Evaluation of CD19+CD5+ B (B1) Lymphocytes and CD20+ CD38 Low Preplasmablast Cells in Patients with Behçet's Disease

Behçet Hastalarında CD19+CD5+ B (B1) Lenfositler ile CD20+ CD38 Düşük Preplazmablast Hücrelerinin Değerlendirilmesi

Başak KANDİ, MD,[a]
Fulya İLHAN, MD,[b]
Demet ÇİÇEK, MD,[a]
Nesrin DEMİR, MD,[b]
Vedat BULUT, MD,[b]
Haydar UÇAK, MD,[c]
Nurhan HALİSDEMİR[d]

Departments of
[a]Dermatology
[b]Immunology
[d]Statistic
Fırat University Faculty of Medicine,
[c]Department of Dermatology,
Elazığ Education and Research Hospital,
Elazığ

Geliş Tarihi/*Received:* 30.03.2011
Kabul Tarihi/*Accepted:* 21.09.2011

Yazışma Adresi/*Correspondence:*
Demet ÇİÇEK, MD
Fırat University Faculty of Medicine,
Department of Dermatology, Elazığ
TÜRKİYE/TURKEY
dr.demetcicek@hotmail.com

ABSTRACT Objective: Behcet's disease (BD) is a chronic, recurrent, inflammatory disease. CD19+CD5+ B cells are currently defined as B1 cells and they produce polyreactive antibodies. CD20+CD38 low B cells can cause endothelial cell adhesion and are responsible for specific antibody synthesis. The aim of this study was to investigate the presence of CD19+CD5+ B cells and B cells containing CD20+CD38 low molecule, which plays a role in B cell differentiation and activation. Moreover, the ratio of these cells in BD patients was also evaluated. **Material and Methods:** In this study, 20 BD patients and 20 healthy control subjects were compared. Blood samples of the patients and the control group were stained with standard procedure using CD3, CD19, CD20, CD5, CD38 monoclonal antibodies with flow cytometric method, and B lymphocyte subgroups were evaluated. **Results:** There were no significant differences between total T and B lymphocyte ratios of two groups. However, CD19+CD5+ B lymphocytes and CD20+CD38 low preplasmablasts were significantly higher in BD patients compared to the control group. **Conclusion:** It was determinated that high levels of CD20+CD38low and CD19+CD5+ B lymphocytes in BD concerns the possible role of humoral immunity or force of T cell independent response. On the other hand, immediate differentiation of IgM producing cells indicates B cell activation and all the others support the possible role of CD38 in the etiology of vasculitis, which is the unchangeable characteristic and the basis of defining BD as an autoinflammatory disease.

Key Words: Behçet syndrome; B-lymphocytes; lymphocytes

ÖZET Amaç: Behçet hastalığı (BH), kronik, tekrarlayıcı, inflammatuar bir hastalıktır. CD19+CD5+ B hücreleri yakın zamanda B1 hücreleri olarak tanımlanmış ve çokyanıtlı antikorlar üretmektedirler. CD20+CD38 düşük B hücreleri, endotelyal hücre adhezyonuna neden olabilmektedir ve spesifik antikor sentezinden sorumludurlar. Bu çalışmanın amacı, B hücre farklılaşmasında ve aktivasyonunda rol alan CD19+CD5+ B hücrelerini ve CD20+CD38 düşük molekül içeren B hücrelerini araştırmaktı. Ayrıca, bu hücrelerin BH'li hastalardaki oranını değerlendirmekti. **Gereç ve Yöntemler:** Bu çalışmada BH'li 20 hasta ve sağlıklı 20 kontrol olgusu karşılaştırılmıştır. Hastaların ve sağlıklı kontrol grubunun kanları, flow sitometrik metodla CD3, CD19, CD20, CD5, CD38 monoklonal antikorlar kullanılarak standart yöntemlerle boyanmış ve B lenfosit alt grubları değerlendirilmiştir. **Bulgular:** Her iki grubun T ve B hücre oranları arasında anlamlı fark yoktu. Ancak, BH' li hastalarda CD19+CD5+ B lenfositleri ve CD20+CD38 düşük preplasmablastlar kontrol grubuyla karşılaştırıldığında anlamlı olarak yüksek idi. **Sonuç:** CD20+CD38düşük ve CD19+CD5+ B hücrelerinin BH'li hastalardaki yüksek düzeyi, hümoral immünitenin olası rolünü veya T hücre bağımsız cevabın gücünü etkilediğini düşündürmüştür. Diğer taraftan, Ig M üreten hücrelerin doğrudan farklılaşması, B hücre aktifleşmesini ve tüm diğerlerinin CD38' in otoimmün bir hastalık olarak BH' nın tanımlanmasında esas ve değişmez bir özellik olan vaskülitin etiyolojisindeki olası rolünü desteklediğini göstermekte olduğu belirlenmiştir.

