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Letter to the Editor

Possible role of Th17 cells and IL-17 in the pathogenesis of atopic dermatitis in northern China

To the Editor,

Atopic dermatitis (AD) is a common, chronic relapsing, inflammatory skin disease, which is usually associated with other systemic atopic disorders such as allergic asthma and rhinitis [1,2]. It is well known that AD is attributed to the interaction of multiple genetic, immunologic and environmental factors. Traditionally, Th cells are thought to differentiate into Th1 and Th2 subsets. Recently, a new CD4⁺ T-cell subset, Th17 was identified and characterized by the production of IL-17 [3]. The pathogenic roles of Th17 cells and IL-17 in a variety of autoimmune and inflammatory conditions have been well proven [4,5]. AD is originally regarded as a Th2-mediated disease. Interestingly, it has been demonstrated that Th17 cells and IL-17 play an important role in the pathogenesis of allergic asthma, another Th2-mediated allergic disease [6]. And from a genetic perspective, an association between IL-17 promoter G152A polymorphism and asthma was observed [7]. While, so far few studies on the role of Th17 cells and IL-17 in the pathogenesis of AD were performed, as well as the correlation of IL-17 polymorphism and AD was unknown. In this study, Th17 cells percentage, IL-17 mRNA level in peripheral blood mononuclear cells (PBMCs), and IL-17 serum concentration were detected, as well as the association of IL-17 G152A polymorphism with AD was investigated.

181 AD patients (3–16 years old) and 218 ethnic-matched healthy control subjects (6–16 years old) were included to screen IL17-G152A polymorphism by restriction fragment length polymorphism and DNA sequencing. Genotypes and allele frequencies were compared by χ^2 test. Th17 cells percentage, IL-17 mRNA level, and IL-17 serum concentration were measured by flow cytometric analysis, real-time quantitative reverse transcriptase-polymerase chain reaction and enzyme-linked immunosorbent assay in 49 AD children (6–16 years old) and 30 age-matched healthy controls. The quantitative data were expressed as median (25–75 percentile). Mann–Whitney *U*-test and Spearman's correlation were used for statistical analysis. All participants were

nonconsanguineous Chinese living in northern China and without systemic diseases, ongoing infection or immunosuppression. The study was approved by the Ethics Committee of Binzhou Medical University, and written informed consent was obtained from all participants or their guardians.

AD patients showed an obvious increase in Th17 cells percentage compared to healthy controls [1.60 (1.36–1.80)% vs. 0.40 (0.30–0.50)%, $Z = -7.438$, $P < 0.01$, Fig. 1]. The IL-17 mRNA level in PBMCs [6.87 (5.62–7.95) vs. 1.68 (1.40–2.07), $Z = -7.426$, $P < 0.01$] and serum concentration [32.60 (28.55–37.85) pg/ml vs. 11.45 (9.78–12.55) pg/ml, $Z = -7.425$, $P < 0.01$] were both significantly higher in AD patients than healthy controls (Fig. 1). In addition, the disease severity of AD was determined by the SCORAD (SCORing Atopic Dermatitis) index. And the SCORAD index correlated positively with Th17 cells percentage ($r = 0.421$, $P < 0.05$), IL-17 mRNA level ($r = 0.372$, $P < 0.05$) and serum concentration ($r = 0.362$, $P < 0.05$).

Table 1 showed the genotypes and allele frequencies of IL17-G152A polymorphism between AD patients and control subjects. It was in Hardy–Weinberg equilibrium for both of them ($P > 0.05$). In the whole dataset, the AA genotype and A allele frequency in AD group were significantly higher than those in control group (Table 1). In gender stratified comparison, there were no significant differences between each AD subgroup and healthy controls. Furthermore, when AD patients were subdivided according to different confounding factors (Table 1), the AA genotype and A allele frequency were significantly more frequent in early-onset AD patients than later-onset AD patients and in AD patients with rhinitis and/or asthma than simple AD patients.

In the 49 AD children, Th17 cells percentage of AA ($n = 15$), AG ($n = 14$) and GG ($n = 20$) genotypes carriers was 1.70 (1.60–2.00)%, 1.65 (1.44–1.77)% and 1.50 (0.98–1.70)%, respectively. IL-17 mRNA level was 7.64 (6.50–8.98), 6.40 (5.62–7.79) and 6.35 (4.61–7.12), respectively. IL-17 serum concentration was 36.81 (32.90–40.08) pg/ml, 33.75 (28.55–37.15) pg/ml and 31.99 (27.81–34.16) pg/ml, respectively. In further comparison, Th17 cells percentage, IL-17 mRNA level and IL-17 serum concentration in A allele carriers (AA and AG genotypes) were significantly higher than GG genotype carriers [Th17 cells percentage: 1.70

