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Blood Donors with Different Types of Human Constitution Demonstrate Different Level of Cytokines

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Objective: This study was aimed to determine possible relationship between the types of human constitution used in Mongolian traditional medicine and certain types of immune response in healthy blood donors. **Materials and methods:** Ninety-three blood donors were enrolled in this cross-sectional study. The type of human constitution was determined using the method of Sachs R (1995) and modified by Batchimeg et al. (2003), in which the titer of cytokines (Human IL-2, IL-6, IL-10, IFNγ and TGFβ) in blood plasma and in supernatant of 12-hour PBMC culture were measured by ELISA. **Results:** Analysis and comparison of different cytokine titers in different constitution groups produced the following findings: Subjects with Badgan (ᠪᠠᠳᠭᠠᠨ, Tibetan-badken, or phlegm, or bile) type of constitution had a lower activity of Th2 mediated immune response; subjects with Shar (ᠰᠢᠷ᠎ᠠ, Tibetan-mkrispa [kris-pa] or mucus) humour domination had a higher activity of Th2 mediated response; and subjects with Khii humour domination may demonstrate higher activity of Th1 mediated response. **Conclusion:** Human typology types used in Mongolian traditional medicine are likely related to activity or intensity of certain types of adaptive immune responses and authors see an essential need to continue research in this field of study.

Keywords: body constitution, cytokine, traditional medicine, blood donor, Mongolia

Introduction

Human constitutional typology system used in traditional Mongolian medicine is based on the constitutional concepts of Indian and Tibetan medicine and have been adapted into the culture of nomadic Mongolian people living in Central Asian continental plateau during the last several centuries [1]. This typology system explains not only the differences in physical characteristics, but somatic, mental, spiritual and behavioral peculiarities of individuals as well [1-3]. In traditional Mongolian medicine, the typology system prescribes total 7 human constitutional types including 3 pure and 3 mixed (or combined)

and 1 collected type. All of these types are in accordance with domination of abstract substances (or humours, or notions, or elements) in human body. Pure types are "Khii" (ཁྲལ, Tibetan-rlung [loong] or wind, or vital energy, or air), "Shar" (ཤར, Tibetan-mkrispa [kris-pa] or mucus) and "Badgan" (བདགན, Tibetan-badken, or phlegm, or bile), and mixed types are Khii-Shar, Khii-badgan, Shar-badgan [4-6]. According to this typology concept, each individual has own inherited balanced ratio or combination of these humours and it is this balance determines an individual's vital or existence essence and illness or healing in an individual depends on the change in ratio of khii, Shar and Badgan elements. [1, 3-5, 7, 8]

The immune system in mammalians is the organ system responsible for antigenic environment in the body and immune response is the principal mechanism to establish optimal antigenic homeostasis. The types, forms and efficacy of the specific immune response triggered by foreign antigen exposure are correlated, on one hand, from natural properties of the exposed antigen, and its quantity and route of exposure and on other hand by the individual peculiarities of mammalian host [9, 10]. The end result of the immune response to microbial antigens in individuals can determine, for example, their congenital and/or acquired susceptibility or resistance to parasitic, viral and bacterial infections [11-15]. Our theory is that the variation in immune response observed in modern medicine may correlate with above mentioned concepts of illness or healing in traditional Mongolian medicine.

A great number of research reports have been dedicated to the possible relationship between basic concepts of traditional medicine and modern medicine. In particular, relationship of modern medicine with Sasang typology in Korean medicine, Yin-Yang typology in Chinese medicine, and typology in Ayurveda medicine have been published. Ambaga M (2017) suggests that behind all the concepts around living rLung, Mkhris, Badgan in traditional Mongolian medicine are due to regulations in the membrane - redox potentials three - state line system dependent - full 9 stepped cycle of proton conductance inside human body [16-21]. But searching the available literature sources did not yield reports focused on relationship between types of immune response and typology systems in Oriental medicine.

The purpose of this study was to determine possible relationship between types of human constitution used in traditional Mongolian medicine and certain types of immune response in healthy blood donors.

