HUMAN RECOMBINANT INTERLEUKIN 4 INDUCES Fcε RECEPTORS (CD23) ON NORMAL HUMAN B LYMPHOCYTES

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We have recently reported (1) the isolation of a cDNA sequence coding for human IL-4 B cell stimulatory factor 1 (BSF_1).[1] This lymphokine is a T cell–derived glycoprotein consisting of 129 amino acids with two potential *N*-glycosylation sites. Human IL-4 is able to induce the proliferation of activated B lymphocytes (Defrance, T., B. Vanbervliet, J. P. Aubry, et al., manuscript submitted for publication) and activated T lymphocytes (Spits, H., H. Yssel, Y. Takebe, et al. manuscript submitted for publication). During the course of our studies aimed at characterizing the phenotype of the B lymphocyte population proliferating in response to IL-4, we studied the expression of several activation markers. The most striking phenotypic modification mediated by IL-4 was the induction on B lymphocytes of the low-affinity receptor (R_L) for IgE ($Fc\epsilon R_L$/CD23) (2, 3), as determined by the binding of the $Fc\epsilon R_L$/CD23-specific mAb 25. We also show in this report that IFN-γ specifically inhibits the IL-4-mediated induction of $Fc\epsilon R_L$/CD23.

Materials and Methods

Reagents. Insolubilized rabbit anti–human IgM (Bio-Rad Laboratories, Richmond, CA) was used at the final concentration of 5 μg/ml. The anti $Fc\epsilon R_L$ (CD23 antigen)-specific mAb 25 was produced after immunizing mice with RPMI 8866 cells (2). The FITC-conjugated goat anti–mouse Ig used in the indirect immunofluorescence assays was purchased from Grub (Vienna, Austria). OKT mAbs were from Ortho Diagnostic Systems Inc. (Westwood, MA); Leu mAbs were from Becton Dickinson Monoclonal Center (Mountain View, CA); B1, MO2, and MO1 were from Coulter Immunology (Hialeah, FL).

Escherichia coli–derived rIFN-γ (10^7 IU/mg) was obtained from Schering Research, Bloomfield, NJ. IL-4 was obtained as supernatants from COS-7 cells transfected with pcD vector containing the human IL-4 cDNA clone (1). 1 U of IL-4 is defined as the amount providing a half-maximal [^{3}H]TdR uptake in activated PHA blasts (1). Some experiments were performed with purified IL-4. Mock preparations consisting of culture supernatants of COS-7 cells transfected with a nonrelated cDNA were also used. Human rIL-2 was

[1] *Abbreviations used in this paper:* AET, amino ethylisothiouronium bromide; BCGF, B cell growth factor; BSF_1, B cell stimulatory factor 1; cBCGF, commercial BCGF; EBV LCL, EBV-transformed lymphoblastoid cell lines; $Fc\epsilon R_L$, low-affinity receptor for IgE on lymphoid cells. FLS, forward light scatter; PLS, perpendicular light scatter; PY, pyronin Y.

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obtained as *E. coli* lysates from Dr. R. Kastelein at DNAX and as a purified protein from Amgen Biologicals (Thousand Oaks, CA). Human rIL-1α was obtained from Dr. Zurawski at DNAX in the form of *E. coli* lysates. It was purified by SDS-PAGE and the IL-1 was eluted from its migration area in the gel by reverse electrophoresis. A commercial preparation of a low-molecular-weight B cell growth factor (BCGF) purified from the culture supernatants of PHA-stimulated PBL was obtained from Cellular Products Inc. (Buffalo, NY) and is referred to in the text as commercial BCGF (cBCGF). This preparation was free from IL-2 and IFN-γ activity, as determined by measurement of the [^{3}H]-TdR uptake by the IL-2-dependent mouse T cell line CTLL-2 and an ELISA assay, respectively.

