

Regulation of Cytokine Production by Soluble CD23: Costimulation of Interferon γ Secretion and Triggering of Tumor Necrosis Factor α Release

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Summary

Soluble CD23 (sCD23) has multiple IgE-independent biological activities. In the present study, we examined the regulatory effect of sCD23 on cytokine production by human peripheral blood mononuclear cells (PBMC). We show that sCD23 enhances by about 80-fold the interleukin 2 (IL-2)-induced interferon γ (IFN- γ) production and by about 10-fold the response to IL-12. This potentiating activity is time and dose dependent and is not associated with a significant effect on DNA synthesis. The sCD23 costimulatory activity for IFN- γ synthesis is drastically reduced in monocyte-depleted PBMC, suggesting that monocytes may be the target for sCD23. This hypothesis was supported by the following observations. First, sCD23 alone is a potent inducer of tumor necrosis factor α (TNF- α) production by PBMC and this effect disappears after monocyte depletion. The triggering of TNF- α release is specifically inhibited by neutralizing anti-CD23 monoclonal antibody (mAb). In addition, IL-2 and IL-12 synergize with sCD23 to induce TNF- α production. Second, sCD23 triggers the release of other inflammatory mediators such as IL-1 α , IL-1 β , and IL-6. Finally, TNF- α production in response to IL-2 and sCD23 precedes IFN- γ and IFN- γ secretion is significantly inhibited by anti-TNF- α mAb, indicating that the sCD23 costimulatory signal for IFN- γ production may be partially mediated by TNF- α release. It is proposed that sCD23 is a proinflammatory cytokine that, in addition, may play an important role in the control of the immune response via the enhancement of IFN- γ production.

The CD23 antigen (low affinity receptor for IgE) (FceRII) is a 45-kD membrane type II glycoprotein mainly expressed on B lymphocytes and monocytes (1). However, it can also be found on a variety of hematopoietic cells including eosinophils, platelets, and T cells (1). Membrane CD23 is cleaved by autoproteolysis into soluble forms of various molecular sizes (2, 3). Although CD23 and its soluble products were demonstrated to be involved in IgE regulation (4, 5), most of the activities ascribed to soluble CD23 are pleiotropic and IgE independent. These include costimulation with IL-1 of prothymocyte maturation (6), myeloid precursor cell growth (7), prevention of apoptosis of germinal center B cells (8), and increase of histamine release by human basophils (9). The last two activities are shared by some anti-CD21 mAbs (8, 9), inasmuch as CD21 is reported to be a novel ligand for CD23 (10).

IL-4 and, more recently, IL-13, are the most potent inducers of CD23 and sCD23 in B cells (11, 12). In addition to IL-4, both IL-3 and GM-CSF increase CD23 expression and sCD23 release by human monocytes (13). IFN- γ modulates CD23 expression by inhibiting the IL-4-induced CD23 expression on B cells (11). On monocytes, IFN- γ induces

sCD23 release, whereas its effects on surface CD23 expression is still debated (14–16). In the studies presented here, we investigated the regulatory activities of soluble CD23 (sCD23)¹ on cytokine production by unfractionated PBMC. We demonstrate that sCD23 costimulates IL-2 or IL-12-induced IFN- γ production and directly triggers TNF- α , IL-1 α , IL-1 β , and IL-6 release by human PBMC.

Materials and Methods

Reagents. Human recombinant IL-2 was kindly provided by Dr. D. Bron (Institut Bordet, Brussels, Belgium). Human recombinant IL-12 was a generous gift from Dr. M. Gately (Hoffmann-La Roche, Nutley, NJ). Affinity-purified recombinant sCD23, mAb to CD23 (clone 63), and class-matched control mAbs were prepared in our laboratory (17, 18). Neutralizing anti-TNF- α mAb was purchased from R & D Systems, Inc. (Minneapolis, MN). All mAbs, cytokines, media, and additives contained low endotoxin levels (<15 pg/ml) as determined by the chromogenic Limulus amoebocyte lysate (QCL-1000; BioWhittaker, Inc., Walkersville, MD).

¹ Abbreviation used in this paper: sCD23, soluble CD23.

Cell Preparation and Culture Conditions. PBMC were isolated by density gradient centrifugation of heparinized blood using Lymphoprep (Nycomed, Oslo, Norway). Monocyte depletion was achieved with anti-CD14 (Becton Dickinson & Co., Mountain View, CA)-coated goat anti-mouse IgG Dynabeads (Dyna, Oslo, Norway). PBMC and monocyte-depleted PBMC were cultured in quadruplicate at 10^6 /ml in 96-well flat-bottomed Falcon plates (Becton Dickinson, Lincoln Park, NJ) in complete serum-free HB101 medium (GIBCO BRL, Gaithersburg, MD) supplemented with 2 mM glutamine, 1 mM sodium pyruvate, 10 mM Hepes, 100 IU penicillin, and 100 μ g/ml streptomycin. For proliferation assay, cells were pulsed with 0.5 μ Ci [3 H]thymidine (Amersham Corp., Arlington Heights, IL) during the last 6 h of the culture period and [3 H]thymidine incorporation was measured by a standard liquid scintillation counter. For TNF- α , IL-1 α , IL-1 β , and IL-6 production, cultures were performed at 10^6 /ml in 5-ml sterile Falcon tubes (Becton Dickinson).