Anahtar Kelimeler: Behçet sendromu; B-lenfositler; lenfositler

doi:10.5336/medsci.2011-23993

Turkiye Klinikleri J Med Sci 2011;31(6):1521-6

Behcet's disease (BD) is a multisystemic and chronic inflammatory disease. All components of immune system may change during inflammation process.[1] Although there are studies evaluating the roles of immune system cells such as T lymphocytes, monocytes, macrophages and neutrophils in BD, investigations on the function of B lymphocytes in BD are very limited.[2-4] It is known that immunoglobulin (Ig) secreting B cell count and Ig levels increase in BD.[5,6] Meanwhile, increased immunocomplex levels and presence of anti-lymphocyte, anti-intermediate filament, anti-endothelial cell, and anti-HSP 65 antibodies indicate an increased B cell activity in BD.[7-10]

In autoimmune diseases such as rheumatoid arthritis, Sjogren's syndrome and systemic lupus erythematosus, the relationship between the increase of autoantibodies and CD5+ B cells was established.[11,12] CD5+ B cells (B1 lymphocytes) constitute 15-25% of B cell population in secondary lymphoid tissues in adults. Large numbers of B1 cells are found as a self-renewing population in the peritoneum and mucosal sites.[13] Although they are found in fetus extensively, a decrease in cell counts occurs by increasing age. CD5+ B cells differ from T dependent antigens by producing low-affinity polyreactive natural antibodies in response to polyclonal activators.[11-14] B1 cells generally mediate T cell independent response to circulating pathogens, they response and differentiate short-lived IgM producing cells.[13]

CD19 is a member of Ig superfamily and is expressed by most of B cells. CD19, together with CD20 and CD22 are the main markers currently used to identfy human B cells.[15] B cell activation forms a coreceptor complex with CD21 and CD18 to deliver signals that synergize B cell antigen receptor complex.[16]

CD38 molecule is a 45-kDa type II integral membrane protein found in active B and T cells, natural killer (NK) cells, monocytes, plasma cells, and medullary thymocytes. CD38 molecule is presented to B cell line in early phases of B cell development, diminishes during maturation phase, and presented again to plasma cell during the final differentiation phase. As it is not found in mature resting lymphocytes, it is used as an activation marker. However, its role in B cell differentiation is not completely understood.[17-19] CD38 molecule is also an enzyme that has activities such as nicotine amic acid (NAD) glycohydrolase, adenosine diphosphate (ADP) ribosyl cyclase, and cyclic adenosine diphosphate (cADP) ribose hydrolase (cADPR). The most important functions of CD38 are Ca++ messenger production such as cADPR and nicotinic acid-adenine dinucleotide phosphate (NAADP), Ca++ release from intracellular channels via cADPR and as a result increase in intracellular Ca++ levels, and endothelial cell adhesion.[20-24]

CD20 is an integral non- glycolysated membrane protein. It has three isoforms with molecular weights of 33, 35, 37 kDa. Although it is found in all B lymphocytes, it is not seen in plasma cells. Thus, plasma cells are defined as $CD38^{high}$ CD20-/^{low}, and plasmablasts as CD20+ $CD38^{low}$.[25] Preplasmablasts are defined as CD20+ $CD38^{low}$ CD138-.[26]

MATERIAL AND METHODS

The study protocol was approved by the Local Ethics Committee of Firat University Medical Faculty. A total of 20 (male/female 9/11) BD patients, classified according to international criteria[27] as active (10 patients) or inactive (10 patients), and 20 (male/female 12/8) healthy controls were included in the study (Table 1).

