Cytokine 69 (2014) 120–124

Contents lists available at ScienceDirect

Cytokine

journal homepage: www.journals.elsevier.com/cytokine

Association of IL-17 gene polymorphisms and serum level with graft versus host disease after allogeneic hematopoietic stem cell transplantation

Mohammad Hossein Karimi [a], Sanaz Salek [a], Ramin Yaghobi [a,*], Mani Ramzi [b], Bita Geramizadeh [a], Sara Hejr [a]

[a] Transplant Research Center, Shiraz University of Medical Sciences, Shiraz, Iran
[b] Hematology Research Center and Bone Marrow Transplant Unit, Shiraz University of Medical Sciences, Shiraz, Iran

ARTICLE INFO

Article history:
Received 12 November 2013
Received in revised form 20 April 2014
Accepted 12 May 2014
Available online 16 June 2014

Keywords:
Hematopoietic stem cell transplantation
GVHD
Gene polymorphism
IL-17

ABSTRACT

Background: Cytokines are important factors determining the outcome of transplantation. Host ability in cytokine production may be affected by cytokine genes polymorphisms. The aim of the present study was to investigate the effect of IL-17 gene polymorphisms on outcome of Hematopoietic stem cell transplantation.

Materials and methods: A total of 60 bone marrow recipients were included in this study. Twenty-five recipients (41.66%) underwent a GVHD. IL-17 gene polymorphisms were evaluated by PCR-RFLP method and the serum levels were also checked by ELISA.

Results: No significant differences in distribution of the IL-17(A/G) (rs3819025) genotypes and alleles were observed between two groups. But, IL-17 (A/G, -197) GG genotype was found to be significantly higher in GVHD group compared to those of non-GVHD group ($P = 0.04$). Interestingly, after stratification of patients according severity of GVHD, IL-17 (rs3819025) G allele was remained significantly higher in GVHD grade (0–I) group compared to those of grade (II–IV) group ($P = 0.05$). In addition, after categorization of patients according to their sex, IL-17-197 GG genotype showed a significant association with non-GVHD in male patients ($P = 0.05$). IL-17 serum levels did not show any significant difference between GVHD and non GVHD groups.

Conclusion: Results indicated that IL-17197 GG genotype, G allele of (rs3819025) and its serum level have predictive values for severity of GVHD. Also, IL-17-197 GG genotype is a sex dependent genetic risk factor for development of GVHD, but this subject need to be studied in different population.

1. Introduction

Allogeneic Hematopoietic stem cell transplantation (HSCT) is a potentially curative therapy for various hematopoietic malignancies and immunologic diseases [1]. Graft versus host disease (GVHD) is a major complication of allogeneic BMT and causes significant morbidity and mortality [2]. Acute GVHD is a proinflammatory process mediated in part by mature donor T cells present in the stem cell or marrow inoculum that are polarized toward a Th1 phenotype and recognize minor or major histocompatibility disparities between the donor and host [3]. During the early stages after HSCT, alloreactive CD4 + T cells secrete proinflammatory cytokines that play an important role in the pathophysiology of GVHD by causing activation of immune cells and by direct tissue damage [4]. Both Th1 and Th2 cells are generated in response to alloantigens and contribute to the development of GVHD [5].

Recently, a newly identified CD4 + T cell subset, Th17, distinct from Th1 or Th2, is characterized by the production of interleukin-17A (IL-17A) [6]. IL-17 gene is located on chromosome 6 (location: 6p12) and is linked to many immune/autoimmune related diseases including rheumatoid arthritis (RA) [7,8], asthma [9], lupus erythmatosus [10,11], multiple sclerosis (MS) [12], allograft rejection [13]. IL-17 has important roles in bridging innate and adaptive immunity, and is involved in the host defense against extracellular pathogens, the pathophysiology of autoimmune diseases, and allograft rejection of solid organs [14,15]. In fact, recent studies have shown the prominent role of Th17 cells in the development of acute renal allograft rejection. It has been shown that IL-17 can be considered as an early diagnostic marker of acute renal allograft rejection [16]. Moreover, several reports

* Corresponding author. Tel./fax: +98 711 6476331.
E-mail addresses: Karimimh@sums.ac.ir (M.H. Karimi), rayaviro@yahoo.com (R. Yaghobi).

http://dx.doi.org/10.1016/j.cyto.2014.05.011
1043-4666/

have so far shown that Th17 cells and IL-17 has a significant impact on the development of acute GVHD in mouse models [17–20].