B Cell Preparations and Cultures. B cells were isolated either from tonsils or from blood cytapheresis residues. Mononuclear cells were separated by the standard Ficoll/Hypaque gradient method. Tonsil B cells were obtained by twice rosetting with amino ethyl isothiouronium bromide (AET)-treated SRBC, while blood B cells were submitted to a single rosetting with AET-treated SRBC followed by complement-mediated lysis of the remaining T cells with the use of anti-T3 (CD3), -T4 (CD4), -T8 (CD8), -T11 (CD2) mAbs. Depletion of blood monocytes, null cells and large granular lymphocytes was achieved by L-leucine methyl ester treatment according to the method described by Thiele et al. (4). The B cell–enriched populations obtained were typically >95% surface Ig-positive, >95% B1 antigen (CD20)-positive. <1% of the cells were positively stained by the T cell markers Leu-1, OKT4, OKT8, and OKT11 or by the monocyte markers: Leu-M3, MO1 (CD11), MO2 (CD14). <1% of the cells reacted with the NK cell markers: Leu-7 and Leu-11 (CD16).

Purified B cells were cultured at 10^6 cells/ml in Iscove's medium enriched with 50 μg/ml human transferrin, 5 μg/ml bovine insulin, 0.5% BSA, oleic, linoleic, and palmitic acids (all from Sigma Chemical Co., St. Louis, MO) as described by Yssel et al. (5). 2% FCS was added to the medium.

Analysis with a FACS. Fluorescence analysis was performed with a FACS 440 (Becton Dickinson & Co., Sunnyvale, CA) equipped with a 5 W argon laser running at 488 nm, 0.5 W. Fluorescence parameters were collected using a built in logarithmic amplifier after gating on the combination of forward light scatter (FLS) and perpendicular light scatter (PLS), which was used to discriminate viable from nonviable cells.

Cell Staining. 4×10^5 cells were incubated with 50 μl of the appropriately diluted mAb in 0.2-ml microtiter plate wells. After two washes with PBS containing 1% BSA, 0.01% sodium azide, cells were incubated with fluoresceinated $F(ab')_2$ fragments of goat anti-mouse Ig (Grub) for 30 min at 4°C. After three washes with PBS/BSA/azide, the cells were analyzed with the FACS.

Simultaneous Measurement of RNA Content and Surface Antigen Expression. The procedure used was adapted from Shapiro (6). 10^6 cells/ml in PBS/1% BSA/0.01% sodium azide were incubated at 37°C for 45 min with 5 μM pyronin Y (PY; Aldrich Chemical Co., Milwaukee, WI). After centrifugation the cells were resuspended in cold PBS/BSA containing 4 μM PY (PBS/PY) and the mAb was added at the appropriate dilution. After an incubation of 30 min at 4°C the cells were washed twice in cold PBS/PY then resuspended in PBS/PY containing the fluorescent-conjugated goat anti-mouse Ig. After 30 min at 4°C, the cells were washed twice with cold PBS/PY and resuspended in PBS/PY. Analyses were performed within 15 min after staining. 15,000 cells were recorded. The green fluorescence (530 nm) specific for antibody staining is recorded with logarithmic amplification; the red fluorescence (>600 nm) specific for RNA staining is recorded with linear amplification.

Results

IL-4 Specifically Induces the Expression of Fcε Receptors/CD23 on Normal Human B Cells. Highly purified tonsil B lymphocytes not stimulated or stimulated by insolubilized anti-IgM antibody were cultured with or without IL-4 (80 U/ml of a COS-7 cells transfection supernatant). After 24 or 48 h, cells were stained with

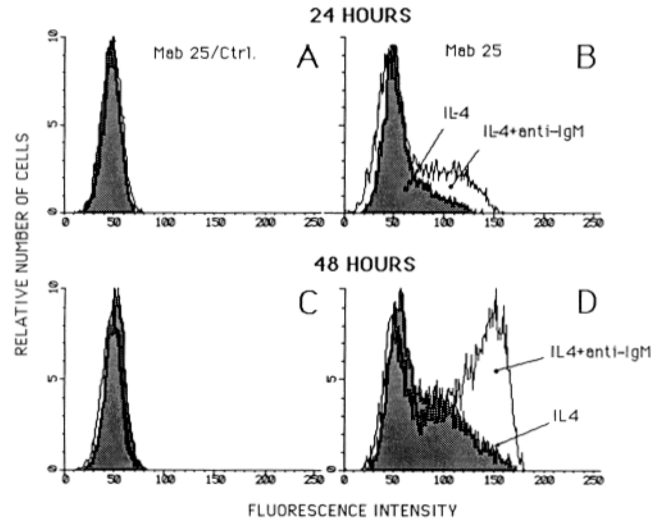

FIGURE 1. IL-4 induces the expression of $Fc\epsilon R_L$/CD23 on purified tonsil B cells. $Fc\epsilon R_L$/CD23 is detected by immunofluorescence flow cytometry with mAb 25, an anti-$Fc\epsilon R_L$/CD23 mAb. Purified tonsil B cells were cultured for 24 h (*A* and *B*) or 48 h (*C* and *D*) without (*A* and *C*) or with (*B* and *D*) IL-4, without or with insolubilized anti-IgM antibody (5 μg/ml). The IL-4 was a COS-7 transfection supernatant used at 80 U/ml.

