

系统性红斑狼疮患者血清白细胞介素-2受体 α 水平及其临床意义

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[摘 要] **目的:** 探究系统性红斑狼疮(systemic lupus erythematosus, SLE)患者血清中白细胞介素-2受体 α (interleukin-2 receptor α , IL-2R α)水平在临床中的意义。**方法:** 收集2019年1月至2020年12月就诊于北京大学人民医院的107例SLE患者病历资料,依据SLE疾病活动度指数(SLE disease activity index 2000, SLEDAI-2K)评估患者的病情活动情况,并选取年龄、性别分别匹配的39例健康人作为健康对照。采用酶联免疫吸附法测定SLE患者组和健康对照组的血清IL-2R α 水平,比较其差异并分析SLE患者IL-2R α 水平与临床指标及实验室指标的相关性。采用 t 检验或Mann-Whitney U 检验、 χ^2 检验和Spearman秩相关性分析进行统计学分析。**结果:** SLE患者血清IL-2R α 水平[830.82(104.2~8940.48) ng/L]较健康对照组[505.1(78.65~1711.52) ng/L]明显升高($P < 0.001$)。相关性分析显示,血清IL-2R α 水平与SLEDAI-2K评分及抗核小体抗体滴度呈正相关($r = 0.357, P < 0.001; r = 0.25, P = 0.027$)。107例SLE患者中36例(33.6%)合并狼疮性肾炎,合并狼疮性肾炎的患者血清IL-2R α 水平[1102.14(126.52~8940.48) ng/L]较未合并狼疮性肾炎患者[743.89(104.19~4872.06) ng/L]明显升高($P = 0.032$)。高IL-2R α 水平组合并狼疮性肾炎者(40.8%)较低水平组(19.4%)明显升高($P = 0.031$),高IL-2R α 水平组SLEDAI-2K评分更高[10(3~21) vs. 7(3~16), $P = 0.001$]。SLE患者常规治疗12周后血清IL-2R α 水平[1119.1(372.25~2608.86) ng/L]随病情改善较基线时[1556.73(373.08~8940.48) ng/L]明显下降($P = 0.042$)。**结论:** 血清IL-2R α 可作为SLE病情活动评估指标,与肾脏受累有一定相关性。

[关键词] 受体, 白细胞介素-2; 红斑狼疮, 系统性; 狼疮肾炎; T淋巴细胞

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Serum interleukin-2 receptor α as a clinical biomarker in patients with systemic lupus erythematosus

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ABSTRACT Objective: To investigate the clinical relevance of serum interleukin-2 receptor α (IL-2R α) in patients with systemic lupus erythematosus (SLE). **Methods:** One hundred and seven SLE patients and 39 healthy controls with comparable age and gender were recruited at Peking University People's Hospital from January 2019 to December 2020. Complete clinical data in 107 SLE patients at baseline and follow-up were collected. SLE disease activity index 2000 (SLEDAI-2K) was used to assess the disease activity of the SLE patients. The serum level of IL-2R α in the SLE patients and healthy controls was measured using enzyme-linked immunosorbent assay (ELISA). The association between serum IL-2R α and clinical and laboratory parameters was investigated. Mann-Whitney U test or t test, Chi-square test and Spearman correlation were used for statistical analysis. **Results:** The serum IL-2R α levels were significantly higher in the SLE patients [830.82 (104.2 – 8940.48) ng/L], compared with those in the healthy controls [505.1 (78.65 – 1711.52) ng/L] ($P < 0.001$). Association analysis showed that the increased serum IL-2R α was positively associated with SLEDAI-2K scores and anti-nucleosome antibody ($r = 0.357, P < 0.001; r = 0.25, P = 0.027$, respectively). Thirty-six of 107 (33.6%) SLE patients had lupus nephritis. Serum IL-2R α levels were significantly higher in the patients accompanied with lupus nephritis [1102.14 (126.52 – 8940.48) ng/L] than in the patients without lupus nephritis [743.89 (104.19 – 4872.06) ng/L] ($P = 0.032$). The patients in the high IL-2R α group had more lupus nephritis compared with those in the low IL-2R α group (40.8% vs. 19.4%, $P = 0.031$). Meanwhile, SLEDAI-2K scores were found significantly higher in the high IL-2R α group than in the low IL-

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2R α group [10 (3-21) vs. 7 (3-16), $P=0.001$]. With the improvement of disease activity in the SLE patients after conventional treatments, serum levels of IL-2R α [1 119.1 (372.25-2 608.86) ng/L] in the week 12 decreased significantly compared with the baseline [1 556.73 (373.08-8 940.48) ng/L] ($P=0.042$). **Conclusion:** Serum IL-2R α may be used as a biomarker of disease activity in patients with SLE. There is certain correlation between serum IL-2R α and renal involvement in SLE.