Given the importance of Th17 cells and their related cytokines in the development of GVHD, genetic variations in the genes of IL-17 may play a significant role in the outcome of HSCT [21]. Recent reports have shown association of SNPs in the IL-17 gene with autoimmune diseases such as gastric cancer [22], acute GVHD [23] and coronary artery disease [24]. A functional G-to-A transition at position -197 in the promoter region of IL-17 gene (rs2275913) has been studied extensively [25,21] and it has been shown that healthy individuals possessing the -197A allele produced significantly more IL-17 than those without the -197A allele [21]. The association of this polymorphism with susceptibility to ulcerative colitis [26] and acute graft-versus-host disease (GVHD) after unrelated HSCT have also been reported [21]. Considering the importance of Th17 and its related cytokines in the HSCT outcome, the aim of the present study is to investigate the association of single nucleotide polymorphisms in the genes of IL-17 (rs2275913 and rs3819025) as well as the serum levels of the IL-17 with GVHD in HSCT recipients.

2. Material and methods

2.1. Patients

A total of 60 HSCT recipients who underwent surgery at the Namazi hospital, Shiraz, Iran, were consecutively recruited from 2005 to 2011. Their ages ranged from 6 to 55 years. All of the patients were Iranian and had transplantation at the Transplant center of Namazi hospital affiliated to Shiraz University of Medical Sciences. In this study, the patients were divided into two groups according to the presence (GVHD group) or absence (non-GVHD group) of GVHD. Acute GVHD has been graded according to the classic Glucksbeg–Seattle criteria (GSC) and the International HSCT Registry (IBMTR) [27–29]. Also, non-GVHD patients were considered as the control group. Signs and symptoms were identified by an expert hematologist team based on European group for blood and marrow transplantation criteria. This study was approved by Research Ethics Committee of our institute (The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki). Conditioning chemotherapy regimen included busulfan 16 mg/kg or busulfex IV (80% of oral dose) and cyclophosphamide 120–200 mg/kg in leukemia patients (acute myelogenous leukemia, acute lymphogenous leukemia, and chronic myelogenous leukemia) and cyclophosphamide 60–120 mg/kg + ATG 90 kg/mg for severe aplastic anemia and Fanconi's anemia. GVHD disease prophylaxis consisted of cyclosporine and methotrexate. Prophylactic antibiotic, antifungal, and antiviral drugs were prescribed for all patients. All blood products were irradiated with gamma rays to prevent post transfusion GVHD. The HLA typing is routine in our center.

2.2. DNA extraction

The Buffy coat of the whole blood from bone marrow transplanted patients was available in the sample bank affiliated to Shiraz Transplant Research Center. Genomic DNA was extracted from Buffy coat, using a QIAamp DNA mini kit (Qiagen, Germany) according to the manufacturer's instructions.

2.3. Genotyping

The SNPs of IL-17 genes including: IL-17 (rs3819025 A/G, rs2275913-197A/G were evaluated by PCR-RFLP methods as previously described [30,31]. PCR conditions, cycles, restriction enzymes and primers are summarized in Table 1. PCR-RFLP method in a final volume of 25 μL was employed for determining the IL-17 (rs3819025 A/G, rs2275913-197A/G) gene polymorphism. The PCR products were digested by MaeII (Fermentas, Lithunia) and BstENI (Vivantis, Singapore) restriction enzymes and the amplified products were monitored by agarose gel electrophoresis (Figs. 1a and b).

2.4. ELISA

IL-17 serum level was evaluated by ELISA method. The case group consisted 24 of patients with GVHD and the control group included 30 patients without GVHD. All samples were taken in the first week after transplantation before corticoid treatments. Plasma samples were isolated immediately and stored at −80 °C until required and using an ELISA kit (eBioscience, USA) according to the manufacturer's instructions.

