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Meta-Analysis

Association between circulating transforming growth factor-β1 level and polymorphisms in systemic lupus erythematosus and rheumatoid arthritis: A meta-analysis

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Abstract: This study systemically reviewed evidence regarding the relationship between circulating blood transforming growth factor-β1 (TGF-β1) levels and systemic lupus erythematous (SLE) and rheumatoid arthritis (RA), and associations between TGF-β1 polymorphisms and susceptibility to SLE and RA. We conducted a meta-analysis on the serum/plasma TGF-β1 levels in SLE and RA patients and healthy controls, and the associations between TGF-β1 +869 T/C, +915 C/G, and -509 T/C polymorphisms and SLE or RA risk. Twenty-eight studies were considered in this meta-analysis. Circulating TGF-β1 levels were significantly lower in the SLE group than in controls (SMD = -1.164, 95% CI = -2.257 – -0.070, $P = 0.037$). Serum/plasma TGF-β1 levels were not significantly different between RA and control groups (SMD = 0.699, 95% CI = -0.379 – 1.717, $p = 0.211$). No association between TGF-β1 +869 T/C polymorphism and SLE was found. However, meta-analysis showed an association between the TGF-β1 +869 T allele and RA in all subjects (OR = 1.282, 95% CI = 1.118–1.470, $P = 3.8 \times 10^{-4}$). Analysis after stratification by ethnicity indicated that the T allele was significantly associated with RA in Asians and Arabs (OR = 1.429, 95% CI = 1.179–1.733, $P = 2.9 \times 10^{-4}$; OR = 1.352, 95% CI = 1.097–1.668, $P = 0.005$), but not Europeans. However, no association was found between TGF-β1 +915 G/C or -509 C/T polymorphisms and RA or SLE. Meta-analysis revealed a significantly lower circulating TGF-β1 level in SLE patients, and a significant association between TGF-β1 +869 T/C polymorphism and RA development.

Key words: TGF-β1; level; Polymorphism; SLE; RA.

Introduction

Systemic lupus erythematosus (SLE) is a prototypic autoimmune disease, characterized by B cell hyperactivity, high level of autoantibody production, immune-complex deposition, and multiple organ damage (1). Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease that predominantly affects the synovial joints, characterized by infiltration of the synovium with neutrophils, macrophages, T cells, B cells, plasma cells, and dendritic cells (DCs) (2,3), causing hyperplasia of synovial cells and formation of new blood vessels, and bone erosions and joint deformity. Although their causes are not fully understood, it has been established that genetic and environmental factors contribute to the pathogenesis of SLE and RA.

TGF-β1 is a pleiotropic cytokine produced by T lymphocytes, DCs, and monocytes/macrophages, which exerts both immunoregulatory and proinflammatory properties (4). It suppresses T and B cell proliferation and plays an important role in the generation of CD8+ T cells that downregulate B cell function (4). TGF-β1 knockout mice develop autoimmunity and multi-organ inflammatory syndrome by producing autoantibodies and exhibiting enhanced lymphocyte proliferation (5). TGF-β1 deficiency may induce autoimmune diseases by influencing lymphocyte activation and differentiation, and regulatory T cell function (5). It has been reported that TGF-β1 production from lymphocyte is reduced in patients with SLE,(6) and TGF-β1 has been detected in the synovial tissue of patients with RA (7). Because of its capacity to regulate inflammatory reactions and immune responses, the TGF-β1 gene, located at 19q13, is viewed as a candidate gene for SLE and RA (8). TGF-β1 polymorphisms that regulate its level of expression may have a propensity to develop autoimmune diseases. The most frequently studied TGF-β1 polymorphisms are +869 T/C, +915 C/G, and -509 T/C, and have been shown to be associated with TGF-β1 production (9-11).

Studies on circulating TGF-β1 levels in SLE and RA patients compared to healthy controls have reported heterogeneous results, and TGF-β1 polymorphisms have been reported to be associated with susceptibility to SLE and RA in some, but not all, studies. In order to overcome the limitations of individual studies and resolve inconsistencies (12,13), we performed this meta-analysis. The aim of this meta-analysis was to systematically review the evidence on serum/plasma TGF-β1 levels in SLE and RA patients compared to those in healthy controls, as well as determine whether TGF-β1 polymorphisms are associated with susceptibility to SLE and RA.

