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CORRELATION RISK ANALYSIS OF SERUM RAGE AND HLI LEVELS IN PATIENTS WITH IMMUNE DISEASES

ANALIZA POVEZANOSTI I FAKTORA RIZIKA U VEZI SA SERUMSKIM NIVOIMA RAGE I HLI KOD PACIJENATA SA BOLESTIMA IMUNOG SISTEMA

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Summary

Background: To explore the roles of Human Leukocyte Interferon (HLI) and Receptor for Advanced Glycation Endproducts (RAGE) in the occurrence and development of systemic lupus erythematosus (SLE), as well as their associations with the disease activity and clinical symptoms of SLE, and to evaluate the clinical application value of their detection.
Methods: The levels of serum RAGE and HLI in SLE patients were detected via ELISA. The immunomagnetic bead method was used to measure the amounts of interleukin (IL)-1β, IL-2, IL-4, IL-5, and IL-6. Serum HLI and RAGE levels were measured in the active and inactive groups to assess the trial's effectiveness.
Results: The SLE group had higher levels of HLI and RAGE than the RA group ($P<0.05$), while the RA group had lower levels of IL-2 and IL-6 ($P<0.05$). The active group had higher levels of RAGE, IL-6, and HLI than the inactive group ($P<0.05$). Positive correlations were found between RAGE and HLI ($r=0.79$, $P=0.015$) and between RAGE and HLI and the SLEDAI ($r=0.65$, $P=0.016$;

Kratak sadržaj

Uvod: Cilj je bio da se ispita uloga humanog leukocitnog interferona (HLI) i receptora za krajnje produkte uznapredovale glikacije (RAGE) u nastanku i progresiji sistemskog eritemskog lupusa (SLE), kao i njihova povezanost sa aktivnošću bolesti i kliničkim manifestacijama SLE, te da se proceni klinički značaj njihovog određivanja.
Metode: Serumski nivoi RAGE-a i HLI-ja kod pacijenata sa SLE su određivani metodom ELISA. Koncentracije interleukina (IL)-1β, IL-2, IL-4, IL-5 i IL-6 merene su metodom imunomagnetnih kuglica. Njihov potencijalni klinički značaj je procenjivan poređenjem serumskih nivoa HLI-ja i RAGE-a između grupa sa aktivnim i neaktivnim oblikom bolesti.
Rezultati: Pacijenti sa SLE su imali više serumske nivoe HLI-ja i RAGE-a u poređenju sa pacijentima sa reumatoidnim artritisom (RA) ($P<0,05$), dok su u grupi sa RA zabeleženi niži nivoi IL-2 i IL-6 ($P<0,05$). U grupi sa aktivnim oblikom bolesti utvrđeni su viši nivoi RAGE-a, IL-6 i HLI-ja nego u neaktivnoj grupi ($P<0,05$). Utvrđena je pozitivna korelacija između RAGE i HLI ($r=0,79$;

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r=0.44, P=0.034). RAGE is related to the cytokines IL-1β, IL-4, and IL-5, whereas HLI is related to IL-1β and IL-4.
Conclusion: HLI and RAGE support one another and play a role in the onset and progression of SLE. Both HLI and RAGE are associated with disease activity and clinical manifestations such as fever and kidney damage in patients with SLE. Their detection has significant clinical utility for distinguishing active from inactive SLE patients.

Keywords: systemic lupus erythematosus, correlation analysis, prognosis assessment, human leukocyte interferon, receptor for advanced glycation endproducts

P=0,015), kao i između nivoa RAGE i HLI i SLEDAI skora (r=0,65; P=0,016; r=0,44; P=0,034). RAGE je bio povezan sa nivoima IL-1β, IL-4 i IL-5, dok je HLI bio povezan sa IL-1β i IL-4.
Zaključak: HLI i RAGE imaju značajnu i međusobno povezanu ulogu u nastanku i progresiji SLE. Oba biomarkera su povezana sa aktivnošću bolesti i kliničkim manifestacijama, uključujući povišenu telesnu temperaturu i oštećenje bubrega, kod pacijenata sa SLE. Njihovo određivanje može imati značajnu kliničku primenu u razlikovanju aktivnog od neaktivnog oblika SLE.

