Brief Definitive Report

RANTES and Macrophage Inflammatory Protein 1α Selectively Enhance Immunoglobulin (IgE) and IgG4 Production by Human B Cells

By Hajime Kimata,*‡ Akira Yoshida,§ Chihiro Ishioka,‖ Masayuki Fujimoto,¶ Ivan Lindley,** and Kenshi Furusho‡

*From the *Department of Pediatrics, Yunichika Central Hospital, Uji City, Kyoto 611; the ‡Department of Pediatrics, Kyoto University Hospital, Kyoto 606-01; the §Department of Pediatrics, Japanese Red Society Wakayama Medical Center, Wakayama 640; the ‖Department of Pediatrics, Shimada Municipal Hospital, Shimada, Shizuoka 427; ¶the Department of Pediatrics, National South Kyoto Hospital, Kyoto 610-01, Japan; and the **Department of Dermatology, Sandoz Research Institute, A-1235 Vienna, Austria*

Summary

We studied the effects of various chemokines including neutrophil-activating peptide 2 (NAP-2), β-thromboglobulin (β-TG), platelet factor 4 (PF-4), melanoma growth stimulating activity (GRO), γ interferon-induced protein (IP-10), regulated on activation, normal T expressed and secreted (RANTES), macrophage inflammatory protein 1α (MIP-1α), MIP-1β, and monocyte chemotactic protein 1 (MCP-1) on Immunoglobulin (IgE) and IgG4 production by human B cells. None of these chemokines with or without interleukin (IL-4), anti-CD40 or -CD58 monoclonal antibody (mAb), induced IgE and IgG4 production by B cells from nonatopic donors. However, RANTES and MIP-1α selectively enhanced IgE and IgG4 production induced by IL-4 plus anti-CD40 or -CD58 mAb without affecting production of IgM, IgG1, IgG2, IgG3, IgA1, or IgA2, whereas other chemokines failed to do so. Enhancement of IgE and IgG4 production by RANTES and MIP-1α was specifically blocked by anti-RANTES mAb and anti-MIP-1α antibody (Ab), respectively, whereas anti-IL-5 mAb, anti-IL-6 mAb, anti-IL-10 Ab, anti-IL-13 Ab, and anti–tumor necrosis factor-α mAb failed to do so. Purified surface IgE positive ($sIgE^+$) and $sIgG4^+$ B cells generated either in vitro or in vivo spontaneously produced IgE and IgG4, respectively, whereas $sIgE^-$ and $sIgG4^-$ B cells failed to do so. RANTES and MIP-1α enhanced spontaneous IgE and IgG4 production in $sIgE^+$ and $sIgG4^+$ B cells, respectively, whereas neither RANTES nor MIP-1α did so in $sIgE^-$ or $sIgG4^-$ B cells. Purified $sIgE^+$ and $sIgG4^+$, but not $sIgE^-$ or $sIgG4^-$ B cells, generated in vitro and in vivo expressed receptors for RANTES and MIP-1α, whereas they failed to express receptors for other chemokines. These findings indicate that RANTES and MIP-1α enhance IgE and IgG4 production by directly stimulating $sIgE^+$ and $sIgG4^+$ B cells.

Human IgE and IgG4 production is regulated by various cytokines and factors. IL-4 and IL-13 induced IgE and IgG4 production in mononuclear cells or in B cells stimulated with anti-CD40 mAb by isotype switching (1–3). IL-5, -6, -9, -10, and TNF-α enhance IL-4– and IL-13–induced IgE and IgG4 production (1–6), whereas IFN-α, IFN-γ, TGF-β, and IL-12 inhibit their production depending on the condition of culture (1, 4, 6, 7). Moreover, IL-4 plus anti-CD58 mAb also induced IgE production by purified B cells, and this production was IFN-γ and IL-6 independent (8). We have also reported that some neuropeptides selectively modulated IL-4 induced and spontaneous IgE and IgG4 production, which was not mediated by these cytokines (9, 10).

The chemokines consists of α subfamily members including IL-8, melanoma growth-stimulating activity (GRO), neutrophil-activating peptide 2 (NAP-2), β-thromboglobulin (β-TG), γ interferon-induced protein (IP-10), and platelet factor 4 (PF-4), and β subfamily members including regulated on activation, normal T expressed and secreted (RANTES), macrophage inflammatory protein 1α (MIP-1α), MIP-1β, and monocyte chemotactic protein 1 (MCP-1) (11). Recently, it has been reported that these chemokines act on various cell types, including neutrophils, eosinophils, basophils, monocytes, myeloid progenitors, and T and B cells (11–15). In addition, we have found that IL-8 selectively inhibited IgE and IgG4 production induced by IL-4 (16). Here, we demonstrate that RANTES and MIP-1α

 J. Exp. Med. © The Rockefeller University Press • 0022-1007/96/05/2397/06 $2.00
Volume 183 May 1996 2397–2402

selectively enhance IgE and IgG4 production, whereas other chemokines fail to do so.

