Japan), IFN- $\alpha$  and IFN- $\gamma$  (Takeda Chemical Industries, Osaka, Japan), and GH and rabbit anti-GH Ab (Sumitomo Pharmaceuticals, Osaka, Japan). Mouse IgG1 anti-GH receptor mAb (MAB 263) was purchased from Agen Biomedical Ltd. (Qld, Australia) (13). Human recombinant IL-13 was purchased from Pepro Tech Inc. (Rocky Hill, NJ). Human recombinant IGF-I, IGF-II, insulin, rabbit anti-IGF-I Ab, mouse IgG1 anti-IGF-I receptor mAb ( $\alpha$ IR-3), mouse IgM anti-CD40 mAb (MA6), rabbit anti-IL-13 Ab, control rabbit IgG, and control mouse IgG1 were purchased from

Cosmo Bio Co. (Tokyo, Japan) (2, 3). The culture medium was a serum- and hormone-free type, DME, supplemented with Ham's Nutrient (DME/F-12) (Sigma Chemical Co., St. Louis, MO), 0.5% BSA, and 50  $\mu$ g/ml transferrin (14).

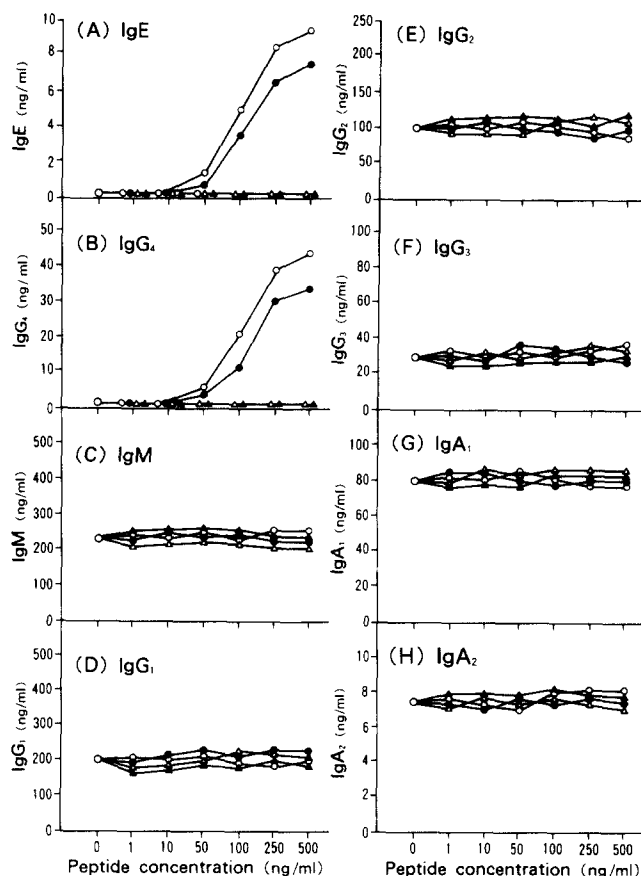
**Cell Cultures.** Tonsillar MNC were obtained from nonatopic donors (serum IgE level <50 U/ml) and atopic patients (serum IgE level 1,129–13,129 U/ml). MNC were depleted of sIgE<sup>+</sup> and sIgG4<sup>+</sup> B cells by panning (10, 15). The percentage of sIgE<sup>+</sup> and sIgG4<sup>+</sup> B cells was <0.1%. They were cultured ( $3 \times 10^5/0.2$  ml/well) in 96-well U-bottomed microtiter plates (Costar, Cambridge, MA) for 14 d with various factors as described in Results. Highly purified B cells were obtained by SRBC rosetting, followed by L-leucine methyl ester incubation as described previously (10, 15). Purified B cell fractions contained, <1% CD3<sup>+</sup> T cells, <1% CD14<sup>+</sup> monocytes, <1% CD16<sup>+</sup> NK cells and >98% CD20<sup>+</sup> B cells. Purified B cells were depleted of sIgE<sup>+</sup> and/or sIgG4<sup>+</sup> B cells by panning. The percentages, respectively, of sIgE<sup>+</sup> and sIgG4<sup>+</sup> B cells in the sIgE<sup>-</sup> and sIgG4<sup>-</sup> B cell fractions were <0.1%. Alternatively, sIgE<sup>+</sup> and sIgG4<sup>+</sup> B cells were enriched from tonsils of atopic patients by repeated panning. Purified sIgE<sup>+</sup> and sIgG4<sup>+</sup> B cell fractions contained >98% sIgE<sup>+</sup> B cells and >98% sIgG4<sup>+</sup> B cells, respectively (10, 15). In nonatopic donors, sIgE<sup>+</sup> and sIgG4<sup>+</sup> B cell fractions could not be obtained because of paucity of these cells. They were cultured for 14 d as described in Results. Control cultures for the evaluation of preformed Ig were carried out in the presence of cycloheximide (100  $\mu$ g/ml). The amount of IgE, IgG subclasses, IgM, and IgA subclasses in the supernatants were determined by ELISA (10, 13).

