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ORIGINAL ARTICLE

Baculoviral inhibitor of apoptosis family of proteins repeat-containing 5 gene methylation status in peripheral blood mononuclear cells and plasma survivin levels in patients with Behçet's disease

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ABSTRACT

Objectives: This study aims to evaluate the baculoviral inhibitor of apoptosis repeat-containing 5 (BIRC5) gene methylation in the peripheral blood mononuclear cells (PBMCs) in patients with Behçet's disease (BD) compared to healthy controls and the association of survivin with BD activity.

Patients and methods: A cross-sectional study was conducted on 43 BD patients (22 males, 21 females; mean age 36.6±10.1 years; range, 18 to 66 years) and 44 age- and sex-matched healthy controls (23 males, 21 females; mean age 35.4±7.5 years; range, 18 to 61 years) between August 2019 and December 2019. Sample size was calculated guided by taking into account the difference of 1.5 units between the mean expression of BIRC5 gene in the BD and control groups, as well as considering α=0.5 and power=80%. We assessed the methylation status of the BIRC5 gene in PBMCs of BD and control groups by methylation-specific polymerase chain reaction (MS-PCR). Plasma levels of survivin were measured by enzyme-linked immunosorbent assay.

Results: Oral aphthous ulcer, genital ulcer, and skin lesions were the most common clinical manifestations in BD group. MS-PCR showed that the deoxyribonucleic acid samples of BD and control groups were not different in methylated and unmethylated areas and alleles were heterozygote. No significant difference was observed in the plasma levels of survivin in BD (98.86±25.5 pg/mL) and control (118.16±37.4 pg/mL) groups. There was no significant correlation between survivin plasma levels and BD activity.

Conclusion: Our study did not show any evidence of association between the alteration in the BIRC5 gene methylation, survivin production, and apoptosis dysregulation in BD.

Keywords: Apoptosis, Behçet's disease, methylation, survivin.

Behçet's disease (BD) is an autoimmune/autoinflammatory disorder with a broad range of clinical manifestations including recurrent oral aphthous ulcers, genital ulcers, uveitis, erythema nodosum, pseudofolliculitis, and arthritis. Although the etiology of BD is unknown, immune system dysregulation triggered by environmental factors, including microbial agents, vitamin D deficiency, and smoking play an important role.[1-3] Many studies revealed the role of genetic background in the immune system dysregulation and autoimmunity development in BD.[4-6] In BD, innate and acquired immune system dysfunction lead to presentation of microbial and

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self antigens to the T-cells and hyperactivation of them.[7,8] Regulatory mechanism can control immune response and prevent autoimmunity. Apoptosis is one of the mechanisms that by deleting hyperreactive T-cells control immune response and plays a key role in the pathogenesis of many autoimmune diseases.[7,8] Many studies introduced the role of apoptosis dysregualtion in the pathogenesis of BD.[9-14]

Survivin belong to a group of proteins named inhibitor of apoptosis proteins (IAPs), which stop apoptosis by inhibiting function of caspases 3 and 9.[7] Baculoviral IAPs repeat-containing 5 (BIRC5) gene has the function of encoding survivin.[7] Survivin expression is dysregulated in various autoimmune diseases including systemic lupus erythematous, systemic sclerosis, and rheumatoid arthritis (RA).[7,15,16] Higher survivin levels in the sera of RA patients in comparison to healthy controls suggested that survivin could be considered as a possible biomarker for the diagnosis and monitoring of RA disease activity.[17,18] A preliminary study showed high expressions of the BIRC5 gene in the peripheral blood mononuclear cells (PBMCs) of patients with BD and higher plasma levels of survivin in BD patients compared with controls.[19] However, differences in the plasma levels of survivin did not reach significant levels.[19] We hypothesized that a type II error occurred and by increasing the sample size, we could prove an increased production of survivin. In addition, we hypothesized that epigenetic mechanisms may be responsible for the higher expression of the BIRC5 gene and increased production of survivin in BD patients. The epigenetic mechanism has been shown to affect the genes expression by altering the physical structure of deoxyribonucleic acid (DNA).[20] DNA methylation is an epigenetic mechanism that affects the expression of specific genes by adding a methyl group to the part of DNA that occurs most frequently at the 5' end of guanine in CpG (cytosine-phosphate-guanine) dinucleotide.[20] Recent studies showed the role of DNA methylation in the pathogenesis of BD.[21-24] Therefore, in this study, we aimed to evaluate the BIRC5 gene methylation in the PBMCs and plasma levels of survivin in patients with BD compared to healthy controls and the association of survivin with BD activity.