All BD patients fulfilled the criteria of the International Study Group for BD.[27] At the time of the clinical assessment, patients were included in the active group if they had at least two of the following clinical findings: oral ulcers, genital ulceration, active uveitis, recent artritis, papulopustular or pseudofollicular cutaneous lesions, neurological involvement and pathergy test positivity.

Peripheral blood samples of active patients who were not taking any immunosuppressive drugs, control group and inactive patient group were stained according to standard procedures, and B

TABLE 1: Clinical values of patients with Behcet's disease.

No	Age	Gender	OA	GU	UV	ACN	PT	AT	ATG	CNS	GUS	GIS	DVT	EN
1	30	M	2	2	0	2	0	0	0	0	2	0	0	0
2	28	F	2	0	2	0	2	0	0	0	0	0	0	0
3	37	M	2	2	0	2	0	0	0	2	0	2	2	0
4	43	F	2	0	0	2	2	2	0	0	0	0	0	0
5	29	F	2	2	0	2	0	0	0	0	0	0	0	0
6	32	F	2	2	0	0	2	0	0	0	0	0	0	0
7	34	M	2	0	0	0	2	0	2	0	0	0	0	0
8	29	F	2	2	2	0	0	0	0	0	0	0	0	2
9	28	M	2	2	2	0	2	0	0	0	0	0	0	0
10	31	M	2	2	0	0	0	0	0	0	0	0	0	0
11	32	F	1	1	2	1	0	1	1	0	0	0	0	1
12	34	M	1	0	0	0	1	0	0	0	1	0	0	0
13	33	F	1	2	1	0	1	0	1	0	0	0	0	0
14	44	F	2	1	0	1	0	0	0	1	0	0	0	0
15	42	M	1	0	0	1	0	1	1	0	0	0	1	0
16	34	F	2	1	1	0	0	0	0	0	0	0	0	1
17	41	M	1	0	1	0	1	0	0	0	0	0	0	0
18	29	F	1	2	1	1	0	1	1	0	0	0	0	0
19	26	M	2	1	0	1	0	0	0	0	0	0	0	0
20	24	F	1	2	0	1	0	1	1	0	0	0	0	0

OA: oral aphthae, GU: genital ulcer, UV: uveitis, ACN: acneiform lesions, EN: erythema nodosum, PT: Pathergy, AT: Arthritis, ATG: Arthralgia, CNS: central nervous system symptoms, GUS: genitourinary system symptoms, DVT: Deep vein thrombosis, GIS: Gastrointestinal system symptoms.
0 - Unobserved 1-Inactive 2- Active

lymphocyte subgroups were evaluated by flow cytometric method using CD3, CD19, CD20, CD5, CD38 monoclonal antibodies. CD20+CD38^{low} cells were evaluated as preplasmablast cells. The blood samples obtained for flow cytometry were evaluated within two hours. All monoclonal antibodies used for the analysis were purchased from Beckman Coulter (Miami, USA). Analytic flow cytometry was performed by using Coulter EPICS XL-MCL (Beckman Coultere USA). A total of 10 000 cells were counted and interpretations were made after adjustment of required voltage and by using isotypic controls for each patient. Statistical analyses were carried out by employing the Statistical Package for Social Sciences software 11.0 for Windows package software (SPSS, Inc., Chicago, IL). The Mann-Whitney U and Kruskal-Wallis tests were used and a p value less than 0.05 were considered as statistically significant. The correlation between data was evaluated by using Spearman's correlation test.

RESULTS

The mean age of active patient group was 33± 2 years (range 24 – 44), of inactive patient group was 32 ± 1 years (range 28 – 43). The mean age of healthy control group was 30 ± 1 years (range 25 – 38). The mean duration of disease was 6 ± 1 years in active patient group and 6 ± 1 years in inactive patient group (Table 2).

CD3+ T lymphocytes (total T lymphocyte) and CD19+ cells (total B lymphocytes) determined as to

TABLE 2: Demographic characteristics of Behcet's patients and control subjects.