In some experiments, MNC ( $3 \times 10^5/0.2$  ml/well) or B cells ( $1 \times 10^5/0.2$  ml/well) were cultured with or without factors for 4 d, and concentrations of GH, IGF-I, or IL-4 were measured by ELISA or RIA (16, 17).

## Results

Preliminary experiments have shown that in MNC, medium alone failed to induce IgE (<0.15 ng/ml,  $n = 10$ ) or IgG4 (<0.3 ng/ml,  $n = 10$ ) production, whereas GH and IGF-I at 250 ng/ml induced IgE ( $4.1 \pm 2.7$  and  $5.2 \pm 2.4$  ng/ml, respectively,  $n = 10$ ) and IgG4 ( $33.0 \pm 7.4$  and  $41.7 \pm 7.2$  ng/ml, respectively,  $n = 10$ ) production. To rule out the possibility that GH- and IGF-I-induced IgE and IgG4 production may result from the expansion of a small sIgE<sup>+</sup> and sIgG4<sup>+</sup> B cell population, MNC were depleted of sIgE<sup>+</sup> and sIgG4<sup>+</sup> B cells, and they were cultured with peptides. As shown in Fig. 1, A–H, GH and IGF-I induced IgE and IgG4 production in a dose-dependent fashion, whereas they failed to induce IgM, IgG1, IgG2, IgG3, IgA1, and IgA2 production. In contrast, IGF-II and insulin failed to induce IgE (<0.15 ng/ml) or IgG4 (<0.3 ng/ml) or other Ig production (Fig. 1, A–H).

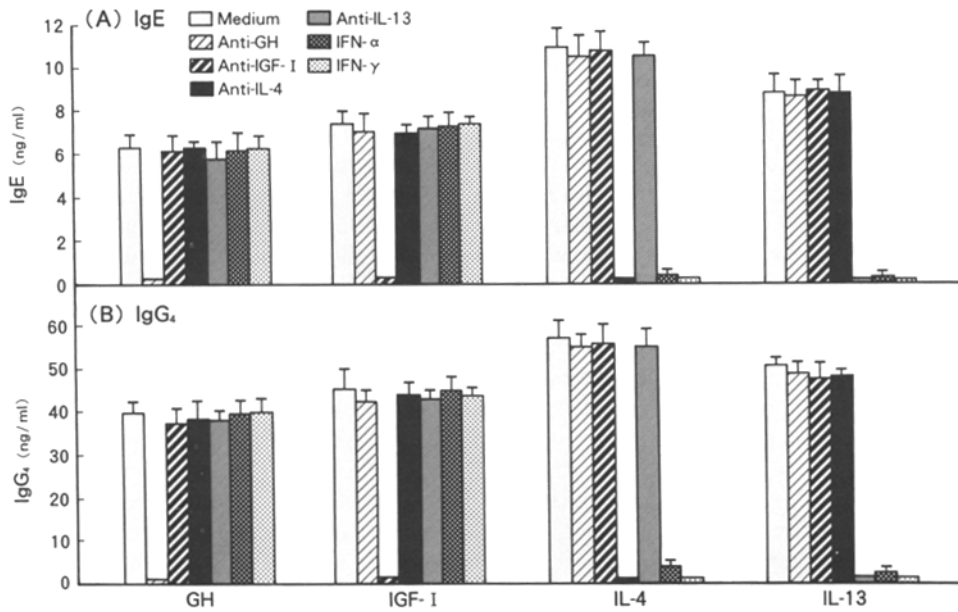
It has been reported that GH-induced stimulation was mediated by endogenously produced IGF-I (17, 18), although we and others (13, 19, 20) have reported the direct enhancing effect of GH. It has also been reported that IL-4 and IL-13 induced IgE and IgG4 production, and that IFN- $\alpha$  and IFN- $\gamma$  antagonized induction by them (1, 3, 11, 12, 21). Therefore, we compared the inducing effects of GH and IGF-I with those of IL-4 and IL-13. As shown in Fig. 2, GH-induced IgE and IgG4 production was blocked by anti-GH Ab, whereas neither anti-IGF-I Ab nor anti-IL-4 Ab nor anti-IL-13 Ab did



