Brief Definitive Report

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

By H. Kimata and M. Fujimoto

From the Department of Pediatrics, Kyoto University Hospital, Kyoto 606, Japan

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 $sIgE^+$ and $sIgG4^+$ 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 α (IFN-α) or IFN-γ, 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 $sIgE^-$, $sIgG4^-$ 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 $sIgE^+$, but not $sIgE^-$, B cells from atopic patients spontaneously produced IgE. GH or IGF-I with anti-CD40 mAb failed to enhance IgE production by $sIgE^+$ B cells, whereas they induced IgE production by $sIgE^-$ B cells. Similarly, whereas GH or IGF-I with anti-CD40 mAb failed to enhance IgG4 production by $sIgG4^+$ B cells from atopic patients, they induced IgG4 production by $sIgG4^-$ 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-α or IFN-γ (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-α or IFN-γ (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-α–, and IFN-γ–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 $sIgE^-$, $sIgG4^-$ 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-α and IFN-γ (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 (αIR-3), mouse IgM anti-CD40 mAb (MA6), rabbit anti-IL-13 Ab, control rabbit IgG, and control mouse IgG1 were purchased from

 J. Exp. Med. © The Rockefeller University Press • 0022-1007/94/08/0727/06 $2.00
Volume 180 August 1994 727–732

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 μg/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 $sIgE^+$ and $sIgG4^+$ B cells by panning (10, 15). The percentage of $sIgE^+$ and $sIgG4^+$ B cells was <0.1%. They were cultured (3×10^5/0.2 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% $CD3^+$ T cells, <1% $CD14^+$ monocytes, <1% $CD16^+$ NK cells and >98% $CD20^+$ B cells. Purified B cells were depleted of $sIgE^+$ and/or $sIgG4^+$ B cells by panning. The percentages, respectively, of $sIgE^+$ and $sIgG4^+$ B cells in the $sIgE^-$ and $sIgG4^-$ B cell fractions were <0.1%. Alternatively, $sIgE^+$ and $sIgG4^+$ B cells were enriched from tonsils of atopic patients by repeated panning. Purified $sIgE^+$ and $sIgG4^+$ B cell fractions contained >98% $sIgE^+$ B cells and >98% $sIgG4^+$ B cells, respectively (10, 15). In nonatopic donors, $sIgE^+$ and $sIgG4^+$ 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 μg/ml). The amount of IgE, IgG subclasses, IgM, and IgA subclasses in the supernatants were determined by ELISA (10, 13).

In some experiments, MNC (3×10^5/0.2 ml/well) or B cells (1×10^5/0.2 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 ± 2.7 and 5.2 ± 2.4 ng/ml, respectively, $n = 10$) and IgG4 (33.0 ± 7.4 and 41.7 ± 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 $sIgE^+$ and $sIgG4^+$ B cell population, MNC were depleted of $sIgE^+$ and $sIgG4^+$ 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-α and IFN-γ 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