KEY WORDS Receptor, interleukin-2; Lupus erythematosus, systemic; Lupus nephritis; T-lymphocytes

系统性红斑狼疮(systemic lupus erythematosus, SLE)是一种累及全身多系统的自身免疫性疾病,发病机制复杂,其中T细胞和B细胞的过度活化及细胞因子的失衡在SLE发病中发挥重要作用^[1]。白细胞介素-2(interleukin-2, IL-2)是一种具有多向性作用的T细胞生长因子^[2],新近的研究发现,低剂量IL-2治疗SLE是极具前景的免疫治疗新方法^[3-4]。IL-2受体(IL-2 receptor, IL-2R)由3个不同的亚基组成,分别为 α 链(即CD25)、 β 链(即CD122)和 γ 链(即CD132)。血清IL-2R α ,又称可溶性CD25(soluble CD25, sCD25),是由膜IL-2R α 蛋白水解产生的^[5],研究发现血清IL-2R α 是T细胞活化的标志^[6-8]。本研究旨在检测SLE患者血清IL-2R α 水平,并评估其与临床的相关性,为SLE患者的病情评估寻找新的监测指标。

1 资料与方法

1.1 研究对象

选取2019年1月至2020年12月就诊于北京大学人民医院风湿免疫科的SLE患者107例,临床资料及辅助检查资料完整。所有患者符合1997年美国风湿病学SLE分类标准^[9],并排除合并明确诊断了其他自身免疫性疾病、慢性感染和炎症疾病的患者。同时选取39例年龄及性别分别匹配的本科室在职员工作为健康对照组,均无风湿免疫病相关临床表现或家族史。本研究获得北京大学人民医院伦理委员会批准,所有研究对象(包括患者和健康人)均已签署知情同意书。

1.2 临床和实验室相关指标

收集患者临床资料(包括性别、年龄、病程、各器官系统受累情况等)和实验室检查资料(血常规、自身抗体谱、免疫球蛋白、补体、红细胞沉降率、C反应蛋白、尿蛋白等),同时进行SLE疾病活动指数(SLE disease activity index 2000, SLEDAI-2K)评估,其中0~4分定义为基本无活动,5~9分定义为轻度活动,10~14分定义为中度活动, ≥ 15 分定义为重度活动^[10]。

1.3 酶联免疫吸附法检测血清IL-2R α 水平

严格按照R&D公司试剂盒说明书用酶联免疫

吸附法(enzyme-linked immunosorbent assay, ELISA)检测血清中IL-2R α 。

1.4 统计学处理

采用SPSS 24.0统计软件进行统计学分析。符合正态分布的计量资料采用均数 \pm 标准差表示,非正态分布的计量资料以中位数(范围)表示,计数资料用百分数表示。计量资料采用 t 检验或者Mann-Whitney U 检验,计数资料组采用 χ^2 检验,相关性采用Spearman秩相关分析。以 $P < 0.05$ 为差异有统计学意义。

2 结果

2.1 患者一般资料及血清IL-2R α 水平检测

研究共纳入107例SLE患者,其中女性100例(93.5%),男性7例(6.5%),中位年龄29(18~66)岁,病程2(0.1~23)年。健康对照39例,其中女性37例(94.9%),男性2例(5.1%),年龄28(23~60)岁,与SLE组在性别、年龄上差异无统计学意义($P > 0.05$)。SLE患者组血清IL-2R α 水平明显高于健康对照组[830.82(104.2~8 940.48) ng/L vs. 505.1(78.65~1 711.52) ng/L, $P < 0.001$,图1A]。

