Dysfunction of CD27⁺IgD⁺B Cells Correlates With Aggravated Systemic Lupus Erythematosus

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Abstract

Objective The apoptotic signaling pathway is obviously disordered in systemic lupus erythematosus (SLE). Natural IgM (nIgM) is important in clearing apoptotic cells and preventing them from triggering deleterious autoimmunity. B-1- and innate-like B- (ILBs) cells are the main nIgM producers. Human CD27⁺IgD⁺B cells (un-switched memory B cells) are considered ILBs. However, their functional properties in SLE remain undefined.

Methods Peripheral blood samples of 50 SLE patients and 50 healthy control were collected, and twelve SLE patients were assessed in a follow-up study. The amounts of CD27⁺IgD⁺B cell was analyzed by flow cytometry. The IgM and IL-10 levels of CD27⁺IgD⁺B cell were assessed by ELISPOT and qRT-PCR. SPSS 17.0 (SPSS, USA) was employed for data analysis. $P < 0.05$ indicated statistical significance.

Result 92.0% were females, 17-67 years. CD27⁺IgD⁺B cell amounts are significantly decreased in SLE patients than healthy control ($p < 0.01$). CD27⁺IgD⁺B cell amounts were positively correlated with WBC ($r = 0.337$, $p = 0.017$), platelet count ($r = 0.396$, $p = 0.004$) and serum C3 levels ($r = 0.415$, $p = 0.003$), CD27⁺IgD⁺B cell amounts showed negative correlations with serum creatinine levels ($r = -0.285$, $p = 0.045$), SLEDAI ($r = -0.724$, $p = 0.000$), anti-dsDNA ($r = -0.477$, $p = 0.000$) and CRP ($r = -0.398$, $p = 0.004$). The IgM and IL-10 levels of CD27⁺IgD⁺B in SLE were decreased than healthy control ($p < 0.001$), moreover CD27⁺IgD⁺B cells are increased in SLE cases after treatment in SLE patients than before treatment ($p < 0.001$).

Conclusion CD27⁺IgD⁺B cell amounts are significantly decreased and it was correlated with clinical and immunological features in SLE patients. CD27⁺IgD⁺B cells had impaired function regarding IgM and IL-10 production in SLE, however, CD27⁺IgD⁺B cells amounts are recovered in SLE cases with treatment-related disease remission.

1. Introduction

Systemic lupus erythematosus (SLE), a major systemic autoimmune disorder, affects humans with genetic susceptibility in certain environmental conditions(1). Its pathogenetic mechanisms remain unclear. It is admitted that autoantibodies represent the main determinants of SLE's pathological signs. Antibodies could harm self-tissues via complement-mediated inflammatory reactions, programmed cell death and immune-complexes associated injury. However, the exact role of antibodies in SLE remains unraveled(2).

Apoptosis is strictly controlled by cell surface proteins (e.g., Fas) and intracellular proto-oncogenes such as Bcl-2 and Bax family members(3). It has been demonstrated that the apoptosis signaling pathway is obviously disordered in SLE. Abnormal production of a large number of apoptotic signaling molecules, including TNF-related apoptosis inducing ligand (TRAIL), TNF-like weak inducer of apoptosis (TWEAK) and death ligand FasL (Fas ligand), leads to abnormal increase of apoptosis(4, 5). In addition, individuals with SLE have trouble clearing apoptotic cells. Cell death (programmed cell death, necrosis and NETosis

[affecting neutrophils via NETs]), provides most of the self-dsDNA that induces immune reactions and causes autoimmune disorders(6).

Natural immunity enables the identification and elimination of injured and apoptotic cells. Meanwhile, it also performs the intricate regulation of inflammatory response and enhances immune tolerance. Natural IgM (nIgM) represents a critical part of innate immunity in humans, reacting with multiple epitopes found in self-and non-self antigens(7). Therefore, nIgM deficiency increases the tendency toward the development of autoimmune disorders; nIgM is indeed very important in clearing apoptotic cells and preventing them from triggering autoimmunity.

B-1 and innate-like B (ILBs) cells constitute the main natural IgM producers. It is admitted that 80% of serum natural IgM is produced by B1 cells(8). On the other hand, ILBs represent a heterogeneous group of atypical B cells possessing innate sensing and responding features. Mouse ILBs comprise B1, marginal zone (MZ) B and other related B cells. CD19⁺CD27⁺IgD⁺ B cells (or unswitched memory B cells) have been considered ILBs in humans(9). ILBs keep natural IgM amounts at the steady state, and quickly gain immune modulatory features via secretion of natural IgM and IL-10 after innate activation(10). Recent studies have shown that abnormalities of the B cell subsets homeostasis might contribute to the pathogenesis of SLE and ILBs play a role in the pathogenesis of this disease(11, 12), Frequencies of ILBs were lower in new-onset SLE patients(13). Our previous study indicated CD27⁺IgD⁺B cell impairment in rheumatoid arthritis (RA), likely contributing to disease perpetuation(14). However, CD27⁺IgD⁺ B cell properties and function in SLE remain undefined.