Materials and Methods

Identification of eligible studies and data extraction

We performed a literature search for studies that examined circulating (serum or plasma) TGF-β1 level

in SLE or RA patients and controls, and associations between the polymorphisms of TGF-β1 and SLE or RA. PUBMED, EMBASE, and Cochrane databases were searched to identify all available past articles (up to September 2016). The following key words and subject terms were used in the search: "TGF-β1," "serum or plasma," "polymorphism," "systemic lupus erythematosus," and "rheumatoid arthritis." All references cited were also reviewed to identify additional studies not covered by the above-mentioned electronic databases. Studies were considered eligible if: (1) they were case-control studies, (2) they provided data on TGF-β1 levels in case and control groups, (3) they studied TGF-β1 polymorphisms in case and control groups. No language restriction was applied. Studies were excluded if: (1) they contained overlapping or insufficient data, or (2) they were reviews or case reports. Data on methods and results were extracted from original studies by two independent reviewers. Discrepancies between the reviewers were resolved by consensus. The meta-analysis was conducted in accordance with PRISMA guidelines. (14) The following information was extracted from each study: primary author, year of publication, country, ethnicity, number of participants, mean and standard deviation (SD) of TGF-β1 levels, and the genotype and allele frequencies of the TGF-β1 polymorphisms. When the data given were medians, interquartile ranges, or ranges, we computed the mean and SD using previously described formulae (15,16).

Evaluation of statistical associations

We performed a meta-analysis examining the relationship between TGF-β1 level in SLE or RA. We also performed meta-analyses using 1) allelic contrast, 2) recessive models, 3) dominant models, and 4) homozygote contrast of the TGF-β1 polymorphisms. For continuity of data, results were presented as standardized mean differences (SMDs) and 95% confidence intervals (CIs). SMDs were calculated by dividing the mean difference between two groups according to the pooled SD, and were used when different scales were integrated to measure the same concept. This measure compares case and control arms in terms of standardized scores. The magnitude of SMD was considered as follows: 0.2–0.5, small effect; 0.5–0.8, medium effect; ≥0.8, large effect (17). Odds ratios (ORs) and 95% confidence intervals [CIs] were calculated for dichotomous data. We assessed within-study and between-study variations and heterogeneities using Cochran's Q-statistics (18). The heterogeneity test was used to assess the null hypothesis that all studies were evaluating the same effect. When the significant Q-statistic ($p < 0.10$) indicated heterogeneity across studies, the random effects model was used for the meta-analysis.(19) If not, the fixed effects model was used. It assumed that all studies estimated the same underlying effect, and it considered within-study variation only (18). We quantified the effect of heterogeneity using $I^2 = 100\% \times (Q\text{-}df)/Q$,(20) where I^2 measured the degree of inconsistency between studies and determined whether the percentage total variation across studies was due to heterogeneity rather than due to chance. I^2 ranged between 0% and 100%; I^2 values of 25%, 50%, and 75% were referred to as low, moderate, and high estimates, respectively (20). Statistical manipulations were undertaken using the Comprehensive Meta-Analysis computer program (Biosta, Englewood, NJ, USA).

Evaluation of heterogeneity and publication bias

To examine potential sources of heterogeneity observed in the meta-analysis, subgroup analysis was performed using the following variables: ethnicity, or data type. Although funnel plots are often used to detect publication bias, they require diverse study types of varying sample sizes, and their interpretation involves subjective judgment. In light of this, we evaluated publication bias using Egger's linear regression test (21), which measured funnel plot asymmetry using a natural logarithm scale of ORs.

Results

Studies included in the meta-analysis

We identified 455 studies using electronic and manual search methods. Thirty-two of these were selected for full-text review based on the title and abstract. Four of these were excluded because they had duplicate data, data on other polymorphism, or data on review. Thus, 28 articles including 10 studies on TGF-β1 levels and 18 studies on the TGF-β1 polymorphisms satisfied the inclusion criteria (Table 1, Figure 1) (22-47). Me-

Table 1. Characteristics of individual studies included in the meta-analysis.