Materials and methods

A cross sectional study design was used. Ninty-three (females 48, males 45) blood donors aged 20-54 year (mean age 33.42±9.68), who registered as an active blood donators at the Blood Transfusion Research Center (MoH, Mongolia) and who have been passed routine medical examination within last 3 months, were enrolled in the study. The type of human constitution in each participant was determined using the method developed by Sachs R (1995) and modified by Batchimeg et al. (2003) [2, 22]. This included 100 blood serum tests which were compared to findings of anamnesis, observation, and physical examination and all of these tests were grouped in four sections such as body characteristics (25 tests), general properties (15 tests), individual's imagination (41 tests) and special properties (19 tests). Test results were expressed as scores in three columns corresponding to Khii, Shar and Badgan humours. Constitution of each subject was determined by totaling the column scores.

Titers of cytokines in blood plasma of all participants and in supernatant of 12-hour peripheral blood mononuclear cell (PBMC) culture of randomly selected donors (5 subjects from each constitutional type group) were measured according with protocol attached by manufacturer (Human IL-2, IL-6, IL-10, IFNγ and TGFβ ELISA kits, Biolegend, USA) [23]. Results that exceeded the standard deviation after double sample testing and following repeated testing were excluded from calculation.

The data were analyzed statistically. Pearson's correlation coefficient (r) was calculated for correlation of different plasma and supernatant cytokines and independent-samples T test (t) was used for comparison of mean titer of cytokines in subjects with different constitutional types. Microsoft Windows Excel and SPSS-17 programs were used for statistical calculation.

Results

Constitutional testing of participants was divided into 3 pure types, as "Khii" (n=8), "Shar" (n=19), "Badgan" (n=7) and 5 mixed types as "Khii-Badgan" (n=12), "Khii-Shar" (n=28), "Shar-Badgan" (n=10), "Badgan-Khii" (n=2), and "Shar-Khii" (n=7). Furthermore, all participants were classified into 3 groups by dominantly expressed humours, namely, "Khii" dominated

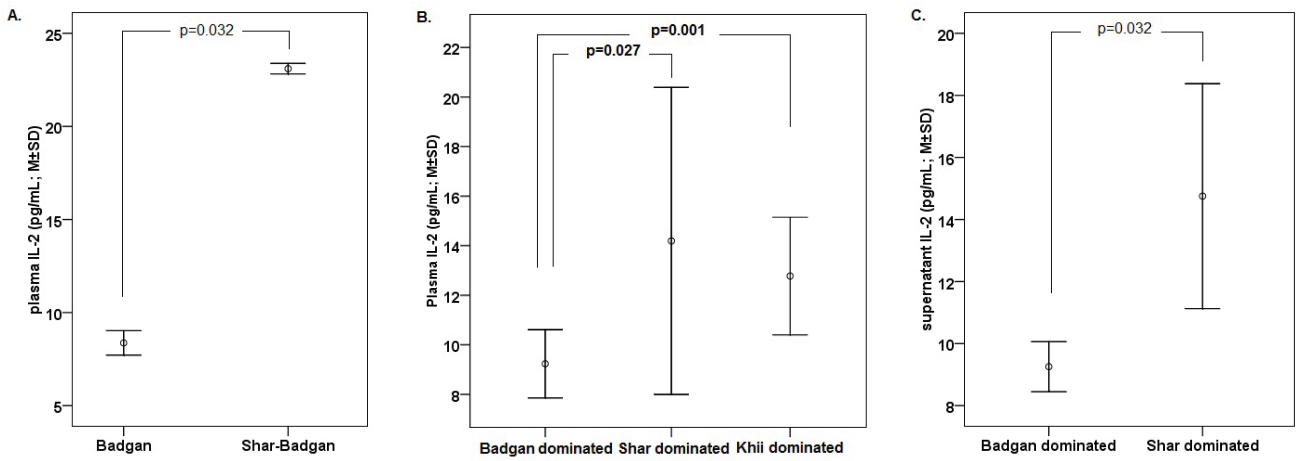

Figure 1. Titer of IL-2 in subjects with different constitutional types

(included pure Khii, Khii-Shar and Khii-Badgan subjects, n=49, 52.7%), "Shar" dominated (included pure Shar, Shar-khii and Shar-Badgan subjects, n=35, 37.6%) and "Badgan" dominated (included pure Badgan and Badgan-khii subjects, n=9, 9.7%) groups. We did not find any significant difference in the distribution of constitution types with age or gender.

