Perturbations of peripheral B lymphocyte homoeostasis in children with systemic lupus erythematosus

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Objective: To investigate the distribution of peripheral B cell subpopulations of children with active and inactive systemic lupus erythematosus (SLE) compared with healthy controls.

Methods: Peripheral B cell subpopulations of 11 children with SLE (6 with active and 5 with inactive disease) and 14 age matched normal healthy children were analysed. Active disease was diagnosed in children with a flare of SLE, who received treatment by IV cyclophosphamide or IV methylprednisolone pulse to control the disease. Additionally, the peripheral B cells of the children with SLE were compared with those of 13 consecutive patients with adult onset SLE.

Results: No major difference was found in the frequency and total number of CD27+/CD19− naive B cells and CD27+/CD19− memory B cells between patients with active and inactive lupus and healthy controls, but there was a significant increase in CD27+/CD19− expressing plasma blasts in patients with active SLE. These cells coexpress CD38+, HLA-DR+, surface IgM and lack the expression of CD20 but are clearly positive for intracellular Ig, indicative of early plasma cells. Most CD138+ cells coexpress CD27+/CD19−. The enhanced frequency of peripheral plasma blasts in children with active SLE is consistent with previous findings in adult patients with SLE, whereas a relative predominance of CD27+ memory B cells was only identified in the adult patients.

Conclusions: Profound abnormalities in the distribution of B cell compartments are more pronounced in older patients with SLE, but an enhanced frequency and cell number of peripheral plasma blasts is characteristic of both diseases during active stages. Thus detection of CD27+ plasma blasts significantly correlates with active lupus in both children and adults.

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Systemic lupus erythematosus (SLE) is a prototype of an autoimmune disease with a broad variety of clinical manifestations, particularly affecting the kidneys and the central nervous system. Autoantibodies against dsDNA and a number of other nuclear and cytoplasmic antigens as well as spontaneous immunoglobulin (Ig) producing cells are characteristic of SLE, reflecting an aberrant immune response. Although the disease may affect anyone, it is uncommon in children, and data about the relevant B cell distribution among children are limited. Information about this would be of interest because the cause of the disease and the nature of the mechanisms leading to the generation of autoantibodies remain enigmatic in children and in adults.

In vivo, after an immune response to a pathogen, B cells binding antigen through their B cell receptor (surface Ig) become activated, selected, and clonally expanded during germinal centre reactions by Tg cells. It is commonly believed that under normal circumstances, Ig isotype switching and hypermutation of V region genes and differentiation into either memory B cells or plasma cells occur in germinal centres, somatically diversifying the B cell receptor gene repertoire and providing an appropriate variability of specificities for sufficient selection of high affinity antibodies. This dichotomy of B cell differentiation into the memory cell pool or, alternatively, into the plasma cell pool is reflected by the differential expression of certain surface antigens. Whereas expression of CD20 becomes down regulated during differentiation of naïve and memory cells towards plasma cells, expression of CD38 and CD138 (syndecan-1) is up regulated by plasma cells. Recently, the expression of CD27 has been shown to be restricted to antigen experienced B cells carrying somatically mutated V genes. Most recently, a study identified an enhanced number of peripheral plasma cells expressing CD27high in adult patients with SLE. A significant increase of CD27 expressing B cells was found in most of these patients, resulting from a reduction of naïve CD27− B cells that accounted for an overall B lymphocytopenia. Further characterisation of the peripheral blood B cells showed that cells expressing high levels of CD27 are recently generated plasma blasts/cells, and their number and frequency seemed to correlate with the disease activity in adult patients with SLE. Despite a marked reduction of CD19−CD27− naïve B cells and predominating CD19−CD27+ memory B cells and CD19+/CD27high plasma cells, molecular analysis of immunoglobulin V genes in one patient showed that these B cell subpopulations differed in their Vh gene usage. These findings in adult patients with SLE prompted us to investigate whether similar disturbances of B cell homoeostasis are also characteristic of children with SLE. Altogether, the current data provide evidence that the detection of an enhanced fraction of persistent plasma blasts/cells and a reduction of naïve B cells in the periphery of patients with SLE are characteristic of active disease stages, independent of age and disease duration.