2.2 血清IL-2R α 水平与病情活动及血清学指标的相关性

SLE患者组SLEDAI-2K评分9(0~24)分,其中基本无活动者23例(21.5%),血清IL-2R α 水平313.09(123.76~2 441.96) ng/L;轻度活动者34例(31.8%),血清IL-2R α 水平722.83(104.19~4 872.06) ng/L;中度活动者34例(31.8%),血清IL-2R α 水平994.08(223.31~8 856.53) ng/L;重度活动者16例(15%),血清IL-2R α 水平1 374.94(184.76~8 940.48) ng/L。SLE病情活动者(≥ 5 分)血清IL-2R α 水平较无活动者(0~4分)明显升高[883.15(104.19~8 940.48) ng/L vs. 313.09(123.76~2 441.96) ng/L, $P = 0.027$]。相关性分析显示,血清IL-2R α 水平与SLEDAI-2K评分及抗核小体抗体(anti-nucleosome antibodies, AnuA)呈正相关($r = 0.357, P < 0.001; r = 0.25, P = 0.027$;图1B和1C),但与免疫球蛋白、补体C3及C4、抗双链

DNA(anti-double-stranded DNA, dsDNA)抗体水平的相关性差异无统计学意义($P > 0.05$)。

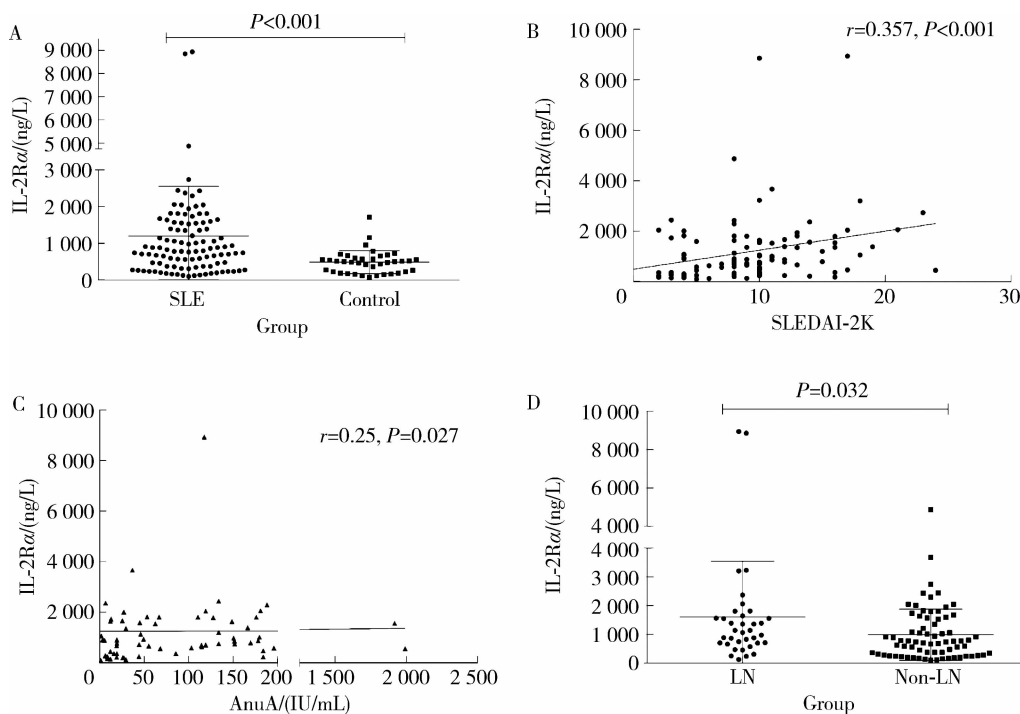
2.3 血清 IL-2R α 水平与 SLE 系统受累的相关性

107 例 SLE 患者中有 36 例(33.6%)合并狼疮性肾炎(lupus nephritis, LN),其血清 IL-2R α 水平较未合并 LN 患者明显升高[1 102.14(126.52 ~ 8 940.48) ng/L vs. 743.89(104.19 ~ 4 872.06) ng/L, $P = 0.032$, 图 1D]。根据健康对照组 95% 置信区间计算,将 SLE 患者血清 IL-2R α 水平等于或高于正常上限(590.48 ng/L)定义为高水平组(71 例, 66.4%),低于该水平定义为低水平组(36 例,

33.6%),两组间年龄、性别和病程差异无统计学意义($P > 0.05$, 表 1),高水平组合并 LN 者明显多于低水平组[29 例(40.8%) vs. 7 例(19.4%), $P = 0.031$],高水平组 SLEDAI-2K 更高($P = 0.001$, 表 1)。