Lymphokine Determinations. IFN- γ was measured by two-site solid-phase RIA using anti-IFN- γ mAb (clone 42.25) to coat the solid phase and 125 I-labeled anti-IFN- γ mAb (clone KM48, provided by Dr. S. Alkan, Ciba-Geigy, Basel, Switzerland) as detecting probe. The cytokine-specific ELISA and their sensitivities were: IL-1 α (3.9 pg/ml), IL-1 β (3.9 pg/ml), and IL-6 (4.6 pg/ml) (R & D Systems, Inc.). TNF- α was assessed using a sandwich ELISA employing mouse mAb to human TNF- α (clone T144.B, kindly given by Dr. T. Nakajima, St. Mariana University School of Medicine, Kawasaki, Japan) and a polyclonal rabbit anti-TNF- α antibody received from Dr. J. Tavernier (Roche Research Institute, Ghent, Belgium). The assay was calibrated against the TNF- α standard obtained from the National Institute of Biological Standards and Control (Hertfordshire, England). The limit of detection for the TNF- α ELISA was 150 pg/ml.

Results

sCD23 Enhances IFN- γ Production. To determine the regulatory effects of sCD23 on IFN- γ production, normal human PBMC were stimulated for 3 d with either IL-2 or IL-12 in the presence of sCD23. As shown in Fig. 1, sCD23 strongly increases by \sim 80-fold the IL-2-induced IFN- γ production and enhances by \sim 10-fold the response to IL-12. Of note, sCD23 alone is unable to induce IFN- γ production. The costimulatory activity of sCD23 is observed at various cytokine concentrations ranging from 25 to 500 U/ml for IL-2 (Fig. 2), and from 10 to 60 pM for IL-12 (data not shown) suggesting that sCD23 lowers the threshold for cytokine-induced IFN- γ production by PBMC. To further investigate the regulation of IFN- γ production by sCD23, we examined the effect of varying the stimulation period and titrating the concentrations of sCD23. Time course analysis showed that the sCD23 potentiating activity is already observed at day 1 (mean \pm SD of three separate experiments: 228 ± 8 U/ml of IFN- γ in treated vs 8.6 ± 3.2 U/ml in untreated cultures) reaching plateau at day 5 (Fig. 3). sCD23 costimulates IFN- γ secretion in a dose-dependent manner (Fig. 4). Its effect is significant at 3 ng/ml whereas optimal enhancement of IFN- γ production is observed at concentrations between 25 and 50 ng/ml (data not shown). These data also indicate that sCD23 has little or no effect on IL-2- or IL-12-induced DNA synthesis strongly suggesting that the increase in IFN- γ production is not related to cell prolifera-

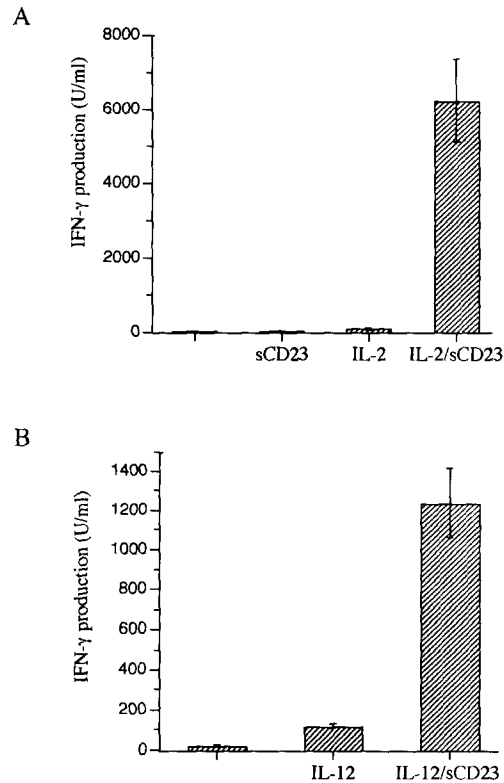


Figure 1. sCD23 increases IL-2- or IL-12-induced IFN- γ production. (A) PBMC were cultured with or without IL-2 (25 U/ml) or sCD23 (25 ng/ml) and in the presence of IL-2 plus sCD23. (B) PBMC were cultured with or without IL-12 (40 pM) and in the presence of IL-12 plus sCD23 (25 ng/ml). After 3 d, IFN- γ was measured in the culture supernatants. Data represent mean \pm SD of (A) 15 and (B) 11 experiments.