PATIENTS AND METHODS

Patients

Heparinised whole blood (5–10 ml) from children with SLE was obtained from the Department of Paediatric Immunology and Pneumology, Charité, Berlin. In a cross sectional study we
analysed 11 white children (age 5–17 years) with SLE fulfilling the 1982 revised criteria (table 1). Patients with active disease (n=6) received either intravenous (IV) cyclophosphamide or IV methylprednisolone pulse, or both, to control the disease. The others were grouped as inactive patients (n=5). Table 1 presents their clinical and therapeutic characteristics. Fresh blood was also obtained for analysis from 14 apparently normal healthy age matched children recruited outside the hospital as a control.

Preparation of PBMC
Peripheral blood mononuclear cells (PBMC) were prepared by density gradient centrifugation using Ficoll-Hypaque (Pharmacia, Uppsala, Sweden). Briefly, heparinised or EDTA blood was carefully layered on Ficoll, and PBMC were harvested from the white interphase after centrifugation for 30 minutes at 400 g and room temperature and washed with phosphate buffered saline (PBS).

Flow cytometric analysis
Immunofluorescence labelling for flow cytometric analysis was performed by incubating PBMC with biotinylated antihuman CD19 (clone SJ25-C1, Southern Biotechnology Associates (SBA), Birmingham, AL), antihuman CD27 Cy5 (clone 2E4), and either antihuman HLA-DR FITC (rabbit antihuman IgG, DAKO, Hamburg, Germany), antihuman IgM FITC (rabbit antihuman IgM DAKO), antihuman Igκ FITC (clone G20-193, Pharmingen, San Diego, CA), or antihuman Igλ FITC (clone JDC-12, Pharmingen).

Incubation with antibodies was performed in PBS/0.5% bovine serum albumin (BSA)/5 mM EDTA at 4°C for 10 minutes. Propidium iodide (1 µg/ml, Sigma, Munich, Germany) was added immediately before cytometric analysis to exclude dead cells. Before incubation with streptavidin-phycoerythrin (PE) (0.5 mg/ml; Pharmingen) cells were washed twice.

For intracellular staining, the cells were fixed in 2% wt/vol formaldehyde (Merck, Darmstadt, Germany) for 20 minutes at room temperature, washed, and stored at 4°C in PBS/EDTA/N3. The cells were then incubated in PBS/EDTA, with or without 0.5% (wt/vol) saponin (Sigma, Munich, Germany) and fluoresceinated antibodies for 10 minutes at 4°C, then washed with saponin buffer and PBS. Flow cytometric analysis was performed using FACS Calibur and CellQuest software (Becton Dickinson, San Jose, CA). A total of 50 000–120 000 events were collected for each analysis.

Statistical analysis
For statistical analysis we used GraphPad Prism software (San Diego, CA). Frequencies of B cell subpopulations were calculated using CellQuest software (Becton Dickinson), and differences between blood donor groups were compared using the non-parametric Mann-Whitney U test. To analyse the relation between the total white blood cell count and total B cells, the total number of B cells of various phenotypes was calculated per ml of blood, based on the frequencies of those cells among PBMC, and the total numbers of PBMC. Results are given in the text and figures as median values and standard deviation (SD) of cell frequency for each group. Values of p<0.05 (*) and p<0.01 (**) were considered to be significant.

The influence of immunosuppressive treatment on CD27 high plasma blasts/cells was also analysed by multiple regression.

RESULTS
Children with active SLE show significantly increased cell numbers and frequency of CD27 high CD19+ B cells and reduced naive B cells. Peripheral blood CD19+ B cells of 11 children with SLE fulfilling the 1982 revised criteria(1) and 14 age matched normal healthy children were analysed for the