Here, we determined the amounts and natural antibody-like IgM and IL-10 producing capacity of CD27⁺IgD⁺B cells in SLE patients. In addition, we analyzed their clinical associations and revealed their tendency after therapy.

2. Materials And Methods

2.1 Patients and samples

Totally 50 SLE and 50 healthy control (HC) patients were enrolled. Individuals with SLE were treated in the First Affiliated Hospital of Baotou Medical College that applied the American College of Rheumatology criteria for the classification of SLE(15). SLE patients routinely performed some laboratory assessments; complete blood cell count, serum C3, C4, Creatinine, anti-dsDNA, urinary proteins, CRP, C1q. Serum MBL(R&D Systems, USA) level was measured by sandwich enzyme-linked immunosorbent assay according to the manufacturer's company protocol. The main features of the SLE cases are listed in Table 1.

Disease activity was measured by the modified Systemic Lupus Erythematosus Disease Activity Index (SLEDAI-2K)(16), and classified as low disease activity (LDA) (SLEDAI of 0-4, n=34) and active disease (SLEDAI above 4, n=16). This trial had approval from the Institutional Medical Ethics Review Board of Baotou Medical College, and signed informed consent was obtained from each participant.

Twelve SLE patients were assessed in a follow-up study. All patients were treated with glucocorticoid, cyclophosphamide and hydroxychloroquine. Blood specimens were collected prior to treatment and at 4 weeks post-treatment. Patient features pre- and post-treatment are summarized in Table 2

2.2 Flow cytometry analysis

For CD27⁺IgD⁺ B cell detection, 2-ml blood specimens were collected from SLE and HC patients, and 100µl fresh whole blood cells was extracted and incubated with the following antibodies APC-CY7-labeled anti-CD19 (BioLegend, USA), APC-linked anti-CD27 (eBioscience, USA) and FITC-labeled anti-IgD (eBioscience). Then, erythrocyte lysis was carried out with the RBC lysis buffer (MultiSciences, China) and the remaining cells were assessed on a FACS Aria II. Dead cells were excluded based on scatter properties and 7-AAD staining.

2.3 Cell sorting and culture

Fluorescence-activated cell sorting (FACS) was utilized to purify CD27⁺IgD⁺ B cells. Briefly, 10-ml blood specimens were obtained from SLE and HC patients, followed by peripheral blood mononuclear cell (PBMC) isolation by Ficoll density-gradient centrifugation and staining as described above. Next, the target cells were collected in RPMI 1640 containing 10% FBS and 2% antibiotics on a FACS Aria II flow cytometer as directed by the manufacturer (95–99% purity).

2.4 Quantitative real-time RT-PCR (qRT-PCR) analysis

Total RNA extraction from CD27⁺IgD⁺ B cells utilized RNeasy Mini Kit (Qiagen, Germany). Reverse transcription was carried out with the RevertAid First Strand cDNA synthesis kit (Fermentas, USA) as instructed by the manufacturer, followed by qRT-PCR assessment. GAPDH and β-actin were employed for normalization, and the $2^{-\Delta\Delta CT}$ method was applied for data analysis(14).

2.5 ELISPOT

ELISPOT was carried out with ELISpotPLUS Human IgM and IL-10 Kit (MABTECH AB, Sweden). In brief, 10⁴ purified CD27⁺IgD⁺ B cells from SLE and HC patients, respectively, were assessed for IgM and IL-10 after incubation with anti-CD40 (3µg/ml, eBioscience) and CpG (10µg/ml, Invivogen, USA) for 24h. An ImmunoSpot Analyzer (Cellular Technology Ltd., USA) was utilized for data analysis.

2.6 Statistics analysis

SPSS 17.0 (SPSS, USA) was employed for data analysis. Student's t-test, paired t-test, one-way ANOVA and Spearman rank correlation, respectively, were performed for statistical analysis as appropriate. P<0.05 indicated statistical significance.

