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Detection of circulating FcεR2/CD23$^+$ monocytes in patients with rheumatic diseases

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SUMMARY

Recently, *in vitro* studies have demonstrated that expression of FcεR2/CD23 on normal monocytes can be specifically induced by IL-4. In order to investigate the interaction of IL-4 and monocytes in rheumatic diseases, flow cytometry studies were performed. Elevated numbers of circulating FcεR2/CD23$^+$ monocytes were detected in patients with progressive systemic sclerosis (PSS) as compared with controls. In addition, supernatants derived from phytohaemagglutinin-stimulated peripheral blood mononuclear cells of PSS patients contained high activity to induce FcεR2/CD23 on CD14$^+$ monocytes. An increased frequency of FcεR2/CD23$^+$ monocytes was also observed in rheumatoid arthritis, and sequential studies in patients with systemic lupus erythematosus showed a close relationship between FcεR2/CD23$^+$ monocytes and disease activity. It is suggested that IL-4 has an important role in the pathogenesis of PSS by activating monocytes, and might also contribute to monocyte activation in other rheumatic diseases.

Keywords Fcε receptor IL-4 monocytes rheumatic diseases

INTRODUCTION

The low affinity Fcε receptor (FcεR2/CD23) has been detected on B lymphocytes, platelets, eosinophils, and on certain subsets of monocytes and macrophages (Spiegelberg, 1984; Delespesse *et al.*, 1986). Initially, FcεR2/CD23 was described as a B cell-specific activation antigen (Yukawa *et al.*, 1987). More recently, it has been suggested that FcεR2/CD23 has multiple functions, and might be involved in antigen presentation (Gordon *et al.*, 1989).

In vitro studies have demonstrated that expression of FcεR2/CD23 on monocytes can be specifically induced by IL-4 (Vercelli *et al.*, 1988). Of the two identified types of the FcεR2, a and b, IL-4 has been found to induce FcεR2b (Yokota *et al.*, 1988). IL-4 has an important role in IgE responses (reviewed by Delespesse, Sarfati & Heusser, 1990). In atopic subjects, IgE-bearing monocytes have been observed to infiltrate into skin lesions (Leung *et al.*, 1987), and high numbers of FcεR2/CD23$^+$ monocytes have been shown to correlate with serum IgE in Kawasaki disease (Furukawa *et al.*, 1990).

IL-4 is also known to affect a variety of other B cell functions (Defrance *et al.*, 1987, 1988; Shields *et al.*, 1989), and differences in the expression of FcεR2/CD23 antigen on B cells have been observed in diseases characterized by altered B cell reactivity, particularly in rheumatic diseases (Kumagai *et al.*, 1989). Therefore, we were interested to investigate the interaction of IL-4 and monocytes in these conditions. Here we studied FcεR2/CD23$^+$ monocytes in patients with progressive systemic sclerosis (PSS), rheumatoid arthritis (RA), and systemic lupus erythematosus (SLE).

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SUBJECTS AND METHODS

Patients and controls

Ten patients with PSS (nine women and one man aged 29–71 years, mean 53·6), 10 patients with SLE (seven women and three men, aged 22–67 years, mean 39·8), and 14 patients with RA (eight women and six men, aged 40–76 years) were studied. Patients met the ARA criteria (Masi *et al.*, 1980; Tan *et al.*, 1982; Arnett *et al.*, 1988). At initial evaluation, drug treatment included corticosteroids in five PSS patients (daily prednisolone equivalent dose up to 12·5 mg), in six SLE patients (up to 20 mg), and in five RA patients (up to 10 mg). Eight patients with RA received long-acting anti-rheumatic drugs (oral gold, sulfasalazine), 12 were taking non-steroidal anti-inflammatory agents. Seventeen non-atopic individuals (14 women and three men, aged 23–65 years) who did not show any sign of an active disease served as controls.

In patients with SLE, disease activity was assessed by an activity index (AI) rating clinical symptoms (arthritis, serositis, skin and organ involvement, haematological disease manifestations) as previously described (Becker, Schauer & Helmke,

1986). Three of the PSS patients had a recent onset of disease (duration of symptoms less than 2 years). The erythrocyte sedimentation rate (ESR) was measured according to Westergren (first-hour values). Anti-nuclear antibodies (ANA) were detected on rat frozen liver sections, anti-ds DNA antibodies were determined by radioimmunoassay (normal values < 7 U/l; Amersham, Braunschweig, Germany).

