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Original Article

Expression level of plasma Bcl-xL and Bcl-2 in patients with systemic lupus erythematosus

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Abstract: Objective: To investigate the plasma levels of Bcl-xL and Bcl-2 in systemic lupus erythematosus (SLE) patients and their correlations with SLE-associated clinical parameters. Methods: SLE patients and 80 normal controls were recruited, the plasma of them were obtained at the first visit. Plasma Bcl-xL and Bcl-2 levels were evaluated by Enzyme-Linked Immunosorbent Assay (ELISA). Results: When compared with the normal controls, the plasma level of Bcl-xL was significantly lower in SLE patients, while the plasma level of Bcl-2 in SLE patients was significantly higher (both $P<0.05$). Furthermore, the plasma level of Bcl-xL was positively associated with the level of C4 and was inversely correlated with the levels of IgG and IgM. Conclusion: All these findings suggest Bcl-xL and Bcl-2 possible role in the pathogenesis of SLE. However, further studies are needed to confirm these preliminary results.

Keywords: Bcl-xL, Bcl-2, systemic lupus erythematosus

Introduction

Systemic lupus erythematosus (SLE) is a chronic, multifactorial autoimmune disease with the features of the presence of multiple autoantibodies, complement activation, and immune-complex deposition, causing serious injury to various organs or systems [1-3]. So far, although the exact cause of SLE remains unclear, it is sure that the disorder of B cell and T cell immune function plays a key role for the disease pathogenesis, especially B cell.

Bcl-xL and Bcl-2 are inhibitors of apoptotic cell death belonging to the Bcl-2 family proteins. Dysregulated expression of either of the two molecules may result in autoimmunity. Transgenic expression of Bcl-xL or Bcl-2 in murine B cells was shown to modify the repertoire of B cells and to result in the production of pathogenic antibodies and the development of autoimmune diseases including SLE [4, 5]. But The Bcl-xL and Bcl-2 transgenes also act differently during negative selection in immature B cells, as transgenic Bcl-xL has the ability to block negative selection and promote developmental maturation, whereas autoreactive cells transgenic for Bcl-2 remain arrested in development [4, 6]. Fang et al demonstrated that the *Bcl-xL* transgene allowed self-reactive B cells that normally arrest in development and die in the bone marrow (BM) to escape clonal deletion and proposed that Bcl-xL may have a distinct role in controlling survival at the immature stage of B cell development by generating B cell-restricted Bcl-xL transgenic mice [4]. Bcl-xL also play a role in the development, differentiation, and clonal selection of B cells [7, 8]. Mice expressing a Bcl-2 transgene in their B-cells were prone to develop an autoimmune disease resembling SLE [5]. Together, all these evidences indicated that Bcl-xL and Bcl-2 may be involved in SLE pathogenesis. However, the association studies between Bcl-2 SNP markers and SLE have shown different results among different populations [9, 10]. And previous studies has indicated that the expression of Bcl-2 varies among various cells [11-14]. Therefore, the role of Bcl-xL and Bcl-2 in SLE remain to be further elucidated.

Table 1. The general features of study subjects

Parameters	SLE patients (n=80)	Healthy control (n=80)	*P* value
Age	37.81 ± 14.50	35.48 ± 8.97	0.222
Sex (male/female)	7/73	11/69	0.317
Active (SLEDAI ≥10)	43/37	NA	NA
Nephritis (yes/no)	27/53	NA	NA

Note: SLEDAI: SLE disease activity index; NA: not applicable.

Table 2. Comparison of plasma BCL-XL levels and plasma BCL-2 levels between different subgroups

Group	Number	Plasma level (ng/ml) Mean ± SD	*P* value
BCL-XL			
Normal controls	74	74.70 ± 56.80	
SLE patients	51	32.79 ± 16.40	<0.001*
SLE without nephritis	35	30.85 ± 16.95	
SLE with nephritis	16	37.03 ± 14.75	0.215☆
Less active SLE	23	34.15 ± 18.22	
More active SLE	28	31.67 ± 15.00	0.596▲
BCL-2			
Normal controls	71	56.38 ± 36.44	
SLE patients	73	68.56 ± 30.36	0.031*
SLE without nephritis	49	70.69 ± 33.23	
SLE with nephritis	24	64.21 ± 23.48	0.341☆
Less active SLE	33	73.27 ± 37.32	
More active SLE	40	64.67 ± 22.90	0.253▲

Note: *versus normal controls; ☆versus SLE without nephritis; ▲versus less active SLE.