tion. Indeed, sCD23 augments the IL-2-induced steady state IFN- γ mRNA level (data not shown).

sCD23 Triggers TNF- α , IL-1, and IL-6 Release. The effector cells producing IFN- γ in response to IL-2 and IL-12 are

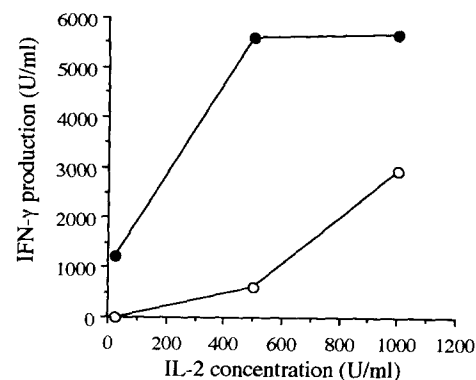


Figure 2. sCD23 lowers the threshold of IL-2-induced IFN- γ production. PBMC were cultured for 2 d with titrated concentrations of IL-2 (5–1,000 U/ml) in the absence (O) or presence (●) of sCD23 (25 ng/ml). IFN- γ was measured in culture supernatants. Data are representative of three experiments.

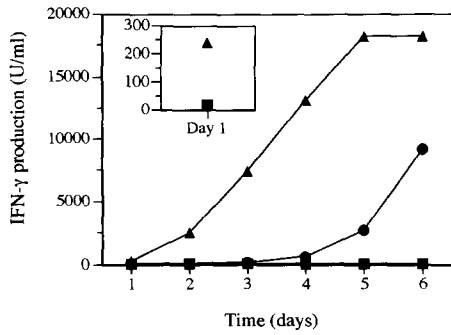


Figure 3. Kinetics of sCD23 enhancement of IL-2-induced IFN- γ production. PBMC were cultured in medium alone (■), IL-2 (25 U/ml) (●), or IL-2 plus sCD23 (25 ng/ml) (▲), and culture supernatants were collected at the indicated times and assessed for IFN- γ content. Data are representative of three experiments.

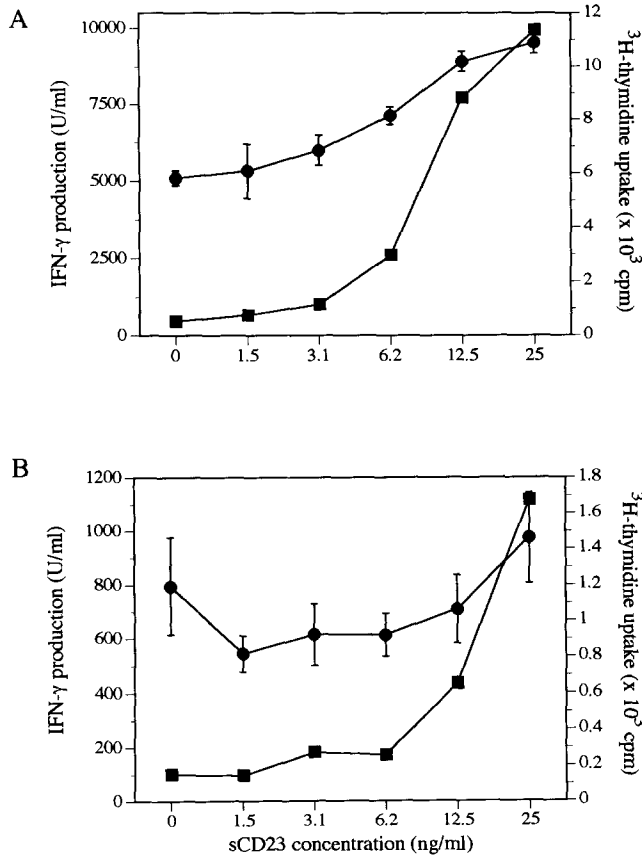


Figure 4. Dose-dependent effect of sCD23 on IL-2- or IL-12-induced IFN- γ production and proliferation. PBMC were incubated for 3 d with (A) IL-2 (25 U/ml) or (B) IL-12 (40 pM) and titrated concentrations of sCD23. Culture supernatants were collected and assessed for IFN- γ content (■), and [^3H]thymidine uptake was measured as described (●). Data represent mean \pm SD of quadruplicate samples and are representative of three experiments.