Flow cytometry analysis

Peripheral blood mononuclear cells (PBMC) were obtained from heparinized venous blood as previously reported (Becker *et al.*, 1986). Cells (2×10^6 per sample) were incubated for 30 min on ice with FITC-conjugated monoclonal antibody to FcεR2/CD23 (Immunotech/Dianova, Hamburg, Germany). Cells were incubated with FITC-labelled isotype-matched control immunoglobulin (Coulter, Krefeld, Germany) in parallel. After three washes (PBS, 0·1% NaN_3), analysis was conducted using a FACScan flow cytometer (Becton Dickinson, Heidelberg, Germany) equipped with a 488-nm argon laser and computer-assisted evaluation of data as reported (Becker *et al.*, 1990). Gates were set on monocytes, and 5000 events per sample were collected. Results were expressed as percentage of monocytes.

Cell cultures

Cells were cultured in RPMI 1640 medium with supplements (10% fetal calf serum, antibiotics, glutamine, Na pyruvate, non-essential amino acids), and incubated at 37°C in 5% CO_2 and air as described in detail (Becker *et al.*, 1986). PBMC were suspended at a density of 2×10^6/ml, and aliquots of 1 ml were set up in tissue culture tubes (Falcon/Becton Dickinson) in the presence of phytohaemagglutinin (PHA) (Biochrom, Berlin, Germany), or an equal volume of medium. A final PHA concentration of 10 μg/ml and 96 h of incubation were found to be optimal. Supernatants were harvested, and were stored at −20°C. Supernatants from sequential studies were collected and tested on one occasion.

To determine their FcεR2/CD23-inducing capacity, supernatants were added to PBMC obtained from a healthy individual. PBMC from one individual were used to test all supernatants from patients and controls. 2×10^6 cells were suspended in 1 ml of supernatant, or in medium containing PHA. In parallel, cells were incubated with various concentrations of a recombinant IL-4 standard (Genzyme, Boston, MA). After preliminary experiments to establish the optimal incubation period, cultures were terminated at 48 h. Cells were washed, incubated for 30 min on ice with PBS/0·2% EDTA (Biochrom), and transferred to test tubes (Falcon) for double fluorescent analysis employing FITC-conjugated anti-FcεR2/CD23, PE-conjugated anti-CD14 antibody (Becton Dickinson), and FITC-labelled and PE-labelled isotype control immunoglobulin (Coulter). To analyse cultured cells, anti-CD14 antibody was used for detection of monocytes since they could not be clearly distinguished from lymphocytes by forward and side scatter characteristics. Percentages of FcεR2/CD23$^+$CD14$^+$ cells were calculated. Values obtained from cells incubated with PHA-containing medium were subtracted from values obtained with supernatants. Isotype immunoglobulin staining of cultured cells was less than 1%.

For inhibition studies, supernatants were pre-incubated with rabbit anti-human IL-4 antibody (Genzyme), or an equal volume of medium for 1 h at 37°C.

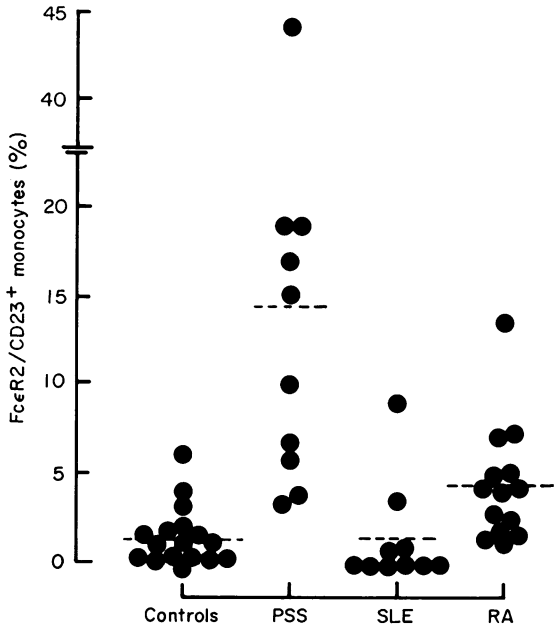

Fig. 1. Increased numbers of FcεR2/CD23$^+$ monocytes in the peripheral blood of patients with progressive systemic sclerosis (PSS) and rheumatoid arthritis (RA), compared with controls and patients with systemic lupus erythematosus (SLE). Data expressed as percentage of monocytes; – – –, mean.

Enriched monocyte fractions were obtained from blood anti-coagulated with EDTA. Dextran sedimentation and subsequent density gradient centrifugation on Nykodenz Monocytes (Molter, Neckargemünd, Germany) were performed. Enriched monocyte fractions contained more than 70% CD14$^+$ cells.

Statistical analysis

The Mann–Whitney *U*-test, and Spearman rank analysis were applied. $P < 0{\cdot}05$ was considered significant.