2.5. Statistical analysis

Allele and genotype frequencies were calculated in patient and control subjects by direct gene counting. Statistical evaluation was carried out using the Statistical Package for the Social Sciences (SPSS), version 15. The frequencies of the alleles/genotypes were compared in cases and controls by Chi-square test and Fisher's exact test. Odds ratios and 95% confidence intervals (CIs) for relative risks were calculated. A probability value of $P > 0.05$ was considered as statistically significant and all the reported p-values were two-tailed. LD2SNPing program V 2.0 (http://www.bio.kuas.edu.tw/LD2SNPing) was used to estimate linkage disequilibrium (LD), Hardy–Weinberg and haplotypes were evaluated using Arlequin V311.

3. Results

3.1. GVHD rate

The age range of bone marrow transplant patients was between 6–55 years old. The 36 of 60 (60%) allogeneic HSCT recipients were male and 24 of 60 (40%) were female with a mean ± SD age of 25.83 ± 12.12 years. Male to female ratio (M/F) was 16/9 (1.77) in GVHD group and 20/15 (1.33) in the non-GVHD group. All patients received a graft from related donors. The 25 of 60 (41.7%) transplant patients were shown GVHD and 35 of 60 (58.3%) patients were shown non-GVHD. GVHD was confirmed in 9 of 25 (36%) grade 0–I and 16 of 25 (64%) grade II = IV patients.

Table 1
The primers, types of PCR, restriction enzyme and thermocycling condition for the IL-17 genotyping.

Locus	Primers	Method	Fragment length (base pairs)	Thermocycling program
IL-17(G-197A) (rs2275913)	Forward primer: 5′GCAGCTCTGCTCAGCTTCTAA3′ Reverse primer: 5′TTCAGGGGTGACACCATTTT3′	PCR-RFLP (BstENI)	AA:155 GG:87 + 68 AG:155,87,68	95 °C, 5 min; 30 cycles. 94 °C, 30 s. 57 °C, 30 s. 72 °C, 30 s; 72 °C, 5 min
IL-17(G/A) (rs3819025)	Forward primer: 5′ ACAAACTCATCCATCCCCAG 3′ Reverse primer: 5′ GCCCCAATATAGCTATCTTTC3′	PCR-RFLP (MaeII)	AA:296 GG:214 + 82 AG:296,214,82	95 °C, 5 min; 30 cycles. 95 °C, 1 min. 59.5 °C, 1 min. 72 °C, 1 min; 72 °C, 5 min

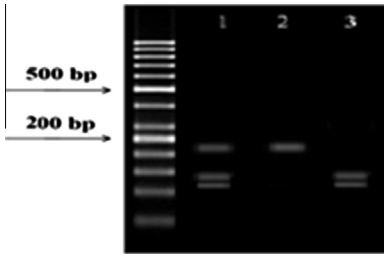

Fig. 1a. Genotyping of the IL-17 (-197A/G) polymorphism by XagI RFLP. Lane 1 AG genotype (155, 87, 68 bp), lane 2 AA genotype (155 bp), lane M DNA size marker (50 bp ladder), and lane 3 indicate GG genotype (87, 68 bp), respectively.

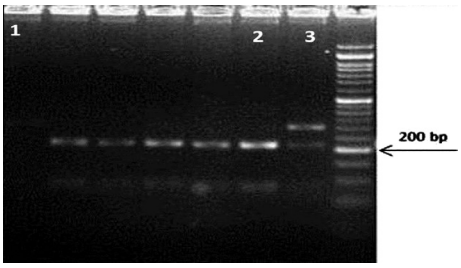

Fig. 1b. Genotyping of the IL-17(A/G) (rs3819025) polymorphism by MaeII RFLP. Lane 1 AA genotype (296 bp), lane 2 GG genotype (214, 82 bp), lane M DNA size marker (50 bp ladder), and lane 3 indicate AG genotype (296, 214, 82 bp), respectively.