Materials and Methods

Reagents. The following recombinant human cytokines and Abs were kindly provided by companies noted previously (2, 4): IL-4 and rabbit anti-IL-4 Ab (Ono Pharmaceutical Company, Osaka, Japan), and IL-2 and IFN-α (Takeda Chemical Industries, Osaka, Japan). Recombinant human IL-13 was purchased from Pepro Tech Inc. (Rocky Hill, NJ) (2). Recombinant human IL-8 and mouse IgG1 anti-IL-8 mAb were obtained from Sandoz Research Institute (Vienna, Austria) (16). Recombinant human IL-10, -6, -12, TGF-β, RANTES, GRO, MIP-1α, MIP-1β, and MCP-1, and mouse IgG1 anti-IL-5, anti-IL-6, anti-TNF-α mAb, anti-RANTES mAb, and goat anti-IL-10 and anti-MIP-1α Ab were purchased from R&D Systems, Inc. (Minneapolis, MN). Recombinant human NAP-2, PF-4, highly purified native human β-TG, IP-10, mouse IgM anti-CD40 mAb (BL-C4), mouse IgG2a anti-CD58 mAb (BRIC5), and rabbit anti-IL-13 Ab were purchased from Cosmo Bio Co. (Tokyo, Japan) (2, 4, 16). The culture medium was DME, supplemented with Ham's Nutrient (DME/F-12) (Sigma Chemical Co., St. Louis, MO), 0.5% BSA, and 50 μg/ml transferrin (2).

Cell Cultures. Tonsillar mononuclear cells were obtained from nonatopic donors (serum IgE level <50 U/ml) and atopic patients (serum IgE level 1,578–12,259 IU/ml). Highly purified B cells were separated by SRBC rosetting, followed by L-leucine methyl ester incubation as described previously (2). Purified B cell fractions contained >98% $CD20^+$ B cells. Purified B cells were depleted of surface IgE positive ($sIgE^+$) and $sIgG4^+$ B cells by panning. The percentage of $sIgE^+$ and $sIgG4^+$ B cells was <0.1%. The $sIgE^-$, $sIgG4^-$ B cells were cultured (2×10^5/0.2 ml/well) in U-bottomed microtiter plates (Costar Corp., Cambridge, MA) for 14 d in the presence or absence of various factors with or without Abs as described in Results. All the Abs to cytokines were used at 10 μg/ml, because anti-IL-5 mAb, anti-IL-6 mAb, anti-IL-10 Ab, anti-IL-13 Ab, and anti-TNF-α mAb (all at 10 μg/ml) completely neutralized induction of IgE and IgG4 production by IL-5 (100 ng/ml), IL-6 (100 ng/ml), IL-10 (100 ng/ml), IL-13 (500 ng/ml), and TNF-α (50 ng/ml), respectively (2, 4, 6). In some experiments, purified $sIgE^-$, $sIgG4^-$ B cells were cultured with IL-4 (1,000 U/ml) plus anti-CD40 mAb (0.1 μg/ml) or IL-4 plus anti-CD58 mAb (0.1 μg/ml) for 5–7 d, and then $sIgE^+$, $sIgE^-$, $sIgG4^+$, and $sIgG4^-$ B cells were purified by panning (2, 4). Alternatively, $sIgE^+$, $sIgE^-$, $sIgG4^+$, and $sIgG4^-$ B cells were purified from tonsillar B cells of atopic patients by panning. Purified $sIgE^+$ and $sIgG4^+$ B cell fractions contained >98% $sIgE^+$ B cells and >98% $sIgG4^+$ B cells, respectively (2, 4). Purified $sIgE^+$ and $sIgG4^+$ B cells were cultured (2×10^4/0.2 ml/well) for 14 d as described in Results. The amounts of IgE, IgG subclasses, IgM, and IgA subclasses in the supernatants were determined by ELISA (2, 4). Results were expressed as the means ± 1 SD of triplicate cultures from one experiment, representative of four or five.

In some experiments, sIg^+ and sIg^- B cells were tested for the binding of chemokines by immunofluorescence using biotinylated chemokines, as previously reported (6, 17). The mean flourencence intensity (MFI) value of biotinylated ligand-specific binding, determined after subtraction of the nonspecific binding in the presence of a 100-fold excess of unlabeled ligand, was expressed as ΔMFI (6, 17). Binding (ΔMFI, $n = 4$) of RANTES, MIP-1α, IP-10, MIP-1β, and MCP-1 in purified human monocytes was 76 ± 14, 68 ± 20, 58 ± 21, 72 ± 17, and 61 ± 18, respectively, whereas binding (ΔMFI, $n = 4$) of NAP-2, β-TG, PF-4, and GRO in purified human neutrophils was 92 ± 31, 89 ± 27, 80 ± 16, and 79 ± 22, respectively.