Ključne reči: sistemski eritemski lupus, analiza povezanosti, procena prognoze, humani leukocitni interferon, receptor za krajnje produkte uznapredovale glikacije

Introduction

The chronic inflammatory condition known as systemic lupus erythematosus (SLE) is brought on by an imbalance in the body's immune system (1). Its clinical manifestations are diverse. Pathogenic autoantibodies that accumulate in the body combine with antigens to form immune complexes (ICs) that deposit in target organs. ICs can activate Toll-like receptors (TLRs) on dendritic cells (DCs), thereby altering the type I interferon (IFN) system (2–4). Abnormal immune regulation results from CD4+ T lymphocytes, CD8+ T lymphocytes, and B cells promoting a cascade of autoimmune reactions, especially abnormal apoptosis and abnormal cytokine secretion (5). During this process, the release of the Receptor for Advanced Glycation End Products (RAGE) increases (6–8). The latter can stabilise immune complexes, promote the endocytosis of RAGE, and trigger additional autoimmune responses upon TLR engagement (9–11). RAGE activates DCs, leading to increased HLI production, which, in turn, further activates immune cells and drives cytokine production (12). RAGE and HLI may promote each other and amplify in a cascade during the pathogenesis of SLE (13–15).

In this study, serum cytokines (HLI, RAGE, and IL-1β) in SLE patients were detected to explore the role of cytokines such as HLI and RAGE in the occurrence and development of SLE and to evaluate the correlation between HLI, RAGE, and the disease activity of SLE patients, as well as the clinical application value of these indices.

Materials and Methods

General information

A total of 140 SLE patients (in the SLE group) diagnosed and treated in our hospital from January 2023 to December 2024 were selected as the research subjects. All of them met the revised SLE classification criteria of the American College of Rheumatology and the European Society of Rheumatology in 2023. SLE patients were further divided into an active group (SLEDAI≥5) and an inactive group (SLEDAI<5) according to the SLE Disease Activity Index (SLEDAI). A comparison of general data between the active and inactive groups is shown in *Table I*. Thirty patients with rheumatoid arthritis (RA) were diagnosed and treated, with an average age of 34.5±7.4 years, including 4 males and 26 females. Seventy healthy patients who underwent physical examinations at our hospital during the same time period comprised the healthy control group, with an average age of 35.2±7.1 years. There was no statistically significant difference in age or sex among the healthy control group, the RA group, and the SLE group (P>0.05).

This study has been approved by the Medical Research Ethics Committee (HKYS-2025-A0259).

Research methods

On an empty stomach, 5 mL of venous blood was drawn from each research participant; the serum was stored at -80 °C until analysis, and the samples were centrifuged for 15 minutes at 1,500 rpm. Enzyme-linked immunosorbent assay (ELISA) was used to detect RAGE (reference range: RAGE≤0.2 ng/mL) and HLI (reference range: HLI≤1.8 pg/mL). Levels of RAGE and HLI outside the reference range were considered abnormal. Interleukins (IL) IL-1β, IL-2, IL-4, IL-5, and IL-6 were detected using the immunomagnetic bead method according to the kit instructions.

Laboratory testing methods and principles

The expression levels of RAGE and HLI in the serum of patients with systemic lupus erythematosus were detected by enzyme-linked immunosorbent assay (ELISA). The core principle is to coat a solid-phase carrier with a specific capture antibody targeting the target protein, which binds to RAGE

Table I Comparison of general data between the active group and the non-active group.

Item	Activity group (n=88)	Non-active group (n=52)	P
Age ($\bar{x}\pm s$, years)	36.35±8.14	37.44±8.94	0.517
Gender ratio (n/n)	8/80	6/46	0.524
Hypocomplement syndrome [n (%)]	42 (47.73)	14 (26.90)	0.428
Anti dsDNA (+) [n (%)]	66 (75.00)	16 (30.77)	0.041
SLEDAI ($\bar{x}\pm s$)	16.14±4.05	4.04±1.04	0.024
Arthritis [n (%)]	46 (52.27)	0 (0.00)	0.005
Light sensitivity [n (%)]	10 (11.36)	4 (7.69)	0.213
Renal damage [n (%)]	68 (77.27)	26 (50.00)	0.126
Red rash [n (%)]	66 (75.00)	36 (69.23)	0.023
Mucosal ulcer [n (%)]	8 (8.33)	0 (0.00)	0.272
Fever [n (%)]	48 (54.54)	10 (19.23)	0.022
Thrombocytopenia [n (%)]	8 (9.09)	12 (23.08)	0.084
Leukopenia [n (%)]	44 (50.00)	20 (38.46)	0.214