3.2. Alleles and genotypes frequencies

Alleles and genotypes frequencies for IL-17 (rs2275913 A/G, rs3819025 A/G), were determined in 25 GVHD group and 35 non-GVHD group. All genotypes were not in agreement with Hardy–Weinberg equilibrium in both groups of patients. Armitag's trend test was used to check the association of genotypes with GVHD and grade whenever the Hardy–Weinberg equilibrium did not meet. No differences in the distribution of the IL-17(A/G) (rs3819025) genotypes and alleles were observed in the GVHD group compared to non-GVHD group. However, as shown in Table 2, the frequency of IL-17 (rs2275913 A/G, -197) GG genotype was found to be significantly higher in GVHD group compared to those of non-GVHD group (48% and 22.85% respectively, $P = 0.04$, OR = 3.12, 95% CI = 0.90–11.08 study power = 54%).

Interestingly, after stratification of patients according severity of GVHD IL-17 (rs3819025) G allele was remained significantly higher in GVHD grade (0–I) group compared to the grade (II–IV) group (94.44% and 71.87% respectively, $P = 0.05$, OR = 0.15, 95% CI = 0.01–1.39, study power = 65%) (Table 3).

After categorization of HSC recipients according to their sex, IL-17-197 GG genotype showed a significance association with GVHD in male patients group compared to non-GVHD in male group (50% and 20% respectively, $P = 0.05$, OR = 4, 95% CI = 0.75–22.94, study power = 50%) (Table 3).

3.3. IL-17 haplotype frequency

The frequency of IL-17 haplotype is shown in Table 4. The frequency of the IL-17 AA haplotype was significantly higher in GVHD patients with grade (II–IV) ($P = 0.02$).

3.4. Linkage disequilibrium determination

A linkage disequilibrium ($D' = 0.89$, $P = 0.012$) was found for two polymorphisms at the positions rs2275913 A/G, rs3819025 A/G in patients who had GVHD and without GVHD symptoms. Linkage disequilibrium was not found for two polymorphisms at the positions (rs2275913 A/G, rs3819025 A/G) between different grades of GVHD in HSCT (Fig. 2).

3.5. Association between coolys anemia and GVHD

The indications for HSCT are summarized in Table 5. Also, the results showed that there was a significant association between coolys anemia as a underlying disease and GVHD in HSC transplanted patients ($p = 0.03$).

3.6. ELISA results

IL-17 serum levels did not show any significant difference between normal populations, GVHD and non GVHD groups. Furthermore, it was not different among grade groups. We compared IL-17 serum level with its genotypes. There was not any significant difference between IL-17 serum level and genotype. Also, there was not any significant difference between IL-17 serum level with age, sex and blood group. Data was not shown.

4. Discussion

Th17 cells and their related cytokines have been implied as the major players in autoimmunity [7–10]. These cells have been reported to produce proinflammatory cytokines like IL-17 [32]. Interestingly, the accelerated allograft rejection was associated with increased production of the proinflammatory cytokines including IL-6, IL-17, and IL-12p40. A number of studies have demonstrated the role of IL-17 in the GVHD inducing in bone marrow transplant recipients [21,23]. Several mouse model experiments have revealed that transfer of IL-17 producing cells induced acute

Table 2
The frequencies of IL-17 (-197A/G) (rs2275913) and 17 (A/G) (rs3819025) genotypes and alleles in bone marrow transplant patients with different grade of GVHD.

Locus	Genotype	GVHD grade (0–I) *N*(%)	GHVD grade (II–IV) *N*(%)	*P* value	OR	95%CI
IL-17(-197A/G) (rs2275913)	AA	3(33.33)	9(56.25)	0.27	0.39	0.05–2.80
	GA	1(11.11)	0(0)	0.17	Undefined	Undefined
	GG	5(55.55)	7(43.75)	0.57	1.61	0.23–11.45
	A allele	11(61.11)	25(78.12)	0.19	0.44	0.10–1.85
	G allele	7(38.88)	7(21.87)			
IL-17(A/G) (rs3819025)	AA	0(0)	2(12.50)	0.26	0	0.0–8.08
	GG	8(88.88)	9(56.25)	0.09	6.22	0.52–166.51
	AG	1(11.12)	5(31.25)	0.25	0.28	0.01–3.49
	A allele	1(5.55)	9(28.12)	**0.05***	0.15	0.01–1.39
	G allele	17(94.44)	23(71.87)			

* Considered significant with *P*-value threshold of 0.05. In genotypes, each *P*-value is the result of comparing corresponding row with the sum of other rows. *N*, absolute number; OR, odd ratio; CI, confidence interval.