reported to be T and NK cells (19). However, this response is enhanced by monocyte-derived cytokines such as TNF- α and IL-1 (20–22). We therefore examined whether the presence of monocytes was required for sCD23 to increase IFN- γ by PBMC. The results in Table 1, show that monocyte depletion strongly reduces sCD23 ability to costimulate IFN- γ production. Most interestingly, these data indicate that sCD23 alone is a potent inducer of TNF- α secretion by PBMC. The absence of detectable amounts of TNF- α in monocyte-depleted PBMC suggests that the sCD23-induced TNF- α is largely derived from monocytes. The triggering of TNF- α release is time and dose dependent (Fig. 5 A) and specific (Fig. 5 B). Indeed, the TNF- α production in response to sCD23 alone or sCD23 and IL-2 is completely abolished by neutralizing anti-CD23 mAb with no effect of isotype-matched control mAb (Fig. 5 B). We next performed kinetic studies and showed that TNF- α secretion in response to IL-2 and sCD23 precedes IFN- γ production suggesting that the sCD23-induced TNF- α secretion by monocytes may partially mediate the costimulatory signal for PBMC IFN- γ production (Fig. 6 A). This hypothesis is supported by the observations that neutralizing anti-TNF- α mAb significantly decreases

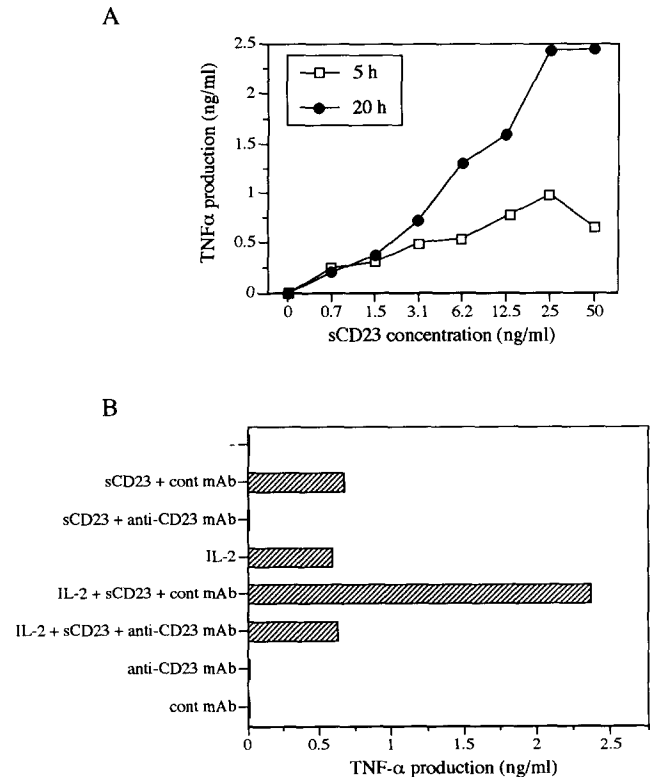


Figure 5. sCD23 specifically induces TNF- α production. (A) PBMC were cultured for 5 or 20 h with titrated concentrations of sCD23 and cell-free supernatants were tested for TNF- α release. Data are representative of two experiments. (B) PBMC were cultured for 20 h in the absence or presence of sCD23 (25 ng/ml), IL-2 (25 U/ml), or IL-2 and sCD23. Some cultures were supplemented with 30 $\mu\text{g/ml}$ of neutralizing anti-CD23 mAb or isotype-matched control mAb. Data are representative of five separate experiments.

Table 1. *TNF- α and IFN- γ Production by PBMC and Monocyte-depleted PBMC*

Stimulus	TNF- α (ng/ml)				IFN- γ (U/ml)			
	PBMC		Monocyte-depleted PBMC		PBMC		Monocyte-depleted PBMC	
	Exp 1	Exp 2	Exp 1	Exp 2	Exp 1	Exp 2	Exp 1	Exp 2
Nil	<0.15	<0.15	<0.15	<0.15	<10	<10	<10	<10
sCD23	1.75	0.51	<0.15	<0.15	<10	<10	<10	<10
IL-2	<0.15	0.27	<0.15	<0.15	72	94	26	<10
IL-2 + sCD23	1.97	0.90	<0.15	<0.15	2958	3374	236	64

PBMC or monocyte-depleted PBMC were cultured in the absence or presence of sCD23 (25 ng/ml), IL-2 (25 U/ml), or IL-2 and sCD23. TNF- α and IFN- γ production were measured in culture supernatants after 20 h and 3 d, respectively.

the IL-2 and sCD23-induced IFN- γ production (Fig. 6 B). Finally, we determined whether sCD23 triggers the release of other inflammatory mediators by PBMC. As illustrated in Table 2, sCD23 induces significant amounts of IL-1 α , IL-1 β , and IL-6 with no additive effect in the presence of IL-2

or IL-12. However, it synergizes with IL-2 ([mean \pm SEM] 1.33 ± 0.24 vs. 0.85 ± 0.15 , $n = 25$, $p < 0.001$) or IL-12 (1.61 ± 0.46 vs. 0.88 ± 0.23 , $n = 14$, $p < 0.05$) to further enhance TNF- α production.