RESULTS

Detection of circulating FcεR2/CD23$^+$ monocytes

In PSS and RA, percentages of FcεR2/CD23$^+$ monocytes were markedly elevated as compared with controls (PSS, $P < 0{\cdot}0001$; RA, $P < 0{\cdot}002$; Mann–Whitney *U*-test, Fig. 1). Values were significantly higher in PSS patients than in patients with RA ($P < 0{\cdot}002$), or SLE ($P < 0{\cdot}001$, Fig. 1). In particular, patients with recently diagnosed PSS had very high numbers of FcεR2/CD23$^+$ monocytes (43·9%, 18·9%, 14·6%). We did not observe any correlation of age or sex with levels of FcεR2/CD23$^+$ monocytes.

At initial evaluation, only one of the SLE patients had a relatively high frequency of FcεR2/CD23$^+$ monocytes (Fig. 1). When sequential studies were performed in six patients with SLE, increasing numbers of FcεR2/CD23$^+$ monocytes could be detected with enhanced disease activity (patients 1–3, Table 1), and were not observed in patients with inactive disease (4a, b and 5, Table 1).

Table 1. Sequential studies in systemic lupus erythematosus

Patient no.	FcεR2/CD23(%) Expressed*	Induced†	AI	ESR (mm)	ANA titre^{-1}	Anti-ds DNA (U/ml)	Treatment
1a	3·5	0	60	60	1280	72	None
b	0	nd	0	22	1280	31	Aza., st.
c	0	nd	0	22	320	28	Aza., st.
d	0·8	0	5	26	1280	29	Aza., st.
2a	0·3	nd	85	73	5120	6	St.
b	0	0	35	44	2560	5	Cyc., st.
c	24·3	28·3	45	73	2560	11	Cyc., st.
3a	8·8	0	15	20	80	0	St.
b	3·5	0	5	27	40	0	St.
c	12·0	0	10	45	80	0	St.
4a	0	4·2	0	23	320	11	None
b	0	0	0	21	640	11	None
c	0·8	nd	5	27	5120	62	None
5a	0	0	0	16	10	0	None
b	0	0	0	12	10	0	None
6a	0	nd	60	78	640	42	St.
b	0·6	nd	35	45	160	17	Cyc, st.

Six patients studied on different occasions (a–d).

ND, not done; AI, activity index; ESR, erythrocyte sedimentation rate; ANA, anti-nuclear antibodies, Aza., azathioprine (100–150 mg); Cyc., cyclophosphamide (50–100 mg); St., steroids.

* Spontaneous expression by circulating monocytes.

† Induction of FcεR2/CD23$^+$ monocytes by supernatants.

Induction of FcεR2/CD23$^+$CD14$^+$ cells by supernatants

When the same supernatants were assayed on different occasions, reproducible results were obtained. For example, percentages of FcεR2/CD23$^+$CD14$^+$ cells induced by supernatants from two healthy individuals tested three times were 7·1%, 5·0%, 5·6% and 1·2%, 3·9%, 3·6%. FcεR2/CD23$^+$CD14$^+$ cells could not be detected when supernatants were pre-incubated with 25 μg/ml rabbit anti-IL-4. Using PBMC, the IL-4 standard induced 3·4±1·4% FcεR2/CD23$^+$CD14$^+$ cells at 1 U/ml, 6·2±0·6% at 10 U/ml, and 17·2±2·5% at 100 U/ml (mean±s.e.m., four different experiments). When enriched monocyte fractions were incubated with IL-4, results were similar (0% at 1 U/ml, 4·2% at 10 U/ml and 27·8% at 100 U/ml).

Supernatants from PBMC of SLE patients contained significantly less FcεR2/CD23$^+$-inducing activity than supernatants obtained from 12 controls ($P<0·01$; Mann–Whitney U-test, Fig. 2). Supernatants from patients with PSS showed the highest activity, although differences did not reach statistical significance ($P<0·09$, Fig. 2). There were no differences in results obtained from patients with early (16·8%, 20·4% and 0%) or long-standing PSS.

In PSS, numbers of circulating FcεR2/CD23$^+$ monocytes were not associated with FcεR2/CD23-inducing activity in supernatants ($r=0·0375$). In SLE patients studied sequentially, a close correlation of FcεR2/CD23-expressing monocytes and FcεR2/CD23-inducing activity could be detected only in two patients (patients 2 and 5, Table 1). A significant relation between FcεR2/CD23 inducing activity and clinical parameters was not observed.