**Figure 1.** Effects of peptides on Ig production by MNC from nonatopic donors. MNC were depleted of sIgE<sup>+</sup> and sIgG4<sup>+</sup> B cells, and were cultured ( $3 \times 10^5$ /well) with medium ( $\diamond$ ) or increasing concentrations of GH ( $\bullet$ ), IGF-I ( $\circ$ ), IGF-II ( $\blacktriangle$ ), or insulin ( $\triangle$ ). After 14 d of culture, IgE (A), IgG4 (B), IgM (C), IgG1 (D), IgG2 (E), IgG3 (F), IgA1 (G), and IgA2 (H) production were determined. Values are means  $\pm$  1 SD of triplicate cultures from two experiments.

so. Addition of anti-GH receptor Ab also blocked induction, whereas anti-IGF-I receptor mAb failed to do so (data not shown). Moreover, neither IFN- $\alpha$  nor IFN- $\gamma$  antagonized the effect of GH (Fig. 2). Conversely, IGF-I-induced IgE and IgG4 production was blocked by anti-IGF-I Ab, whereas none of the anti-GH Ab, anti-IL-4 Ab, anti-IL-13 Ab, IFN- $\alpha$ , or IFN- $\gamma$  had any effect. Addition of anti-IGF-I receptor mAb also blocked induction whereas anti-GH receptor mAb failed to do so (data not shown). In contrast, IL-4- and IL-13-induced IgE and IgG4 production was blocked by anti-IL-4 Ab and anti-IL-13 Ab, respectively, but not by anti-GH or anti-IGF-I Ab, and induction was antagonized by IFN- $\alpha$  and IFN- $\gamma$  (Fig. 2).

We also measured GH, IGF-I, and IL-4 concentrations in culture supernatants. To do this, MNC were cultured with or without GH (250 ng/ml) for measurement of IGF-I or IL-4, and, conversely, they were cultured with or without IGF-I (250 ng/ml) for measurement of GH or IL-4. On the other hand, they were cultured with or without IL-4 (1,000 U/ml) for measurement of GH or IGF-I. Cultured supernatants did not contain detectable levels of GH (<10 pg/ml),