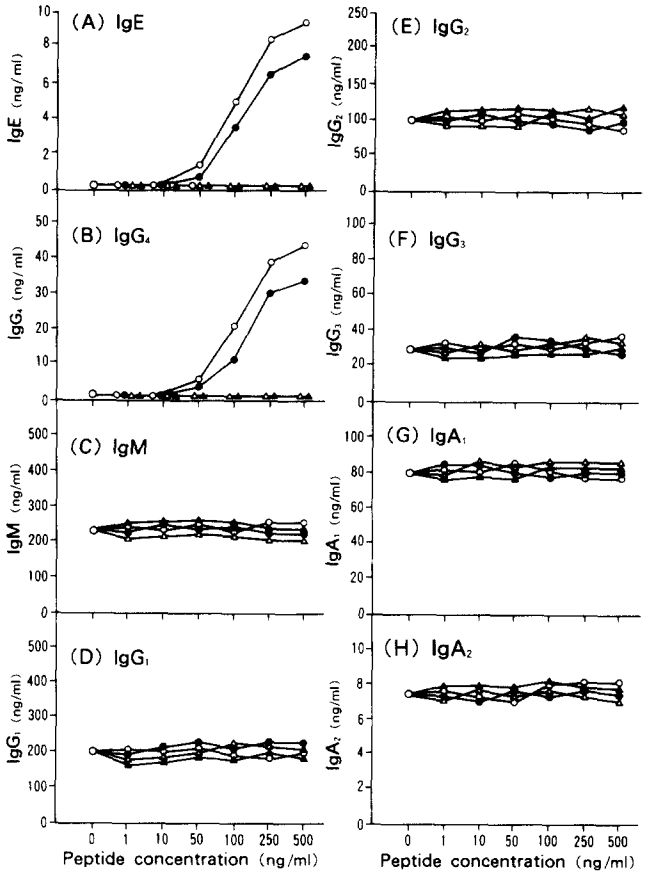

Figure 1. Effects of peptides on Ig production by MNC from nonatopic donors. MNC were depleted of $sIgE^+$ and $sIgG4^+$ B cells, and were cultured (3×10^5/well) with medium (◇) or increasing concentrations of GH (●), IGF-I (○), IGF-II (▲), or insulin (△). After 14 d of culture, IgE (*A*), IgG4 (*B*), IgM (*C*), IgG1 (*D*), IgG2 (*E*), IgG3 (*F*), IgA1 (*G*), and IgA2 (*H*) production were determined. Values are means ± 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-α nor IFN-γ 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-α, or IFN-γ 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-α and IFN-γ (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),

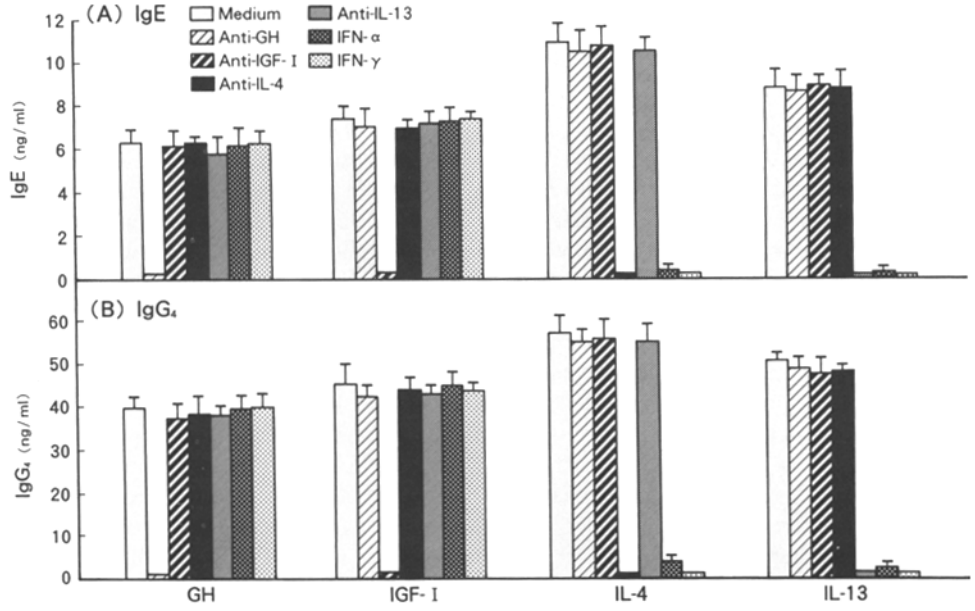

Figure 2. Specificity of the effects of GH and IGF-I on IgE and IgG4 production by MNC from nonatopic donors. MNC from nonatopic donors were depleted of $sIgE^+$ and $sIgG4^+$ B cells, and were cultured (3×10^5/well) with indicated factors. GH was used at 250 ng/ml, IGF-I at 250 ng/ml, IL-4 at 1,000 U/ml, IL-13 at 50 ng/ml, and all the Abs at 10 μg/ml, IFN-α at 1,000 U/ml and IFN-γ at 1,000 U/ml. After 14 d of culture, IgE (*A*) and IgG4 (*B*) production were determined. Values are means ± 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, $sIgE^-$, $sIgG4^-$ 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 $sIgE^-$, $sIgG4^-$ B cells.