The titer of plasma cytokines was normally distributed, and was not significantly different for either age or gender groups. Correlation analysis of plasma cytokine level found a direct linear correlation of interferon γ (IFNγ) with interleukin 2 (IL-2), interleukin-10 (IL-10) and transforming growth factor-beta (TGFβ) (Table 1).

The following findings were identified when comparing the levels of cytokines in the different constitutional groups.

Interleukin-2 (IL-2). Table 2, shows the mean titer of IL-2 in the different constitution groups. Comparison of mean titer of the cytokines in subjects with constitution types demonstrated some significant differences. Both plasma and supernatant IL-2 mean titer in Shar-Badgan subjects was greater than in subjects with pure Badgan type (plasma p=0.032; supernatant p=0.039). The plasma IL-2 mean titer in Badgan dominated subjects was lower than in Shar (p=0.027) and Khii dominated subjects (p=0.001). Measurement of IL-2 in cell culture supernatant also demonstrated a lower mean titer in Badgan dominated subjects compared with Shar dominated (p=0.032).

IL-2 plays important role in differentiation of naive T cells into effector or memory T cells. We observed lower titers of this cytokine in subjects with Badgan humour (Figure 1).

A. Mean titer of plasma IL-2 in subjects with different constitutional types; B. Mean titer of plasma IL-2 in subjects

Table 1. Correlation of plasma cytokine titers in healthy blood donors

Cytokines	Statistics	IL-2	IL-6	IL-10	IFNg	TGFb
IL-2	PCC	1	0.144	-0.135	0.268	0.115
	p-value		0.2	0.236	0.17	0.301
IL-6	PCC	0.144	1	0.137	-0.70	0.129
	p	0.2		0.209	0.529	0.301
IL-10	PCC	-0.135	-0.70	1	0.225	0.158
	p-value	0.236	0.529		0.041	0.149
IFNg	PCC	0.268	-0.70	0.225	1	0.295
	p	0.017	0.529	0.041		0.006
TGFb	PCC	0.115	0.129	0.158	0.295	1
	p-value	0.301	0.232	0.149	0.006	

PCC – Pearson's correlation coefficient

Table 2. Titer of IL-2 in subjects with different types of human constitution

Constitution	n	Mean titer in serum (pg/mL)		Mean titer in supernatant (pg/mL)	
		M	SD	M	SD
By constitution types					
Badgan	5	8.5[a]	0.51	9.2[b]	0.92
Shar	19	14.5	5.56	13.6	3.94
Khii	8	12.7	2.19	12.3	4.06
Khii-Badgan	12	13.1	5.43	12.6	6.00
Khii-Shar	26	13.2	4.46	13.6	3.80
Shar-Badgan	5	17.3	7.98	15.5	3.73
Badgan-Khii	2	11.4	0.28	-	-
Shar-Khii	7	11.1	1.87	13.3	2.44
Total	84*	13.2	4.85	13.1	3.92
By dominating humours					
Badgan	7	9.3[c]	1.50	9.2	0.92
Shar	30	13.9	5.44	14.1	3.34
Khii	47	13.3	4.57	12.8	4.41
Total	84*	13.2	4.85	13.1	3.92

n-number of subjects attended; M-mean of variables; SD-standard deviation of the mean; *-exceeding variables were excluded from calculation; [a]-statistical significance compared with plasma mean titer of Shar-Badgan subjects p=0.032; [b]-statistical significance compared with supernatant mean titer of Shar-Badgan subjects p=0.039; [c]-statistical significance compared with plasma mean titer of Shar (p=0.027) and Khii (p=0.001) dominated subjects