Table 3
The frequencies of IL-17 (-197A/G) (rs2275913) and 17 (A/G) (rs3819025) genotypes and alleles in patients with and without-GVHD.

Locus	Genotype	GVHD Total *N*(%)	Non-GVHD Total *N*(%)	GVHD Male *N*(%)	Non-GHVD Male *N*(%)	GVHD Female *N*(%)	Non-GHVD Female *N*(%)	P_1 value	P_2 value	P_3 value
IL-17(-197A/G) (rs2275913)	AA	12(48)	23(65.75)	7(43.75)	14(70)	5(55.55)	9(60)	0.07	0.11	0.83
	GA	1(4)	4(11.42)	1(6.25)	2(10)	0(0)	2(13.33)	0.30	0.68	0.25
	GG	12(48)	8(22.85)	8(50)	4(20)	4(44.44)	4(26.66)	**0.04***	**0.05***	0.37
	A allele	36(72)	54(77.14)	22(68.75)	32(80)	14(77.77)	22(73.33)	0.52	0.27	0.73
	G allele	14(28)	16(22.85)	10(32.25)	8(20)	4(22.22)	8(26.66)			
IL-17(A/G) (rs3819025)	AA	2(8)	1(2.85)	1(6.25)	0(0)	1(11.11)	1(66.66)	0.36	0.25	0.70
	GG	17(68)	19(54.28)	13(81.25)	12(60)	4(44.44)	7(46.66)	0.28	0.16	0.91
	AG	6(24)	15(42.85)	2(12.5)	8(40)	4(44.44)	7(46.66)	0.13	0.06	0.91
	A allele	10(20)	17(24.28)	4(12.5)	8(20)	6(33.33)	9(30)	0.57	0.39	0.80
	G allele	40(80)	53(75.71)	28(87.5)	32(80)	12(66.66)	21(70)			

P_1 value = Indicate the difference between GHVD and non GHVD group.
P_2 value = Indicate the difference between GHVD and non GHVD group in male patients.
P_3 value = Indicate the difference between GHVD and non GHVD group in female patients.
* Considered significant with *P*-value threshold of 0.05. In genotypes, each *P*-value is the result of comparing corresponding row with the sum of other rows *N*, absolute number; OR, odd ratio; CI, confidence interval.

Table 4
The frequencies of IL-17 haplotypes in GVHD patients. In haplotypes, each *P* value is the result of comparing corresponding row with the sum of other rows.

Haplotype distribution	Grade(0–1)	Grade(2–4)	χ^2	*P* value
AG	11	17	1.39	0.58
AA	0	8	0.00	**0.02***
GG	6	6	2.17	0.24
GA	1	1	1.82	0.67

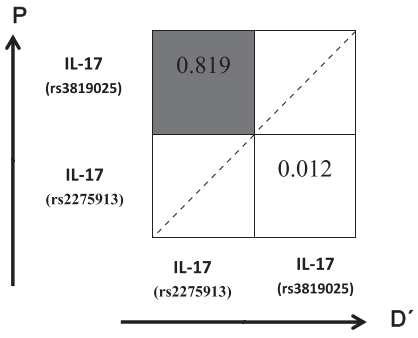

Fig. 2. Linkage disequilibrium plot of IL-17 polymorphisms in *D'* value. Dark color boxes are representative of high linkage disequilibrium (LD) and light color boxes indicate low LD. The left upper boxes indicate the *P* values.

GVHD [33–35]. In contrast, there is a report showing that donor IL-17 producing cells ameliorated acute GVHD [20]. Cytokines are important factors determining the outcome of transplantation [36].