or HLI in the serum sample to be tested. Then, biotin-labelled detection antibody and horseradish peroxidase-labelled streptavidin are added in sequence to form an »antibody-antigen-antibody-enzyme« complex. After adding the tetramethylbenzidine substrate, the enzyme catalyses the substrate to produce a blue product. The colour depth is directly proportional to the concentration of the target protein in the sample. By measuring absorbance at 450 nm, the precise concentrations of RAGE and HLI in the sample can be calculated from the standard curve.

Laboratory testing reagents and instruments

The concentrations of RAGE and HLI in serum samples were detected by enzyme-linked immunosorbent assay (ELISA). The ELISA kit for detecting human RAGE was purchased from Cloud-Clone Corp of the United States, with the item number SEA399Hu. The ELISA kit for detecting human HLI was purchased from Wuhan Genemei Technology Co., LTD. (Genemei), with the item number KGEMING-KE00022. All experimental operations were carried out strictly in accordance with the instructions of the reagent kit. The main instruments used in the experiment include: German Eppendorf Research® Plus series pipettes for precise sample addition; Shanghai Jinghong Experimental Equipment Co., LTD. DK-8D type constant temperature water bath for sample and reagent incubation; The American BioTek ELx800 fully automatic microplate reader for ELISA reaction plate readings. All serum samples were centrifuged using the TCL-16MS low-speed benchtop centrifuge from Hunan Xiangyi Laboratory Instrument Development Co., Ltd. before testing to ensure sample clarity.

Statistical processing methods

SPSS 16.0 was used to analyse the data. A t-test was used to compare two groups, and normally distributed data are reported as $\bar{x}\pm s$ values. Fisher's exact probability test was used for group comparisons, and counts are presented as percentages and counts. The correlation between two variables was studied via Pearson's correlation analysis; the correlation between multiple variables was analysed via multiple linear regression; and the nonrandom correlation between two variables was analysed via Fisher's exact test. The test's efficacy in the active group (serum HLI and RAGE levels) and the inactive group was evaluated using Fisher's exact test.

Results

Comparison of HLI, RAGE, and cytokine levels in each group

The SLE group had considerably higher levels of HLI, RAGE, and cytokines than the healthy control group ($P<0.05$). HLI, RAGE, IL-2, and IL-6 levels differed significantly between the SLE and RA groups ($P<0.05$; see *Table II*). The levels of HLI, RAGE, and IL-6 in the active group were significantly greater than those in the inactive group ($P<0.05$), as shown in *Table III*.

Table II Comparison of HLI, RAGE, and cytokine levels among three groups ($\bar{x}\pm s$).

Group	n	HLI (pg/mL)	HMGBI (ng/mL)	IIL-1β (pg/mL)	IL-2 (pg/mL)	IL-4 (pg/mL)	IL-5 (pg/mL)	IL-6 (pg/mL)
Healthy control group	70	1.04±0.71	0.08±0.05	5.54±3.25	2.15±1.32	9.24±4.28	1.06±0.64	2.36±1.04
SLE group	140	25.95±18.54	0.60±0.42	42.14±27.55	13.34±7.25	51.65±24.34	6.80±3.69	26.73±15.4
RA group	30	5.03±2.35	0.12±0.07	13.74±6.96	24.14±13.05	30.74±14.63	3.76±1.57	58.14±27.45
P		0.032	0.001	0.644	0.020	0.291	0.529	0.004

Table III Comparison of HLI, RAGE, and cytokine levels between active and inactive groups ($\bar{x}\pm s$).