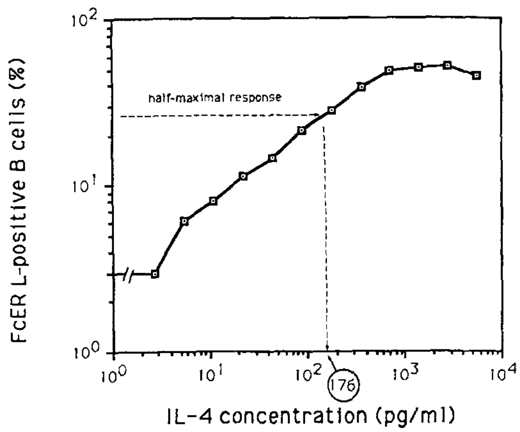

FIGURE 2. Highly purified IL-4 obtained from COS-7 transfection supernatants is able to induce $Fc\epsilon R_L$/CD23 on purified tonsil B cells. Purified tonsil B lymphocytes were cultured for 48 h with insolubilized anti-IgM antibodies and increasing concentrations of IL-4. The number of cells expressing $Fc\epsilon R_L$/CD23 was estimated by immunofluorescence flow cytometry after staining with mAb 25.

mAb 25, which is specific for the $Fc\epsilon R_L$/CD23. FACS histograms (Fig. 1) show that IL-4 is able to induce the expression of $Fc\epsilon R_L$/CD23 on nonactivated B cells but that the concomitant activation with anti-IgM antibodies increases the number of cells expressing $Fc\epsilon R_L$/CD23 as well as the intensity of $Fc\epsilon R_L$/CD23 expression on these cells. The nonactivated and the anti-IgM-activated B lymphocytes cultured with a mock COS-7 transfection supernatant did not significantly express $Fc\epsilon R_L$/CD23. The IL-4-induced expression of $Fc\epsilon R_L$/CD23 was confirmed by the binding of soluble IgE as assessed by flow cytometry after successive incubations of the cells with soluble IgE, an anti-IgE-specific mAb, and a FITC-labeled goat anti-mouse Ig conjugate (data not shown).

To determine the concentration that induces optimal $Fc\epsilon R_L$/CD23 induction, experiments were carried out with highly purified rIL-4 obtained from transfected COS-7 supernatants. Data in Fig. 2 show that the maximum expression of $Fc\epsilon R_L$/CD23 on anti-IgM-activated B cells is obtained with 700 pg/ml IL-4. The half-maximal induction of $Fc\epsilon R_L$/CD23 is obtained with ~176 pg/ml IL-4.

It has been shown that activated B lymphocytes can proliferate in response to

TABLE I
The Induction of Fcϵ Receptor/CD23 on Normal B Cells Is Specific for IL-4

Cytokine added	$Fc\epsilon R_L^+$ cells*	
	No activation	Anti-IgM activated
	%	
0	1 ± 1	3 ± 2
Mock COS-7 (1%)	1 ± 1	1 ± 1
IL-4 (80 U/ml)	20 ± 2	48 ± 4
IL-1α (10 IU/ml)	1 ± 1	2 ± 1
IL-2 (20 IU/ml)	2 ± 1	1 ± 1
IFN-γ (50 U/ml)	2 ± 1	2 ± 1
IFN-γ (1,000 U/ml)	4 ± 1	1 ± 1
cBCGF (20%)	1 ± 1	1 ± 1
UD 58 supernatant (5%)‡	2 ± 1	1 ± 1
RPMI 8866 supernatant (20%)‡	3 ± 2	3 ± 1
HG 120 supernatant (10%)§	2 ± 1	1 ± 1