PATIENTS AND METHODS

This cross-sectional study was conducted at Connective Tissue Diseases Research Center of Tabriz University of Medical Sciences between August 2019 and December 2019. Forty-four patients with BD and 44 age- and sex-matched healthy controls were enrolled in this study. One-to-one matching was performed. However, one of the BD patients was excluded due to a technical problem with DNA isolation. Thus, a total of 43 BD patients (22 males, 21 females; mean age 36.6±10.1 years; range, 18 to 66 years) and 44 age- and sex-matched healthy controls (23 males, 21 females; mean age 35.4±7.5 years; range, 18 to 61 years) were included. Sample size was calculated guided by taking into account the difference of 1.5 units between the mean expression of BIRC5 gene in the BD and control groups, as well as considering α=0.5 and power=80%. The controls were selected from the students and staff of the School of Modern Medical Sciences who were invited to study by advertisements. Three controls were selected for both patients. Inclusion criteria were: *(i)* fulfillment of the International Criteria of Behçet's Disease;[25] *(ii)* age over 16 years, and *(iii)* having active disease. Exclusion criteria for BD and control groups were having underlying diseases including malignancy, human immunodeficiency virus infection, other inflammatory and autoimmune disorders, liver disease, diabetes mellitus, kidney disease, and ever smoking. We measured BD activity using Behçet's Disease Current Activity Form (BDCAF), Iranian Behçet's Disease Dynamic Activity Measure (IBDDAM), and Total Inflammatory Activity Index (TIAI).[26,27] Patients with BDCAF ≥1 were classified as active BD.[28] The study protocol was approved in June 2019 by the Tabriz University of Medical Sciences Ethics Committee (ethical code: IR TBZMED. REC.1397.190). A written informed consent was obtained from each participant. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Five milliliter of blood was drawn from the cubital vein of all the participants after 12 hours of overnight fasting. The blood samples were transferred directly to the sodium citrate tubes. PBMCs were isolated immediately with

Table 1. Sequences of BIRC5 and GAPDH primers

Gene	Sequence	Product size
GAPDH		
Forward	AATGGGCAGCCGTTAGGAAA	79
Reverse	GCCCAATACGACCAAATCAGAG	
Survivin-methylation		
Methylated forward	GGCGGGAGGATTATAATTTTCG	164bp
Methylated reverse	CCGCCACCTCTACCAACG	
Survivin-methylation		
Unmethylated forward	GGTGGGAGGATTATAATTTTTG	168bp
Unmethylated reverse	ACCACCACCACCTCTACCAACA	

GAPDH: Glyceraldehyde-3-phosphate dehydrogenase; BIRC5: Baculoviral inhibitor of apoptosis repeat-containing 5.

Ficoll method using a density-gradient centrifuge (Lymphodex, Inno-Train, Kronberg, Germany) and were directed to a -70°C refrigerator until next step. Total ribonucleic acid (RNA) was extracted from PBMCs by RNA isolation kit (BioFACTTM Total RNA Prep Kit, Daejeon, South Korea) according to the manufacturer's instructions. DNA isolation from PBMCs was performed using Blood Genomic DNA extraction mini kit (Favorgen Biotech, Corp., Ping-Tung, Taiwan). DNA integrity was checked by 2% agarose electrophoresis.