| Table 1 Demographic data, peripheral B cells, and drugs of the patients with SLE analysed and normal healthy controls |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Donor | Diagnosis | Sex | Age (years) | WBC (10⁹/l) | Number of CD19+ cells (10⁹ cells/l) | Frequency of CD19+ B cells (%) | Treatment |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| 1 | SLE | M | 5 | 9.89 | 1039 | 10.5 | Methotrexate (1) Azathioprine (2) Prednisolone (3) Hydroxychloroquine (4) |
| 2 | SLE | F | 14 | 5.30 | 843 | 15.9 | Yes No No No |
| 3 | SLE | F | 16 | 5.20 | 432 | 8.3 | No No No Yes |
| 4 | SLE | F | 17 | 4.50 | 432 | 9.6 | No No No Yes |
| 5 | SLE | F | 17 | 5.50 | 358 | 6.5 | No No No Yes |
| 6 | Active SLE | F | 17 | 3.50 | 760 | 21.7 | No No Yes Yes |
| 7 | Active SLE | F | 17 | 3.20 | 674 | 21.4 | No No Yes Yes |
| 8 | Active SLE | M | 14 | 5.30 | 689 | 13.0 | No Yes Yes Yes |
| 9 | Active SLE | F | 11 | 5.50 | 220 | 4.0 | No No Yes Yes |
| 10 | Active SLE | F | 7 | 5.55 | 328 | 5.9 | Yes No No No |
| 11 | Active SLE | F | 14 | 7.30 | 344 | 4.7 | No Yes No Yes |
| 12 | Healthy control | F | 13 | 6.83 | 1045 | 15.3 | – – – – |
| 13 | Healthy control | F | 8 | 6.98 | 559 | 8.0 | – – – – |
| 14 | Healthy control | M | 15 | 4.65 | 325 | 7.0 | – – – – |
| 15 | Healthy control | F | 7 | 5.57 | 524 | 9.4 | – – – – |
| 16 | Healthy control | M | 13 | 8.30 | 1659 | 20.1 | – – – – |
| 17 | Healthy control | F | 8 | 6.75 | 979 | 14.5 | – – – – |
| 18 | Healthy control | F | 14 | 7.35 | 603 | 8.2 | – – – – |
| 19 | Healthy control | M | 14 | 5.65 | 615 | 10.9 | – – – – |
| 20 | Healthy control | M | 16 | 7.79 | 600 | 7.7 | – – – – |
| 21 | Healthy control | F | 16 | 5.74 | 586 | 10.2 | – – – – |
| 22 | Healthy control | M | 14 | 5.24 | 440 | 8.4 | – – – – |
| 23 | Healthy control | M | 12 | 4.58 | 605 | 13.2 | – – – – |
| 24 | Healthy control | M | 15 | 5.75 | 547 | 9.5 | – – – – |
| 25 | Healthy control | M | 4 | 7.40 | 777 | 10.5 | – – – – |

Patient 1 required cyclosporin A 5 mg/kg body weight daily; patients 6, 8, 10 and 11 methylprednisolone pulse; patients 7 and 9 methylprednisolone and cyclophosphamide pulse.

(1) Methotrexate (MTX) 15 mg/m² once a week; (2) azathioprine 2 mg/kg body weight daily; (3) prednisolone <0.2 mg/kg body weight daily; (4) hydroxychloroquine 200 mg/day.
expression of CD27, a marker which has been previously characterised as a memory B cell marker. Figure 1 shows that the clinical manifestations of the patients varied to some extent, although all met at least four American College of Rheumatology (ACR) criteria for SLE. By analysing the peripheral blood of children with active SLE, three distinct populations of CD19\(^+\) B cells became apparent (fig 2). The frequency of these three subpopulations, expressing CD27 at different levels, were calculated according to the thresholds set in reference as shown in fig 2.

At the time of the analysis, six children had active disease. These children showed a distinct CD27\(^{high}\)/CD19\(^+\) B cell subpopulation in the peripheral blood similar to that found in an earlier study of adult patients with active SLE. The five remaining patients were considered to be in the group with inactive SLE.

**Peripheral B cells**

The frequency of peripheral B cells expressing CD27 was not significantly different in children with active SLE (median (SD) 37.1 (15.5)\%) from that in children with SLE showing no evidence of a flare (22.0 (7.2)\%) and healthy blood donors (22.9 (8.2)\%). There was no significant difference in the total number of peripheral B cells between children with a lupus flare (509 (231)\times 10^6 cells/l), children with inactive SLE (432 (302)\times 10^6 cells/l), and healthy blood donors (602 (334)\times 10^6 cells/l).