Since host ability in cytokine production may be affected by cytokine genes polymorphisms, the aim of the present study was to investigate the effect of IL-17 rs2275913 and rs3819025 at the IL-17 gene polymorphisms with GVHD after allogeneic stem cell transplantation. Our results showed that IL-17 (rs2275913 A/G, -197) GG genotype was found to be significantly higher in GVHD group compared to those of non-GVHD group. Interestingly, after stratification of patients according severity of GVHD IL-17 (rs3819025) G allele was remained significantly higher in GVHD grade (0–I) group compared to those of grade (II–IV) group. There are controversies about the association of genotypes of IL-17 in different disease. The study on the basis of myeloablative transplantation showed that the IL-17-197A genotype on the recipient side was associated with a risk of higher grades; the validation study has demonstrated the association between the recipient -197A genotype and the increased incidence of chronic GVHD [23]. Espinoza JL and et al. in 2011were showed that the -197A allele of the IL-17 gene in the donor was associated with a higher risk of acute GVHD after unrelated fully HLA-matched Hematopoietic stem cell transplantation [23]. Previous studies have reported an association between the G-197A SNP in the IL-17 promoter region and the susceptibility of the Japanese population to ulcerative colitis [37], as well as to rheumatoid arthritis in the Caucasian population [38]. Ramsey et al. reported that rare allele G of the IL-17 F His162Arg polymorphism is inversely associated with development of asthma [39].

As IL-17 G-197A polymorphism is located in the promoter region of IL-17gene, it is conceivable that it may exert some roles in the transcriptional regulation of IL-17 secretion. After gender classification IL-17(-197) GG genotype showed a significance association with non-GVHD in male patients. There have not been any

Table 5
Relationship between GVHD and underlying disease the prevalence of underlying disease of bone marrow transplant patients.

Underlying disease	GVHD *N*(%)	Non-GVHD *N*(%)	*P* value	OR	95%CI
AML M4	10(40)	18(51.4)	0.38	0.63	0.2–2.01
ALL	5(20)	10(28.6)	0.44	0.63	0.15–2.45
CML	3(12)	3(8.6)	0.66	1.45	0.21–10.23
Coolys anemia	3(12)	0(0)	**0.03***	Undefined	Undefined
A plastic anemia	0(0)	2(5.7)	0.22	0.00	0.00–5.88
Thalassemia	2(8)	2(5.7)	0.72	1.43	0.13–15.72
Myelodysplastic syndrome	2(8)	0(0)	0.08	Undefined	Undefined

N, absolute number; OR, odd ratio; CI, confidence interval.
* Considered significant with *P*-value threshold of 0.05. In genotypes, each *P* value is the result of comparing corresponding row with the sum of other rows.

published studies on relationships between IL-17 polymorphisms with GVHD in gender. So we could not compare our results with others'.

In conclusion, we suggest IL-17 promoter polymorphism in IL-17 as a regulatory cytokine could be a genetic risk factor for the development of GVHD. GVHD is a multifactor phenomenon, and cytokines have major role in this aspect. Given that the -197A allele is significantly associated with the higher production of IL-17, G-197A genotyping may be used to predict the susceptibility organ allograft rejection.

Acknowledgments

This study was financially supported by the Transplant Research Center. The authors would like to thank Dr. Nasrin Shokrpour at Center for Development of Clinical Research of Nemazee Hospital for editorial assistance.