2.4 血清 IL-2R α 水平治疗前后的变化

107 例 SLE 患者中 39 例完成 12 周治疗随访,常规治疗 12 周后血清 IL-2R α 水平较基线时明显下降[1 119.1(372.25 ~ 2 608.86) ng/L vs. 1 556.73(373.08 ~ 8 940.48) ng/L, $P = 0.042$, 图 2A],同时 SLEDAI-2K 评分也较基线时明显改善[4(0 ~ 12) vs. 11(8 ~ 23), $P < 0.001$, 图 2B]。



IL-2R α , interleukin-2 receptor α ; SLE, systemic lupus erythematosus; SLEDAI-2K, SLE disease activity index 2000; AnuA, anti-nucleosome antibody; LN, lupus nephritis. A, serum IL-2R α level in SLE group was significantly higher than that in control group; B, serum IL-2R α level was positively correlated with SLEDAI-2K score; C, serum IL-2R α level was positively correlated with AnuA titer; D, serum IL-2R α levels in SLE patients with LN were significantly higher than those without LN.

图 1 血清 IL-2R α 水平与临床相关性

Figure 1 Correlation between serum IL-2R α level and clinical significance

3 讨论

SLE 具有多器官受累、病情复杂及容易复发等特点,评估疾病病情活动对指导临床治疗至关重要,目前临床多采用结合临床表现、血清学免疫指标检测等手段综合评估^[11]。但由于 SLE 临床表现的复杂性,临床病情评估及监测方面仍存在不足,寻求评估病情活动或器官受累情况的新标志物具有重要临床意义。

本研究发现,血清 IL-2R α 水平与 SLEDAI-2K 评分呈正相关,且伴有脏器受累,如狼疮性肾炎的

SLE 患者中 IL-2R α 水平升高更为显著,进一步分析发现血清 IL-2R α 水平与血清 AnuA 滴度呈正相关,这些结果提示血清 IL-2R α 水平与 SLE 疾病活动度密切相关,可作为评估 SLE 活动的客观指标,其升高可能预示患者肾脏受累的风险。血清 IL-2R α 水平是 T 细胞活化的标志^[6-8],但血清 IL-2R α 的生物学相关性以及其对 T 细胞功能的影响仍不明确。动物研究发现,尽管血清 IL-2R α 不与 T 细胞表面结合,但可与分泌的 IL-2 竞争性特异性结合,从而造成 T 细胞的失衡^[12]。IL-2 是调节性 T 细胞(regular T cell, Treg)分化发育的重要细胞因子,SLE 中 IL-2

水平的下降造成调节免疫耐受的 Treg 细胞功能障碍,是 SLE 重要的发病机制之一^[13-14]。同样,SLE 患者血清中升高的 IL-2R α 通过竞争性抑制 IL-2 与 Treg 细胞表面 IL-2R α 结合可导致 Treg 细胞功能障碍,可能参与了 SLE 的发病过程。考虑到疾病活动

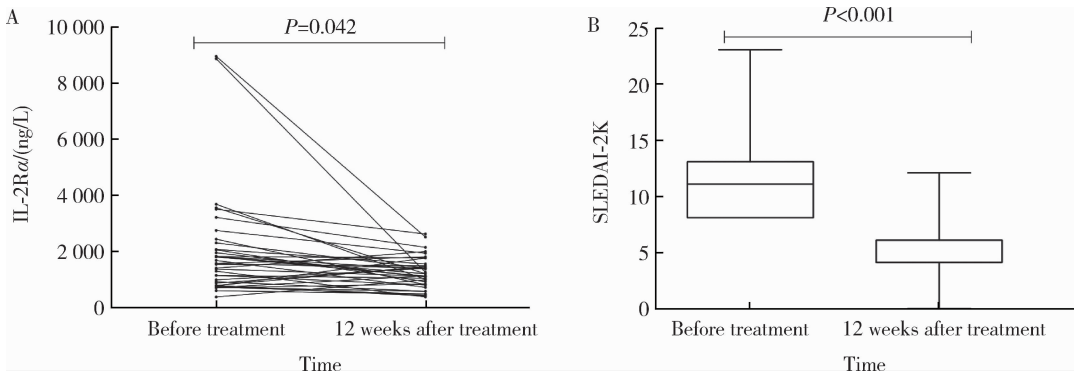
期 SLE 患者血清 IL-2R α 水平升高,外源性的低剂量 IL-2 治疗可能重建调节性 T 细胞和效应性 T 细胞之间的免疫平衡,从而达到治疗目的。最近的研究表明,低剂量 IL-2 治疗 SLE 是极具前景的免疫治疗新方法^[3-4]。