Table 3. Titer of IL-6 in subjects with different types of human constitution

Constitution	n	Mean titer in serum (pg/mL)		Mean titer in supernatant (pg/mL)	
		M	SD	M	SD
By constitution types					
Badgan	7	6.6[a]	1.56	7.9	2.13
Shar	19	9.3	4.13	11.4	4.89
Khii	8	7.4	0.66	9.7	0.94
Khii-Badgan	12	8.2	1.51	10.5	1.83
Khii-Shar	25	9.4	2.97	12.3	3.43
Shar-Badgan	10	7.2	1.06	8.6	1.38
Badgan-Khii	2	19.5	2.21	-	-
Shar-Khii	7	7.1	2.20	8.8	2.62
Total	90*	8.7	3.56	9.9	2.91
By dominating humours					
Badgan	9	10.3	7.42	7.9[b]	2.13
Shar	35	8.2	3.33	9.6	3.33
Khii	46	8.8	2.47	10.8	2.41
Total	90*	8.7	3.56	9.9	2.91

n-number of subjects attended; M-mean of variables; SD-standard deviation of the mean; *-exceeding variables were excluded from calculation; [a]-statistical significance compared with plasma mean titer of Khii-Shar subjects p=0.042; [b]-statistical significance compared with supernatant mean titer of Khii (p=0.027) dominated subjects

with dominantly expressed humours; C. Mean titer of cell culture supernatant IL-2 in subjects with dominantly expressed humours;

Interleukin 6 (IL-6). Table 3 shows the mean titer of IL-6 for the different constitution groups. Independent-sample T test analysis showed lower plasma IL-6 mean titer in subjects with Badgan type comparing with Khii-Shar mixed type subjects (p=0.042) and lower supernatant level in Badgan dominated type comparing with Khii dominated subjects (p=0.027).

Table 4. Titer of IL-10 in subjects with different types of human constitution

Constitution	n	Mean titer in serum (pg/mL)		Mean titer in supernatant (pg/mL)	
		M	SD	M	SD
By constitution types					
Badgan	7	7.6	1.80	7.9	2.13
Shar	19	7.8	1.50	11.4	4.89
Khii	7	6.8	1.13	9.7	.94
Khii-Badgan	10	7.8	1.54	10.5	1.83
Khii-Shar	27	8.4	1.51	12.3	3.43
Shar-Badgan	10	7.8	1.22	8.6	1.38
Badgan-Khii	1	8.1	-	-	-
Shar-Khii	7	8.6	1.87	8.8	2.62
Total	88*	7.9	1.53	9.9	2.91
By dominating humours					
Badgan	8	7.7	1.68	8.8	1.98
Shar	35	7.9	1.52	9.1a	1.50
Khii	45	8.0	1.54	8.3	2.03
Total	88*	7.9	1.53	8.7	1.79

n-number of subjects attended; M-mean of variables; SD-standard deviation of the mean; *-exceeding variables were excluded from calculation; [c]-statistical significance compared with supernatant mean titer of Khii (p=0.006) dominated subjects

