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Serum levels of cytokines in systemic lupus erythematosus

Association study in a Chinese population

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease, characterized by auto-antibodies production, complement activation and immune-complex deposition, causing tissue and organ damage. Although the clear pathogenesis of SLE has not been fully elucidated, cytokine-mediated immunity has been found to play an important role. Serum IL-6 levels were significantly elevated in SLE patients compared with normal controls and correlated with the SLE activity index (SLEDAI), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) [1, 2].

Evidence has indicated that blocking the effects of IL-6 in SLE is effective and safe, such as the anti-IL-6 receptor monoclonal antibody tocilizumab [3]. As one of the main players in the pathogenesis of SLE, the serum TNF-α level was significantly elevated in SLE patients compared to controls, and anti-TNF-α treatment for SLE has, thus, been applicable [2, 4]. It is notable that some patients treated with infliximab (anti-TNFα monoclonal antibody) had infectious conditions, such as urinary tract infection and *Escherichia coli* bacteremia [5]. In addition, infliximab treatment may induce deep-vein thrombosis, central nervous system lymphoma, and legionella pneumonia [6]. Therefore, the search for new cytokines that are associated with disease onset of SLE and have therapeutic potential continues.

The aim of this study was to investigate serum levels of cytokines (IL-19, IL-24, IL-26, IL-31, IL-32, IL-36) in SLE, in comparison with normal controls. A total of 65 patients with SLE from the Chinese population (59 women, 6 men; mean age 32±11 years; disease activity (SLEDAI) <6 [7]) were recruited from the Department of Rheumatology at Anhui Provincial Hospital and the First Affiliated Hospital of Anhui Medical University. Patients were treated with steroids and antimalarial agents. The diagnosis of SLE was established by the presence of four or more American College of Rheumatology (ACR) diagnostic criteria [8]. As normal controls, 65 healthy volunteers of Chinese population (58 females, 7 males; mean age 30±7 years) with no history of autoimmune disorders, major infection, and other inflammatory diseases were included. Demographic data, clinical data, and laboratory data were obtained by reviewing medical records or a questionnaire and reviewed by experienced physicians. This study was approved by the ethics committee of Anhui Medical University, and informed consent was obtained from all the participants. Serum levels of IL-19, IL-24, IL-26, IL-31, IL-32, and IL-36 were detected by enzyme-linked immunosorbent assay (ELISA) kits (R&D Systems, Minneapolis, MN, USA) according to the manufacturer's instructions. Statistical differences were analyzed with the Mann–Whitney test using SPSS 11.01 software. A two-tailed p value <0.05 was considered statistically significant.

Our results showed that serum levels of IL-19, IL-24, IL-26, IL-31, IL-32, and

Tab. 1 Comparison of serum levels of cytokines between SLE and controls

Variable	SLE patients	Healthy controls	p value
pg/ml	Median (interquartile range)	Median (interquartile range)	
IL-19	31.97 (13.07–55.21)	23.93 (8.12–50.76)	0.328
IL-24	13.50 (9.06–22.97)	10.82 (7.43–18.58)	0.105
IL-26	48.31 (25.67–64.70)	44.63 (30.78–58.71)	0.882
IL-31	40.74 (29.59–67.35)	42.11 (22.06–58.01)	0.195
IL-32	39.55 (25.40–55.42)	39.25 (21.00–70.46)	0.906
IL-36	54.23 (40.12–70.29)	55.47 (41.51–66.12)	0.900

IL-36 in SLE patients were not significantly different from the normal controls (Tab. 1). These findings may be attributed to several aspects. Serum levels of cytokines in patients with different disease stage or treated with antirheumatic drugs may be different, such as newly diagnosed severe SLE patients, patients with flared status, patients in remission, or patients in steady state [7]. Pan et al. [9] observed significantly higher levels of serum IL-12 family cytokines (IL-12, IL-23, IL-27, IL-35), IL-6 and anti-dsDNA antibodies in newly diagnosed severe SLE patients compared with healthy controls. After prednisone treatment, the serum levels of IL-12 family cytokines decreased significantly. In addition, Cepika et al. [10] found that circulating DNA is higher in newly diagnosed, untreated SLE patients than in controls, and decreases significantly after chloroquine treatment. Untreated patients had higher serum IL-10 than controls. Corticosteroids decreased and chloroquine completely abolished CpG-mediated CD86 upregulation in B cells and IL-10 secretion. In this study, patients included were in steady state, by which the disease activity SLEDAI was <6, and the patients were treated with steroids and antimalarial agents. Therefore, studies with newly diagnosed, untreated SLE patients should be discussed in the future in order to detect the serum levels of these cytokines. In addition, with 65 patients and 65 healthy controls in the current study, the sample size may be relevantly small. Therefore, further studies with larger sample sizes should be discussed. Furthermore, these cytokines are preferentially expressed by Th cells; it is possible that there is retention and/or migration of Th cells within the tissues or organs in SLE patients, leading to the reduction in peripheral blood expression [11].