Discussion

In the present study, we first report that sCD23 provides a potent costimulus for PBMC IFN- γ production in the presence of IL-2 or IL-12. This potentiating activity is time and dose dependent, and is observed at low IL-2 concentrations. The IFN- γ expression is limited to two normal cell types, T and NK cells (19). Physiological activation of T lymphocytes to induce cytokine production, including IFN- γ , requires TCR occupancy and APC-derived costimulatory signals (23). More precisely, monocytes are reported to enhance IFN- γ synthesis by mitogen-stimulated T cells via direct cell-cell contact involving CD2 signaling (24). However, IL-1 (20) or TNF- α (21) in synergy with IL-2 may partially replace the monocyte-mediated IFN- γ production signal. Similarly, IFN- γ production by stimulated SCID splenocytes (NK cells) required TNF- α synthesis (22). In this SCID model, IL-2 was synergistic with IL-12 or IL-12 plus TNF- α to induce IFN- γ release, but not with TNF- α alone (25).

In agreement with the above studies, our results indicate that the enhancement of IFN- γ by sCD23 largely depends on the presence of monocytes. Furthermore, we show that sCD23 synergizes with IL-2 and IL-12 to induce TNF- α release and that this effect completely disappears upon selective monocyte depletion. Taken together, it is tempting to speculate that the sCD23 costimulatory activity for IFN- γ production is mediated by TNF- α release and that monocytes are the target for sCD23 and the source of TNF- α production. This hypothesis is supported by the observations that TNF- α production precedes IFN- γ secretion and that neutralizing anti-TNF- α mAb partially inhibits the IL-2- and sCD23-induced IFN- γ production. It should be mentioned that NK cells are also capable of producing TNF- α (26).

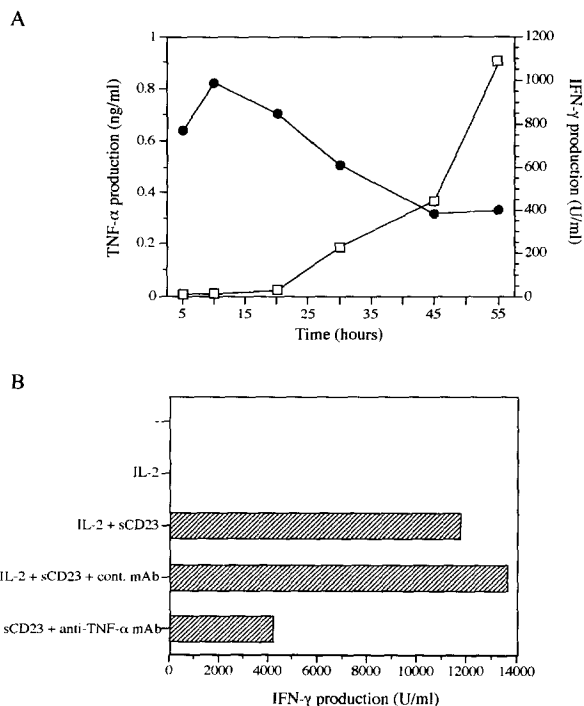


Figure 6. IFN- γ production by PBMC stimulated with IL-2 and sCD23 is partially mediated by TNF- α release. (A) PBMC were cultured with IL-2 (25 U/ml) and sCD23 (25 ng/ml) and culture supernatants were collected at the indicated times and assessed for TNF- α (●) or IFN- γ (□). Data are representative of two experiments. (B) PBMC were cultured with IL-2 (25 U/ml) and sCD23 (25 ng/ml) in the presence of anti-TNF- α mAb or isotype-matched control mAb (10 μ g/ml) and culture supernatants were tested for IFN- γ production. Data are representative of three experiments.

Table 2. *sCD23 Triggers Monokine Release*

Stimulus	TNF- α	IL-1 α	IL-1 β	IL-6
	ng/ml	pg/ml	pg/ml	pg/ml
Nil	<0.15	<3.9	<3.9	25 \pm 0.7
sCD23	2.1 \pm 0.95	211 \pm 16	182 \pm 41	645 \pm 24
IL-2	<0.15	12 \pm 11	73 \pm 75	179 \pm 53
IL-2 + sCD23	3.62 \pm 0.9	378 \pm 41	149 \pm 8.5	613 \pm 27
IL-12	<0.15	12 \pm 16	125 \pm 168	123 \pm 91
IL-12 + sCD23	4.6 \pm 2.0	347 \pm 3	154 \pm 13	724 \pm 31

PBMC were cultured for 20 h with sCD23 (25 ng/ml), IL-2 (25 U/ml), IL-12 (40 pM), or sCD23 and IL-2 or IL-12. Culture supernatants were harvested for cytokine determination as described. Data are the mean \pm SD of two experiments.