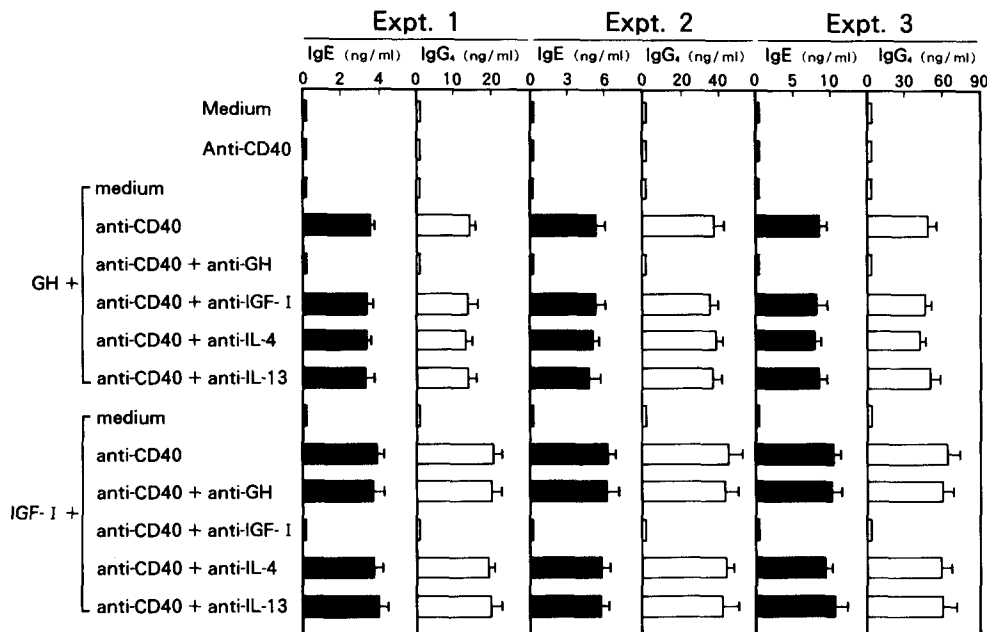
**Figure 2.** Specificity of the effects of GH and IGF-I on IgE and IgG4 production by MNC from nonatopic donors. MNC from nonatopic donors were depleted of sIgE<sup>+</sup> and sIgG4<sup>+</sup> B cells, and were cultured ( $3 \times 10^5$ /well) with indicated factors. GH was used at 250 ng/ml, IGF-I at 250 ng/ml, IL-4 at 1,000 U/ml, IL-13 at 50 ng/ml, and all the Abs at 10  $\mu$ g/ml, IFN- $\alpha$  at 1,000 U/ml and IFN- $\gamma$  at 1,000 U/ml. After 14 d of culture, IgE (A) and IgG4 (B) production were determined. Values are means  $\pm$  1 SD of triplicate cultures.

IGF-I (<30 pg/ml), or IL-4 (<40 pg/ml), and addition of GH, IGF-I, or IL-4 failed to induce them.

We next studied the effects of GH and IGF-I on IgE and IgG4 production by purified B cells with or without anti-CD40 mAb (2, 4-6). As shown in Fig. 3, sIgE<sup>-</sup>, sIgG4<sup>-</sup> B cells failed to produce detectable levels of IgE or IgG4. Neither anti-CD40 mAb nor GH induced them. However, GH plus anti-CD40 mAb induced IgE and IgG4 production which was blocked by anti-GH Ab and anti-GH receptor mAb (data not shown), whereas none of the anti-IGF-I Ab, anti-IGF-I receptor mAb (data not shown), anti-IL-4 Ab, or anti-IL-13 Ab did so. Similarly, IGF-I plus anti-CD40 mAb

induced IgE and IgG4 production, whereas IGF-I alone failed to do so. Induction by IGF-I plus anti-CD40 mAb was specifically blocked by anti-IGF-I Ab or anti-IGF-I receptor mAb (data not shown), but not by anti-GH Ab, anti-GH receptor mAb (data not shown), anti-IL-4 Ab, or anti-IL-13 Ab. Moreover, no detectable levels of GH, IGF-I or IL-4 were induced in cultures of these B cells. In contrast to GH and IGF-I, neither IGF-II plus anti-CD40 mAb nor insulin plus anti-CD40 mAb induced IgE (<0.15 ng/ml) or IgG4 (<0.3 ng/ml) production by sIgE<sup>-</sup>, sIgG4<sup>-</sup> B cells.

We then studied the effects of GH and IGF-I on spontaneous IgE and IgG4 production by atopic patients' B cells.



**Figure 3.** Effects of GH and IGF-I on IgE and IgG4 production by B cells from nonatopic donors. B cell from nonatopic donors were depleted of sIgE<sup>+</sup> and sIgG4<sup>+</sup> cells (sIgE<sup>-</sup>, sIgG4<sup>-</sup> B cells), and they were cultured ( $10^5$ /well) with indicated factors. Anti-CD40 mAb were used at 0.1  $\mu$ g/ml, GH at 250 ng/ml, IGF-I at 250 ng/ml, and all the Abs at 10  $\mu$ g/ml. After 14 d of culture, IgE (■) and IgG4 (□) production were determined. Values are means  $\pm$  1 SD of triplicate cultures.