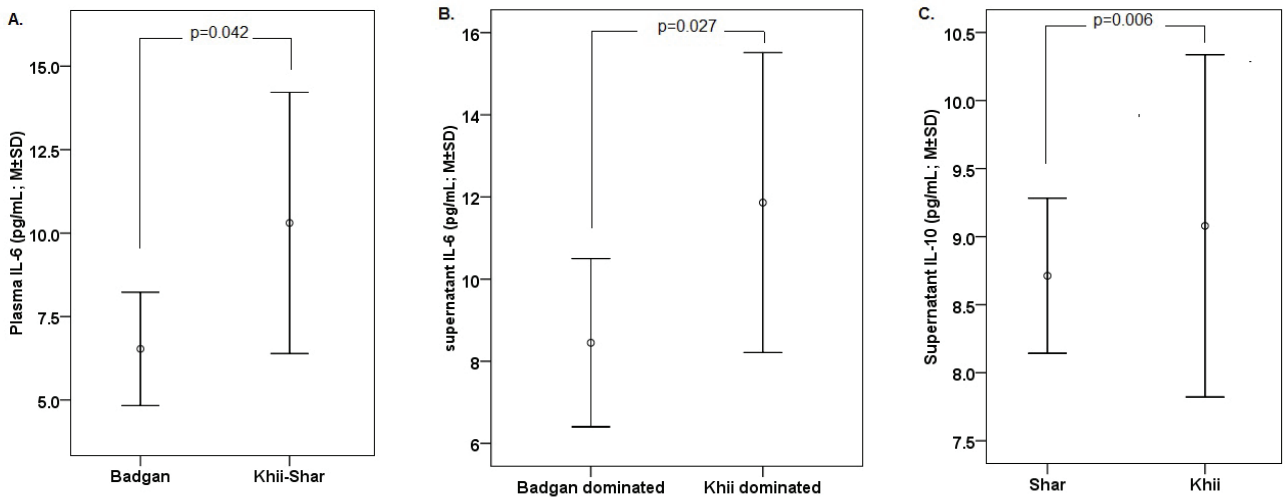

Figure 2. Titer of Il-6 and IL-10 in subjects with different constitutional types

Interleukin 10 (IL-10). Table 4 shows the mean titer of IL-10 in the different constitution groups. Comparison of mean supernatant IL-10 in different constitutional groups showed a higher mean titer of IL-10 in pure Shar subjects comparing with Khii subjects (p=0.006).

IL-6 and IL-10 cytokines play a key role in triggering of T helper 2 (TH2) mediated immune reaction and their level was greater in subjects with Shar humours and lower in subjects with Badgan humours (Figure 2).

A. Mean titer of plasma IL-6 in subjects with different constitutional types; B. Mean titer of cell culture supernatant IL-6 in subjects with dominantly expressed humours; C. Mean titer of cell culture supernatant IL-10 in subjects with different constitutional types;

Interferon gamma (IFNγ). Table 5 shows the mean titer of IL-10 in different constitution groups. Shar subjects have a decreased mean titer of supernatant IFNγ compared with Shar-Badgan mixed type subjects (p=0.049).

IFNγ is a key cytokine produced by activated TH1 lymphocytes and the presence of Badgan humour increased the IFNγ level in subjects with Shar pure constitutional type (Figure 3).

Table 5. Titer of IFNγ in subjects with different types of human constitution

Constitution	n	Mean titer in serum (pg/mL)		Mean titer in supernatant (pg/mL)	
		M	SD	M	SD
By constitution types					
Badgan	6	70.8	17.75	94.5	24.68
Shar	19	69.6	16.64	87.4a	14.25
Khii	7	71.0	16.13	92.9	24.14
Khii-Badgan	12	78.9	21.03	112.4	32.51
Khii-Shar	26	68.1	17.85	92.3	22.59
Shar-Badgan	8	91.4	29.40	134.8	43.51
Badgan-Khii	1	69.6	-	-	-
Shar-Khii	7	68.2	17.52	89.6	12.15
Total	86*	72.6	19.70	100.5	29.13
By dominating humours					
Badgan	7	70.6	16.21	94.5	24.68
Shar	33	74.6	22.26	103.9	33.93
Khii	46	71.4	18.47	99.2	26.61
Total	86*	72.6	19.70	100.5	29.13

n-number of subjects attended; M-mean of variables; SD-standard deviation of the mean; *-exceeding variables were excluded from calculation; [a]-statistical significance compared with supernatant mean titer of Shar-Badgan mixed subjects p=0.049

Transforming Growth Factor Beta (TGFβ). Table 6 shows mean titer of TGFβ in different constitutional groups. Analysis of variance comparing mean TGFβ titers across different constitution types did not show a significant difference.

Table 6. Titer of TGFβ in subjects with different types of human constitution

Constitution	n	Mean titer in serum (pg/mL)		Mean titer in supernatant (pg/mL)	
		M	SD	M	SD
By constitution types					
Badgan	6	477.7	73.9	789.8	126.5
Shar	19	504.9	275.0	865.0	522.9
Khii	8	513.1	211.9	838.2	364.9
Khii-Badgan	12	553.8	249.3	931.5	495.4
Khii-Shar	28	578.8	278.1	893.0	187.3
Shar-Badgan	8	407.9	138.6	736.4	299.4
Badgan-Khii	2	688.6	38.4	-	-
Shar-Khii	7	603.4	217.2	984.1	393.5
Total	90*	536.5	241.7	862.6	343.0
By dominating humours					
Badgan	8	530.4	115.9	789.8	126.5
Shar	33	489.3	232.4	861.8	398.7
Khii	49	569.2	260.2	887.6	346.0
Total	90*	536.5	241.7	862.6	343.0

n-number of subjects attended; *-exceeding variables were excluded from calculation; M-mean of variables; SD-standard deviation of the mean

Discussion

Direct linear correlation of IFNγ with IL-2, IL-10 and TGFβ may be explained with balanced cross-regulation of Th1 and Th2 mediated response in healthy subjects [10, 24].

