Complement receptor expression of relevance to apoptotic cell clearance in SLE

Sir, The autoantigens of human systemic lupus erythematosus (SLE) are exposed on the surface of apoptotic cells and increased numbers of apoptotic cells in SLE may contribute to autoantigen generation [1]. Apoptotic cells and bodies are normally rapidly recognized and cleared, especially by local monocyte-derived macrophages, thus limiting the possibility of antigenic exposure. The mechanisms of recognition, engulfment and clearance of apoptotic cells by macrophages are being defined, and a number of different molecules may play a role. There is evidence to suggest that decreased phagocytosis of apoptotic cells by monocyte-derived macrophages does occur in SLE [2]. We have recently reported reduced expression of CD44 on monocytes and neutrophils in SLE, which may contribute to the impaired clearance of apoptotic neutrophils [3], while CD36 expression was not different in SLE compared with controls [4].

Mevorach et al. [5] have shown that, in the presence of serum, the human macrophage complement receptors for iC3b (CR3 and CR4) are involved in a 3- to 5-fold increase in macrophage phagocytosis of apoptotic lymphocytes and neutrophils. Also, monoclonal antibodies to CR3 and CR4 significantly block engulfment of the apoptotic cells. Reduced expression of complement receptor molecules on erythrocytes has been demonstrated in SLE [6, 7], and we hypothesized that reduced expression of CR3 or CR4 on SLE monocytes/macrophages may contribute to the impaired clearance of apoptotic cells.

We studied 31 Caucasian SLE patients (28 female, median age 50 yr), 19 Caucasian healthy controls (17 female, median age 48 yr) and 19 Caucasian patients with rheumatoid arthritis (RA; 17 female, median age 51 yr) and determined the expression of CR3 (CD11b, clone 2LPM19c; Dako, Ely, UK) and CR4 (CD11c, clone KB90; Dako) using whole-blood immunofluorescence labelling and flow cytometric analysis as previously described [3].

The percentage of monocytes expressing CR3 was increased in SLE compared with healthy controls (median 98.6 \( \text{vs} \) 95.7, \( P = 0.018 \), Mann–Whitney test), but not significantly different in SLE compared with RA controls (median 98.0, \( P = 0.390 \)). The percentage of monocytes expressing CR3 was also increased in RA compared with healthy controls (\( P = 0.012 \)).

The density of monocyte surface CR3 expression (Fig. 1) was higher in SLE compared with healthy controls [median MCF (mean channel fluorescence) 7.13 \( \text{vs} \) 5.37, \( P = 0.001 \)], but not significantly different from that in RA (median MCF 7.37, \( P = 0.342 \)). The density of monocyte CR3 expression was also higher in RA compared with healthy controls (\( P < 0.001 \)).

Median expression of monocyte CR4 was 94.0% in SLE, 90.4% in healthy controls and 90.6% in RA. Median density of monocyte CR4 expression (MCF) was 1.37 in SLE, 1.19 in healthy controls and 1.50 in
RA. There were no significant differences between the three groups in the percentage of monocytes expressing CR4 or in the density of surface CR4 expression on monocytes.

We have demonstrated higher percentages of monocytes expressing CR3 and a higher density of monocyte surface CR3 expression in both SLE and RA compared with healthy controls. SLE and RA samples were not significantly different. This may be a feature of their activation in these inflammatory diseases. This is in keeping with previous studies that described increased CR3 expression on RA monocytes \[8, 9\]. In our study, 19 SLE patients and seven RA patients were receiving oral corticosteroids (median dose 10 mg prednisolone/day in both groups). The prednisolone dose did not correlate with any measure of CR3 or CR4 expression. We have demonstrated no difference in monocyte CR4 expression between the three groups. To the best of our knowledge, such findings have not been reported previously. They do not support the hypothesis that the impaired monocyte/macrophage clearance of apoptotic leucocytes in SLE is due to reduced monocyte CR3 or CR4 expression. However, further work would be necessary to determine the effect of macrophage maturation on complement receptor expression, and to study complement receptor function during apoptotic cell phagocytosis. Serum complement levels are often reduced in active SLE and this may impair complement receptor-mediated clearance. Deficient expression or function of other clearance-related molecules may, however, play a role in SLE pathogenesis.

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