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

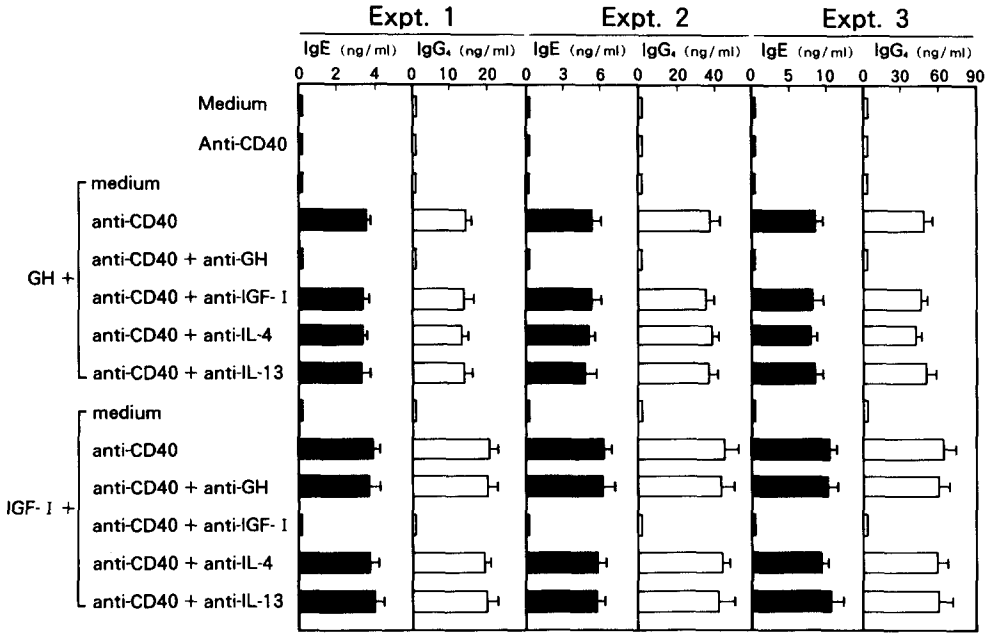

Figure 3. Effects of GH and IGF-I on IgE and IgG4 production by B cells from nonatopic donors. B cell from nonatopic donors were depleted of $sIgE^+$ and $sIgG4^+$ cells ($sIgE^-$, $sIgG4^-$ B cells), and they were cultured (10^5/well) with indicated factors. Anti-CD40 mAb were used at 0.1 μg/ml, GH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

To do this, sIgE$^+$, sIgE$^-$, sIgG4$^+$, and sIgG4$^-$ B cells from atopic patients were separated and cultured with medium or factors. As shown in Fig. 4 *A*, sIgE$^+$ 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-α or IFN-γ (*Expt. 3*) affected IgE production by sIgE$^+$ B cells. In contrast, sIgE$^-$ 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$^-$ 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-α or IFN-γ (*Expt. 3*).

Identical results were observed in IgG4 production by sIgG4$^+$ or sIgG4$^-$ 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$^+$ B cells, whereas they induced IgG4 production by sIgG4$^-$ 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-α or IFN-γ (*Expt. 3*).

Discussion

We have demonstrated that GH and IGF-I specifically induced IgE and IgG4 production by normal donors' MNC depleted of sIgE$^+$ and sIgG4$^+$ B cells, whereas IGF-II and insulin failed to do so. The detailed mechanisms of differential effects of these peptides are currently under investigation. 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-α and IFN-γ 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$^-$, sIgG4$^-$ 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$^+$ and sIgG$^+$ B cells. This was directly shown by using sIgE$^+$, sIgG4$^+$, sIgE$^-$, or sIgG4$^-$ 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$^-$ and sIgG4$^-$ B cells, respectively, they