Interleukin-2 (IL-2). This cytokine is produced by activated CD4+ T lymphocytes and regulates differentiation of the T cells, including differentiation of naive T cells into effector or memory

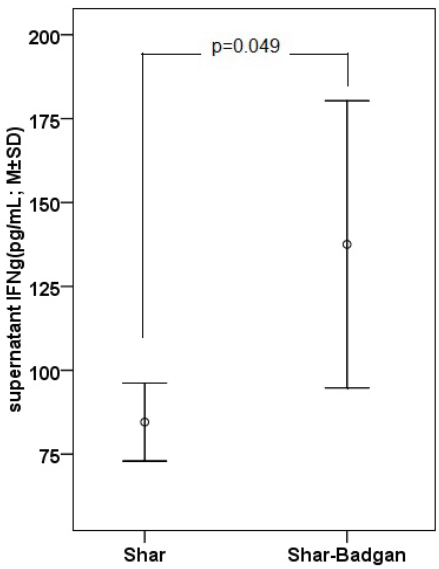

Figure 3. Titer of IFNγ in subjects with different constitutional types.

T cells and differentiation of autoreactive thymocytes into Treg cells [10, 25, 26]. Clinical trial use of this cytokine demonstrated inhibitory effect of T helper 1 (Th1) mediated inflammation in patients with autoantibody and/or immune complex mediated diseases such as diabetes mellitus type I, atherosclerosis, systemic lupus erythematosus (SLE) and rheumatoid arthritis [27]. In our study we found 1) elevated IL-2 titer in Shar-Badgan subjects comparing with pure Badgan type; decreased IL-2 mean titer in Badgan dominated subjects comparing with Shar (p=0.027) and Khii dominated subjects (p=0.001); and 3) lower mean IL-2 titer in Badgan dominated subjects comparing with Shar dominated subjects. These findings can be summarized that Badgan humour may be inversely correlated with T cell differentiation activity.

Interleukin 6 (IL-6). This is a well-known pyrogenic, acute-phase pro-inflammatory cytokine produced by activated T lymphocytes and macrophages. It plays key role in triggering of Th2-mediated immune reaction and neurohumoral regulation of inflammatory reaction [10, 28]. There role of IL-6 the in development of certain cancers, autoimmune and autoinflammatory diseases such as diabetes mellitus, atherosclerosis, Alzheimer's disease, SLE, multiple myeloma, prostate cancer, Behcet's disease and rheumatoid arthritis has been established [29-36].

Here we found lower plasma IL-6 mean titer in subjects with Badgan type compared with Khii-Shar mixed type subjects; and lower supernatant IL-6 level in Badgan dominated type compared with Khii dominated subjects (p=0.027). Based on these data, we propose that domination of Badgan humour may be related with lower activity of Th2 mediated immune response.

Interleukin 10 (IL-10). This cytokine is known as Human Cytokine Synthesis Inhibitory Factor (CSIF) [10]. The cytokine is released from activated Th2 cells and inhibits production of Th1 dependent cytokines from activated Th1 cells. It also the decreases expression of MHC class II and costimulatory molecules on the surface of macrophages, and thus supports negative regulation of Th1 and Th2 response [10, 37]. There are reports that therapeutic use of recombinant IL-10 resulted in clinical improvement of patients with Crohn's disease and advanced cancer [38, 39]. Our analysis of IL-10 levels showed higher a mean titer in pure Shar subjects comparing with Khii subjects and this may indicate the higher activity of Th2 mediated response related with Shar humour domination.