The methylation levels of BIRC5 gene were assessed by methylation-specific PCR (MS-PCR) technique according to the manufacturer's instructions. The bisulfite modification was performed by EZ DNA Methylation-GoldTM Kit (Zymo Research, Cat No. D5006, The Epigenetics Company, Irvine, CA, USA). The primer sequences for unmethylated promoter sequences were previously designed.[29] The expression levels of methylated and unmethylated survivin were measured by real time quantitative PCR

Table 2. Demographic, clinical, and laboratory characteristics of participants

	BD group (n=43)					Control group (n=44)					
	n	%	Mean±SD	Median	IQR	n	%	Mean±SD	Median	IQR	*p*
Age (year)			36.6±10.1					35.4±7.5			0.234
Sex											0.508
Male	22	51.2				23	52.3				
Female	21	48.8				21	47.7				
Disease duration before diagnosis (month)				37	21				-	-	
Oral aphthous ulcer	40	93.0									
Genital ulcer	29	67.4									
Positive pathergy	23	53.5									
Arthritis	21	48.8									
Erythema nodosum	18	41.8									
Uveitis	15	34.9									
Pseudofolliculitis	6	14.0									
CNS involvement	4	9.3									
HLA-B5	23	53.5									
HLA-B51	22	51.2									

BD: Behçet's disease; SD: Standard deviation; IQR: Interquartile range; CNS: Central nervous system; HLA: Human leukocyte antigen.

Table 3. Plasma survivin levels in patients with various demographic and clinical manifestations of Behçet's disease

	Frequency		Plasma survivin levels	
	n	%	Mean±SD	*p*
Sex				
Male	22	51.2	96.2±25.7	0.855
Female	21	48.8	102.0±24.1	
Genital ulcer				
Yes	29	67.4	98.6±22.9	0.993
No	14	32.6	98.7±26.8	
Uveitis				
Yes	15	76.1	94.9±23.5	0.666
No	28	23.9	99.8±26.1	
Positive pathergy				
Yes	23	53.5	97.7±26.3	0.855
No	20	46.5	99.9±24.3	
Skin lesions				
Yes	18	41.9	95.8±25.9	0.619
No	25	58.1	101.6±25.3	
Arthritis				
Yes	21	48.8	100.7±32.1	0.490
No	22	51.2	97.3±24.5	

SD: Standard deviation.

LightCycler 96 instrument (Roche Diagnostics GmbH, Mannheim, Germany, and made in Switzerland) according to the manufacturer's instructions. The specific primers and PCR program are indicated in Table 1. We used glyceraldehyde-3-phosphate dehydrogenase as reference gene. All experiments were triplicated.

Plasma levels of survivin were measured by Human survivin ZellBio GmbH enzyme-linked immunosorbent assay (ELISA) kit (Cat. No: ZB-13904C-H9648, Ulm, Germany) according to the manufacturer's instructions. We expressed results as picogram of survivin per milliliter plasma (pg/mL).

Statistical analysis

Statistical analysis was performed using the SPSS version 16.0 (SPSS Inc., Chicago, IL, USA) and GraphPad Prism version 7.03 software (GraphPad, San Diego, USA). We reported continuous variables as means ± standard deviation and categorical variables as frequency and percentage. We compared categorical variables in studied groups by chi-squared test. Independent samples t-test or Mann-Whitney U test as appropriate was used for comparing continuous variables. P value less than 0.05 was considered as statistically significant.

RESULTS

There were no significant differences in sex and age between BD and control groups. The demographic and clinical characteristics of participants are shown in Table 2. Oral aphthous ulcer, genital ulcer, and skin lesions were the most common clinical manifestations of BD patients.

The methylation status of BIRC5 gene in PBMCs of BD and control groups was assessed using MS-PCR. Real-time PCR showed that the DNA samples of BD and control groups were not different in methylated and unmethylated areas and alleles were heterozygote (Figure 1).