To do this, sIgE<sup>+</sup>, sIgE<sup>-</sup>, sIgG4<sup>+</sup>, and sIgG4<sup>-</sup> B cells from atopic patients were separated and cultured with medium or factors. As shown in Fig. 4 A, sIgE<sup>+</sup> B cells spontaneously produced IgE, which was not enhanced by GH plus anti-CD40 mAb or by IGF-I plus anti-CD40 mAb. (Expts. 1–3). Fig. 4 A also showed that none of anti-GH or anti-IGF-I Ab (Expt. 1), or anti-IL-4 or anti-IL-13 Ab (Expt. 2), or IFN- $\alpha$  or IFN- $\gamma$  (Expt. 3) affected IgE production by sIgE<sup>+</sup> B cells. In contrast, sIgE<sup>-</sup> B cells did not produce IgE with medium alone. However, GH plus anti-CD40 mAb or IGF-I plus anti-CD40 mAb induced IgE production by sIgE<sup>-</sup> B cells, which was blocked by anti-GH and anti-IGF-I Ab, respectively (Expt. 1), but not by anti-IL-4 or anti-IL-13 Ab (Expt. 2), or by IFN- $\alpha$  or IFN- $\gamma$  (Expt. 3).

Identical results were observed in IgG4 production by sIgG4<sup>+</sup> or sIgG4<sup>-</sup> B cells. As shown in Fig. 4 B, neither GH plus anti-CD40 mAb nor IGF-I plus anti-CD40 mAb affected IgG4 production by sIgG4<sup>+</sup> B cells, whereas they induced IgG4 production by sIgG4<sup>-</sup> B cells. Induction by GH and IGF-I was specifically blocked by anti-GH Ab and anti-IGF-I Ab, respectively (Expt. 1), whereas it was not blocked by any of the anti-IL-4 Ab or anti-IL-13 Ab (Expt. 2), or by IFN- $\alpha$  or IFN- $\gamma$  (Expt. 3).

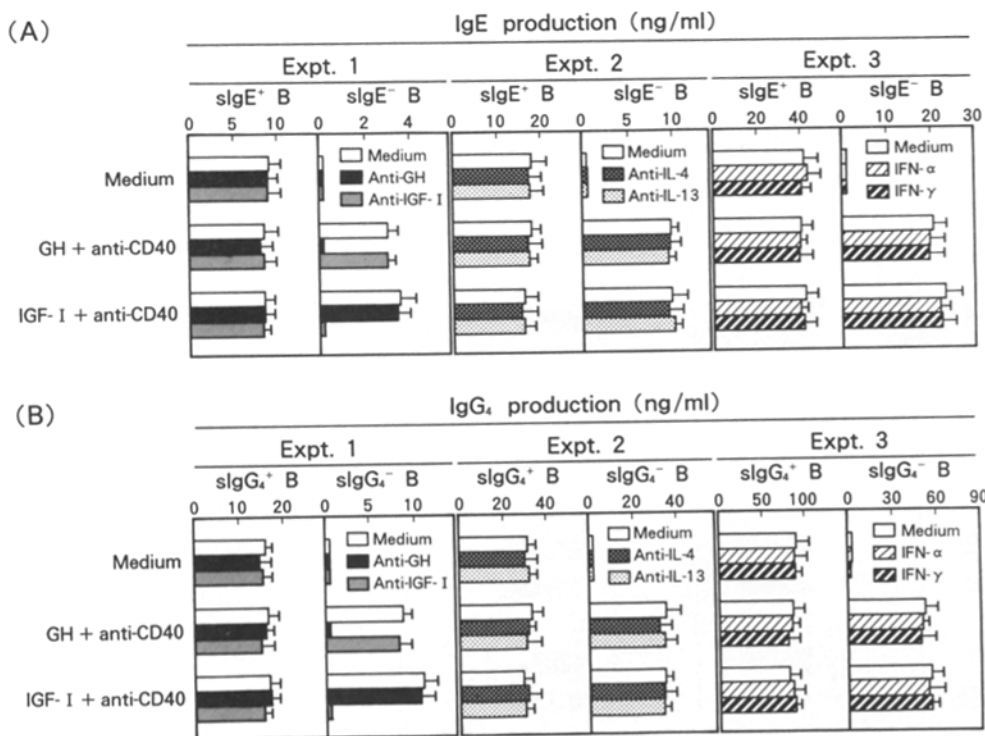
## Discussion

We have demonstrated that GH and IGF-I specifically induced IgE and IgG4 production by normal donors' MNC depleted of sIgE<sup>+</sup> and sIgG4<sup>+</sup> B cells, whereas IGF-II and insulin failed to do so. The detailed mechanisms of differential effects of these peptides are currently under investiga-

tion. However, this is not surprising. We and others (13, 22, 23) have reported that GH and IGF-I stimulated plasma cells, pre-T cells, and neutrophils, whereas IGF-II or insulin were either less stimulatory or without effect.