	Active Patient	Inactive Patient	Control
n	10	10	20
Gender (M/F)	4/6	5/5	12/8
Age (years)	33 ± 2	32 ± 1	30 ± 1
Duration of the disease	6 ± 1	6 ± 1	_

be normal in all groups and there were no statistically significant differences between groups. On the other hand, CD19+CD5+ B lymphocytes were significantly higher in active and inactive patients compared to healthy controls (the p values obtained by the comparison of active / control and inactive / control groups were p = 0.001, p = 0.008, respectively) (Table 3).

CD20+CD38^{low} B lymphocytes were found to be higher in active BD patients compared to inactive BD patients and healthy controls (the p values obtained by the comparison of active / inactive and active / control groups were p = 0.009, p = 0.03, respectively) (Table 3).

There was a significant correlation between CD19+ B lymphocytes (total B lymphocytes) and CD19+CD5+ B lymphocytes, and CD19+ B lymphocytes and CD20+CD38^{low} B lymphocytes (r = 0.027 and r < 0.001, respectively) but not a significant correlation were found between CD19 and disease activity or duration (Figure 1, 2).

CONCLUSION

BD is not classified in classical autoimmune diseases, as there are no female dominance and no antinuclear antibody positivity.[28] Th-1 type cytokine profile dominates in BD similar to many other autoimmune diseases. T cells producing Th-1 type proinflammatory cytokines such as interleukin (IL)2, IL-12 and interferon-gamma (IFN-gamma) are shown to be increased in BD and correlated with the activity of the disease.[29,30] Moreover, these cytokines released by Th-1 cell line were found to be decreased following treatment and remained high in patients that are resistant to treatment.[31]

TABLE 3: Laboratory values of Behcet's disease patients and control subjects.

	Active patient n=10	Inactive patient n=10	Control n=20
CD3* (Total T lymphocyte)	68.87 ± 3.25	62.04 ± 3.83	67.39 ± 0.76
CD19+* (Total B lymphocyte)	15.56 ± 2.39	14.73 ± 1.49	12.91 ± 0.89
CD19+CD5+B* (Total B1 lymphocyte)	2.52 ± 0.61[a]	2.06 ± 0.53[b]	0.86 ± 0.13[a,b]
CD20+CD38 low preplasmablast*	4.32 ± 0.37[c,d]	4.11 ± 0.75[c]	2.78 ± 1.29[d]

*(Mean ± SD)

[a] p= 0.001 active patients vs healthy controls

[b] p= 0.008 inactive patients vs healthy controls

[c] p= 0.009 active patients vs inactive patients

[d] p= 0.03 active patients vs healthy controls

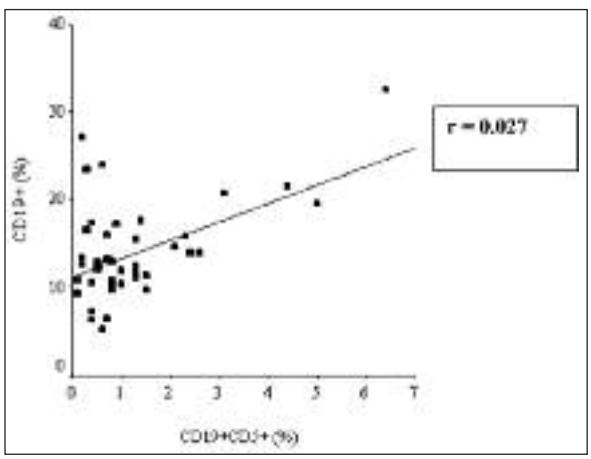

FIGURE 1: Correlation between CD19+ B lymphocytes and CD19+CD5+ B lymphocytes.

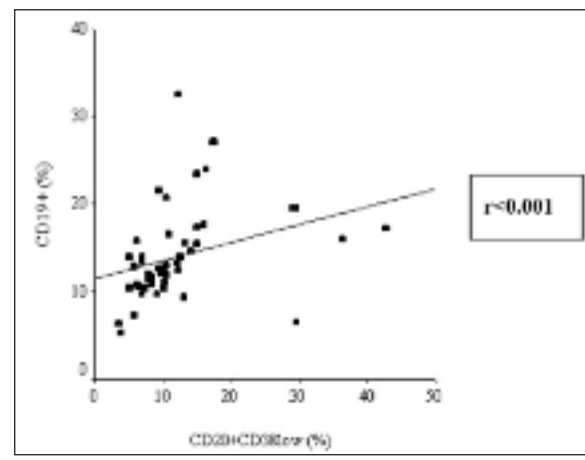

FIGURE 2: Correlation between CD19+ B lymphocyte and CD20+CD38 low B- lymphocytes.