We measured the plasma levels of survivin in BD and control groups with ELISA. No significant difference was observed in plasma levels of survivin in BD (98.86±25.5 pg/mL) and control (118.16±37.4 pg/mL) groups (Figure 2). In addition, differences in plasma survivin levels in patients with various demographic and clinical manifestations of BD were not significant (Table 3). There was no significant correlation between survivin plasma levels and BD activity assessed by BDCAF (r=0.117, p=0.569), IBDDAM (r=-0.132, p=0.552), and TIAI (r=0.361, p=0.191) (Table 4).

Table 4. Correlation between survivin plasma levels and Behçet's disease activity

	BDCAF		IBDDAM		TIAI	
	Pearson correlation	*p*	Pearson correlation	*p*	Pearson correlation	*p*
Plasma survivin (pg/mL)	0.117	0.569	-0.132	0.522	0.361	0.191

BDCAF: Behçet's Disease Current Activity Form; IBDDAM: Iranian Behçet's Disease Dynamic Activity Measure; TIAI: Total Inflammatory Activity Index.

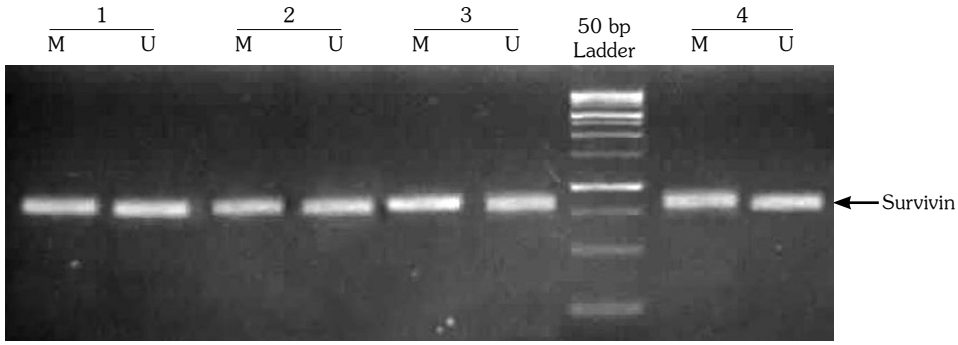

Figure 1. Methylation-specific polymerase chain reaction product analysis of blood baculoviral inhibitor of apoptosis repeat-containing 5 genes by agarose gel electrophoresis and ethidium bromide staining. Lanes 3-4: normal blood samples, lanes 1-2: Behçet's disease patients' blood samples. Each sample was represented by two successive lanes, one for methylated (M) band and another for unmethylated (U) band.

DISCUSSION

Activated auto-reactive lymphocytes play an essential role in the pathogenesis of BD. Failure to remove activated lymphocytes can result in augmented inflammatory reaction.[30] Apoptosis is one the mechanisms that control inflammatory response by removing activated cells. Several studies considered the role of apoptosis in the pathogenesis of BD. Hamzaoui et al.,[10] in a study on 50 BD patients reported a high serum soluble Fas/APO (sFas/APO-1) level in active BD compared with healthy controls. sFas/APO-1 is a soluble receptor which, by binding to Fas ligand (FasL), prevents this ligand's interaction with Fas. This process leads to the down-regulation of apoptosis. Hamzaoui et al.,[9] in another study assessed B-cell lymphoma 2 (BcL-2) expression in the lymphocytes obtained from body fluids including blood, cerebrospinal fluid, and bronchoalveolar lavage of patients with BD. They found higher levels of Bcl-2 expression in the lymphocytes of BD patients compared with the controls. Yang et al.[13] found resistance to Fas-mediated apoptosis in the PBMCs of patients with BD. They induced apoptosis in the PBMCs by using anti-Fas antibody and noted lesser apoptosis in the PBMCs of patients with BD (19.7%) compared with controls (26.1%). Interestingly, in another study, they showed higher Fas expression on the T cells of BD patients.[14] Todaro et al.[31] reported resistance to spontaneous and cluster