IFNγ is also known as Th1 dependent cytokine and is produced by activated natural killer (NK), natural killer T (NKT), CD4+ T (Th) and CD8 (cytotoxic T lymphocyte-CTL) cells during the adaptive immune response. It plays key role in inhibition of viral replication, cancer growth control, activation of macrophages, formation of granulomas during intracellular infection, and in sum upregulation of cellular immune response and downregulation of Th2 mediated humoral immune response [10, 40]. In this study, Shar subjects had a decreased mean titer of supernatant IFNγ compared with Shar-Badgan mixed type subjects. This may indicate the Badgan humour is related to higher activity of Th1 mediated response.

Transforming Growth Factor Beta (TGFβ). This pleotropic cytokine produced by leukocytes such as lymphocytes and monocytes, mainly by Treg CD4+ CD25+ cells and support development and further differentiation of Treg cells in a autocrine manner and differentiation of Th17 cells in a paracrine manner [10, 24]. Its role in the inhibition of Th1 mediated anticancer response and maintenance of fibroblast activation and collagenogenic efficacy has been established in both animal model and clinical studies [24, 41, 42].

Conclusion. Based on our findings in this study, we propose the following relationships. First, Badgan humour may be associated with lower Th2 activity comparing with Khii and Shar humours. Second, Shar humour may be associated with

Higher Th2 activity comparing with Khii humours. Third, on one hand, mixed Shar-Badgan subjects had a higher level of IFNγ comparing with pure Shar subjects; on other hand, we did not find direct evidence for a difference in Th1 response activity in the different types of constitutions, but according to the cytokine negative cross-regulation concepts we suggest higher IFNγ levels or higher efficacy of Th1 responses in Khii subjects via higher IL-10 level in Shar subjects. So, we hypothesize that Khii humour is associated with higher activity of Th1 mediated response [10].

Th1 mediated response matched with Khii humour is a powerful mechanism against intracellular infection [40, 43]. A high intensity of this type of response is normally related to resistance to intracellular infections caused by many kinds of viruses and bacterias such as Mycobacterium tuberculosis, Bartonella henselae, Francisella tularensis, Listeria monocytogenes, Salmonella typhi, Brucella, Legionella, Yersinia, Neisseria meningitidis, fungi such as Histoplasma capsulatum, Cryptococcus neoformans and ptotozoans such as Plasmodium spp., Toxoplasma gondii, Cryptosporidium parvum, Leishmania spp., Trypanosoma cruzi, but people with a high level of Th1 mediated response may be susceptible to infections with pyogenic bacteria and their toxins (43). Abnormal Th1 response have been established as a important pathogenetic factor for development of atherosclerosis [44]. The observations of Burmaa B (2010) and Tserentsoo Ts (2014) showed a relatively high prevalance of Khii dominated subjects among patients with circulatory pathologies and theorized that this may be explained with abnormal Th1 response [45, 46].

Th2 mediated response matched with Shar humours is responsible for humoral immunity [10]. High intensity of this type of adaptive immune response is normally related to resistance to infection by extracellular bacteria and fungi, but not intracellular infection [10]. A high prevalence of Shar dominated subjects with Shar or Badgan dominated humours among patients with chronic digestive disorders may be explained by presence of persistent intracellular infections of digestive organs caused by weak Th1 response in these patients [46].

We did not find results of other studies describing the relationship between types of adaptive immune response and types of human body typology used in other traditional Oriental medicine. However, some studies reported the relationship between human body constitution types and certain pathologies. Sohn et al. (2012) in their meta-analysis reported the significant difference among Sasang types of typology system used in Korean traditional medicine in distribution of genotypes or haplotypes related with development of coronary and metabolic diseases, HLA phenotypes and drug resistance [16]. Wan et al. (2010) observed no significant difference in mean titer of IL-1β and IL-2 in subjects with yin-deficiency constitution and gentle constitution according Chinese traditional medicine, although yin-deficiency subjects demonstrated increased level of cortisol, adrenocorticotropic hormone and cyclic guanosine monophosphate compared to subjects with gentle constitution [19].

In this study participants were not investigated for all quantitative and functional features of cellular and humoral immunity and types of immune response were estimated only with cytokines produced mainly by Th1 and Th2 lymphocytes. In the future, immune function variance and its relation with human typology should be investigated using protocols that quantify immune cell phenotypes, evaluate of antibody production, and the innate immunity function in both healthy populations and groups of patients with certain immune disorder pathologies.

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