Th-1 response can cause major autoimmune disease and tissue damage such as diabetes mellitus and rheumatoid arthritis.[32] Furthermore, counts of B cells that are secreting Ig and serum Ig levels are reported to be increased and some autoantibodies are shown to be positive in BD.[5,6]

Based on these scientific data and definition of BD as an autoinflammatory disease, evaluation of B lymphocyte profile, particularly B1 and preplasmablast cell ratios and exhibition of the difference between patients were aimed in this study.

Eksioglu et al.[32] evaluated humoral immunity in BD patients, and despite their findings that total B lymphocyte counts were normal, and autoantibody producing CD5+CD19+ B lymphocyte levels were low, they showed that CD80 and CD28 molecules, which are the markers of B lymphocyte activation were increased. In this study, although we found that T lymphocyte and total B lymphocyte ratios were normal, in contradiction to previous studies, we determined an increase in CD5+CD19+ B lymphocyte levels in both active and inactive BD patients. Similar investigations were made on other autoimmune disorders like SLE because B1 cells considered to be involved in IgM autoantibody production, however no direct evidence for the development of SLE has been provided. Pathogenic IgG autoantibody production by B1 cells may be initiated in the thymus in the presence of autoreactive $CD4^+$ T cells and mature myeloid DCs.[33] B1 cells expressed higher levels of costimulatory molecules and showed a potent antigen-presenting activity. Interestingly, B1 cells stimulated proliferation of autologous thymic $CD4^+$ T cells in the presence of IL-2. These results indicate that aberrant B1 cell trafficking into the thymus due to ectopic high expression of BLC (B lymphocyte chemokine) may result in an activation of self-reactive T cells in the development of murine lupus.[34]

CD38 in membrane rafts is able to initiate and propagate several activating signaling pathways, possibly by facilitating critical associations within other raft subsets, for example LAT rafts, via its capacity to interact with Lck and CD3ζ .These increases are not specific for T cells because the B and the NK cell compartments showed significant differences in CD38 expression between SLE patients and healthy controls when evaluated in PBMC by dual staining for CD38 and CD19 (B cells), or CD38 and CD56 (NK cells).[35]

The CD38 cell surface receptor is a potent activator for B lymphocytes. In one research of CD38 signaling which regulates B lymphocyte activation, it was demonstrated that CD38 initiated a novel signaling cascade leading to Btk-, phosphatidylcholine (PC)-metabolizing enzymes, (PC-PLC and phospholipase D), PC-PLC-, and phospholipase D-dependent, PLC-gamma2-independent, B lymphocyte activation.[36]

CD3- CD20+$CD38^{low}$ preplasmablasts are cells causing endothelial cell adhesion, which plays a role in vasculitis etiology and responsible for production of specific antibody synthesis.[17-19] Secondary roles of these molecules are B cell activation markers. In this study, we determined that CD38 expression and preplasmablast cell rates increase parallel to the activity of BD at clinical presentation.

In conclusion, in accordance with the studiy of Donis-Hernandez et al.,[19] in which it was shown that CD38 played a role in endothelial cell adhesion, and studies of Bjil et al.[37] and Arce et al.,[38] in which they obtained a higher CD38+ cell count in SLE, a disease vasculitis is the main underlying cause, this study also shows the role of CD38 in the etiology of vasculitis in BD patients. Determination of high levels of CD20+$CD38^{low}$ B lymphocyte levels in BD, which is basically a vasculitis-triggered by immune system, supports the possible role of CD38 in the etiology of vasculitis, which is the unchangeable characteristic and the basis of defining BD as an autoinflammatory disease. We also strongly believe that the role of CD38 in B cell activation as a potent activator both enzimatically and by signaling molecules and/or endothelial cell adhesion must be further evaluated in experimental models of the disease.

Acknowledgements

Thanks to Hasan Filik for his contribution to English translation.