We next demonstrate that sCD23 is a proinflammatory cytokine inasmuch as sCD23 alone directly triggers TNF- α , IL-1 α , IL-1 β , and IL-6 release by PBMC. The sCD23-induced TNF- α occurs rapidly (already detectable after 5 h) and is specific since neutralizing anti-CD23 mAb abolishes sCD23 or IL-2 and sCD23-induced TNF- α production. Although monocytes release TNF- α and IL-1 after stimulation with endotoxin, PMA or gram-positive bacterial components, some more physiological triggers have been described such as LFA-3, CD44, and CD45 engagement (27). Alderson et al. (28), recently reported that CD40L-transfected cells costimulated TNF- α production by purified monocytes in the presence of GM-CSF, IL-3, or IFN- γ . Finally, ligation of membrane CD23 on IL-4-treated monocytes by anti-CD23 mAb (29) or by IgE-immune complexes (30) triggers inflammatory mediator release, further suggesting that the CD23 Ag may be considered as a proinflammatory molecule. Of note, and in agreement with our previous report (29), anti-CD23 mAb alone does not trigger inflammatory mediator release in unstimulated monocytes (Fig. 5 B).

The present observations that the costimulus provided by sCD23 for PBMC IFN- γ and TNF- α production disappears after monocyte depletion and that sCD23 alone is a potent inducer of inflammatory mediators strongly suggest that monocytes express a ligand for CD23. In addition to the well-established IgE molecule, CD21 has been proposed to serve as a second ligand for CD23 (10). However, CD21 Ag is primarily expressed on B cells and follicular dendritic cells but not on monocytes (31). We recently reported (32) that sCD23 binds to a novel ligand different than IgE and CD21. Our unpublished data indicate that monocytes express this sCD23 binding molecule, suggesting without demonstrating, that this novel ligand may be a functional receptor.

Whether the in vivo overexpression of CD23 is involved in the increased levels of inflammatory cytokines seen in certain disease states remains to be determined. For instance, in patients with rheumatoid arthritis, IL-1, TNF- α , and GM-CSF has been found in synovial fluid (33). Also, their sera contained elevated levels of serum sCD23 (16 ng/ml in rheumatoid arthritis vs 4.5 ng/ml in control sera) (34). The possibility therefore exists that GM-CSF, which has been shown to induce CD23 expression on monocytes (13), may be involved in the progression of the disease. In that regard, Hellen et al. (35), have reported that high CD23 expression in synovial biopsy from patients with all forms of arthritis may be related to the severity of the inflammatory infiltrate. Similarly, in patients suffering of chronic renal failure, increased levels of serum sCD23 were shown to be correlated with TNF- α and IL-6 (36). We hypothesize that T cell and monocyte activation, reported in this disease (36), reflects the costimulatory activity of sCD23 described in vitro. In addition, the activated mononuclear cells may contribute to increased CD23 expression inasmuch as activated monocytes readily express CD23 (14) and activated T cells are potent inducers of CD23 on B cells (37). Finally, affinity-purified native sCD23 was reported to induce monophasic fever in rabbits, further supporting the present in vitro data that sCD23 triggers the release of proinflammatory mediators (38).

IFN- γ and TNF- α are two critical molecules that play a central role in the macrophage-mediated host defense against intracellular pathogens (39). In addition, IFN- γ is important in the regulation of physiological processes including Th1 development and Ig-class switch (40). Therefore, the ability of sCD23 to enhance IFN- γ and to trigger TNF- α production underlines its potential role in the control of the immune response.