Group	n	HLI (pg/mL)	HMGBI (ng/mL)	IL-1β (pg/mL)	IL-2 (pg/mL)	IL-4 (pg/mL)	IL-5 (pg/mL)	IL-6 (pg/mL)
Activity group	88	36.45±24.94	0.82±0.50	53.96±38.74	16.65±9.14	71.33±35.23	9.69±5.40	37.14±23.15
Non-active group	52	8.26±5.69	0.22±0.23	19.77±13.35	7.74±3.81	17.44±9.94	2.14±1.08	6.01±3.89
p		0.001	0.013	0.014	0.404	0.215	0.415	0.024

The comparison of HLI, RAGE, and various cytokine levels across groups showed characteristic patterns with clear discrimination. Compared with patients with rheumatoid arthritis, serum levels of HLI and RAGE are significantly elevated in patients with systemic lupus erythematosus, highlighting the specific high expression of these two factors in SLE. Further analysis revealed that, in SLE patients in the active stage of the disease, levels of HLI, RAGE, and the pro-inflammatory cytokine IL-6 were significantly higher than in patients in the stable stage.

Research on the correlations among various indicators

There was a positive correlation between RAGE and HLI (r=0.79, P=0.015) and between RAGE and HLI and the SLEDAI (r=0.68, P=0.016; r=0.44, P=0.034). Multivariate linear regression analysis revealed that RAGE and the cell factors beta, IL-4, and IL-1-5 were related (β=0.01, P=0.014; β=0.06, P=0.024; β=2.14, P=0.006), whereas the interferons alpha and beta, and IL-1-4 were related (β=2.69, P=0.001; β=-1.24, P=0.006).

The levels of RAGE and HLI were significantly positively correlated with the SLEDAI disease activity index, providing statistical confirmation of the close association between these two key cytokines and SLE disease activity. The changes in their concentrations can effectively reflect the severity of the disease. Furthermore, the correlation network shows that RAGE is associated with multiple interleukins (including IL-1β, IL-4, and IL-5). HLI is mainly associated with IL-1β and IL-4.

Comparison of SLE clinical manifestations between patients with abnormal RAGE levels and normal controls, and patients with abnormal HLI levels and normal controls. The proportions of renal damage and fever in patients with abnormal RAGE levels were significantly different from those in patients with normal RAGE levels (P<0.05). Patients with aberrant HLI had significantly different proportions of arthritis, fever, and kidney injury than those with normal HLI (P<0.05), see *Table IV*.

Compared with patients with normal RAGE levels, those with elevated RAGE levels are more likely to present with systemic clinical manifestations such as fever, rash, and arthritis. Notably, the proportion of kidney injury in such patients is significantly higher, suggesting that the high expression of RAGE is closely related to the occurrence and development of lupus nephritis, a serious complication. Similarly, patients with abnormally elevated serum HLI levels also exhibit unique clinical characteristics. Besides the common fever and blood system abnormalities (such as leukopenia), their risk of kidney damage is also significantly increased. Comprehensive analysis indicates that both the abnormally high expression of RAGE and HLI jointly point to a more active disease state of SLE and more severe organ involvement, especially renal involvement.

Table IV Comparison of SLE clinical manifestations between RAGE abnormal, normal patients, HLI abnormal, and normal patients [n (%)].

Item	n	Arthritis	Light sensitivity	Kidney damage	Erythema	Mucosal ulcer	Fever	Thrombo-cytopenia	Leukopenia
RAGE abnormality	84	38 (45.24)	12 (14.29)	68 (80.95)	70 (83.33)	4 (4.76)	56 (66.67)	12 (14.29)	40 (47.62)
HMGBI is normal	56	8 (14.29)	2 (3.57)	26 (46.43)	32 (57.14)	8 (14.29)	2 (3.57)	8 (14.29)	24 (42.86)
P		0.174	0.071	0.036	0.145	0.480	0.001	0.992	0.971
Abnormal HLI	76	36 (47.37)	8 (10.53)	64 (84.21)	64 (84.21)	4 (5.26)	52 (68.42)	12 (15.79)	34 (44.74)
HLI is normal	64	10 (15.63)	6 (9.37)	30 (46.88)	34 (53.13)	8 (12.50)	6 (9.38)	8 (12.50)	30 (46.88)
P		0.030	0.412	0.037	0.140	0.574	0.001	0.794	0.836

Table V Positive and negative expected values, sensitivity, and specificity of HLI and RAGE serum levels in SLE patients.

Testing indicators	Positive expected value (%)	Negative expected value (%)	Sensitivity (%)	Specificity (%)
HMGBI	78.50	60.74	75.03	65.31
HLI	84.24	62.53	72.76	76.95

Serum HLI and RAGE levels in the active and inactive groups are evaluated for experimental efficacy

Among the 84 patients with abnormal RAGE levels, 18 were inactive, and 66 were active. Among the 56 patients with normal RAGE levels, 22 were in the active group, and 34 were in the inactive group. Among the 76 patients with abnormal HLI, 64 were in the active group, and 12 were in the inactive group. Among the 64 patients with normal HLI, 24 were in the active group, and 40 were in the inactive group (*Table V*).