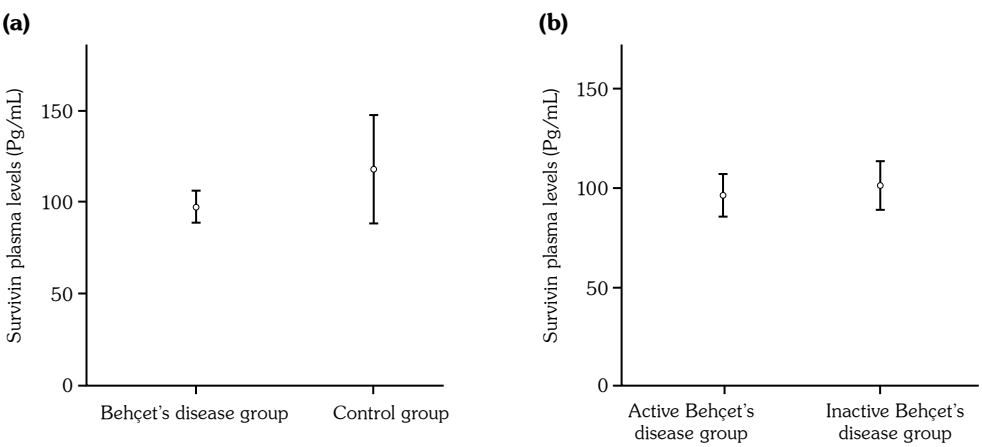

Figure 2. Survivin plasma levels in studied groups: **(a)** Behçet's disease group compared with control group, **(b)** active Behçet's disease group compared with inactive Behçet's disease group.

of differentiation (CD) 95-induced apoptosis in T cells of patients with BD. They found that a higher expression of nuclear factor-κβ in lymphocytes leads to a higher expression of cellular FLICE [FADD-like interleukin (IL)-1 beta-converting enzyme]-inhibitory protein and Bcl-extra large, and resistance to apoptosis.[31] Baris et al.[12] performed immunohistochemical staining for Bcl-2 and Fas in biopsies from skin lesions from 29 patients with BD and 10 patients with non-specific chronic inflammatory skin lesions. They found staining for Bcl-2 in 76% of cutaneous lesions lymphocytes in BD patients and in 20% of controls. Fas staining was not detected in cutaneous lesions lymphocytes of BD group.[12] However, lymphocytes in 33% of biopsies of control group stained for Fas. IL-12 by suppression of CD95-induced cell death causes resistance to activation-induced cell death in T cells of patients with BD and proliferation of auto-reactive T helper type I cells and prolong inflammatory attack.[12]

Survivin with expression in the nucleus, cytoplasm, and mitochondria of proliferating cells, like activated T cells, exert several regulatory functions including: *(i)* aiding cell division by forming a chromosomal passenger complex after attaching to borealin, inner centromere protein, and Aurora in the G2/M phase of mitosis, *(ii)* suppression of apoptosis by forming a complex with X-linked IAPs and inhibiting caspase-3 in the cytoplasm. It also prevents the activation of caspase-9 by inhibiting the release of the second mitochondria derived activator of caspases (Smac/Diablo).[7,8] Despite many studies about FasL/Fas-mediated apoptosis dysregulations in patients with BD, limited data exist about survivin-mediated apoptosis dysregulation in BD. In the present study, there were no significant differences in the methylation of the BIRC5 gene and plasma survivin levels in patients with BD compared with healthy controls.

This study has some limitations. With this study, we cannot rule out the role of survivin in the apoptosis dysregulation in BD. At first, a relatively small number of patients may have led to type II error. In addition, alteration in posttranslational modifications of survivin including phosphorylation and acetylation that play a key role in regulating survivin function may have been involved.

In conclusion, our study did not show any evidence of association between alteration in the BIRC5 gene methylation, survivin production, and apoptosis dysregulation in BD patients.

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Declaration of conflicting interests

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