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References

1. Delespesse, G., M. Sarfati, S. Fournier, C.Y. Wu, and M. Letellier. 1992. The low affinity receptor for IgE (FcεRII/CD23). *Immunol. Rev.* 125:77.
2. Letellier, M., T. Nakajima, G. Pulido-Cejudo, H. Hofstetter, and G. Delespesse. 1990. Mechanism of formation of human IgE-binding factor (soluble CD23): III. Evidence for a receptor (FcεRII)-associated proteolytic activity. *J. Exp. Med.* 172:693.
3. Letellier, M., M. Sarfati, and G. Delespesse. 1989. Mechanisms of formation of IgE-BFs (soluble CD23). I. FcεRII bearing B cells generate IgE-binding factors of different molecular weights. *Mol. Immunol.* 26:1105.
4. Sutton, B.J., and H.J. Gould. 1993. The human IgE network. *Nature (Lond.)* 366:421.
5. Flores-Romo, L., J. Shields, Y. Humbert, P. Graber, J.-P. Aubry, J.-F. Gauchat, G. Ayala, B. Allet, M. Chavez, H. Bazin, et al. 1993. Inhibition of an in vivo antigen-specific IgE response by antibodies to CD23. *Science (Wash. DC)* 261:1038.
6. Mossalayi, M.D., J.-C. Lecron, A.H. Dalloul, M. Sarfati, J.-M. Bertho, H. Hofstetter, G. Delespesse, and P. Debre. 1990. Soluble CD23 (FcεRII) and interleukin 1 synergistically induce early human thymocyte maturation. *J. Exp. Med.* 171:959.
7. Mossayali, M.D., M. Arock, J.M. Bertho, C. Blanc, A.H. Dalloul, H. Hofstetter, M. Sarfati, G. Delespesse, and P. Debré. 1990. Proliferation of early human myeloid precursors induced by interleukin-1 and recombinant soluble CD23. *Blood* 75:1924.
8. Bonnefoy, J.-Y., S. Henchoz, D. Hardie, M.J. Holder, and J. Gordon. 1993. A subset of anti-CD21 antibodies promote the rescue of germinal center B cells from apoptosis. *Eur. J. Immunol.* 23:969.
9. Bacon, K., J.-F. Gauchat, J.-P. Aubry, S. Pochon, P. Graber, S. Henchoz, and J.-Y. Bonnefoy. 1993. CD21 expressed on basophilic cells is involved in histamine release triggered by CD23 and anti-CD21 antibodies. *Eur. J. Immunol.* 23:2721.
10. Aubry, J.-P., S. Pochon, P. Graber, K.U. Jansen, and J.-Y. Bonnefoy. 1992. CD21 is a ligand for CD23 and regulates IgE production. *Nature (Lond.)* 358:505.
11. DeFrance, T., J.P. Aubry, F. Rousset, B. Vandervliet, J.Y. Bonnefoy, N. Arai, Y. Takebe, T. Yokota, F. Lee, K. Arai, et al. 1987. Human recombinant interleukin 4 induces Fcε receptors (CD23) on normal human B lymphocytes. *J. Exp. Med.* 165:1459.
12. Punnonen, J., G. Aversa, B.G. Cocks, A.N.J. McKenzie, S. Menon, 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.
13. Alderson, M.R., T.W. Tough, S.F. Ziegler, and R.J. Armitage. 1992. Regulation of human monocyte cell-surface and soluble CD23 (FcεRII) by granulocyte-macrophage colony-stimulating factor and IL-3. *J. Immunol.* 149:1252.
14. Delespesse, G., M. Sarfati, and R. Peleman. 1989. Influence of recombinant IL-4, IFNα, and IFN-γ on the production of human IgE-binding factor (soluble CD23). *J. Immunol.* 142:134.
15. TeVelde, A.A., F. Rousset, C. Peronne, J.E. DeVries, and C.G. Figdor. 1990. IFNα and IFN-γ have different regulatory effects on IL-4-induced membrane expression of FcεRIIb and release of soluble FcεRIIb by human monocytes. *J. Immunol.* 144:3052.
16. Vercelli, D., H.H. Jabara, B.-W. Lee, N. Woodland, R.S. Geha, and D.Y.M. Leung. 1988. Human recombinant interleukin 4 induces FcεR2/CD23 on normal human monocytes. *J. Exp. Med.* 167:1406.
17. Mossalayi, M.D., M. Arock, G. Delespesse, H. Hofstetter, B. Bettler, A.H. Dalloul, E. Kilchherr, F. Quaaaz, P. Debré, and M. Sarfati. 1992. Cytokine effects of CD23 are mediated by an epitope distinct from the IgE binding site. *EMBO (Eur. Mol. Biol. Organ.) J.* 11:4323.
18. Rector, E., T. Nakajima, C. Rocha, D. Duncan, D. Lestourgeon, R.S. Mitchell, J. Fisher, A.H. Sehon, and G. Delespesse. 1985. Detection and characterization of monoclonal antibodies specific to IgE receptors on human lymphocytes by flow cytometry. *Immunology* 55:481.
19. Farrar, M.A., and R.D. Schreiber. 1993. The molecular cell biology of interferon-γ and its receptor. *Annu. Rev. Immunol.* 11:571.
20. Fischer, H., G. Hedlund, T. Kalland, H.-O. Sjögren, and M. Dohlsten. 1990. Independent regulation of IFN-γ and tumor necrosis factor by IL-1 in human T helper cells. *J. Immunol.* 145:3767.
21. Scheurich, P., B. Thoma, U. Ücer, and K. Pfizenmaier. 1987. Immunoregulatory activity of recombinant human tumor necrosis factor (TNF)-α: induction of TNF receptors on human T cells and TNF-α-mediated enhancement of T cell responses. *J. Immunol.* 138:1786.
22. Tripp, C.S., S.F. Wolf, and E.R. Unanue. 1993. Interleukin 12 and tumor necrosis factor α are costimulators of interferon γ production by natural killer cells in severe combined immunodeficiency mice with listeriosis, and interleukin 10 is a physiologic antagonist. *Proc. Natl. Acad. Sci. USA* 90:3725.
23. Mueller, D.L., M.K. Jenkins, and R.H. Schwartz. 1989. Clonal expansion versus functional clonal inactivation: a costimulatory signalling pathway determined the outcome of T cell antigen receptor occupancy. *Annu. Rev. Immunol.* 7:445.
24. Gjørloff Wingren, A., K. Dahlenborg, M. Björklund, G. Hedlund, T. Kalland, H.-O. Sjögren, A. Ljungdahl, T. Olsson, H.-P. Ekre, D. Sansom, and M. Dohlsten. 1993. Monocyte-regulated IFN-γ production in human T cells involves CD2 signaling. *J. Immunol.* 151:1328.
25. Locksley, R.M. 1993. Interleukin-12 in host defense against microbial pathogens. *Proc. Natl. Acad. Sci. USA* 90:5879.
26. Naume, B., M. Gately, and T. Espevik. 1992. A comparative study of IL-12 (cytotoxic lymphocyte maturation factor)-, IL-2-, and IL-7-induced effects on immunomagnetically purified CD56⁺ NK cells. *J. Immunol.* 148:2429.
27. Webb, D.S.A., Y. Shimizu, G.A. Van Seventer, S. Shaw, and T.L. Gerrard. 1990. LFA-3, CD44, and CD45: physiologic triggers of human monocyte TNF and IL-1 release. *Science (Wash. DC)* 249:1295.
28. Alderson, M.R., R.J. Armitage, T.W. Tough, L. Strockbine,