It has been reported that GH-induced stimulation was mediated by IGF-I, although a direct stimulating effect of GH was also reported (13, 17–20). Moreover, IL-4 and IL-13 have been shown to induce IgE and IgG4 production (1–3, 11, 12). However, our results indicate that GH effect was specific, and was not mediated by IGF-I, IL-4, or IL-13, because GH-induced IgE and IgG4 production was blocked by anti-GH Ab, but not by anti-IGF-I Ab, anti-IL-4 Ab, or anti-IL-13 Ab. In addition, whereas IFN- $\alpha$  and IFN- $\gamma$  inhibited IL-4- and IL-13-induced IgE and IgG4 production, they had no effect on GH- or IGF-I-induced IgE and IgG4 production. Furthermore, no IGF-I or IL-4 was detectable in the culture supernatants with GH. Conversely, IGF-I-induced induction was not mediated by GH, IL-4, or IL-13, because it was blocked by anti-IGF-I Ab, but not by anti-GH Ab, anti-IL-4, Ab or anti-IL-13 Ab. Moreover, no GH or IL-4 was produced by IGF-I.

GH and IGF-I also induced IgE and IgG4 production by normal donors' sIgE<sup>-</sup>, sIgG4<sup>-</sup> B cells in the presence, but not absence, of anti-CD40 mAb. Again, this induction was specific to each peptide. These results indicate that GH- and IGF-I-induced IgE and IgG4 production was due to switching but not to expansion of sIgE<sup>+</sup> and sIgG4<sup>+</sup> B cells. This was directly shown by using sIgE<sup>+</sup>, sIgG4<sup>+</sup>, sIgE<sup>-</sup>, or sIgG4<sup>-</sup> B cells from atopic patients. Whereas GH plus anti-CD40 mAb or IGF-I plus anti-CD40 mAb induced IgE and IgG4 production by sIgE<sup>-</sup> and sIgG4<sup>-</sup> B cells, respectively, they



**Figure 4.** Effects of GH and IGF-I on IgE and IgG4 production by sIg<sup>+</sup> and sIg<sup>-</sup> B cells from atopic patients. Purified sIgE<sup>+</sup> or sIgE<sup>-</sup> (A), and sIgG4<sup>+</sup> or sIgG4<sup>-</sup> (B) B cells from atopic patients were cultured ( $2 \times 10^4$ /well) with indicated factors. Anti-CD40 mAb was used at 0.1  $\mu$ g/ml, GH at 250 ng/ml, IGF-I at 250 ng/ml, all the Abs at 10  $\mu$ g/ml, IFN- $\alpha$  at 1,000 U/ml, and IFN- $\gamma$  at 1,000 U/ml. After 14 d of culture, IgE (A) and IgG4 (B) production were determined. Values are means  $\pm$  1 SD of triplicate cultures.

failed to do so by sIgE<sup>+</sup> and sIgG4<sup>+</sup> B cells, respectively.

The in vivo influence of GH and IGF-I remains to be elucidated. However, it has been reported that alveolar macrophages from patients with lung disease produced IGF-I, and that IgE concentrations in bronchoalveolar lavage (BAL) fluid was elevated in those patients (24, 25). In accordance with this, we have found that GH and IGF-I concentrations in BAL fluid were elevated in asthmatic patients: GH and IGF-I concentrations in BAL fluid in asthmatic patients ( $n = 5$ ) were  $45 \pm 12$  and  $61 \pm 10$  pg/ml ( $n = 5$ ), respec-

tively, whereas those in normal donors ( $n = 5$ ) were  $<10$  and  $<30$  pg/ml, respectively. Moreover, there are cases with IgE deficiency and GH deficiency and low serum levels of IGF-I (26).

GH and IGF-I seem to be excellent reagents in the study of IgE and IgG4 regulation. We and others (1-3, 5, 21) have reported that various factors modulate IL-4-induced IgE and IgG4 production. The interaction of GH and IGF-I with those factors is currently under investigation.

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