IL-19, IL-24, and IL-26 belong to the IL-10 cytokine family. Concentrations of IL-19 and IL-26 were significantly elevated in rheumatoid arthritis (RA) patients compared with healthy volunteers [12, 13]. IL-19 expression was up-regulated in both T cells and macrophages derived from RA patients [12]. Similarly, immunohistochemical analysis showed IL-19 was predominantly expressed in the hyperplastic lining layers of RA synovial tissues [14]. In psoriasis patients, etanercept (anti-TNFα monoclonal antibody) suppresses regenerative hyperplasia in psoriasis by acutely down-regulating epidermal expression of IL-19 and IL-24 [15]. In addition, expression of IL-32 and IL-36 was increased in RA patients and ankylosing spondylitis (AS) patients compared with healthy controls [16–18]. IL-32 injected into knee joints of collagen-induced arthritis mice induced significantly higher expression of IL-1β, TNF-α, IL-18, and IFNγ, as well as higher expression of IL-17, IL-21, and IL-23 in relation to controls [19]. Immunohistochemical analysis revealed strong inhibition of IL-32 protein in synovial biopsies from RA patients after anti-TNF-α treatment [20]. These findings suggest that IL-19, IL-24, IL-26, IL-32, and IL-36 are related to the pathogenesis of autoimmune diseases, such as psoriasis, RA, and AS.

Abstract · Zusammenfassung

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Serum levels of cytokines in systemic lupus erythematosus. Association study in a Chinese population

Abstract

Background. Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by abnormal production of autoantibodies and proinflammatory cytokines. The clear pathogenesis of SLE has not been fully elucidated. Cytokine-mediated immunity has been showed to be involved in the pathogenesis of SLE.

Objectives. The aim of this study was to investigate serum levels of cytokines (IL-19, IL-24, IL-26, IL-31, IL-32, IL-36) in SLE patients, in comparison with normal controls in a Chinese population.

Materials and methods. A total of 65 patients with SLE and 65 healthy volunteers were recruited for the current study. All serum levels of cytokines were measured by enzyme-linked immunosorbent assay (ELISA) kits.

Results. Serum levels of IL-19, IL-24, IL-26, IL-31, IL-32 and IL-36 in SLE patients were not significantly different from the normal controls (all p>0.05).

Conclusion. Serum levels of IL-19, IL-24, IL-26, IL-31, IL-32 and IL-36 in SLE patients were not markedly different from the normal controls. However, functional research should be discussed in future studies to elucidate the roles of these cytokines in SLE.

Keywords

Interleukins · Autoantibodies · Genetic polymorphism · Synovial membrane · Lupus nephritis

Zytokin-Serumkonzentrationen bei systemischem Lupus erythematodes. Assoziationsstudie an einem Kollektiv in China

Zusammenfassung

Hintergrund. Der systemische Lupus erythematodes (SLE) ist eine Autoimmunerkrankung, bei der es zu einer anormalen Produktion von Autoantikörpern und proinflammatorischen Zytokinen kommt. Die Pathogenese der SLE ist im Einzelnen noch nicht vollständig geklärt, erwiesen ist allerdings, dass die zytokinvermittelte Immunität eine Rolle spielt.

Zielsetzung. Ziel dieser Studie war die Bestimmung der Konzentrationen von Zytokinen (IL-19, IL-24, IL-26, IL-31, IL-32, IL-36) im Serum von SLE-Patienten im Vergleich mit denen eines nichterkrankten Kontrollkollektivs in einer chinesischen Population.

Material und Methoden. Insgesamt 65 SLE-Patienten und 65 gesunde freiwillige Probanden wurden für die Studie rekrutiert. Sämtliche Serumkonzentrationen der Zytokine wurden mit ELISA("enzyme-linked immunosorbent assay")-Kits bestimmt.

Ergebnisse. Die Serumkonzentrationen von IL-19, IL-24, IL-26, IL-31, IL-32 und IL-36 unterschieden sich in der Gruppe der SLE-Patienten nicht signifikant (alle p>0,05) von denen der gesunden Kontrollgruppe.

Fazit. Zwar bestanden keine erheblichen Unterschiede zwischen den Serumkonzentrationen von IL-19, IL-24, IL-26, IL-31, IL-32 und IL-36 bei SLE-Patienten und Nichterkrankten, dennoch sollte die Rolle dieser Zytokine bei SLE in künftigen (Funktions-)Studien weiter diskutiert und erforscht werden.

Schlüsselwörter

Interleukine · Autoantikörper · Genpolymorphismus · Synovialmembran · Lupusnephritis

IL-26 can induce the generation of the pro-inflammatory cytokines IL-1β, IL-6, and TNF-α by human monocytes and also up-regulate the expression of the chemokine CCL20 [13]. Intriguingly, IL-26-stimulated monocytes selectively promote the production of RORγt$^+$ Th17 cells, through IL-1β secretion by monocytes [13]. In addition, IL-17 mRNA levels in human CD4+ T cells were upgraded by IL-32 stimulation, and expression of RORγt, a transcription factor for Th17 differentiation, was increased by IL-32 stimulation [21]. It has been found that expression of RORγt and IL-17 are elevated in SLE patients and positively correlated with the SLEDAI [22]. Functional studies have confirmed that RORγt and IL-17 play an important role in the disease onset of SLE [23]. Therefore, IL-26 and IL-32 may induce the aberrant expression of RORγt and IL-17 via the Th17 signaling pathway, which has been demonstrated to be related to the pathogenesis of SLE.