A. TGF-β1 level

Author	Country	Ethnicity	Disease	Number		TGF-β1 level (pg/mL)		Correlation findings		
				Case	Control	Case	Control	SMD	Magnitude*	P-value
Sayed, 2014(22)	Egypt	Arab	SLE	56	40	247.4	556.4	-3.809	Large	$< 1.0 \times 10^{-8}$
Antiga, 2011(23)	Italy	European	SLE	15	20	24.3[a]	44.6[a]	-1.776	Large	1.0×10^{-5}
Becker, 2010(24)	Norway	European	SLE	22	31	705.5	746.7	-0.142	No effect	0.611
Hammad, 2006(25)	Egypt	Arab	SLE	32	15	14.5[a]	21.6	-0.596	Medium	0.062
Lu, 2004(26)	Taiwan	Asian	SLE	55	40	818.0	1042.8	-1.084	Large	1.1×10^{-6}
Bennett, 1997(27)	USA	Mixed	SLE	50	76	202.7	149.6	0.313	Small	0.087
Harman, 2016(28)	Turkey	Turkish	RA	38	28	449.0[b]	283.0[b]	0.480	Small	0.057
Mieliauskaite, 2009(29)	Lithuania	European	RA	23	20	51.7[a]	31.6[a]	2.188	Large	1.5×10^{-8}
Rico, 2008(30)	USA	Mixed	RA	20	13	10139.8[c]	4571.0[c]	0.753	Large	0.041
Eriksson, 2004(31)	Sweden	European	RA	15	15	63.2[a]	71.5[a]	-0.723	Large	0.055

SMD, Standard mean difference, * Magnitude of Cohen's d effect size: 0.2 to 0.5: small effect, 0.5 to 0.8: medium effect, 0.8 and higher: large effect. [a]: ng/mL, [b]: ng/L, [c]: unknown.

B. TGF-β1 polymorphisms

Author	Country	Ethnicity	Disease	Number		TGF-β1 polymorphisms
				Case	Control	
Rezai, 2015(32)	Iran	Arab	SLE	55	138	+869 T/C, +915 G/C
Sayed, 2014(22)	Egypt	Arab	SLE	56	40	+869 T/C
Wang, 2007(33)	Japan	Asian	SLE	196	106	+869 T/C
Guarinizo, 2007(34)	Colombia	Latin American	SLE	120	102	+869 T/C, +915 G/C
Lu, 2004(26)	Taiwan	Asian	SLE	138	182	+869 T/C, +915 G/C, -509 C/T
Caserta, 2004(35)	Iran	Arab	SLE	23	32	-509 C/T
Schotte, 2003(36)	Germany	European	SLE	203	158	+915 G/C
Shaker, 2016(37)	Egypt	Arab	RA	104	90	+869 T/C
Saad, 2015(38)	Egypt	Arab	RA	105	105	+869 T/C
Hussein, 2014(39)	Egypt	Arab	RA	160	168	+869 T/C
Li, 2011(40)	China	Asian	RA	112	201	+869 T/C
Kobayashi-1, 2009(41)	Japan	Asian	RA	137	117	+869 T/C
Kobayashi-2, 2009(41)	Japan	Asian	RA	137	108	+869 T/C
Panoulas, 2009(42)	UK	European	RA	395	401	+869 T/C
Alayli, 2009(43)	Turkey	Turkish	RA	131	133	+869 T/C
Wang, 2007(40)	China	Asian	RA	105	100	+869 T/C
Zhu, 2006(44)	China	Asian	RA	76	100	+869 T/C
Kim, 2004(45)	Korea	Asian	RA	143	148	+869 T/C
Pokorny, 2003(47)	New Zealand	European	RA	117	140	+869 T/C
Sugiura, 2002(46)	Japan	Asian	RA	155	110	+869 T/C

NS: Not significant.