* Purified tonsil B cells were cultured for 48 h with the different cytokines and the $Fc\epsilon R_L$/CD23 expression was assessed by flow cytometry using mAb 25.
‡ Supernatants from EBV-transformed cell lines containing BCGF activity as determined on anti-IgM-preactivated B cells but no IL-4, as determined by Northern analysis of isolated mRNA.
§ Supernatant from an allogeneic IL-2-dependent T cell clone stimulated by its specific alloantigen and containing IL-2, IFN-γ, and BCGF activities.

many different lymphokines: IL-4 (Defrance, T., B. Vanbervliet, J. B. Aubrey, et al., manuscript submitted for publication), a low-molecular-weight BCGF (7), a high-molecular-weight BCGF (8), B cell–derived BCGFs (9, 10), IL-2 (11), IL-1 (12, 13), and IFN-γ (14, 15). However, IL-2, IL-1α, IFN-γ, a low-molecular-weight BCGF (cBCGF as obtained from Cellular Products Inc.), B cell–derived BCGF (as obtained from EBV-transformed B cell line supernatants), and a T cell clone supernatant (containing IL-2, IFN-γ, and BCGF) were unable to induce $Fc\epsilon R_L$/CD23 expression (Table I). cBCGF that cooperates with IL-4 for the proliferation of activated B lymphocytes (Defrance, T., B. Vanbervliet, J. B. Aubrey, et al., manuscript submitted for publication) does not alter the induction of $Fc\epsilon R_L$/CD23 on B cells (data not shown). The induction of $Fc\epsilon R_L$/CD23 on normal B cells by IL-4 therefore seems to be a specific property of this lymphokine.

IFN-γ Inhibits the IL-4-induced $Fc\epsilon R_L$/CD23 Expression. Since we failed to demonstrate the presence of $Fc\epsilon R_L$/CD23-inducing activity in many T cell clone supernatants, including clone 2F1 from which the IL-4 cDNA was isolated, we investigated whether these T cell clone supernatants would contain factors inhibiting the IL-4-induced $Fc\epsilon R_L$/CD23 expression on normal B lymphocytes. Recombinant lymphokines (IL-1, IL-2, IFN-γ) were assayed for their potential inhibitory action on the IL-4-induced $Fc\epsilon R_L$/CD23 on B cells. The supernatant of clone 2F1 was found to strongly inhibit the IL-4-induced expression of $Fc\epsilon R_L$/CD23 (data not shown). Among the three recombinant lymphokines

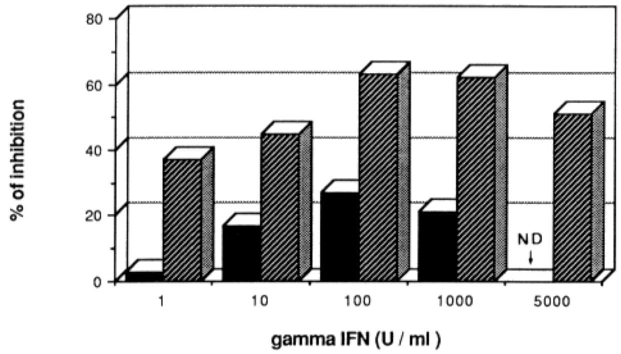

FIGURE 3. IFN-γ strongly inhibits the IL-4-induced FcϵR$_L$/CD23 expression on normal B lymphocytes. B cells were cultured with insolubilized anti-IgM antibody and IL-4 (COS-7 transfection supernatant 80 U/ml) for 24 h (■) or 48 h (▨). The percentage of FcϵR$_L$/CD23-positive cells was estimated by immunofluorescence flow cytometry after staining with mAb 25. The culture point 5,000 U/ml was not tested at 24 h.

tested, IFN-γ was found to be a very potent inhibitor of the IL-4-induced FcϵR$_L$/CD23 expression, while neither IL-1 nor IL-2, nor cBCGF affected the induction of the FcϵR$_L$/CD23 (data not shown). Data in Fig. 3 show that concentrations of IFN-γ as low as 1 U/ml can partially inhibit the FcϵR$_L$/CD23 induction. Inhibition of IL-4-induced FcϵR$_L$/CD23 expression by IFN-γ was observed after 24 h of culture, but optimal inhibition was obtained after a 48-h incubation period. At optimal concentrations of IL-4, IFN-γ did not totally block the induction of FcϵR$_L$/CD23, while a complete inhibition of FcϵR$_L$/CD23 induction could be obtained with IFN-γ when suboptimal concentrations of IL-4 were used (data not shown). These data demonstrate that IFN-γ strongly antagonizes IL-4-induced FcϵR$_L$/CD23 expression on B cells.