3. Results

3.1. CD27⁺IgD⁺ B cell amounts are significantly decreased in SLE patients

B cells were grouped into 4 subtypes according to CD27 and IgD levels, including naïve (CD27⁺IgD⁺), innate-like (CD27⁺IgD⁺), switched memory (CD27⁺IgD⁻) and double negative (CD27⁻IgD⁻) B cells (Figure 1A). To examine the function of CD27⁺IgD⁺B cells in SLE pathogenesis, their amounts were firstly compared between SLE and HC patients. The 50 HCs showed remarkably higher circulatory CD27⁺IgD⁺B cell amounts compared with the 50 individuals with SLE (Figure 1B and C).

3.2. CD27⁺IgD⁺ B cell amounts correlate with clinical and immunological features in SLE patients

The associations of CD27⁺IgD⁺ B cell amounts with demographic and clinical characteristics were analyzed. As shown in Figures 2A–O and Table 3, WBC, platelet count and serum C3 levels were positively correlated with CD27⁺IgD⁺B cell amounts. Besides, CD27⁺IgD⁺B cell amounts showed negative correlations with serum creatinine levels, SLEDAI anti-dsDNA and CRP. However, no associations of CD27⁺IgD⁺B cells with disease duration, ESR, serum C4 levels and serum IgA, IgG IgM, C1q and MBL levels were found. The above findings indicated that CD27⁺IgD⁺ B cell amounts correlate with clinical and immunological features in SLE patients.

3.3. CD27⁺IgD⁺B cells are less competent in producing IgM and IL-10 in SLE

To examine CD27⁺IgD⁺B cells' functional changes, their ability to produce IgM and IL-10 were assessed in SLE patients. CD27⁺IgD⁺B cells isolated from SLE cases and HCs underwent ELISPOT and qRT-PCR. As depicted in Figure 3A and B, ELISPOT revealed significantly reduced IgM-producing ability for CD27⁺IgD⁺B cells in SLE, which was confirmed by decreased IgM mRNA levels as examined by qRT-PCR (Figure 3C). As depicted in Figure 3D and E, ELISPOT revealed significantly reduced IL-10-producing ability for CD27⁺IgD⁺B cells in SLE, which was confirmed by decreased IL-10 mRNA levels as examined by qRT-PCR (Figure 3F). Jointly, the above data indicated that CD27⁺IgD⁺B cells had impaired function regarding IgM and IL-10 production in SLE.

3.4. CD27⁺IgD⁺ B cells amounts are recovered in SLE cases with treatment-related disease remission

To ascertain CD27⁺IgD⁺ B cells' usefulness as a biomarker of disease activity, whether they are restored following effective treatment was assessed. Totally 12 patients previously diagnosed with SLE were assessed during relapse and 4 weeks post-treatment initiation. As expected, treatment markedly decreased disease activity based on the SLEDAI (Table 2). In addition, anti-dsDNA and 24h urinary protein amounts were reduced, with serum C3 and C4 level normalization to a certain degree. Total leukocyte and platelet levels were heightened post-treatment.

Next, CD27⁺IgD⁺B cell amounts and IgM-production were assessed pre-treatment and at 4 weeks post-treatment initiation (Figure 4A-D). As measured by the SLEDAI, all cases had a significant reduction in disease activity after treatment (Figure 4B); meanwhile, CD27⁺IgD⁺B cell amounts were remarkably

elevated (Figure 4C). However, the ability to produce IgM of CD27⁺IgD⁺B cell was no significant increased (Figure 4D). Jointly, the above findings suggested that CD27⁺IgD⁺B cell amount impairment in SLE patients could be alleviated by effective treatment.

4. Discussion

The current study revealed that CD27⁺IgD⁺B cells displayed reduced amounts and functional impairment regarding the production of natural IgM and IL-10 in patients with SLE compared with healthy controls. In addition, CD27⁺IgD⁺B cell amounts were associated with clinical characteristics in SLE patients, and were restored by effective treatment.

In SLE, the number of apoptotic cells increases while phagocytosis is impaired(17, 18). Concurrent occurrence of increased apoptotic cell death and deficient phagocytosis represents a major factor in SLE pathogenesis, promoting autoantigen accumulation and subsequent autoantibody production and autoimmune disorders(19). Apoptotic cells undergo phagocytosis by professional phagocytic cells (e.g., macrophages) under normal conditions. However, apoptotic cell clearance depends not only on functional phagocytes, but also on soluble proteins acting as opsonins and/or bridging materials. Phagocytosis of apoptotic cells can be increased by C-reactive protein (CRP), serum amyloid P component (SAP), C1q, IgM, MBL and other proteins, forming a redundant backup mechanism. These opsonins were associated with disease activity in SLE; for example, serum CRP(20) levels were positively correlated with SLEDAI score, and C1q(21) and MBL(22) levels were negatively correlated with SLEDAI score. Previous studies have found that macrophages are three- to four-fold less phagocytic in the absence of IgM(23). Decreased amounts of natural IgM in SLE patients might reduce apoptotic cell clearance, with dead cells accumulating in blood(24). Individuals with SLE show anti-PC natural IgM level reduction, which correlates with disease duration. In addition, decreased anti-PC natural IgM amounts are associated with a higher frequency of cardiovascular events in human SLE (25). However, the causes of natural IgM defects in SLE patients remain largely unknown.