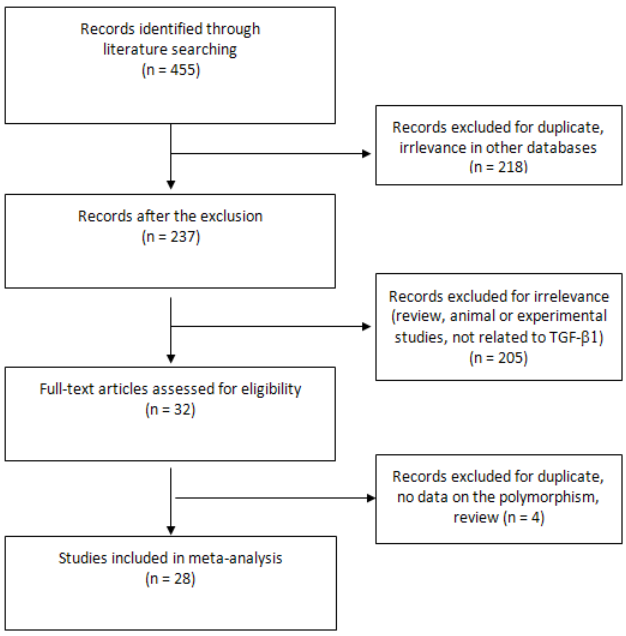

Figure 1. Flow diagram of the study selection process.

ta-analysis of the TGF-β1 polymorphisms was performed if there were at least 2 comparisons. Due to the limited number of studies on polymorphisms, 3 types of meta-analyses were performed: TGF-β1 +869 T/C (rs1982073), +915 G/C (rs1800471) in the coding region, and -509 C/T (rs1800469) in the promoter. The polymorphism at position +869 changes codon 10 (Leu→Pro), and that at position +915 changes codon 25 (Arg→Pro). The characteristic features of the studies included in the meta-analysis are summarized in Table 1.

Meta-analysis of circulating TGF-β1 level in SLE or RA patients compared to controls

Meta-analysis revealed that the circulating TGF-β1 level was significantly lower in the SLE group than in the control group (SMD = -1.164, 95% CI = -2.257 – -0.070, P = 0.037) (Table 2, Figure 2). Serum/plasma TGF-β1 level was not significantly higher in the RA group than in the control group (SMD = 0.699, 95% CI = -0.379 – 1.717, p = 0.211) (Table 2). However, stratification by data type showed a significantly higher TGF-β1 level in the RA group by original data, but not by calculated data (SMD = 1.114, 95% CI = 0.116−2.111, p = 0.029; SMD = -0.723, 95% CI = -1.462−0.015, p = 0.055) (Table 2, Figure 2).

Meta-analysis of the TGF-β1 polymorphisms and susceptibility to SLE or RA.

No association between the TGF-β1 +869 T/C polymorphism and SLE was found using the allele contrast, recessive, dominant, or homozygote models in all study subjects (OR for T allele = 1.050, 95% CI =

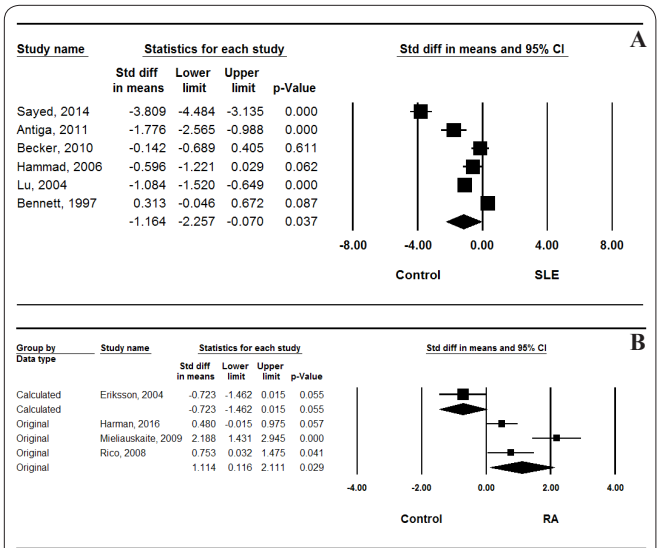

Figure 2. Meta-analysis of the relationship between TGF-β1 levels and SLE in all subjects (A) and RA according to data type (B).

Table 2. Meta-analysis of TGF-β1 levels in SLE or RA patients compared to controls.