Results and Discussion

Preliminary experiments showed that none of the chemokines (1 pM–1 μM) with or without IL-4, anti-CD40 mAb, or anti-CD58 mAb induced IgE (<0.3 ng/ml), IgG4 (<0.3 ng/ml), or other Ig (data not shown) production by purified B cells. However, as shown in Fig. 1, *A* and *B*, of the various chemokines tested, RANTES and MIP-1α enhanced IgE and IgG4 production induced by IL-4 plus anti-CD40 mAb in a dose-dependent fashion, but failed to enhance IgM, IgG1, IgG2, IgG3, IgA1, and IgA2 production (Fig. 1, *C* and *D*). In contrast, none of the other chemokines, including NAP-2, β-TG, PF-4, GRO, IP-10, MIP-1β, and MCP-1 had any effect on the production of IgE, IgG4 (Fig. 1, *A* and *B*) or other Igs (data not shown) at any concentrations tested. Similarly, RANTES and MIP-

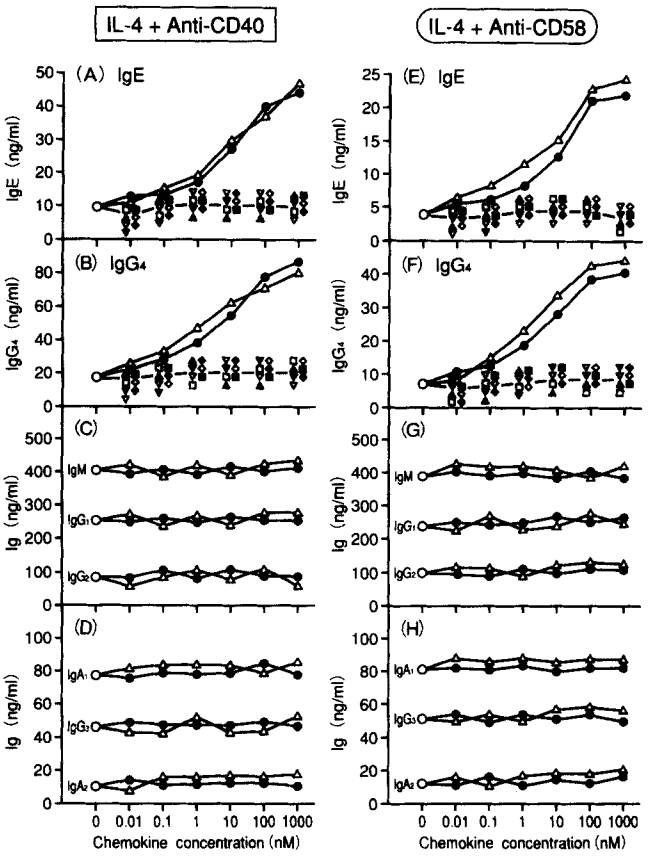

Figure 1. Effects of chemokines on Ig production. Nonatopic donors' IgE^-, $sIgG4^-$ B cells were cultured with IL-4 (1,000 U/ml) plus anti-CD40 mAb (0.1 μg/ml) (*A–D*), or IL-4 plus anti-CD58 mAb (0.1 μg/ml) (*E–H*). Medium (○) or various concentrations of RANTES (●), MIP-1α (△), GRO (▲), NAP-2 (▽), β-TG (▼), PF-4 (□), IP-10 (■), MIP-1β (◇), or MCP-1 (◆) were added, and production of IgE (*A* and *E*), IgG4 (*B* and *F*), IgM, IgG1, and IgG2 (*C* and *G*), or IgG3, IgA1, and IgA2 (*D* and *H*) was determined.

1α enhanced IgE and IgG4 production induced by IL-4 plus anti-CD58 mAb, but did not enhance the production of other Igs (Fig. 1, *E–H*). None of NAP-2, β-TG, PF-4, GRO, IP-10, MIP-1β, or MCP-1 had any effect on the production of IgE, IgG4 (Fig. 1, *E* and *F*), or other Igs (data not shown). In five experiments performed, the ranges of enhancement of IgE and IgG4 production by RANTES (100 nM) and MIP-1α (100 nM) were 3.3–5.1-fold and 2.9–5.2-fold, respectively, in cultures stimulated with IL-4 plus anti-CD40 mAb, and 2.7–5.2-fold and 2.5–4.9-fold, respectively, in cultures stimulated with IL-4 plus anti-CD58 mAb.