IL-4 Induces the Expression of FcϵR$_L$/CD23 on B Cells in the G_0 Phase of the Cycle. Although IL-4 induces FcϵR$_L$/CD23 on tonsil B cells without preactivation, it has to be taken into account that the B cells studied here were obtained from donors with tonsillitis. This implies that a significant proportion of the B cells used were preactivated in vivo. To determine whether IL-4 induced FcϵR$_L$/CD23 on nonpreactivated B cells, the RNA content of the cells expressing FcϵR$_L$/CD23 was measured simultaneously. IL-4 alone (Fig. 4*A*) or in combination with insolubilized anti-IgM antibody (Fig. 4*B*) induced FcϵR$_L$/CD23 on a fraction of nonactivated B cells with low RNA contents but on an activated B cell fraction with relatively high RNA contents. The notion that preactivation of the B cells is not required for the induction of FcϵR$_L$/CD23 by IL-4 is also supported by the finding that IL-4 induced a strong expression of FcϵR$_L$/CD23 on peripheral blood B cells that are in the G_0 phase of the cell cycle, as well as on high-density tonsillar B cells obtained after Percoll-gradient centrifugation (data not shown).

Taken together these data strongly suggest that resting B cells express functional IL-4 receptors and demonstrate that not all the activated B cells express FcϵR$_L$/CD23 upon culture with IL-4.

Discussion

In the present study we have demonstrated that human rIL-4 (BSF$_1$) (1) is able to induce the expression of FcϵR$_L$/CD23 on human B lymphocytes. This has been demonstrated using the binding of the FcϵR$_L$/CD23 mAb 25 (2) or the binding of soluble IgE (data not shown). Concomitant B cell activation by

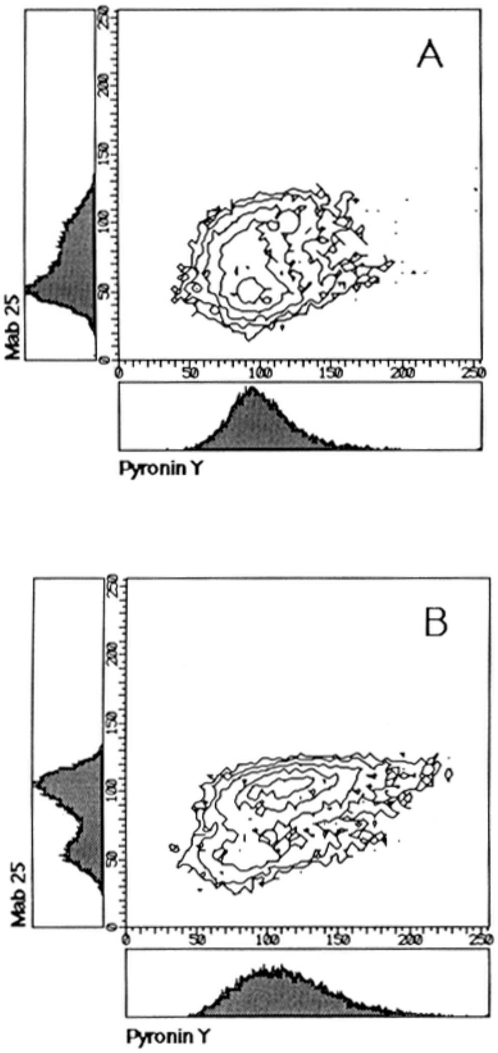

FIGURE 4. IL-4 induces $Fc\epsilon R_L$/CD23 on B cells in the G_0 phase of the cycle. Purified tonsil B cells were cultured for 24 h with IL-4 (*A*) or IL-4 and anti-IgM antibody (*B*). Cells were stained with biotinylated mAb 25/FITC-conjugated avidin (green fluorescence, ordinate, log scale) and PY (red fluorescence, abscissa, linear scale) and were analyzed by double-fluorescence flow cytometry as described under Materials and Methods. The IL-4 was a COS-7 transfection supernatant used at 80 U/ml.