Population	No. of studies	Population	Numbers		Test of association			Test of heterogeneity			Publication bias P-value
			SLE	Control	SMD*	95% CI	P-value	Model	P-value	I^2	
SLE	6	Overall	230	220	-1.164	-2.257 – -0.070	0.037	R	0.000	96.0	0.135
	2	European	37	51	-0.933	-2.534 – 0.667	0.253	R	0.000	91.0	
	2	Arab	88	55	-2.200	-5.439 – 0.949	0.171	R	0.001	97.8	
	1	Asian	55	40	-1.084	-1.520 – -0.649	$1.1x10^{-6}$	na	na	na	
	1	Mixed	50	76	0.313	-0.046 – 0.672	0.087	na	na	na	
RA	4	Overall	96	76	0.699	-0.379 – 1.717	0.211	R	0.000	89.8	0.826
	3	Original	81	61	1.114	0.116 – 2.111	0.029	R	0.001	85.7	
	1	Calculated	15	15	-0.723	-1.462 – 0.015	0.055	na	na	na	

SLE: Systemic lupus erythematosus, RA: Rheumatoid arthritis, SMD: Standard mean difference; CI: Confidence interval; * Magnitude of Cohen's d effect size (SMD): 0.2–0.5, small effect; 0.5–0.8, medium effect; ≥0.8, large effect, R: Random effects model; na: Not available.

Table 3. Meta-analysis of the association between the TGF-β1 polymorphisms and SLE.

Polymorphism	Population	No. of studies	Test of association			Test of heterogeneity		
			OR	95% CI	P-value	Model	P-value	I^2
TGF-β1 +869T/C T vs. C	Overall	5	1.050	0.885-1.246	0.573	F	0.701	0
TT + TC vs. CC (Dominant)	Overall	5	1.070	0.797-1.437	0.652	F	0.758	0
TT vs. TC+ CC (Recessive)	Overall	5	1.078	0.801-1.451	0.619	F	0.688	0
TT vs. CC	Overall	5	1.137	0.782-1.653	0.502	F	0.672	0
TGF-β1 +915 G/C C vs. G allele	Overall	4	1.707	0.619-4.711	0.302	R	0.001	81.5
TGF-β1 -509 C/T C vs. T allele	Overall	2	0.846	0.632-1.132	0.260	F	0.572	0

OR odds ratio, *CI* confidence interval, *F* fixed model, *R* random model.

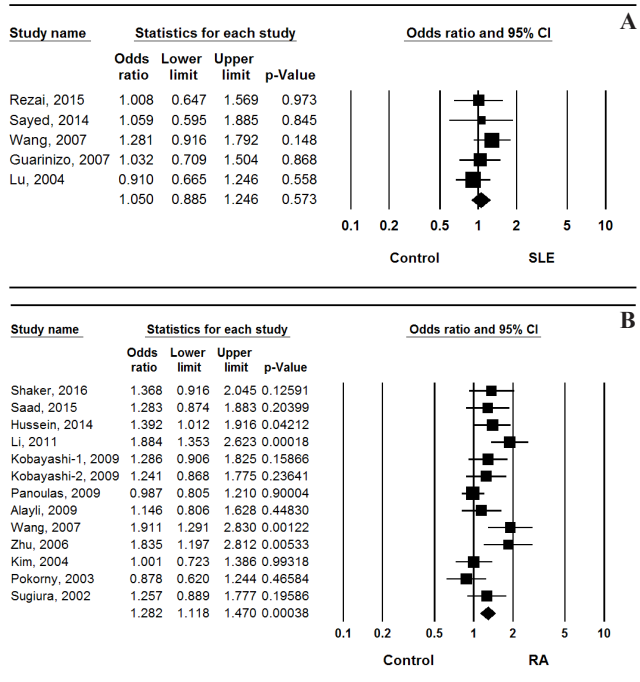

Figure 3. ORs and 95% CIs of individual studies and pooled data for the allelic associations between the TGF-β1 +869 T/C polymorphism and SLE (A) or RA (B).

0.885–1.246, $P = 0.573$) (Table 3, Figure 3). In addition, meta-analysis revealed no association between SLE and the TGF-β1 +915 G/C or -509 C/T polymorphisms (Table 3). However, meta-analysis showed an association between the TGF-β1 +869 T allele and RA in all subjects (OR = 1.282, 95% CI = 1.118–1.470, $P = 3.8 \times 10^{-4}$) (Table 4, Figure 3). Analysis after stratification by ethnicity indicated that the T allele was significantly associated with RA in Asians and Arabs (OR = 1.429, 95% CI = 1.179–1.733, $P = 2.9 \times 10^{-4}$; OR = 1.352, 95% CI = 1.097–1.668, $P = 0.005$), but not in Europeans (Table 3). The same pattern was found in dominant and homozygote models (Table 4). However, no association between the TGF-β1 +915 G/C or -509 C/T polymorphisms and RA was found (Table 4).