We and others have previously reported that IL-4–prestimulated B cells produce IgE spontaneously in vitro after switching to $sIgE^+$ B cells (18, 19). Therefore, in this study, $sIgE^-$, $sIgG4^-$ B cells were prestimulated with IL-4 plus anti-CD40 mAb or IL-4 plus anti-CD58 mAb, and $sIgE^+$, $sIgG4^+$, $sIgE^-$, and $sIgG4^-$ B cells were purified. We also studied the effects of RANTES and MIP-1α on in vivo–generated $sIgE^+$ and $sIgG4^+$ B cells obtained from atopic patients. As shown in Fig. 2, *A–C*, RANTES and MIP-1α enhanced IgE production in $sIgE^+$ B cells induced by IL-4 plus anti-CD40 mAb, IL-4 plus anti-CD58 mAb, and in vivo, but failed to induce IgE production in $sIgE^-$ B cells. Enhancement of IgE production by RANTES was specific, since it was blocked by anti-RANTES mAb but not by anti-MIP-1α Ab or control mouse IgG1 (data not shown). Conversely, enhancement of IgE production by MIP-1α was blocked by anti-MIP-1α Ab, but not by anti-RANTES mAb or control goat IgG (data not shown). Identical results were obtained for IgG4 production (Fig. 2, *D–F*).

These findings indicate that RANTES and MIP-1α directly stimulated $sIgE^+$ and $sIgG4^+$ B cells generated in vitro and in vivo, but had no effect on $sIgE^-$ and $sIgG4^-$ B cells. Kinetic experiments showed that enhancement of IgE and IgG4 production could be detected on day 4 (Fig. 3). That enhancement was caused by stimulation of Ig production and not by proliferation of $sIgE^+$ and $sIgG4^+$ B cells, since RANTES and MIP-1α had no effect on cell number on any day tested (Fig. 3).

We and others have reported that IL-6, IL-10, and TNF-α each enhances IgE and IgG4 production induced by IL-4 plus anti-CD40 mAb (4–6). As shown in Fig. 4 *A*, addition of anti-IL-6 mAb and anti-IL-10 Ab each inhibited IgE and IgG4 production in $sIgE^+$ and $sIgG4^+$ B cells, respectively, induced by IL-4 plus anti-CD40 mAb, whereas anti-TNF-α mAb, IFN-α, and IFN-γ failed to do so. In contrast, anti-IL-10 Ab and anti-TNF-α mAb each inhibited IgE and IgG4 production in those cells induced by IL-4 plus anti-CD58 mAb, whereas anti-IL-6 mAb, IFN-α, and IFN-γ each failed to do so (Fig. 4 *B*). On the other hand, anti-IL-6 mAb, anti-IL-10 Ab, and anti-anti-TNF-α mAb