表 1 IL-2R α 高水平组 (≥ 590.48 ng/L)与低水平组 (< 590.48 ng/L)对比

Table 1 Comparison between high IL-2R α group (≥ 590.48 ng/L) and low IL-2R α group (< 590.48 ng/L)

| Items | High IL-2R α (n = 71) | Low IL-2R α (n = 36) | P value |
|------------------------------------|------------------------------|-----------------------------|---------|
| Gender, Female/Male | 6/65 | 1/35 | 0.419 |
| Age/year, median (range) | 31 (18 - 66) | 36 (29 - 52) | 0.741 |
| Duration/year, median (range) | 2.0 (0.1 - 23.0) | 2.0 (0.2 - 12.0) | 0.355 |
| LN, n (%) | 29 (40.8) | 7 (19.4) | 0.031 |
| SLEDAI-2K, median (range) | 10 (3 - 21) | 7 (3 - 16) | 0.001 |
| IgG/(g/L), median (range) | 13.7 (1.9 - 35.9) | 16.55 (8.2 - 29.9) | 0.862 |
| C3/(g/L), median (range) | 0.453 (0.118 - 1.46) | 0.656 (0.239 - 0.821) | 0.685 |
| C4/(g/L), median (range) | 0.117 (0.04 - 0.544) | 0.097 (0.032 - 0.227) | 0.627 |
| Anti-dsDNA/(IU/mL), median (range) | 223.98 (25 - 1 845.6) | 277.12 (20 - 1 665.8) | 0.375 |
| AnuA/(IU/mL), median (range) | 133.87 (2 - 1 918.3) | 85.72 (2 - 1 991.9) | 0.197 |
| ESR/(mm/h), median (range) | 31 (6 - 110) | 40 (11 - 42) | 0.786 |
| CRP/(mg/dL), median (range) | 4.65 (1.05 - 93.2) | 2.49 (1.03 - 10.8) | 0.952 |

IL-2R α , interleukin-2 receptor α ; LN, lupus nephritis; Anti-dsDNA, anti-double-stranded DNA antibody; SLEDAI-2K, systemic lupus erythematosus disease activity index 2000; IgG, immunoglobulin G; C3, complement 3, C4, complement 4; AnuA, anti-nucleosome antibodies; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.



Abbreviations as in Figure 1. A, the serum IL-2R α level in SLE patients decreased significantly after 12 weeks; B, SLEDAI-2K improved significantly after 12 weeks.

图 2 血清 IL-2R α 水平及 SLEDAI-2K 在 SLE 治疗前后的变化

Figure 2 Changes of serum IL-2R α level and SLEDAI-2K before and after treatment in SLE

LN 是 SLE 最常见的器官受累表现,是 SLE 患者常见的死亡原因之一。肾损伤预测指标的监测有助于临床早诊断、早治疗,改善临床预后。本研究表明,SLE 合并 LN 患者血清 IL-2R α 水平较未合并 LN 者明显升高,提示血清 IL-2R α 可能能够作为一个有助于肾脏损伤预测的指标之一。有研究发现血清 IL-2R α 水平在增殖性 LN 患者较非增殖性 LN 患者

明显升高,且与组织学疾病慢性活动指数相关^[8, 15],这与我们的研究结果一致,提示了 LN 患者中长期的慢性炎症状态。

在 SLE 患者漫长的病程中,评估其疾病活动情况往往既依赖于临床表现,又依赖于自身抗体(如 AnuA、抗 dsDNA 抗体)的滴度。当这些自身抗体为阴性时,如何评估 SLE 患者的疾病严重程度将会面

临挑战。本研究发现血清 IL-2R α 水平与 AnuA 滴度相关,与抗 dsDNA 抗体相关性无统计学差异。但临床上 AnuA 及抗 dsDNA 滴度与病情活动相关,血清 IL-2R α 水平可能为 SLE 疾病活动和自身抗体阴性 SLE 患者的疾病活动度提供重要参考信息,这仍需要将来进行大样本研究以证实。

综上所述,SLE 患者血清 IL-2R α 水平明显升高,与 SLEDAI-2K 呈正相关,可作为评估 SLE 疾病活动的客观指标,且伴有 LN 者 IL-2R α 升高更显著,提示血清 IL-2R α 可能能够作为一个有助于肾脏损伤预测的指标之一。

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