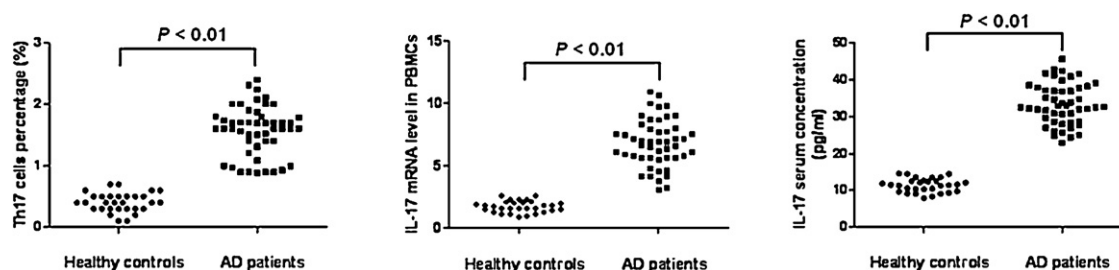


Fig. 1. Th17 cells percentage, IL-17 mRNA level and IL-17 serum concentration of AD patients and control subjects.

Table 1

Genotype and allele frequencies of IL-17 G-152A for AD patients vs. healthy control subjects.

Groups	N	Genotype			χ^2	P	Allele		χ^2	P
		GG	GA	AA			G	A		
Control subjects	218	76	107	35			259	177		
AD patients	181	57	72	52	9.531	0.009 ^{a1}	186	176	5.160	0.023 ^{a2}
Early-onset AD	100	26	38	36	6.429	0.040 ^{b1}	90	110	7.285	0.007 ^{b2}
Later-onset AD	81	31	34	16			96	66		
AD + rhinitis/asthma	112	27	50	35	7.485	0.024 ^{c1}	104	120	5.770	0.016 ^{c2}
Simple AD	69	30	22	17			82	56		

^{a1}AD patients vs. Control subjects.^{a2}OR = 1.385, 95% CI: 1.045–1.834.^{b1}Early-onset AD vs. Later-onset AD.^{b2}OR = 1.778, 95% CI: 1.169–2.704.^{c1}AD + rhinitis/asthma vs. Simple AD.^{c2}OR = 1.690, 95% CI: 1.100–2.596.

(1.54–1.95)% vs. 1.50 (0.98–1.70)%, $Z = -2.122$, $P = 0.034$; IL-17 mRNA level: 7.43 (6.02–8.67) vs. 6.35 (4.61–7.12), $Z = -2.014$, $P = 0.044$; IL-17 serum concentration: 35.10 (31.75–38.05) pg/ml vs. 31.99 (27.81–34.16) pg/ml, $Z = -2.289$, $P = 0.022$. While, there were no significant differences in Th17 cells percentage [1.50 (1.00–1.70)% vs. 1.70 (1.49–1.93)%, $Z = -1.647$, $P = 0.100$], IL-17 mRNA level [6.12 (4.77–7.12) vs. 7.27 (5.72–8.66), $Z = -1.765$, $P = 0.078$] or IL-17 serum concentration [31.90 (27.90–36.80) pg/ml vs. 32.75 (30.84–39.25) pg/ml, $Z = -1.672$, $P = 0.094$] between simple AD patients ($n = 19$) and AD patients with concomitant respiratory allergic diseases ($n = 30$).

Our results showed that Th17 cells percentage, IL-17 mRNA level and serum concentration were elevated in AD patients and correlated with the severity of AD, which was in accordance with the study from Koga and colleagues [8] and indicated that Th17 cells and IL-17 participate in the development of AD further. To the best of our knowledge, there have been no previous studies on genetic variation in IL17-G152A and AD risk. Our present results showed that AA genotype was significantly higher in a portion of AD from northern China than control subjects (28.73% vs. 16.06%). In further stratified analysis, there were higher AA genotype frequencies in simple AD patients than control subjects (24.64% vs. 16.06%), in AD patients with concomitant respiratory allergic diseases than simple AD patients (31.25% vs. 24.64%) and in early-onset AD patients than later-onset AD patients (36.00% vs. 19.75%), which indicated that genetic variation in IL17-G152A may be a risk factor for AD occurrence and development, more possibly, for AD patients with concomitant respiratory allergic diseases and early-onset AD patients. And we also found that AD patients with AA and AG genotypes had a higher Th17 cells percentage, IL-17 mRNA and protein expressions than AD patients with GG genotype. Taken together, the preliminary results of the present study implicate that Th17 cells and IL-17 participate in the pathogenesis of AD and IL17-G152A A allele confers an increased risk of susceptibility to AD and associates with its higher IL-17 expression.

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