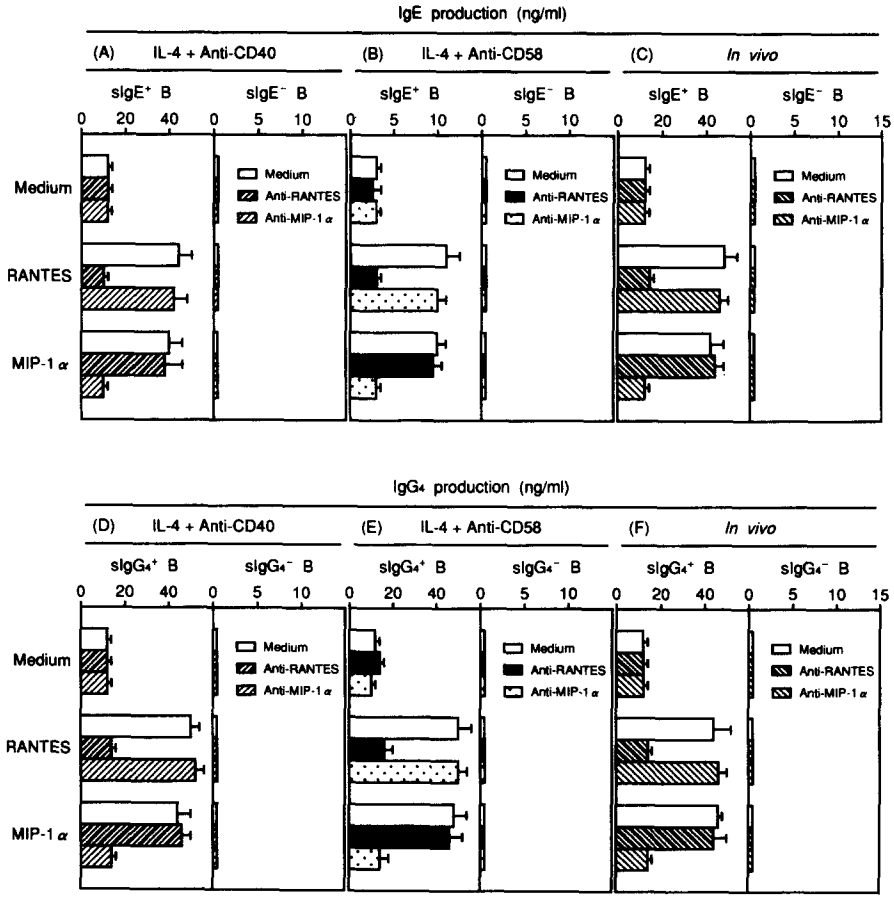

Figure 2. Effects of RANTES or MIP-1α on IgE and IgG4 production in sIg^+ or sIg^- B cells. $sIgE^+$ or $sIgE^-$ B cells (*A–C*), and $sIgG4^+$ or $sIgG4^-$ B cells (*D–F*) induced by IL-4 plus anti-CD40 mAb (*A* and *D*), IL-4 plus anti-CD58 mAb (*B* and *E*), or in vivo (*C* and *F*) were cultured with RANTES (100 nM) or MIP-1α (100 nM) in the presence or absence of Abs (10 μg/ml), and production of IgE (*A–C*) and IgG4 (*D–F*) was determined.

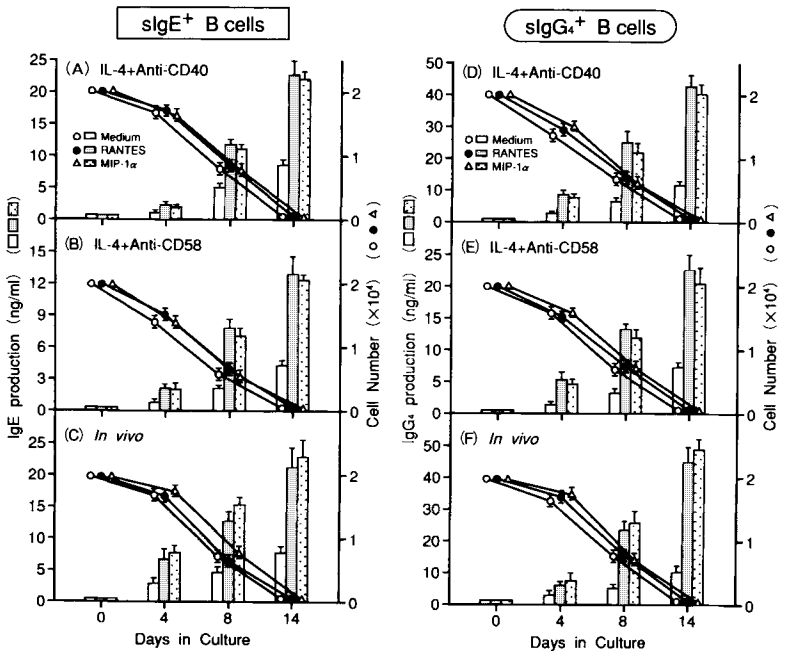

Figure 3. Kinetic study of the effects of RANTES and MIP-1α on sIgE$^+$ and sIgG4$^+$ B cells. Purified sIgE$^+$ B cells (*A–C*) or sIgG4$^+$ B cells (*D–F*) induced by IL-4 plus anti-CD40 mAb (*A* and *D*), IL-4 plus anti-CD58 mAb (*B* and *E*) or in vivo (*C* and *F*) were cultured with medium, RANTES (100 nM), or MIP-1α (100 nM), and Ig production and cell number were determined on days 0–14.

each inhibited IgE and IgG4 production in *in vivo*–generated sIgE$^+$ and sIgG4$^+$ B cells, although neither IFN-α nor IFN-γ inhibited those responses (Fig. 4 *C*). However, none of these Abs inhibited enhancement induced by RANTES or MIP-1α (Fig. 4, *A–C*). None of IL-1β, -2, -3, -7, or -9 at 300 U/ml, and none of IL-5, -11, -12, or -13 at 500 ng/ml affected IgE and IgG4 production by sIgE$^+$ and sIgG4$^+$ B cells, respectively, in these culture systems. Moreover, Abs to these cytokines also were without effects (<20% enhancement or inhibition). The effective neutralizing effects of endogenously produced cytokines with neutralizing Abs may be due to the FCS-free medium used in our culture system, since FCS induced TNF-α production endogenously (20). We also measured IL-10 production by *in vivo*–generated sIgE$^+$ and sIgG4$^+$ B cells. After 3 d of culture, IL-10 production (picograms per milliliter) by sIgE$^+$ and sIgG4$^+$ B cells cultured with medium, RANTES (100 nM) and MIP-1α (100 nM) was 322 ± 41 and 410 ± 62, 338 ± 57 and 425 ± 31, and 309 ± 48 and 402 ± 55, respectively (n = 4). Similarly, neither RANTES nor MIP-1α induced mRNA for IL-10 by PCR (<20% enhancement of control by densitometry). Similar findings were observed in sIgE$^+$ and sIgG4$^+$ B cells induced by IL-4 plus anti-CD40 mAb, or by IL-4 plus anti-CD58 mAb (our manuscript in preparation).