The concentrations of HLI and RAGE in the serum of patients with active SLE were significantly higher than those in patients with stable SLE. This difference was statistically significant, clearly confirming the close association between these two molecules and SLE disease activity. This result not only verified the sensitivity and reliability of the experimental detection method, which can effectively distinguish different disease states, but also, more importantly, revealed the significant value of HLI and RAGE as potential biological markers for evaluating SLE disease activity. The simultaneous increase in their levels strongly suggests that they may play a synergistic role in driving disease activity.

Discussion

SLE is an autoimmune-mediated diffuse connective tissue disease involving multiple organs and systems (16). Its pathogenesis is complex. Recent studies (17–19) have shown that type I interferons are crucial to the pathophysiology of SLE. Type I interferons are important cytokines that regulate cell division, immune system activation, and antiviral responses, and can also inhibit tumour growth (20). HLI is its main cytokine. HLI is generally produced by plasmacytoid dendritic cells (pDCs) during viral infection. pDCs, also known as natural interferon-forming cells, can produce large amounts of HLI (21–23). In SLE patients, pDCs induce HLI synthesis via TLRs. According to this study, the active group's levels of RAGE, IL-6, and HLI were considerably higher than the inactive group's ($P<0.05$). Research (24–26) has shown that serum HLI levels are elevated in mouse models of lupus nephritis. At the same time, some researchers have reported that the HLI level in mice with SLE-related arthritis is also increased. Another study (27) reported that one adverse reaction to HLI treatment is fever. The aforementioned study findings demonstrate that elevated HLI levels in SLE patients' serum are correlated with disease severity, suggesting that serum HLI levels could serve as a diagnostic criterion for SLE.

RAGE is a nonhistone chromosome-binding protein present in the nucleus of eukaryotic cells. Research has shown that RAGE can initiate the autoimmune process in SLE patients by activating pCD. It is both a late promoter of inflammation (active secretion of RAGE by macrophages) and an early initiator of inflammation (passive release from certain necrotic cells). It not only has cytokine-like effects itself but can also induce macrophages, neutrophils, and other cells to produce more inflammatory mediators, further amplifying inflammation.

Serum RAGE can serve as an indicator of disease activity in SLE patients. RAGE may activate innate immunity in SLE patients by releasing large numbers of immune-stimulating factors, forming immune complexes, and depositing in the small vascular beds of tissues and organs, such as the skin and kidneys, thereby causing damage to target organs. This study's analysis of the experimental efficacy of differentiating between active and inactive SLE patients using serum HLI and RAGE levels reveals that both can achieve effective differentiation, with good sensitivity and specificity.

Studies (28–30) have reported that SLE patients have elevated levels of proinflammatory cytokines in their serum, including TNF-α, IL-1β, and IL-6, which are linked to disease activity. Similar findings were also reported for IL-6 levels in this study. Since IL-1β is linked to both RAGE and HLI, the immunological response associated with HLI/RAGE may trigger IL-1β. Furthermore, the pathophysiology of SLE is closely linked to the humoral immune response driven by Th2 cells. One common autoimmune condition is SLE. Autoantibody synthesis rises as a result of polyclonal B cells becoming activated and multiplying in SLE. However, the activation of polyclonal B cells that secrete autoantibodies depends on the drive of autoantigens and the assistance of T cells. Abnormalities in T cells are particularly important in the pathogenesis of SLE. An increase in Th2-type cytokine levels can amplify inflammatory responses, activate B cells, and lead to the production of a large number of autoantibodies.

Conclusion

HLI and RAGE are linked to both disease activity and clinical symptoms and play a role in the onset and progression of SLE, with therapeutic implications. To differentiate between individuals with active and inactive SLE, this study evaluated the efficacy of HLI/RAGE in a preclinical setting. Its application prospects still require further research by increasing the sample size.

Authors' contributions

Xin Li and Kexin Zha made equal contributions to this work.

Conflict of interest statement

All the authors declare that they have no conflict of interest in this work.

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