REFERENCES

1. Emmi L, Brugnolo F, Salvati G, Marchione T. Immunopathological aspects of Behçet's disease. Clin Exp Rheumatol 1995;13(6):687-91.
2. Hasan A, Fortune F, Wilson A, Warr K, Shinnick T, Mizushima Y, et al. Role of gamma delta T cells in pathogenesis and diagnosis of Behcet's disease. Lancet 1996;347(9004): 789-94.
3. Esin S, Gül A, Hodara V, Jeddi-Tehrani M, Dilsen N, Koniçe M, et al. Peripheral blood T cell expansions in patients with Behcet's disease. Clin Exp Immunol 1997;107(3):520-7.
4. Charteris DG, Barton K, McCartney AC, Lightman SL. 4+ lymphocyte involvement in ocular Behçet's disease. Autoimmunity 1992;12(3): 201-6.
5. Suzuki N, Sakane T, Ueda Y, Tsunematsu T. Abnormal B cell function in patients with Behcet's disease. Arthritis Rheum 1986;29(2): 212-9.
6. Taylor PV, Chamberlain MA, Scott JS. Autoreactivity in patients with Behçet's disease. Br J Rheumatol 1993;32(10):908-10.
7. Günaydin I, Yazici H, Ozbakir F, Hamuryudan V, Yurdakul S. Lymphocytotoxic antibodies in the healthy children of patients with Behçet's syndrome. J Rheumatol 1992;19 (12):1996-8.
8. Akoğlu T, Kozakoğlu H, Akoğlu E. Antibody to intermediate filaments of the cytoskeleton in patients with Behçet's disease. Clin Immunol Immunopathol 1986;41(3):427-32.
9. Direskeneli H, Keser G, D'Cruz D, Khamashta MA, Akoğlu T, Yazici H, et al. Anti-endothelial cell antibodies, endothelial proliferation and von Willebrand factor antigen in Behçet's disease. Clin Rheumatol 1995;14(1):55-61.
10. Direskeneli H, Hasan A, Shinnick T, Mizushima R, van der Zee R, Fortune F, et al. Recognition of B-cell epitopes of the 65 kDa HSP in Behçet's disease. Scand J Immunol 1996;43(4):464-71.
11. Smith HR, Olson RR. CD5+ B lymphocytes in systemic lupus erythematosus and rheumatoid arthritis. J Rheumatol 1990;17(6):833-5.
12. Zeher M, Surányi P, Nagy G, Szegedi G. B cells expressing CD5 in minor labial salivary glands of patients with primary Sjögren's syndrome. Arthritis Rheum 1990;33(3):453.
13. Abbas AK, Lichtman AH, Pillai S. Lmphocyte Development and the rearrengement and expression of antigen receptor genes. Cellular and Molecular Immunology. 6th ed. St. Louis: Saunders Elsevier; 2007. p.153-87.
14. Dono M, Cerruti G, Zupo S. The CD5+ B-cell. Int J Biochem Cell Bio 2004;36(11):2105-11.
15. Male D. T cell receptors and major histocompatibility complex molecules. In: Roitt I, Brostoff J, Male D, eds. Immunology. 6th ed. New York: Mosby; 2001. p.87-103.
16. Abbas AK, Lichtman AH, Pober JS. B cell activation and antibody production. Cellular and Molecular Immunology. 4th ed. Philadelphia: WB. Saunders Company; 2000. p.182-207.
17. Ferrero E, Saccucci F, Malavasi F. The making of a leukocyte receptor: origin, genes and regulation of human CD38 and related molecules. Chem Immunol 2000;75:1-19.
18. Campana D, Suzuki T, Todisco E, Kitanaka A. CD38 in hematopoiesis. Chem Immunol 2000;75:169-88.
19. Donís-Hernández FR, Parkhouse RM, Santos-Argumedo L. Ontogeny, distribution and function of CD38-expressing B lymphocytes in mice. Eur J Immunol 2001;31(4):1261-7.
20. Lee HC, Munshi C, Graeff R. Structures and activities of cyclic ADP-ribose, NAADP and their metabolic enzymes. Mol Cell Biochem 1999;193(1-2):89-98.
21. Howard M, Grimaldi JC, Bazan JF, Lund FE, Santos-Argumedo L, Parkhouse RM, et al. Formation and hydrolysis of cyclic ADP-ribose catalyzed by lymphocyte antigen CD38. Science 1993;262(5136):1056-9.