Heterogeneity and publication bias

Between-study heterogeneity was identified during the meta-analyses of TGF-β1 levels in SLE patients (Table 2). Between-study heterogeneity was found during the meta-analyses of the TGF-β1 polymorphisms in RA, but not in SLE (Table 2, 3). However, heterogeneity decreased or resolved in subgroup analysis by ethnicity (Table 2, 3). Publication bias causes a disproportionate number of positive studies, and poses a problem for meta-analyses. However, we found no evidence of publication bias for all study subjects (Egger's regression test p-values > 0.1).

Discussion

In this meta-analysis, we combined the evidence of circulating TGF-β1 levels in SLE and RA, and the association between TGF-β1 polymorphisms and susceptibility to SLE and RA. This meta-analysis showed that the circulating TGF-β1 level was significantly lower in the SLE group than in the control group. However, the TGF-β1 level was not significantly different between the RA group and the control group. Meta-analysis showed no association between TGF-β1 +869 T/C, +915 C/G, and -509 T/C polymorphisms and SLE, but it identified a significant association between the TGF-β1 +869 T/C

Table 4. Meta-analysis of the association between the TGF-β1 polymorphism and RA.

Polymorphism	Population	No. of studies	Test of association			Test of heterogeneity		
			OR	95% CI	p-val	Model	p-val	I^2
TGF-β1 +869T/C T vs. C	Overall	13	1.282	1.118-1.470	$3.8x10^{-4}$	R	0.014	52.5
	Asian	7	1.429	1.179-1.733	$2.9x10^{-4}$	R	0.059	50.5
	Arab	3	1.352	1.097-1.668	0.005	F	0.947	0
	European	2	0.958	0.804-1.142	0.634	F	0.571	0
TT + TC vs. CC (Dominant)	Overall	13	1.571	1.187-2.078	0.002	R	0.001	65.2
	Asian	7	1.760	1.244-2.490	0.001	F	0.035	55.6
	Arab	3	2.206	1.532-3.176	0.003	F	0.238	30.6
	European	2	0.858	0.614-1.197	0.368	F	0.639	0
TT vs. TC+ CC (Recessive)	Overall	13	1.233	1.014-1.499	0.036	R	0.049	43.1
	Asian	7	1.454	1.170-1.809	0.001	F	0.127	39.7
	Arab	3	0.951	0.529-1.681	0.864	R	0.069	62.6
	European	2	1.000	0.778-1.285	0.998	F	0.700	0
TT vs. CC	Overall	13	1.583	1.193-2.101	0.001	F	0.013	52.8
	Asian	7	2.035	1.360-3.046	0.001	R	0.043	52.5
	Arab	3	1.671	1.082-2.579	0.021	F	0.964	0
	European	2	0.879	0.608-1.270	0.492	F	0.613	0

OR odds ratio, *CI* confidence interval, *F* fixed model, *R* random model.

polymorphism and RA susceptibility. These data indicate that a decreased TGF-β1 level is associated with SLE, and that TGF-β1 +869 T/C polymorphism is associated with RA risk.

Low TGF-β1 level in SLE may be explained partly by increased interleukin (IL)-10 in SLE. IL-10 promotes B cell differentiation and autoantibody production. IL-10 may also suppress the ability of T cells, monocytes, and NK cells to produce TGF-β1, thus leading to low TGF-β1 level in SLE (48). It is necessary to explain potential influences on the relationship between TGF-β1 level and SLE. A reduction in circulating TGF-β1 level may predispose to susceptibility to autoimmune diseases including SLE (5). TGF-β1 knockdown mice may develop an autoimmune disease including SLE-like autoantibodies and lymphoproliferation (5). TGF-β1 enhances CD8 expression, and costimulates CD8+ T cells to downregulate cell hyperactivity. TGF-β1 inhibits T and B cell proliferation, and induces apoptosis in B cells, plasma cells, and NK cells (4). Decreased plasma TGF-β1 levels may be one of the factors responsible for B cell hyperactivity, promoting development of SLE (49).