References

[1] van den Brink MR, Burakoff SJ. Cytolytic path-ways in haematopoietic stem-cell transplantation. Nat Rev Immunol 2002;2:273–81.
[2] Shlomchik WD. Graft-versus-host disease. Nat Rev Immunol 2007;7:340–52.
[3] Anderson BE, McNiff JM, Jain D, Blazar BR, Shlomchik WD, Shlomchik MJ. Distinct roles for donor- and host-derived antigen-presenting cells and costimulatory molecules in murine chronic graft-versus-host disease: requirements depend on target organ. Blood 2005;105:2227–34.
[4] Ferrara JL, Abhyankar S, Gilliland DG. Cytokine storm of graft-versus-host disease: a critical effector role for interleukin-1. Transplant Proc 1993;25:1216–7.
[5] Sykes M, Abraham VS, Harty MW, Pearson DA. Selective inhibition of CD4 graft-versus-host activity in IL-2-treated mice. Transplant Proc 1993;25:1225–6.
[6] Cooke A. Th17 cells in inflammatory conditions. Rev Diabet Stud 2006;3(2):72–5.
[7] Kotake S, Yago T, Kawamoto M, Nanke Y. Role of osteoclasts and interleukin-17 in the pathogenesis of rheumatoid arthritis: crucial 'human osteoclastology'. J Bone Miner Metab 2012;30(2):125–35.
[8] Zrioual S, Ecochard R, Tournadre A, Lenief V, Cazalis MA, Miossec P. Genome-wide comparison between IL-17A- and IL-17F-induced effects in human rheumatoid arthritis synoviocytes. J Immunol 2009;182:3112–20.
[9] Wang YH, Wills-Karp M. The potential role of interleukin-17 in severe asthma. Curr Allergy Asthma Rep 2011;11(5):388–94.
[10] Oh SH, Roh HJ, Kwon JE, Lee SH, Kim JY, Choi HJ, et al. Expression of interleukin-17 is correlated with interferon-α expression in cutaneous lesions of lupus erythematosus. Clin Exp Dermatol 2011;36(5):512–20.
[11] Nalbandian A, Crispín JC, Tsokos GC. Interleukin-17 and systemic lupus erythematosus: current concepts. Clin Exp Immunol 2009;157(2):209–15.
[12] Wang HH, Dai YQ, Qiu W, Lu ZQ, Peng FH, Wang YG, et al. Interleukin-17-secreting T cells in neuromyelitis optica and multiple sclerosis during relapse. J Clin Neurosci 2011;18(10):1313–7.
[13] Loverre A, Divella C, Castellano G, Tataranni T, Zaza G, Rossini M, et al. T helper 1, 2 and 17 cell subsets in renal transplant patients with delayed graft function. Transpl Int 2011;24(3):233–42.
[14] Ciprandi G, De Amici M, Murdaca G, Fenoglio D, Ricciardolo F, Marseglia G, et al. Serum interleukin-17 levels are related to clinical severity in allergic rhinitis. Allergy 2009;64(9):1375–8.
[15] Fujino S, Andoh A, Bamba S, Ogawa A, Hata K, Araki Y, et al. Increased expression of interleukin 17 in inflammatory bowel disease. Gut 2003;52:65–70.
[16] Loong CC, Hsieh HG, Lui WY, Chen A, Lin CY. Evidence for the early involvement of interleukin 17 in human and experimental renal allograft rejection. J Pathol 2002;197:322–32.
[17] Yi T, Chen Y, Wang L, Du G, Huang D, Zhao D, et al. Reciprocal differentiation and tissue-specific pathogenesis of Th1, Th2, and Th17 cells in graft-versus-host disease. Blood 2009;114:3101–12.
[18] Yang J, Fan H, Hao J, Ren Y, Chen L, Li G, et al. Amelioration of acute graft-versus-host disease by adoptive transfer of ex vivo expanded human cord blood CD4 + CD25+ forkhead box protein 3+ regulatory T cells is associated with the polarization of Treg/Th17 balance in a mouse model. Transfusion 2012;52(6):1333–47.
[19] Tawara I, Maeda Y, Sun Y, Lowler KP, Liu C, Toubai T, et al. Combined Th2 cytokine deficiency in donor T cells aggravates experimental acute graft-vs-host disease. Exp Hematol 2008;36(8):988–96.
[20] Yi T, Zhao D, Lin CL, Zhang C, Chen Y, Todorov I, et al. Absence of donor Th17 leads to augmented Th1 differentiation and exacerbated acute graft-versus-host disease. Blood 2008;112(5):2101–10.
[21] Espinoza JL, Takami A, Nakata K, Onizuka M, Kawase T, Akiyama H, et al. A genetic variant in the IL-17 promoter is functionally associated with acute graft-versus-host disease after unrelated Hematopoietic stem cell transplantation. PLoS One 2011;6(10):e26229.