Furthermore, peripheral blood mononuclear cells-induced dendritic cells treated with IL-19, IL-24, IL-31, IL-36 produced higher expression of inflammatory cytokines, such as IL-10, IL-12, TNF-α, IL-18, and IL-23 [24–27]. These cytokines have also been recognized to correlate with the pathogenesis of SLE, where serum levels of IL-10, IL-12, TNF-α, IL-18, and IL-23 are elevated in SLE patients and are related to SLEDAI [28, 29]. Meta-analysis of IL-10, IL-18, and TNF-α suggested that gene polymorphisms of these cytokines are associated with the development of SLE [30–32]. MRL/lpr lupus-prone mice treated with a rat anti-IL-23p19 antibody for 6 weeks resulted in delaying the onset of nephritis [33]. IL-23 receptor-deficient lupus-prone C57BL/6-lpr/lpr mice display decreased numbers of CD3(+)CD4(−)CD8(−) cells and IL-17-producing cells in the lymph nodes and produce less anti-DNA Abs [34]. Exogenous IL-18 inhibits endothelial differentiation in control endothelial progenitor cells (EPCs)/circulating angiogenic cells (CACs) and neutralization of IL-18 in SLE EPC/CAC cultures restores their capacity to differentiate into mature endothelial cells, supporting a deleterious effect of IL-18 in vascular repair [35]. Therefore, IL-19, IL-24, IL-31, and IL-36 may play a role in SLE through their roles in the induction of abnormal expression of pro-inflammatory cytokines, which have also been confirmed to be correlated with disease onset of SLE. However, all these speculated mechanisms should be elucidated in future studies.

Conclusion

Serum levels of IL-19, IL-24, IL-26, IL-31, IL-32, and IL-36 in SLE patients were not markedly different from the normal controls. Functional research should be discussed in future studies to elucidate the roles of these cytokines in SLE. For instance, vectors infected with these cytokines and then transferred into lupus mice can be used to discuss the roles of these cytokines in vivo, or the vectors infected with these cytokines and then transferred into T cells, B cells to interpret the roles of these cytokines in vitro.

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Compliance with ethical guidelines

Conflict of interest. M. Zhang, W.-D. Xu, Y. Zhu, P.-F. Wen, R.-X. Leng, H.-F. Pan, and D.-Q. Ye state that there are no conflicts of interest.

All studies on humans described in the present manuscript were carried out with the approval of the responsible ethics committee and in accordance with national law and the Helsinki Declaration of 1975 (in its current, revised form). Informed consent was obtained from all patients included in studies.

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Buchbesprechungen

Wolfgang U. Eckart

Geschichte, Theorie und Ethik in der Medizin

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In der Approbationsordnung für Ärzte wurde im Rahmen des Querschnittsbereichs „Geschichte, Theorie, Ethik der Medizin" der medizinhistorische, medizintheoretische und medizinethische Unterricht in die klinische ärztliche Ausbildung integriert und im Examen geprüft.

Einen Überblick über das Querschnittsfach gibt – bereits in der siebten Auflage – das vorliegende Taschenbuch.

Die moderne wissenschaftliche Medizin fußt auf der Grundlage der Heilkunst, die in der griechischen und römischen Antike geschaffen wurden. Fernwirkungen haben die Persönlichkeiten wie Hippocrates und Galen, deren Konzepte von einem Gleichgewicht der Grundelemente, Grundqualitäten und Körpersäften bestimmt war. Diät, Abführmaßnahmen, frühere chirurgische Techniken und pharmakologische Darreichung werden dargestellt und zum Teil mit neuzeitlichen Erfahrungen verknüpft.

Die Medizin der griechischen und römischen Antike, die byzantinische Medizin, die Medizin im Mittelalter und Renaissance wird in einzelnen Kapiteln dem Aufbruch in die moderne Medizin vom 17. bis 21. Jahrhunderts gegenübergestellt.

Der geschichtliche Bogen von der Antike zur modernen Gesellschaft wird spannend und unterhaltsam geschlagen. Die Fakten, Konzepte und die geistliche Haltung werden klar strukturiert dargestellt und miteinander vernetzt.

Die theoretischen Grundlagen der Medizin, Ethik mit den Grenzkonflikten sind weitere Themen.

Fehlentwicklungen der modernen Medizin oder ideologische Verstrickungen im Nationalsozialismus und den Krieg werden kritisch beleuchtet.

In der siebten Auflage wurden die Themen Theorie und Ethik in der Medizin grundlegend überarbeitet und angepasst an die aktuellen Prüfungsanforderungen in eigenständige Kapitel aufgenommen.

Die Medizin wird in allen Epochen kompakt und anschaulich geschildert, so dass der angehende Mediziner sich für die Prüfung gezielt vorbereiten kann.

Die Medizin-Geschichte wird lebendig im Querschnittsfach zum Lernen, Schmökern und Nachschlagen!

J. Sökeland (Berlin)