- W.C. Fanslow, and M.K. Spriggs. 1993. CD40 expression by human monocytes: regulation by cytokines and activation of monocytes by the ligand for CD40. *J. Exp. Med.* 178:669.
29. Paul-Eugene, N., J.-P. Kolb, A. Abadie, J. Gordon, G. Dellespe, M. Sarfati, J.-M. Mencia-Huerta, P. Braquet, and B. Dugas. 1992. Ligation of CD23 triggers cAMP generation and release of inflammatory mediators in human monocytes. *J. Immunol.* 149:3066.
 30. Borish, L., J.J. Mascali, and L.J. Rosenwasser. 1991. IgE-dependent cytokine production by human peripheral blood mononuclear phagocytes. *J. Immunol.* 146:63.
 31. Dörken, B., P. Möller, A. Pezzutto, R. Schwartz-Albiez, and G. Moldenhauer. 1989. B-cell antigens: CD21. In *Leukocyte Typing IV*. W. Knapp, B. Dörken, W.R. Gilks, E.P. Rieber, R.E. Schmidt, H. Stein, and A.E.G. Kr. von dem Borne, editors. Oxford University Press, Oxford, UK. 58.
 32. Ishihara, H., M. Rubio, G. Delespe, and M. Sarfati. 1994. Soluble CD23 (sCD23) does not react with CR2Ag. In *Leukocyte Typing*. V.S. Schlossman, L. Boumsell, J.M. Harlan, T. Kishimoto, C. Morimoto, J. Ritz, S. Shaw, R. Silverstein, T. Springer, T.F. Tedder, and R.F. Todd, editors. Oxford University Press, Oxford, UK. In press.
 33. Firestein, G.S., and N.J. Zvaifler. 1987. The pathogenesis of rheumatoid arthritis. *Rheum. Dis. Clin. North Am.* 447:59.
 34. Chomarat, P., J. Briolay, J. Banchereau, and P. Miossec. 1993. Increased production of soluble CD23 in rheumatoid arthritis, and its regulation by interleukin-4. *Arthritis Rheum.* 36:234.
 35. Hellen, E.A., D.R. Rowlands, T.T. Hansel, G.D. Kitas, and J. Crocker. 1991. Immunohistochemical demonstration of CD23 expression on lymphocytes in rheumatoid synovitis. *J. Clin. Pathol.* 44:293.
 36. Deschamps-Latscha, B., A. Herbelin, A.T. Nguyen, D. De Groote, P. Chauveau, C. Verger, P. Jungers, and J. Zingraff. 1993. Soluble CD23 as an effector of immune dysregulation in chronic uremia and dialysis. *Kidney Int.* 43:878.
 37. Jover, J.A., E.K. Chartash, B. Kushner, S.M. Friedman, and M.K. Crow. 1989. T helper cell-induced CD23 (BLAST-2) expression: an activation marker for the high density fraction of human B cells. *Clin. Immunol. Immunopathol.* 53:99.
 38. Ghaderi, A.A., and D.R. Stanworth. 1991. Affinity-purified soluble FcεRII/CD23 derived from a culture supernatant of an EBV-immortalized B-cell line induced a monophasic fever in rabbits. *Immunology.* 73:510.
 39. Stout, R.D. 1993. Macrophage activation by T cells: cognate and non-cognate signals. *Curr. Opin. Immunol.* 5:398.
 40. Huang, S., W. Hendriks, A. Althage, S. Hemmi, H. Bluethmann, R. Kamijo, J. Vilcek, R.M. Zinkernagel, and M. Aguet. 1993. Immune response in mice that lack the interferon-γ receptor. *Science (Wash. DC).* 259:1742.