In the present study, to further explore the role of Bcl-xL and Bcl-2 in human SLE, we investigated the Bcl-xL and Bcl-2 plasma levels in SLE and their relations with SLE-associated clinical parameters.

Materials and methods

Patients

SLE patients were recruited from the Department of Rheumatology, First Affiliated Hospital of Anhui Medical University and the Department of Rheumatology, Anhui Provincial Hospital. All the patients fulfilled the requirement of at least four criteria of American College of Rheumatology (ACR) classification for SLE [15]. Individual disease activity was scored by the SLE Disease Activity Index (SLEDAI) [16]. The patients with renal disease were defined by persistent proteinuria (0.5 g/24 h) or the presence of active cellular casts; or biopsy evidence of lupus nephritis [17]. Demographic, clinical, and laboratory data were collected from hospital records or by questionnaire and reviewed by experienced physicians. All of 80 controls were clinically assessed to be without SLE, other autoimmune disorders, systemic disorders or family history of autoimmune disorders (including first-, second- and third-degree relatives). Informed consent for the studies was provided by all participants in accordance with the protocol as approved by the Ethics Committee of each hospital.

Method

Extraction of serum and enzyme-linked immunosorbent assay (ELISA): Serum were obtained from 5 ml of whole blood at the first visit of the study subjects and stored at -80°C. Plasma levels of Bcl-xL and Bcl-2 were determined using commercially available sandwich enzyme linked immunosorbent assay (ELISA) developing kits. All kits were derived from R&D Systems (Ambingdon, UK). The assay procedure was performed according to the manufacturer's instructions of the enclosed pamphlet.

Statistical analysis

The numerical data were expressed as mean ± SD. For comparing the means between two different groups, the Student's t-test was used. All statistical analysis was conducted by the Statistical Package for the Social Sciences (SPSS) statistical software for Windows, Version 10.01 (SPSS Inc, IL, USA). *P* Values less than 0.05 were considered statistically significant.

Results

Characteristics of participants

The mean ages of the SLE subjects were 37.81 ± 14.50 years, while the mean ages of controls was 35.48 ± 8.97 years. 73 SLE patients (91%) and 69 subjects (86%) in control group were female. There were no significant differences between patient group with SLE and healthy controls in terms of age and gender distribution (*P* = 0.222, *P* = 0.317, respectively) (**Table 1**).

Table 3. Associations of plasma BCL-XL and BCL-2 levels with clinical parameters of SLE patients

Group	-/+	Number	Plasma level (pg/ml) Mean ± SD	*P* value
BCL-XL				
Vasculitis	-	46	32.63 ± 16.49	0.842
	+	5	34.19 ± 17.44	
Arthritis	-	34	34.45 ± 17.19	0.311
	+	17	29.26 ± 14.62	
Myositis	-	44	33.57 ± 16.89	0.397
	+	7	27.85 ± 12.85	
Rash	-	24	31.53 ± 19.21	0.610
	+	27	33.91 ± 13.73	
Alopecia	-	30	29.74 ± 16.79	0.114
	+	21	37.13 ± 15.18	
Oral ulcer	-	41	34.63 ± 15.63	0.104
	+	10	25.22 ± 18.18	
Pericarditis	-	47	32.68 ± 16.45	0.876
	+	4	34.04 ± 18.25	
Fever	-	37	32.31 ± 16.93	0.738
	+	14	34.05 ± 15.47	
BCL-2				
Vasculitis	-	68	68.08 ± 31.14	0.624
	+	5	75.04 ± 16.85	
Arthritis	-	49	68.99 ± 32.98	0.849
	+	24	67.67 ± 24.77	
Myositis	-	66	67.56 ± 31.19	0.393
	+	7	77.96 ± 20.22	
Rash	-	36	75.09 ± 33.90	0.069
	+	37	62.20 ± 25.31	
Alopecia	-	45	70.50 ± 30.36	0.494
	+	28	65.45 ± 30.65	
Oral ulcer	-	60	68.51 ± 32.09	0.977
	+	13	38.78 ± 21.63	
Pericarditis	-	68	68.74 ± 31.29	0.727
	+	5	66.16 ± 13.46	
Fever	-	53	71.03 ± 31.62	0.261
	-	20	62.02 ± 26.36	

Note: +/-: with/without.

The plasma levels of Bcl-xL and Bcl-2 in SLE patients and controls

The plasma level of Bcl-xL was lower in SLE patients than in normal controls (32.79 ± 16.40 vs. 74.70 ± 56.80, $P<0.001$). Compared with the normal controls, SLE patients had a higher level of Bcl-2 (68.56 ± 30.36 vs. 56.38 ± 36.44, $P = 0.031$) (**Table 2**).