insolubilized anti-IgM antibody resulted in enhanced $Fc\epsilon R_L$/CD23 induction by IL-4, suggesting an increased expression of IL-4 receptors on B cells. The finding that activation of the B cells enhanced IL-4-mediated $Fc\epsilon R_L$/CD23 induction suggested that IL-4 alone was inducing $Fc\epsilon R_L$/CD23 on the in vivo–preactivated B cells that are known to represent a significant proportion of tonsillar B lymphocytes. This however turned out not to be the case since double-fluorescence analysis carried out with mAb 25 and PY demonstrated that IL-4 induced $Fc\epsilon R_L$/CD23 on B cells containing low levels of RNA (a characteristic of cells in the G_0 phase of the cycle) and on B cells with increased levels of RNA (G_1 phase of the cycle).

The induction of $Fc\epsilon R_L$/CD23 on B cells seems to be specific for IL-4. rIL-2, rIFN-γ, rIL-1α, semipurified low-molecular-weight BCGF or the supernatant of EBV lymphoblastoid cell lines (LCL) containing BCGF activity but no IL-4 (as determined by the absence of IL-4 mRNA in the cell line) were unable to induce FcϵR$_L$/CD23 expression on normal B cells. Human rIL-4 has a FcϵR$_L$/CD23-inducing activity comparable to the lymphokine purified from PHA-activated mononuclear cells supernatants studied by Suemura et al. (16). None of the tested lymphokines acted in concert or in synergy with IL-4, but interestingly, IFN-γ strongly inhibited the FcϵR$_L$/CD23-inducing effect of IL-4. Strong inhibitory effects were observed at IFN-γ concentrations of 1 IU/ml. Although considerable blocking effects were obtained after 24 h of incubation with IL-4, the effect was most pronounced after 48 h. The mechanism by which IFN-γ blocks IL-4-induced FcϵR$_L$/CD23 expression is presently under investigation. This inhibitory effect of IFN-γ is in line with the described antagonizing effects of murine IFN-γ on the proliferation of anti-IgM-activated B cells (17), the increase of class II MHC antigens on B cells, the increase in cell size (18, 19), and IgE and IgG1 production by LPS blasts (20) induced by IL-4. By contrast, the IL-4-induced proliferation of preactivated human B cells was stimulated by IFN-γ (Defrance, T., B. Vanbervliet, J. P. Aubrey, et al., manuscript submitted for publication).

At the present time the biological significance of the IL-4-induced FcϵR$_L$/CD23 expression is unclear. The recent suggestion by Gordon et al. (21, 22) that the CD23 antigen may be the receptor for the low-molecular-weight BCGF (7) is worth considering, since it is in line with our data that indicate that IL-4 synergizes with the low-molecular-weight BCGF in inducing the proliferation of preactivated B cells (Defrance, T., B. Vanbervliet, J. P. Aubrey, et al., manuscript submitted for publication). The demonstration that IL-4 is able to induce (*a*) FcϵR$_L$ on human B lymphocytes, (*b*) the proliferation of murine mast cells, and (*c*) IgE production by murine LPS blasts, demonstrates that IL-4 plays a major role in the IgE system at both the regulatory and the effector levels since it has been suggested that FcϵR$_L^+$ B cells play a major role in the regulation of IgE secretion (23). This hypothesis is confirmed by the recent finding that the in vivo injection of a mAb specific for mouse IL-4 (24) into *Nippostrongylus brasiliensis*–infected mice abrogates the induction of IgE production mediated by this treatment (25). The biological functions of FcϵR$_L$/CD23 on B lymphocytes and the biological significance of its modulation by IL-4 and IFN-γ remain to be determined.

Summary

Human rIL-4 is able to induce the expression of low-affinity receptors for IgE (FcϵR$_L$/CD23) on resting B lymphocytes, as determined by the binding of either the anti FcϵR$_L$/CD23-specific mAb 25 or IgE. Stimulation of B cells with insolubilized anti-IgM antibody increases the number of cells expressing FcϵR$_L$/CD23 upon culturing with IL-4 and enhances the level of FcϵR$_L$/CD23 expression on these cells. FcϵR$_L$/CD23 induction is specific for IL-4 since IL-1α, IL-2, IFN-γ, B cell–derived B cell growth factor (BCGF), and a low-molecular-weight BCGF were ineffective. IFN-γ strongly inhibited the induction of FcϵR$_L$/CD23 by IL-4.

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