**Naïve B cells**

There were no significant differences in the median frequency and median total numbers of CD27\(^−\) naïve B cells between patients with active (62.9 (15.5)\%, 326 (225)\times 10^6 cells/l, respectively) and inactive SLE (78.0 (7.2)\%; 361 (280)\times 10^6 cells/l) and the control donors (77.1 (8.2)\%; 466 (293)\times 10^6 cells/l), although patients with a flare of the disease tended to have reduced numbers of naïve peripheral B cells.

**Memory B cells**

There were no statistically significant differences in the median frequency or the absolute numbers of CD27\(^+\)/CD19\(^+\) memory B cells between children with active SLE (29.8 (11.9)\%; 120 (40)\times 10^6 cells/l), and children with inactive disease (18.5 (7.0)\%; 91 (36)\times 10^6 cells/l), or normal healthy controls (21.7 (7.5)\%; 137 (81)\times 10^6 cells/l). The increased frequency of memory B cells in adult patients with active SLE

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**Figure 1** Frequency of clinical manifestations of the children with SLE analysed in the current study. All analysed children showed at least four different clinical manifestations classifying them according to the 1982 revised ACR criteria.

**Figure 2** Expression of CD27 on CD19\(^+\) peripheral B cells from children with SLE and from a normal healthy donor. Viable PBMC were gated for analysis according to light scatter and exclusion of propidium iodide. Staining with CD19 bio/SA-PE versus CD27 Cy5 is shown for (A) a child with active SLE (donor No 6); (B) a child with inactive SLE (donor No 3); and (C) a healthy child recruited outside the hospital (donor No 12). Gates for the statistical evaluation of the frequency of CD27\(^−\), CD27\(^+\), and CD27\(^{high}\) among CD19\(^+\) peripheral B cells are indicated. The respective frequencies are indicated.

**Figure 3** Frequency (A) and total number (B) of CD27\(^{high}\) peripheral plasma cells in patients with active and inactive SLE and in a control group of healthy subjects. The frequencies were determined by cytometric analysis as shown in fig 2. The median value is indicated. *p<0.05; **p<0.01.
(fig 7A) reflects the reduction of peripheral naïve B cells in these patients because the total number of memory B cells was similar to that in the other two groups (fig 7B).

**Plasma blasts/cells**

The median frequency of CD27high/CD19+ B cells in the children with a flare of SLE (8.6 (5.0)%) was significantly increased compared with their frequency in children with inactive disease (2.9 (1.8)%) (p<0.05) and the healthy control group (1.5 (1.4)%) (p<0.01). No significant difference (p=0.138) in the frequency of CD27high/CD19+ B cells was found between children with inactive SLE and normal healthy controls (fig 3A). For the total cell numbers, a significant increase of CD27high expressing B cells was found in children with a flare of the disease (43 (15)×10^6 cells/l) compared with healthy donors (8 (9)×10^6 cells/l) (p<0.01) but not compared with those with inactive SLE (11 (18)×10^6 cells/l) (p=0.082) (fig 3B).

Analysis of the distinct B cell subpopulation expressing CD27 suggests that the increase in the total number of CD27 expressing B cells in children with active SLE compared with children without a flare and normal healthy children results predominantly from a drastic increase of CD27high B cells and a reduction of CD27 naïve B cells.