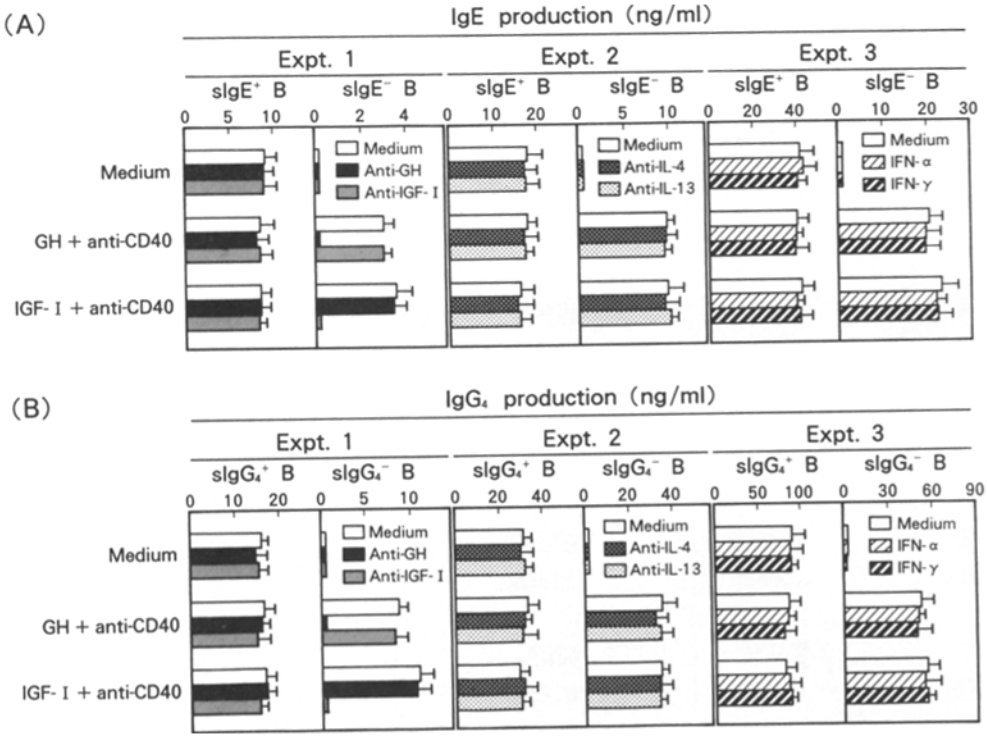

Figure 4. Effects of GH and IGF-I on IgE and IgG4 production by sIg$^+$ and sIg$^-$ B cells from atopic patients. Purified sIgE$^+$ or sIgE$^-$ (*A*), and sIgG4$^+$ or sIgG4$^-$ (*B*) B cells from atopic patients were cultured (2×10^4/well) with indicated factors. Anti-CD40 mAb was used at 0.1 μg/ml,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

failed to do so by $sIgE^+$ and $sIgG4^+$ 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 ± 12 and 61 ± 10 pg/ml (n = 5), respectively, 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.

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

Address correspondence to Dr. H. Kimata, Department of Pediatrics, Kyoto University, 54, Kawahara-cho, Shogoin, Sakyo-Ku, Kyoto 606, Japan.

Received for publication 15 March 1994.

References

1. Péne, J., F. Rousset, F. Brière, I. Chrétien, J.-Y. Bonnefoy, H. Spits, T. Yokota, N. Arai, K. Arai, J. Banchereau, and J.E. de Vries. 1988. IgE production by normal human lymphocytes is induced by interleukin 4 and suppressed by interferon γ and α and prostaglandin E_2. *Proc. Natl. Acad. Sci. USA.* 85:6880.
2. Kimata, H., A. Yoshida, C. Ishioka, I. Lindley, and H. Mikawa. 1992. Interleukin 8 (IL-8) selectively inhibits immunoglobulin E production induced by IL-4 in human B cells. *J. Exp. Med.* 176:1227.
3. Kimata, H., A. Yoshida, C. Ishioka, and H. Mikawa. 1992. Differential effect of vasoactive intestinal peptide, somatostatin, and substance P on human IgE and IgG subclass production. *Cell. Immunol.* 144:429.
4. Jabara, H.H., S.M. Fu, R.S. Geha, and D. Vercelli. 1990. CD40 and IgE: synergism between anti-CD40 monoclonal antibody and interleukin 4 in the induction of IgE synthesis by highly purified human B cells. *J. Exp. Med.* 172:1861.
5. Zhang, K., E.A. Clark, and A. Saxon. 1991. CD40 stimulation provides an IFN-γ-independent and IL-4-dependent differentiation signal directly to human B cells for IgE production. *J. Immunol.* 146:1836.
6. Gascan, H., J.-F. Gauchat, G. Aversa, P.E. Vlasselear, and J.E. de Vries. 1991. Anti-CD40 monoclonal antibodies or $CD4^+$ T cell clones and IL-4 induce IgG4 and IgE switching in purified human B cells via different signaling pathways. *J. Immunol.* 147:8.
7. Kimata, H., E.H. Sherr, and A. Saxon. 1988. Human natural killer (NK) cells produce a late-acting B-cell differentiation activity. *J. Clin. Immunol.* 8:381.
8. Zhang, X., B. Polla, C. Hauser, and R.H. Zubler. 1992. T cells from atopic individuals produce IgE-enhancing activity incompletely blocked by anti-interleukin-4 antibody. *Eur. J. Immunol.* 22:829.
9. Kimata, H., A. Yoshida, C. Ishioka, and H. Mikawa. 1991. Effect of recombinant human erythropoietin on human IgE production *in vitro*. *Clin. Exp. Immunol.* 83:483.
10. Kimata, H., A. Yoshida, F. Masayuki, and H. Mikawa. 1993. Effect of vasoactive intestinal peptide, somatostatin, and substance P on spontaneous IgE and IgG4 production in atopic patients. *J. Immunol.* 150:4630.
11. Punnonen, J., G. Aversa, B.G. Cocks, A.N.J. McKenzie, S. Menson, G. Zurawski, R. de Waal Malefyt, and J.E. de Vries. 1993. Interleukin 13 induces interleukin 4-independent IgG4 and IgE synthesis and CD23 expression by human B cells. *Proc. Natl. Acad. Sci. USA.* 90:3730.
12. Aversa, G., J. Punnonen, B.G. Cocks, R. de Waal Malefyt, F. Vega, Jr., S.M. Zurawski, G. Zurawski, and J.E. de Vries. 1993. An interleukin 4 (IL-4) mutant protein inhibits both IL-4 or IL-13–induced human immunoglobulin G4 (IgG4) and IgE synthesis and B cell proliferation: support for a common component shared by IL-4 and IL-13 receptors. *J. Exp. Med.* 178:2213.
13. Kimata, H., and A. Yoshida. 1994. Differential effect of growth hormone, and insulin-like growth factor-I, insulin-like growth factor-II, and insulin on Ig production and growth in human plasma cells. *Blood.* 83:121.
14. Yoshida, A., C. Ishioka, H. Kimata, and H. Mikawa. 1992. Recombinant human growth hormone stimulates B cell immunoglobulin synthesis and proliferation in serum-free medium. *Acta. Endocrinol.* 126:524.
15. Kimata, H., and H. Mikawa. 1993. Nedocromil sodium selectively inhibits IgE and IgG4 production in human B cells stimulated with IL-4. *J. Immunol.* 151:6723.
16. Hattori, N., A. Shimatsu, M. Sugita, S. Kumagai, and H. Imura. 1990. Immunoreactive growth hormone (GH) secretion by human lymphocyte: Augmented release by GH. *Biochem. Biophys. Res. Commun.* 168:396.
17. Merimee, T.J., M.B. Grant, C.M. Broder, and L.L. Cavalli-Sforza. 1989. Insulin-like growth factor secretion by human B-lymphocytes: A comparison of cells from normal and pygmy subjects. *J. Clin. Endocrinol. & Metabol.* 69:978.
18. Geffner, M.E., N. Bersch, B.M. Lippe, R.G. Rosenfeld, R.L. Hintz, and D.W. Golde. 1990. Growth hormone mediates the growth of T-lymphoblast cell lines via locally generated insulin-like growth factor-I. *J. Clin. Endocrinol. & Metabol.* 71:464.