Taken together, these findings indicate that the require-

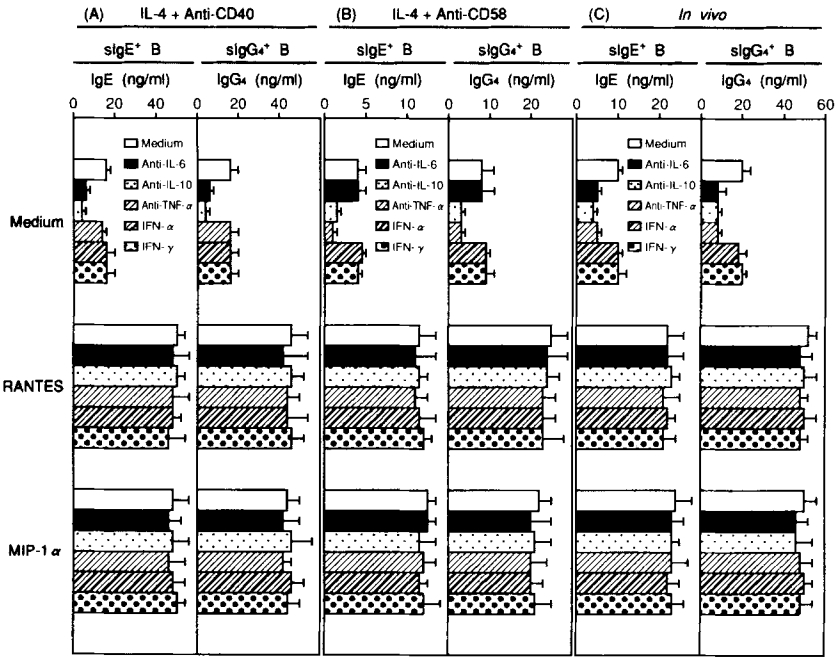

Figure 4. Effects of various factors on enhancement of IgE and IgG4 production by RANTES and MIP-1α. Purified sIgE$^+$ B cells and sIgG4$^+$ B cells induced by IL-4 plus anti-CD40 mAb (*A*), IL-4 plus anti-CD58 mAb (*B*), or in vivo (*C*) were cultured with medium, RANTES (100 nM) or MIP-1α (100 nM) , and various factors were added. All the Abs were used at 10 μg/ml, and IFN-α and IFN-γ at 1,000 U/ml. After 14 d of culture, IgE and IgG4 production were determined.

ment for endogenous cytokines for IgE and IgG4 production in $sIgE^+$ and $sIgG4^+$ B cells differed depending on the inductive stimuli. IL-6 and IL-10, but not TNF-α, were required by $sIgE^+$ and $sIgG4^+$ B cells induced by IL-4 plus anti-CD40 mAb, whereas IL-10 and TNF-α, but not IL-6, were required by $sIgE^+$ and $sIgG4^+$ B cells induced by IL-4 plus anti-CD58 mAb. In contrast, IL-6, IL-10, and TNF-α were all required by $sIgE^+$ and $sIgG4^+$ B cells generated in vivo. These findings were consistent with previous findings that anti-TNF-α mAb failed to block IgE and IgG4 production induced by IL-4 plus anti-CD40 mAb (5), and that IL-6 did not affect IgE production induced by IL-4 plus anti-CD58 mAb (8).

It is possible that the selective stimulation of $sIgE^+$ and $sIgG4^+$, but not $sIgE^-$ and $sIgG4^-$ B cells, by RANTES and MIP-1α may be due to the presence or absence of receptors on these cells. Therefore, expression of receptors for RANTES, MIP-1α, and other chemokines was studied by binding assay. Binding (ΔMFI) of RANTES in $sIgE^+$ and $sIgG4^+$ B cells generated by IL-4 plus anti-CD40 mAb, IL-4 plus anti-CD58 mAb, and in vivo, was 39 ± 11 and 43 ± 16, 42 ± 10 and 34 ± 7, and 48 ± 9 and 46 ± 10, respectively (n = 4). On the other hand, binding (ΔMFI) of MIP-1α in $sIgE^+$ and $sIgG4^+$ B cells generated by IL-4 plus anti-CD40 mAb, IL-4 plus anti-CD58 mAb, and in vivo, was 37 ± 12 and 42 ± 7, 33 ± 6 and 35 ± 7, and 49 ± 8 and 43 ± 8, respectively (n = 4). In contrast, none of the $sIgE^-$ and $sIgG4^-$ B cells generated in vitro or in vivo expressed receptors for RANTES or MIP-1α (<3 ΔMFI) (n = 4). Moreover, none of $sIgE^+$, $sIgG4^+$, $sIgE^-$ or $sIgG4^-$ B cells expressed receptors for NAP-2, β-TG, PF-4, GRO, IP-10, MIP-1β, or MCP-1(<3 ΔMFI) (n = 4).