**Characterisation of CD27high/CD19+ plasma blasts/cells in the periphery of children with active SLE**

Further analysis sought to characterise the identified subpopulations of peripheral B cells in children with active SLE in more detail. CD19 expression on B cells was used to identify the phenotype of peripheral blood B cells in children with SLE. Figures 2, 4, and 5 show that three characteristic and distinct CD19+ B cell subpopulations could be identified in children with active SLE and in one child with inactive disease (patient No 2, 5.6%) based on their expression of CD27. A distinct population of CD27high expressing B cells could be identified in patients with active SLE, similar to that found previously among adult patients with active SLE. Characteristically, CD27high expressing CD19+ B cells are larger than B cells expressing no or intermediate levels of CD27 (fig 4B). The strong expression of CD38, lack of the expression of CD20, down regulation of surface IgM, IgG, and IgD while cytoplasmic Ig is up regulated, high expression of HLA-DR and CD95 identify them as plasma blasts on the
verge of becoming early plasma cells (figs 4C-K). Coexpression of CD27<sup>high</sup>/CD19<sup>+</sup> on the majority of CD138 (syndecan-1) expressing peripheral cells (fig 5B) and drastic down regulation of CD20 (fig 5C) indicate that these cells are on their way to terminally differentiating into plasma cells.

Correlation between CD27<sup>high</sup>/CD19<sup>+</sup> plasma blasts/cells in the periphery of children with active SLE receiving immunosuppressive treatment

In view of recent observations that the frequency of peripheral plasma cells declines with effective immunosuppressive treatment,<sup>14</sup> we also examined the frequency of CD27<sup>high</sup>/CD19<sup>+</sup> plasma cells and the influence of treatment with IV cyclophosphamide or IV methylprednisolone pulse, respectively. Multiple regression analysis showed no significant difference between these variables in the patients examined.

DISCUSSION

This study of the distribution of peripheral B cells in children with SLE provides clear evidence that there are remarkable disturbances in children with active SLE compared with patients with inactive disease and healthy children—namely, the enhanced frequency of CD27<sup>high</sup> expressing B cells and a reduced fraction of naïve B cells in the circulation of these patients. Recently, Arce and coworkers showed that children with SLE have profound B cell lymphopenia due to a reduction in mature B cell subsets.<sup>4</sup> In that study, SLE B cell lymphopenia did not correlate with any modality of treatment, SLE

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**Figure 5** Cytometric characterisation of peripheral CD138<sup>+</sup> cells in a child with a lupus flare (donor No 6). (A) Viable peripheral mononuclear cells of a patient with a lupus flare were gated according to scatter and propidium iodide exclusion and stained for CD138-PE, CD27-Cy5, and either CD19-FITC or CD20-FITC, respectively. Coexpression of CD27 and CD19 (B) or CD20 (C), respectively, on CD138<sup>+</sup> cells, as gated in (A), is shown in a two colour flow cytometric analysis. CD138<sup>+</sup> coexpressing cells in (B) and (C) are depicted in black.

**Figure 6** Comparison of the (A) frequency and (B) total numbers of CD27<sup>−</sup> peripheral naïve B cells in children and adults from a previous study of patients with active and inactive SLE as well as their respective healthy controls. The frequencies were determined by cytometric analysis as shown in fig 2. The median values are indicated. *p<0.05; **p<0.01.
Disease Activity Index (SLEDAI), or anti-dsDNA. In contrast with the reduction in all mature B cell subsets, children with SLE presented a threefold expansion of blood plasma cell precursors that make up to 8.7% of their blood B cell compartment. In that study, only a small proportion of CD20⁻, CD19low, and CD38++ cells in the 68 patients was analysed. The differences between our results and those of Arce et al may be explained by the heterogeneity of the study groups (different ethnic backgrounds, effect of immunosuppressive treatment). Moreover, the CD8⁺ and CD4⁺ T cell subsets expressing CD45RA and CD28 were reported to be specifically reduced, while CD4⁺ and CD8⁺ cells expressing HLA-DR were found to be enhanced. With regard to B lymphocytes, spontaneously activated B cells and polyclonal production of Ig including autoantibodies have been repeatedly demonstrated in the peripheral blood and in the bone marrow in SLE. The identification of an expansion of peripheral plasma blasts is consistent with these previous findings.

CD27 is a member of the tumour necrosis factor receptor family and is expressed on T and B cells. CD27/CD70 interaction is involved in late stage differentiation of B cells, providing a key signal for the maturation of memory B cells into Ig secreting cells in the germinal centre reaction. Expression of CD27 on B cells is apparently induced in germinal centre reactions and is maintained on memory B cells that express somatically hypermutated V genes, regardless of whether they coexpress IgD. It should be noted that cord blood B cells do not express CD27, and the fraction of CD27⁺ memory B cells increases with age. Thus, the differences seen in the frequency of CD27 expressing memory B cells between children and adults with SLE may reflect age differences and it seems less likely that it is influenced by the disease alone. Because the total numbers of memory B cells were comparable between the groups of children analysed, it is likely that they are non-proliferating cells resistant to conventional treatment.