In a previous study, we demonstrated that CD27⁺IgD⁺B cells can readily secrete

IgM with poly-reactivity and low affinity(14). These CD27⁺IgD⁺B cell-associated IgM were coined natural antibody-like IgM. In this study, CD27⁺IgD⁺B cell amounts in SLE patients were remarkably reduced and negatively associated with SLEDAI, anti-dsDNA autoantibodies and CRP. The above findings corroborate previously reported data(12, 26), jointly indicating that B cell-subsets are disordered in SLE patients. Since distinct B cell subsets have different functional characteristics, the imbalance of their proportions would lead to altered immune homeostasis and promote pathological events to some extent. Cytokines including IFN- γ , BAFF, TNF- α , IL-6 and IL-21 in the serum of SLE patients affect the B cell signaling pathway, thereby increasing B cell activation and differentiation(27–29). Therefore, we speculated that the inflammatory environment in SLE patients is one of the factors explaining the reduced CD27⁺IgD⁺B cell amounts, which deserves further investigation.

In addition, qRT-PCR and ELISPOT analyses showed that the ability of CD27⁺IgD⁺B cells to secrete IgM and IL10 in human SLE was markedly reduced, indicating that in SLE patients, CD27⁺IgD⁺B cells have defects not only in quantity, but also in function. Therefore, this may also account for apoptotic cell accumulation and the unbalance of their auto immune function in human SLE. Reduced TCR and/or BCR diversities have been reported in cancer and autoimmune disorders, as potential etiologic factors(30). Our previous research revealed that BCR profile in CD27⁺IgD⁺B cells is abnormal in RA(14). Therefore, we speculated that BCR profile in CD27⁺IgD⁺B cells might also be changed in SLE, and a follow-up study is underway to score CD27⁺IgD⁺B cells' BCR repertoire in SLE patients. In addition, the impairment of natural IgM and IL-10 secretion may be related to their activation and differentiation, and it will be improved and verified in the follow-up research work.

In this study, we also found that the CD27⁺IgD⁺B cells are increased in SLE cases after treatment in SLE patients than before treatment, but the ability of CD27⁺IgD⁺B cells to secrete natural IgM did not increase significantly. It may be that the treatment time is short, the number of CD27⁺IgD⁺B cells has been restored, but their function has not been restored.

5. Conclusion

Overall, the amounts and function of CD27⁺IgD⁺B cells in SLE are altered, which may be one of the reasons for the aggravation of SLE.. After treatment, the amounts of CD27⁺IgD⁺B cells in SLE patients recovered, but their ability to secrete IgM did not change significantly. Therefore, CD27⁺IgD⁺B cells could help reliably detect SLE, although their precise role in SLE development deserves further investigation. The reason of CD27⁺IgD⁺B cell amounts and function defect in SLE patients was not clear in this study, which will be studied in the future.

Abbreviations

SLE□systemic lupus erythematosus

nIgM□Natural IgM

TRAIL□TNF-related apoptosis inducing ligand

TWEAK□TNF-like weak inducer of apoptosis

ILBs□innate-like B cells

HC□healthy control

SLEDAI□Systemic Lupus Erythematosus Disease Activity Index

LDA□low disease activity

PBMC peripheral blood mononuclear cell

Declarations

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Authors' contributions

Study conception and design, W. Z., Y. W. and K.L.; experiments, W. Z. and T.W.; data analysis, W. Z., Y. W. and F. H.; contribution with reagents, materials and analytical tools, L.F., F. H. and Y. W.; manuscript writing, W. Z.; manuscript revision, F. H. and K.L.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Tables

Due to technical limitations, table 1-3 is only available as a download in the Supplemental Files section.

Figures

Figure 1

Circulatory CD27+IgD+B cell amounts are reduced in SLE cases in comparison with healthy control (HC) patients.

Figure 2

Associations of CD27+IgD+B cell amounts with SLE patient disease manifestations

Figure 3

IgM and IL-10 producing abilities of CD27+IgD+B cells in SLE and healthy control patients.

Figure 4

CD27+IgD+B cell amounts are increased after treatment of human SLE.

Supplementary Files

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