22. Lee HC, Graeff RM, Walseth TF. ADP-ribosyl cyclase and CD38. Multi-functional enzymes in Ca+2 signaling. Adv Exp Med Biol 1997;419:411-9.
23. Santos-Argumedo L, Teixeira C, Preece G, Kirkham PA, Parkhouse RM. A B lymphocyte surface molecule mediating activation and protection from apoptosis via calcium channels. J Immunol 1993;151(6):3119-30.
24. Deshpande DA, White TA, Dogan S, Walseth TF, Panettieri RA, Kannan MS. CD38/cyclic ADP-ribose signaling: role in the regulation of calcium homeostasis in airway smooth muscle. Am J Physiol Lung Cell Mol Physiol 2005;288(5):L773-88.
25. Arpin C, Banchereau J, Liu YJ. Memory B cells are biased towards terminal differentiation: a strategy that may prevent repertoire freezing. J Exp Med 1997;186(6):931-40.
26. George A, Cebra JJ. Responses of single germinal-center B cells in T-cell-dependent microculture. Proc Natl Acad Sci U S A 1991;88(1):11-5.
27. Evaluation of diagnostic ('classification') criteria in Behçet's disease--towards internationally agreed criteria. The International Study Group for Behçet's disease. Br J Rheumatol 1992;31(5):299-308.
28. Yazıcı H, Yurdakul S, Hamuryudan V. Behçet's syndrome. In: Maddison PJ, Isenberg DA, Woo P, Glass DN, eds. Textbook of Rheumatology. 2nd ed. Oxford: Oxford University Press; 1998. p.1394-1402.
29. Direskeneli H. Behcet's disease: infectious aetiology, new autoantigens, and HLA-B51. Ann Rheum Dis 2001;60(11):996-1002.
30. Frassanito MA, Dammacco R, Cafforio P, Dammacco F. Th1 polarization of the immune response in Behçet's disease: a putative pathogenetic role of interleukin-12. Arthritis Rheum 1999;42(9):1967-74.
31. Boyd SR, Young S, Lightman S. Immunopathology of the noninfectious posterior and intermediate uveitides. Surv Ophthalmol 2001;46(3):209-33.
32. Ekşioglu-Demiralp E, Kibaroglu A, Direskeneli H, Yavuz S, Karsli F, Yurdakul S, et al. Phenotypic characteristics of B cells in Behçet's disease: increased activity in B cell subsets. J Rheumatol 1999;26(4):826-32.
33. Ishikawa S, Matsushima K. Aberrant B1 cell trafficking in a murine model for lupus. Front Biosci 2007;12:1790-803.
34. Sato T, Ishikawa S, Akadegawa K, Ito T, Yurino H, Kitabatake M, et al. Aberrant B1 cell migration into the thymus results in activation of CD4 T cells through its potent antigen-presenting activity in the development of murine lupus. Eur J Immunol 2004;34(12):3346-58.
35. Pavón EJ, Muñoz P, Navarro MD, Raya-Alvarez E, Callejas-Rubio JL, Navarro-Pelayo F, et al. Increased association of CD38 with lipid rafts in T cells from patients with systemic lupus erythematosus and in activated normal T cells. Mol Immunol 2006;43(7):1029-39.
36. Moreno-García ME, López-Bojórques LN, Zentella A, Humphries LA, Rawlings DJ, Santos-Argumedo L. CD38 signaling regulates B lymphocyte activation via a phospholipase C (PLC)-gamma 2-independent, protein kinase C, phosphatidylcholine-PLC, and phospholipase D-dependent signaling cascade. J Immunol 2005;174(5):2687-95.
37. Bijl M, van Lopik T, Limburg PC, Spronk PE, Jaegers SM, Aarden LA, et al. Do elevated levels of serum-soluble fas contribute to the persistence of activated lymphocytes in systemic lupus erythematosus? J Autoimmun 1998;11(5):457-63.
38. Arce E, Jackson DG, Gill MA, Bennett LB, Banchereau J, Pascual V. Increased frequency of pre-germinal center B cells and plasma cell precursors in the blood of children with systemic lupus erythematosus. J Immunol 2001;167(4):2361-9.