Association of Bcl-xL and Bcl-2 plasma levels with SLE-associated clinical parameters

Both plasma levels of Bcl-xL and Bcl-2 had no significant correlations with LN, SLEDAI score, SLE-associated manifestations including arthritis, vasculitis, rash, alopecia, oral ulcer, pericarditis and fever (**Table 3**), categorical laboratory parameters including Anti-dsDNA, Anti-Sm, Anti-SSA, Anti-SSB, Anti-RNP, Anti-RibosomalP, thrombocytopenia, leukopenia, proteinuria, and blood urine (**Table 4**) and some quantitative laboratory parameters including C3, C-reactive protein(CRP), and IgA. The plasma level of Bcl-xL was correlated with the levels of C4 ($r = 0.293$, $P = 0.041$) and was negatively correlated with the levels of IgG ($r = -0.340$, $P = 0.024$), IgM ($r = -0.352$, $P = 0.019$) (**Table 5**).

Discussion

In recent years, there has been increasing studies on the role of proteins of the Bcl-2 family in regulating apoptotic cell death. Bcl-xL and Bcl-2 are two numbers of the Bcl-2 family proteins participating in the regulating B cell immune response. During B cell ontogeny, Bcl-xL is expressed at highest levels in the small pre-B cell stage of development [18], but at very low levels in pro-B cells and downregulated in immature and mature B resting cells [18, 19]. Fang et al found that the death of pro-B cells with failed immunoglobulin rearrangements occurred by apoptosis and large expansions of pro-B cells developed in bone marrow in transgenic mice expressing Bcl-xL gene in the B lineage. And Bcl-xL can deliver a strong survival signal at the pro-B stage [4]. Takahashi generated Bcl-xL transgene mice in which endogenous Bcl-xL was produced [7]. The transgene mice demonstrated reduced apoptosis in germinal centers B cells and resulted in the expansion of B lymphocytes bearing VDJ rearrangements. The abundance of these noncanonical cells lowered the average affinity of long-lived antibody-forming cells and serum antibody, demonstrating that Bcl-xL influence clonal selection/maintenance for affinity maturation. All these results indicate that Bcl-xL may plays an important role in extending B cells survival, and also reveal an unexpected role of the Bcl-xL in the regulation of B cells function and maintaining self-tolerance. Bcl-2 is highly ex-

Table 4. Associations of plasma BCL-XL and BCL-2 levels with categorical laboratory parameters of SLE patients

Group	-/+	Number	Plasma level (pg/ml) Mean ± SD	*P* value
BCL-XL				
Anti-dsDNA	-	27	32.82 ± 17.21	0.988
	+	24	32.75 ± 15.82	
Anti-Sm	-	36	35.01 ± 16.05	0.134
	+	15	27.44 ± 16.54	
Anti-SSA	-	14	32.87 ± 21.50	0.985
	+	37	32.75 ± 14.38	
Anti-SSB	-	42	75.04 ± 16.85	0.539
	+	9	32.77 ± 21.10	
Anti-RNP	-	32	34.23 ± 15.17	0.419
	+	19	30.35 ± 18.47	
Anti-RibosomalP	-	33	34.18 ± 16.03	0.418
	+	18	30.24 ± 17.24	
Thrombocytopenia	-	36	31.15 ± 14.49	0.275
	+	15	36.70 ± 20.32	
Leukopenia	-	40	32.41 ± 15.68	0.759
	+	11	34.15 ± 19.61	
Proteinuria	-	32	31.41 ± 17.24	0.444
	+	19	35.10 ± 15.06	
Blood urine	-	36	31.06 ± 17.09	0.248
	+	15	36.93 ± 14.32	
BCL-2				
Anti-dsDNA	-	40	72.09 ± 33.66	0.277
	+	33	64.28 ± 25.65	
Anti-Sm	-	53	67.14 ± 31.48	0.518
	+	20	72.33 ± 27.56	
Anti-SSA	-	22	70.65 ± 35.78	0.703
	+	51	37.66 ± 28.04	
Anti-SSB	-	61	68.61 ± 31.56	0.776
	+	12	38.30 ± 24.46	
Anti-RNP	-	44	38.24 ± 29.99	0.913
	+	29	39.04 ± 31.43	
Anti-Ribosomal P	-	52	67.14 ± 31.63	0.534
	+	21	72.07 ± 27.34	
Thrombocytopenia		56	66.14 ± 29.62	0.219
		17	76.52 ± 32.30	
Leukopenia		59	66.07 ± 31.09	0.152
		14	79.05 ± 25.39	
Proteinuria		47	70.79 ± 31.53	0.402
		26	64.52 ± 28.26	
Blood urine	-	51	72.37 ± 32.85	0.057
	-	22	59.72 ± 21.76	