Comparison of B cell subpopulations between childhood and adult SLE

Although the number of children analysed was limited, the clinical parameters of the juvenile patients with SLE were similar to those of the adult patients with SLE (fig 1). Moreover, analyses of B cell subpopulations suggest that they are candidates for disease activity measurement in adults.
and juvenile patients with SLE. Thus, enhanced peripheral plasma cells seem to be of pathogenic importance in lupus, although their ability to produce autoantibodies clearly needs to be shown. One similarity between children and adults with SLE was the reduced frequency of peripheral CD19+ B cells. Secondly, an enhanced peripheral fraction of plasma blasts in the circulation of patients with active disease was found in both children and adults with lupus (fig 8). Further evidence for the relation with disease activity came from the observation that one patient (table 1, No 10) was analysed before a lupus flare but already exhibited an enhanced frequency of this cell population (14.3%). Follow up examinations of adult patients with SLE have shown that the frequency of CD27high plasma cells declined with effective immunosuppressive treatment, coinciding with clinical improvement of the patient.17 Thus, monitoring the peripheral B cell compartments by CD27 candidates could be an early diagnostic tool for detecting abnormalities before flares of the disease. However, there are some major differences between the groups of children and adults with SLE and their respective control groups. Firstly, the frequency and total number of CD27 naïve peripheral B cells was similar in children with inactive SLE and their normal controls, whereas the frequencies and total numbers of these cells were reduced in adults with active and inactive SLE compared with normal subjects (fig 6). However, both children and adults with active SLE tended to have a diminution of naïve cells. Moreover, adults with inactive disease showed an enhanced frequency of peripheral plasma blasts/cells compared with controls, whereas such a difference was not detected in children with inactive lupus with one exception—patient No 2 with 5.6% peripheral CD27high B cells (table 1). On the other hand, comparison of the total number of CD27+ memory B cells gave additional interesting insights (fig 7). Although controls appeared to have slightly more naïve B cells in their periphery, the total numbers of these cells was very similar among all the children’s groups as well as between the adult groups. Thus, the higher frequency (fig 6) of CD27+ B cells in children with active SLE and most remarkably among adults with active and inactive disease was accounted for by a reduction of naïve B cells in these groups. This is consistent with the conclusion that consideration of total numbers is equally important despite relative disturbances of B cell homeostasis in SLE. In the current cross sectional study, immunosuppressive treatment did not have significant influence on the frequency of CD27high plasma cells, although the small number of patients is a limiting factor. Moreover, the influence of treatment needs to be examined by long term follow up studies.

Detailed characterisation of CD27high expressing peripheral B cells

Because the current study identified some differences in the distribution of particular B cell subsets in children with SLE compared with controls and with adults with SLE, the characteristics of the recently identified peripheral CD27high B cells of adults were further analysed in these children. As seen in adults with SLE, this population expresses CD38, CD138 and intracellular, but not surface, Ig. In addition, the down modulation of CD19 on the surface21–26 and lack of CD20 expression further clearly mark them as plasma blasts/cells, consistent with previous data obtained from adults with SLE.24 In a recent study an expansion of a plasma cell clone using a heavily mutated V4–61 gene rearrangement was identified among CD27high cells, supporting the hypothesis that this cell population contains recently activated cells probably homing to the bone marrow.

The current study of peripheral B cell compartments in childhood SLE identified an enhanced fraction of CD27high plasma blasts/cells coinciding with reduced naïve B cell characteristics of patients with active lupus, as identified in adult patients with active SLE.30 Our results suggest that the expression of CD27high plasma cells may play a part in disease exacerbation and therefore pathogenesis of SLE in children, and thus enhanced frequencies of CD27high cells may be a diagnostic marker for disease activity.

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