In conclusion, of various chemokines tested, RANTES and MIP-1α selectively enhanced IgE and IgG4 production by directly stimulating $sIgE^+$ and $sIgG4^+$ B cells generated in vitro and in vivo. The differences between the effects of RANTES and MIP-1β and those of other chemokines were due to selective expression of receptors for RANTES and MIP-1α on $sIgE^+$ and $sIgG4^+$ B cells. In contrast, receptors for other chemokines including NAP-2, β-TG, PF-4, GRO, IP-10, MIP-1β, and MCP-1 were not found on $sIgE^+$ and $sIgG4^+$ B cells. This is not surprising. It has been reported that receptors for RANTES and MIP-1α, but not for MIP-1β, were found in subpopulations of B cells (21, 22). We have previously reported that IL-8 selectively inhibited IgE and IgG4 production (16). Moreover, it is well established that chemokines do differ in their effects depending upon target cells or experimental conditions. For example, MIP-1α inhibited colony formation of myeloid progenitor cells stimulated with steel factor, whereas MIP-1β, GRO, and NAP-2 failed do so (13). RANTES and MIP-1α induced migration of eosinophils, while MIP-1β or MCP-1 did not (23).

The in vivo effects of RANTES and MIP-1α on IgE and IgG4 production remain to be elucidated. However, it has been reported that alveolar macrophages from patients with asthma produced RANTES and MIP-1α, and that IgE and IgG4 concentrations in bronchoalveolar lavage fluid (BALF) were elevated in such patients (2, 24–26). Consistent with this, we found that RANTES and MIP-1α concentrations in BALF were higher in asthmatic patients (58 ± 13 pg/ml RANTES and 48 ± 9 pg/ml MIP-1α, n = 4) with elevated concentrations of BALF IgE (2,785 ± 648 pg/ml) and IgG4 (738 ± 149 ng/ml) than in asthmatic patients (24 ± 5 pg/ml RANTES and 19 ± 4 pg/ml MIP-1α, n = 4) without elevated concentrations of BALF IgE (312 ± 172 pg/ml) or IgG4 (129 ± 42 ng/ml).

We have previously reported that chemokine IL-8 selectively inhibits IgE and IgG4 production, whereas it also inhibits the growth of B cells, and that mRNA for IL-8RI and IL-8RII is found in B cells (16, 27, 28). Conversely, the number of B cells was found to be greatly increased in mice that lacked IL-8R homologue (15). Taken together, these findings indicate that chemokines may play roles in Ig production by and growth of B cells. Detailed molecular analysis of the effects of RANTES and MIP-1α on B cells is currently in progress.

We thank Takeda Chemical Industries for kindly providing the human recombinant IL-2 and IFN-α used in this study, and for their continuing cooperation in our research.

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 Hospital, 54, Kawahara-cho, Shogoin, Sakyo-ku, Kyoto 606-01, Japan.

Received for publication 11 May 1995 and in revised form 12 December 1995.

References

1. 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.* 90:3730–3734.
2. Kimata, H., and M. Fujimoto. 1994. Growth hormone and insulin-like growth factor I induce immunoglobulin (Ig)E and IgG4 production by human B cells. *J. Exp. Med.* 180:

727–732.
3. 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.* 146:1836–1842.
4. Kimata, H, and H. Mikawa. 1993. Nedocromil sodium selectively inhibits IgE and IgG4 production in human B cells stimulated with IL-4. *J. Immunol.* 151:6723–6732.
5. Aversa, G., J. Punnonen, and J.E. de Vries. 1993. The 26-kD transmembrane form of tumor necrosis factor α on activated $CD4^+$ T cell clones provides a costimulatory signal for human B cell activation. *J. Exp. Med.* 177:1575–1585.
6. Kimata, H. 1995. Differential effects of gangliosides on human IgE and IgG4 production. *Eur. J. Immunol.* 25:302–305.
7. Kiniwa, M., M. Gately, U. Gubler, R. Chizzonite, C. Fargas, and G. Delespesse. 1992. Recombinant interleukin-12 suppresses the synthesis of immunoglobulin E by interleukin-4 stimulated human lymphocytes. *J. Clin. Invest.* 90:262–266.
8. Diaz-Sanchez, D., S. Chegini, K. Chang, and A. Saxon. 1994. CD58 (LFA-3) stimulation provides a signal for human isotype switching and IgE production distinct from CD40. *J. Immunol.* 153:10–19.
9. 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.* 144:429–442.
10. Kimata, H., A. Yoshida, M. Fujimoto, and H. Mikawa. 1993. Effect of vasoactive intestinal peptide, somatostatin, and substance P on spontaneous IgE and IgG4 production in atopic patients. *J. Immunol.* 150:4630–4640.
11. Oppenheim, J.J., C.O.C. Zacharide, N. Mukaida, and K. Matsushima. 1991. Properties of the novel proinflammatory supergene "intercrine" cytokine family. *Annu. Rev. Immunol.* 9:617–648.
12. Schall, T.J., K. Bacon, K.J. Toy, and D.V. Goeddel. 1990. Selective attraction of monocytes and T lymphocytes of the memory phenotype by cytokine RANTES. *Nature. (Lond.).* 347:669–671.
13. Broxymer, H.E., B. Sherry, L. Lu, S. Cooper, L. Liu, R. Maze, M.P. Beckmann, A. Cersmi, and P. Ralph. 1993. Comparative analysis of the human macrophage inflammatory protein family of cytokines (chemokines) on proliferation of human myeloid progenitor cells: interacting effects involving suppression, synergistic suppression, and blocking of suppression. *J. Immunol.* 150:3448–3458.
14. Meuer, R., G.V. Riper, W. Feeney, P. Cuningham, D. Hora, Jr., M.S. Springer, D.E. MacIntyre, and H. Rosen. Formation of eosinophilic and monocytic intradermal inflammatory sites in the dog by injection of human RANTES but not human monocyte chemoattractant protein 1, human macrophage inflammatory protein 1α, or human interleukin 8. *J. Exp. Med.* 178:1913–1921.
15. Cacalano, G., J. Lee, K. Kikly, A.M. Ryan, S. Pitts-Meek, B. Hultgren, W.I. Eood, and M.W. Moore. 1994. Neutrophil and B cell expansion in mice that lack the murine IL-8 receptor homolog. *Science (Wash. DC).* 265:682–684.
16. 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.* 176:1227–1231.
17. Kimata, H., and A. Yoshida. 1994. Differential effects of gangliosides on immunoglobulin production and proliferation by human B cells. *Blood.* 84:1194–1200.
18. Kimata, H., A. Yoshida, C. Ishioka, and H. Mikawa. 1991. Effect of recombinant human erythropoietin on human IgE production *in vitro*. *Clin. Exp. immunol.* 83:483–487.
19. Wu, C.Y., M. Sarfati, C. Heusser, S. Fournier, M. Rubio-Trujillo, R. Peleman, and G. Delespesse. 1991. Glucocorticoids increase the synthesis of immunoglobulin E by interleukin 4-stimulated human lymphocytes. *J. Clin. Invest.* 87: 870–877.
20. Rodríguez, C., E. Roldán, G. Navas, and J.A. Brieva. 1993. Essential role of tumor necrosis factor-α in the differentiation of human tonsil *in vivo* induced B cells capable of spontaneous and high-rate immunoglobulin secretion. *Eur. J. Immunol.* 23:1160–1164.
21. Gao, J.-L., D.B. Kuhns, H.L. Tiffany, D. McDermott, X. Li, U. Francke, and P.M. Murphy. 1993. Structure and functional expression of the human macrophage inflammatory protein 1 α/RANTES receptor. *J. Exp. Med.* 177:1421–1427.
22. Schall, T.J., K. Bacon, R. Camp, J.W. Kaspari, and D.V. Goeddel. 1993. Human macrophage inflammatory protein α (MIP-1α) and MIP-1β chemokines attract distinct populations of lymphocytes. *J. Exp. Med.* 177:1821–1825.
23. Rot, A., M. Krieger, T. Brunner, S.C. Bishoff, T.J. Schall, and C.A. Dahinden. 1992. RANTES and macrophage inflammatory protein 1α induce the migration and activation of normal human eosinophil granulocytes. *J. Exp. Med.* 176: 1489–1495.
24. Gosset, P., A.B. Tonnel, M. Joseph, L. Prin, A. Mallart, J. Charon, and A. Capron. 1984. Secretion of a chemotactic factor for neutrophils and eosinophils by alveolar macrophages from asthmatic patients. *J. Allergy. Clin. Immunol.* 74: 827–834.
25. Diaz, P., F.R. Galleguillos, M.C. Gonzalez, C.F.A. Pantin, and A.B. Kay. 1984. Bronchoalveolar lavage in asthma: the effect of disodium cromoglycate (cromolyn) on leukocyte count, immunoglobulin, and complement. *J. Allergy. Clin. Immunol.* 74:41–48.
26. Out, T.A., E.A. Van De Graaf, N.J. Van Den Berg, and H.M. Jansen. IgG subclasses in bronchoalveolar lavage fluid from patients with asthma. *Scand. J. Immunol.* 33:719–727.
27. Kimata, H., and I. Lindley. 1994. Interleukin-8 differentially modulates interleukin-4– and interleukin-2–induced human B cell growth. *Eur. J. Immunol.* 24:3297–3240.
28. Kimata, H., M. Fujimoto, I. Lindley, and K. Furusho. 1995. Interleukin 8 (IL-8) inhibits the interleukin 4 (IL-4)–induced but not the spontaneous growth of human B cells via mechanisms that may involve protein kinase C. *Biochem. Biophys. Res. Commun.* 207:1044–1050.