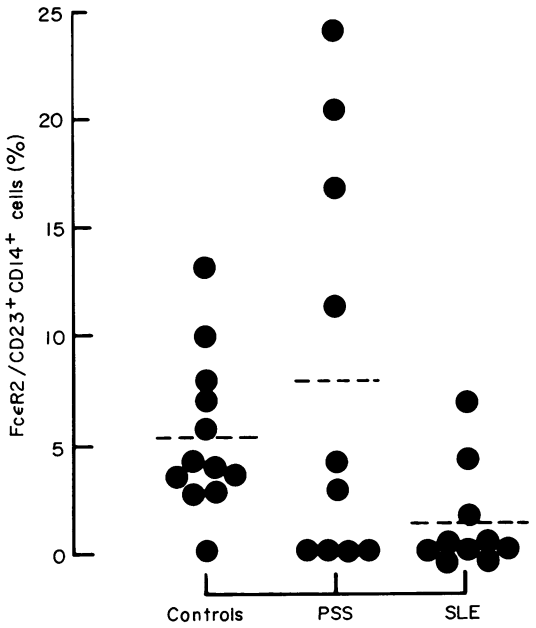

Fig. 2. Induction of FcεR2/CD23$^+$CD14$^+$ cells by supernatants from patients with progressive systemic sclerosis (PSS), systemic lupus erythematosus (SLE), and controls. Data expressed as percentage of CD14$^+$ cells; - - -, mean.

DISCUSSION

We report here elevated numbers of circulating FcεR2/CD23-expressing patients with PSS and RA. Several studies have suggested that increased activation of monocytes/macrophages plays an important role in these diseases. It has been proposed that in RA, altered T cell regulation and cytokine imbalance lead to enhanced monocyte activation (Decker, 1984). Sponta-

neous IL-1 release (Shore, Jaglal & Keystone, 1986), strong HLA-DR expression (Janossy *et al.*, 1981), and enhanced production of tumour necrosis factor-alpha (TNF-α) (Talal & Flescher, 1988) have been demonstrated. Perivascular infiltrates of T cells and macrophages have been described in cutaneous lesions of patients with PSS (Fleischmajer, Perlish & West, 1977). Circulating monocytes spontaneously secreting IL-1 have been observed, particularly in patients with early PSS (Alcocer-Varela, Martinez-Cordero & Alarcon-Segovia, 1985). This is consistent with our observation of high numbers of FcεR2/CD23$^+$ monocytes in patients with recent onset of disease.

Although numbers of FcεR2/CD23$^+$ monocytes were low in patients with SLE, our data from sequential studies suggest that circulating activated monocytes can be observed with increasing disease activity. Others have described impaired IL-1 generation in SLE (Alcocer-Varela, Laffon & Alarcon-Segovia, 1984). However, since IL-4 has been shown to down-regulate IL-1 gene expression *in vitro* (Essner *et al.*, 1989), further studies are necessary to elucidate whether FcεR2/CD23 expression and IL-1 production occur at different phases during the course of SLE.

Detection of high levels of FcεR2/CD23$^+$ monocytes might be related to enhanced IL-4 production in PSS patients. This is suggested by the observation of increased amounts of FcεR2/CD23-inducing activity in supernatants of cultured PBMC from these patients, compared with data from SLE patients. In this regard, anti-IL-4 was shown to inhibit induction of FcεR2/CD23$^+$ monocytes. Moreover, expression of FcεR2/CD23 has been demonstrated to be specifically induced by IL-4 and not by other lymphokines such as IL-1, IL-2, IL-3, IL-5 and interferon-gamma (IFN-γ) (Vercelli *et al.*, 1988). In addition, expression of other monocyte activation markers such as HLA class II antigen is also influenced by IL-4 (Crawford *et al.*, 1987).

Since we employed PBMC to detect induction of FcεR2/CD23$^+$ monocytes, T cell influences exerted by contaminating PHA in supernatants have to be considered. In our study, PBMC and supernatants were co-cultured for short periods of time (48 h) which were not sufficient for generation of FcεR2/CD23-inducing activity in supernatants. All supernatants were assayed on PBMC from the same individual, and supernatants from sequential studies were tested at the same time. Therefore, it is unlikely that contaminating PHA caused the observed differences in FcεR2/CD23 induction on monocytes.

Consistent with our data, hyperactivity of CD4$^+$ T lymphocytes from patients with PSS has been described (Umehara *et al.*, 1988; Kahaleh & LeRoy, 1989), and increased amounts of IL-4 have been detected in supernatants from these patients, employing an enzyme immunoassay (Famularo *et al.*, 1990). Interestingly, IL-4 has been observed to have stimulatory activity on fibroblast proliferation (Monroe *et al.*, 1988), and might contribute to fibrosis in PSS. In contrast, low amounts of FcεR2/CD23-inducing, IL-4-like activity in SLE might be related to T helper cell defects which have been described in association with B cell hyperactivity in this disease (Zubler, Huang & Miescher, 1986). A close correlation of numbers of circulating FcεR2/CD23$^+$ monocytes and FcεR2/CD23-inducing activity was not observed by us. In this regard, differences in migration patterns of T cells and monocytes have to be considered (Westermann & Pabst, 1990).

We conclude that IL-4 has an important role in the pathogenesis of PSS by activating monocytes. Detection of FcεR2/CD23$^+$ monocytes in patients with RA and data from longitudinal studies in SLE suggest that IL-4 contributes to monocyte activation in other rheumatic diseases as well.

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