Note: +/-: with/without.

pressed in the pro-B cells and mature B lymphocytes, but downregulated at the pre-B and immature B cell stages of maturation [20, 21]. In a previous study, Strasser et al generated a transgenic mice harboring human Bcl-2 cDNA under the control of an immunoglobulin heavy chain enhancer (Eμ) which was replaced by a representative transgenic strain Eμ-bcl-2-22 [22]. The mutant mice enforced Bcl-2 expression demonstrated a great excess of B lymphocytes, immunoglobulin-secreting cells, and serum inmmunoglobulins, attributable to increased longevity of B-lineage cells. Pre-B and plasma cells as well as B cells exhibited prolonged survival in culture in the mutant mice. Thus ES-Bcl-2-22 mice constitute a transgenic model for a systemic autoimmune disease resembling human SLE. Collectively, Bcl-xL and Bcl-2 may play an important role in the induction and development of autoimmune diseases.

SLE is considered to be the prototype of human autoimmune diseases. It is a disorder of generalized autoimmunity characterized by multisystem organ involvement, polyclonal B cell activation, and the production of autoantibodies against nuclear, cytoplasmic, and cell surface antigens [10]. More recently, Zhan et al investigated the effects of two inhibitory anti-Bcl-2 (ABT-737, ABT-199) in lupus-prone NZB/W F1 mice and human peripheral blood including SLE and controls in vitro, their results showed that ABT-199 treatment efficiently killed NZB/W plasmacytoid DCs (pDCs) which are major producers of IFN-α and also being a prominent source of B cell activating factor of the tumor necrosis factor family (BAFF) [23]. As we known, IFN-α and BAFF had been proposed to contribute to SLE pathogenesis [24, 25]. Thus they proposed that enhanced cytokine output from pDCs due to their extended survival, mediated by increased BCL-2 levels, could be a significant driver of SLE. All these results support a possible role of Bcl-xL and Bcl-2 in the pathogenesis of SLE.

In the current study, we investigated the plasma Bcl-xL and Bcl-2 levels in SLE patients. Results showed that lower level of Bcl-xL and higher level of Bcl-2 were observed

Table 5. Associations of plasma BCL-XL and BCL-2 levels with quantitative laboratory parameters of SLE patients

Parameters	N	Spearman Correlation coefficient (r/r_s)	*P* value
BCL-XL			
C3	80	0.216	0.128
C4	75	0.293	0.041
CRP	66	0.205	0.183
IgA	71	-0.289	0.057
IgG	71	-0.340	0.024
IgM	71	-0.352	0.019
SLEDAI	79	0.020	0.891
BCL-2			
C3	85	0.205	0.082
C4	79	-0.051	0.675
CRP	70	-0.226	0.082
IgA	75	0.177	0.160
IgG	75	-0.102	0.421
IgM	75	0.027	0.832
SLEDAI	84	-0.129	0.281

in the plasma of SLE patients compared with health controls. In addition, the plasma level of Bcl-xL was correlated with the levels of C4 and was negatively correlated with the levels of IgG, IgM in SLE patients. It is of interest to compare our results to several previous attempts to explore the expression and clinical associations of Bcl-xL and Bcl-2 in SLE patients. A previous study by Rose et al suggest that Bcl-2 expression is unaltered in unfractionated peripheral blood mononuclear cells in patients with SLE and Bcl-2 levels did not correlate with overall disease activity in SLE patients, which are similar to our results [26]. However, another study by Liphaus et al reported upregulation of Bcl-2 protein expression in peripheral blood mononuclear cells from patients with juvenile-onset SLE, and the higher Bcl-2 expression, the active disease [11]. In addition, a decreased Bcl-2 expression in peripheral blood lymphocytes of patients with SLE have also been shown and Bcl was negatively correlated with disease activity [14]. These disparities may be influenced by the difference among various lymphocyte subsets, various disease subgroups, various cells, different demographic characteristics, application of different classification and patient selection criteria.

Taken together, decreased plasma level of Bcl-xL and increased plasma level of Bcl-2, and association of Bcl-xL with C4, IgG and IgM suggest their possible role in the pathogenesis of SLE. However, further studies are needed to confirm these preliminary results.

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Disclosure of conflict of interest

None.

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