Our meta-analysis showed no relationship between TGF-β1 level and RA, but high TGF-β1 level was correlated with RA after excluding one study with calculated data. TGF-β1 is a multifunctional cytokine with immunomodulatory properties to maintain normal immunological homeostasis, but this cytokine may exert an opposing function, dependent on the responding cell type and the state of differentiation (50). We cannot rule out the possibility that circulating TGF-β1 levels are increased in RA, because our study on TGF-β1 level in RA had low statistical power, since only 4 studies with few subjects had sufficient relevant data, and our meta-analysis results for RA were not robust.

Given the potential link between TGF-β1 and autoimmune or inflammatory diseases, TGF-β1 polymorphisms, which may influence TGF-β1 expression, have been studied as potential causes of autoimmune or inflammatory diseases (8). Our meta-analysis revealed an association between the TGF-β1 +869 T/C polymorphism and RA susceptibility, which is in agreement with the results of functional studies conducted on the TGF-β1 polymorphism (9-11). TGF-β1 has regulatory effects on fibroblasts, lymphocytes, DCs, macrophages, chondrocytes, and osteoblasts (7). However, we found no association between SLE and the TGF-β1 polymorphism. This finding suggests that the TGF-β1 +869 T/C polymorphism has a disease-dependent functionality, or that the analysis concerning SLE is underpowered. Our meta-analysis results for the TGF-β1 +915 C/G, and -509 T/C polymorphisms are not consistent with the results of functional studies on TGF-β1 polymorphisms (9-11). Epidemiologic results occasionally do not coincide with the results of functional studies in this regard, because SLE and RA are complex diseases, and multiple genes, different genetic backgrounds, and environmental factors contribute to their development. Moreover, our meta-analysis results for the TGF-β1 polymorphisms may be due to a Type II error (false negative).

The results of our meta-analysis of the association between TGF-β1 +869 T/C polymorphism with RA risk are in good agreement with a similar meta-analysis performed by Zhou et al.[51] Compared with the previous study, our analyses included 3 additional studies on the TGF-β1 +869 T/C polymorphism, 235 more RA patients, and 249 more controls.(37-39) We performed additional meta-analyses with 7 studies to examine potential association of the TGF-β1 polymorphism with SLE in 791 patients and 758 controls. Recent meta-analysis about the relationship between TGF-β1 +869 T/C polymorphisms and autoimmune disease including SLE and RA has been also published (8). However, there have been no meta-analyses on associations between TGF-β1 +915 C/G, and -509 T/C polymorphisms and SLE or RA risk and serum/plasma TGF-β1 levels in SLE and RA patients compared to healthy controls. In addition, several new studies on TGF-β1 polymorphisms in SLE and RA have been published, indicating need of updating the meta-analysis. Therefore, we conducted this meta-analysis.

This meta-analysis has some limitations that need to be considered. First, most of the studies included had

small sample sizes. Thus, the meta-analysis may be underpowered. Second, the studies included in the meta-analysis were heterogeneous in demographic characteristics and clinical features. The heterogeneity, confounding factors, and limited clinical information provided by the study populations may have affected the results. Third, publication bias could have also adversely affected the analysis, because studies that produced negative results may not have been published or may have been missed. Although Egger's regression test was used, the possibility of bias cannot be eliminated. Nevertheless, this meta-analysis also has its strengths. To the best of our knowledge, our meta-analysis is the first study that provides combined evidence for TGF-β1 levels and polymorphisms in patients with SLE or RA. Individual studies included a population size ranging from 15 to 203 in SLE, and from 15 to 219 in RA alone, but our pooled analysis had 965 SLE patients and 1,877 RA patients. Compared to individual studies, our study was able to provide data that were more accurate by increasing the statistical power and resolution through pooling of the results of independent analyses.

In conclusion, our meta-analysis demonstrated that circulating TGF-β1 levels were significantly lower in SLE patients when compared to controls, thereby suggesting that the low TGF-β1 level may be a risk factor for SLE or a consequence of SLE, and that the TGF-β1 +869 T/C polymorphism is associated with RA susceptibility. Our meta-analysis suggested that TGF-β1 likely plays an important role in the pathogenesis of SLE and RA. Further studies are necessary to determine whether TGF-β1 levels and polymorphisms directly contribute to the pathogenesis of SLE and RA.

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