[22] Shibata T, Tahara T, Hirata I, Arisawa T. Genetic polymorphism of interleukin-17A and -17F genes in gastric carcinogenesis. Hum Immunol 2009;70(7):547–51.
[23] Espinoza JL, Takami A, Onizuka M, Kawase T, Sao H, Akiyama H, et al. A single nucleotide polymorphism of IL-17 gene in the recipient is associated with acute GVHD after HLA-matched unrelated BMT. Bone Marrow Transplant 2011;46(11):1455–63.
[24] Zhang X, Pei F, Zhang M, Yan C, Huang M, Wang T, et al. Interleukin-17A gene variants and risk of coronary artery disease: a large angiography-based study. Clin Chim Acta 2011;412(3–4):327–31.
[25] Wang H, Zhong X, Wang K, Qiu W, Li J, Dai Y, et al. Interleukin 17 gene polymorphism is associated with anti-aquaporin 4 antibody-positive neuromyelitis optica in the Southern Han Chinese – a case control study. J Neurol Sci 2012;314(1–2):26–8.
[26] Kim SW, Kim ES, Moon CM, Park JJ, Kim TI, Kim WH, et al. Genetic polymorphisms of IL-23R and IL-17A and novel insights into their associations with inflammatory bowel disease. Gut 2011;60(11):1527–36.
[27] Glucksberg H, Storb R, Fefer A, Buckner CD, Neiman PE, Clift RA, et al. Clinical manifestations of graft-versus-host disease in human recipients of marrow from HLA matched sibling donors. Transplantation 1974;18(4):295–304.
[28] Thomas ED, Storb R, Clift RA, Fefer A, Johnson L, Neiman PE, et al. Bone-marrow transplantation (second of two parts). N Engl J Med 1975; 24; 292(17): 895–902.
[29] Rowlings PA, Przepiorka D, Klein JP, Gale RP, Passweg JR, Henslee-Downey PJ, et al. IBMTR severity index for grading graft-versus-host disease: retrospective comparison with Glucksberg grade. Br J Haematol 1997;97(4):855–64.
[30] Karimi MH, Hejr S, Geramizadeh B. Nikeghbalian1 S, Kamali-sarvestani E, Yaghobi R. Study of the relationships between IL-23R, IL-17, IL-21 polymorphisms and serum level of IL-17, IL-21 with acute graft rejection in Iranian liver transplant recipients. Immunol Invest 2014;43(1):69–85.
[31] Rasouli M, Asaei S, Kalani M, Kiany S, Moravej A. Interleukin-17A genetic variants can confer resistance to brucellosis in Iranian population. Cytokine 2013;61(1):297–303.
[32] Deteix C, Attuil-Audenis V, Duthey A, Patey N, McGregor B, Dubois V, et al. Intragraft Th17 infiltrate promotes lymphoid neogenesis and hastens clinical chronic rejection. J Immunol 2010;184(9):5344–51.
[33] Kappel LW, Goldberg GL, King CG, Suh DY, Smith OM, Ligh C, et al. IL-17 contributes to CD4-mediated graft-versus-host disease. Blood 2009;113:945–52.
[34] Iclozan C, Yu Y, Liu C, Liang Y, Yi T, Anasetti C, et al. Th17 cells are sufficient but not necessary to induce acute graft-versus-host disease. Biol Blood Marrow Transplant 2010;16(2):170–8.
[35] Carlson MJ, West ML, Coghill JM, Panoskaltsis-Mortari A, Blazar BR, Serody JS. In vitro-differentiated TH17 cells mediate lethal acute graft-versus-host disease with severe cutaneous and pulmonary pathologic manifestations. Blood 2009;113:1365–74.
[36] Möller E. Cell interactions and cytokines in transplantation immunity. Transplant Proc 1995 Feb;27(1):24–7.
[37] Arisawa T, Tahara T, Shibata T, Nagasaka M, Nakamura M, Kamiya Y, et al. The influence of polymorphisms of interleukin-17A and interleukin-17F genes on the susceptibility to ulcerative colitis. J Clin Immunol 2008;28:44–9.
[38] Nordang GB, Viken MK, Hollis-Moffatt JE, Merriman TR, Førre ØT, Helgetveit K, et al. Association analysis of the interleukin 17A gene in Caucasian rheumatoid arthritis patients from Norway and New Zealand. Rheumatology (Oxford) 2009;48(4):367–70.
[39] Ramsey CD, Lazarus R, Camargo Jr CA, Weiss ST, Celedón JC. Polymorphisms in the interleukin 17F gene (IL17F) and asthma. Genes Immun 2005;6:236–41.