19. Merchav, S., I. Tatarsly, and Z. Hochberg. 1988. Enhancement of erythropoiesis *in vitro* by human growth hormone is mediated by insulin-like growth factor I. *Br. J. Hematol.* 70:267.
20. Doi, T., L.J. Striker, C. Quaife, F.G. Conti, R. Palmiter, R. Behringer, R.L. Brinster, and G.E. Striker. 1988. Progressive glomerulosclerosis develops in transgenic mice chronically expressing growth hormone and growth hormone-releasing factor but not in those expressing insulin-like growth factor-I. *Am. J. Pathol.* 131:398.
21. Rousset, F., J. Robert, M. Andary, J.-P. Bonnin, G. Souillet, I. Chrétien, F. Brière, J. Pène, and J.E. de Vries. 1991. Shifts in interleukin-4 and interferon-γ production by T cells of patients with elevated serum IgE levels and the modulatory effects of these lymphokines on spontaneous IgE synthesis. *J. Allergy. Clin. Immunol.* 87:58.
22. Gjerset, R.A., J.O. Yeargin, S.K. Volkman, V. Vila, J. Arya, and M. Haas. 1990. Insulin-like growth factor-I supports proliferation of autocrine thymic lymphoma cells with a pre-T cell phenotype. *J. Immunol.* 145:3497.
23. Fu, Y.-K., S. Arkins, B.S. Wang, and K.W. Kelly. 1991. A novel role of growth hormone and insulin-like growth factor-I. Priming neutrophil for superoxide anion secretion. *J. Immunol.* 146:1602.
24. Rom, W.N., P. Basset, G.A. Fells, T. Nukiwa, B.C. Trapnell, and R.G. Crystal. 1988. Alveolar macrophage release an insulin-like growth factor I-type molecule. *J. Clin. Invest.* 82:1685.
25. Diaz, P., F.R. Galleguillos, M.C. Gonzalez, C.F.A. Pantin, and A.B. Kay. Bronchoalveolar lavage in asthma: the effect of disodium cromoglycate (cromolyn) on leukocyte counts, immunoglobulins, and complement. *J. Allergy. Clin. Immunol.* 74:41.
26. Fleisher, T.A., R.M. White, S. Broder, S.P. Nissley, R.M. Blease, J.J. Mulvihill, G. Olive, and T.A. Waldmann. 1980. X-linked hypogammaglobulinemia and isolated growth hormone deficiency. *N. Engl. J. Med.* 302:1429.