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$CD4^+/CD8^+$ 比值异常系统性红斑狼疮患者 PD–L1 和 IFN–α 血清水平检测及其临床意义

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[摘　要]　**目的：**通过检测$CD4^+/CD8^+$比值异常的系统性红斑狼疮(systemic lupus erythematosus，SLE)患者血清程序性凋亡受体配体1(programmed cell death ligand 1，PD-L1)和α-干扰素(interferon-α，IFN-α)水平，探讨PD-L1和IFN-α与SLE患者$CD4^+/CD8^+$比值异常的关系。**方法：**73例SLE患者以$CD4^+/CD8^+$参考范围(1.5~2.5)为标准，分为$CD4^+/CD8^+$倒置组(29例)，$CD4^+/CD8^+$升高组(17)例，$CD4^+/CD8^+$正常组(27例)，另选取20位健康体检者为健康对照组；采用流式细胞术检测SLE患者$CD3^+CD4^+$和$CD3^+CD8^+$T细胞，ELISA法检测血清PD-L1，IFN-α和抗dsDNA抗体水平，分析PD-L1，IFN-α与抗dsDNA抗体的相关性。**结果：**$CD4^+/CD8^+$倒置和升高组补体C3和C4水平显著低于其余二组(均$P<0.01$)。$CD4^+/CD8^+$倒置和升高组C-反应蛋白(C-reactive protein，CRP)水平显著高于正常组和健康组(均$P<0.01$)，而升高组CRP水平显著高于倒置组($P<0.01$)。$CD4^+/CD8^+$倒置及升高组SLE患者抗dsDNA抗体滴度、SLE疾病活动度评分(SLE disease activity index，SLEDAI)明显高于正常和健康组(均$P<0.01$)。$CD4^+/CD8^+$倒置和升高组PD-L1，IFN-α水平均显著高于健康组(均$P<0.05$)；倒置组PD-L1，IFN-α水平均显著高于正常组，而升高组IFN-α与正常组差异无统计学意义($P>0.05$)。$CD4^+/CD8^+$倒置和升高组SLE患者血清PD-L1和IFN-α均与抗dsDNA抗体滴度成正相关(均$P<0.01$)。$CD4^+/CD8^+$异常组SLE患者病原体感染率显著高于其余二组(均$P<0.01$)。**结论：**病原体感染是SLE患者$CD4^+/CD8^+$比值异常的直接原因，$CD4^+/CD8^+$异常SLE患者血清PD-L1和IFN-α水平均升高且与抗dsDNA抗体呈正相关，提示PD-L1和IFN-α调节T细胞活化共同参与免疫过程。

[关键词]　系统性红斑狼疮；$CD4^+/CD8^+$异常；程序性凋亡受体配体1；α-干扰素

Detection of serum PD-L1 and IFN-α levels and its clinical significance in patients with systemic lupus erythematosus with abnormal $CD4^+/CD8^+$ ratio

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Abstract **Objective:** To discuss the relationship between serum level of programmed cell death 1 ligand 1 (PD-L1), interferon-α (IFN-α) and abnormal ratio of $CD4^+/CD8^+$ ratio in patients with systemic lupus erythematosus (SLE). **Methods:** A total of 73 cases of SLE patients were divided into $CD4^+/CD8^+$ inversion, $CD4^+/CD8^+$elevated, $CD4^+/CD8^+$ normal group, and the cases were 29, 17, 27 respectively; moreover, 20 healthy persons were collected as the control group. $CD3^+CD4^+$and $CD3^+CD8^+$T cells in SLE patients were detected by flow cytometry. The serum levels of PD-L1, IFN-α and anti-dsDNA antibodies were detected by ELISA, and the correlation between PD-L1, IFN-α and anti dsDNA antibody was analyzed. **Results:** The serum levels of complement C3 and C4 in $CD4^+/CD8^+$ inversion and elevated group were significantly lower than the other two groups (all $P<0.01$). The serum levels of C-reactive protein (CRP) in the inversion and uprising groups were significantly higher than healthy and normal group ($P<0.05$), and the inversion group was significantly lower than the uprising group ($P<0.05$). The titers of anti-dsDNA antibody and SLE disease activity index (SLEDAI) in $CD4^+/CD8^+$ inversion and elevation SLE patients were significantly higher than the healthy and normal groups (all $P<0.05$). The serum levels of PD-L1 and INF-α in $CD4^+/CD8^+$ inversion and the uprising group were significantly higher than the healthy control group ($P<0.05$). PD-L1 and INF-α serum levels in the $CD4^+/CD8^+$ inversion group were significantly higher than the normal group ($P<0.01$), but INF-α serum level in the uprising group had no statistical significance compared with the normal group ($P>0.05$). PD-L1 and IFN-α serum levels were positively correlated with anti dsDNA antibody titers in $CD4^+/CD8^+$ inversion and elevated SLE patients (all $P<0.01$). The infection rates of SLE in $CD4^+/CD8^+$ abnormal group were significantly higher than other two groups (all $P<0.01$). **Conclusion:** The pathogen infection is the direct cause of the abnormal $CD4^+/CD8^+$ ratio in SLE patients. PD-L1 and IFN-α serum levels in $CD4^+/CD8^+$ abnormal group were elevated and positively correlated with anti dsDNA antibody, suggesting that PD-L1 and IFN-α could regulate the activation of T cells and participate in the immune process together.

Keywords systemic lupus erythematosus; $CD4^+/CD8^+$ abnormal; programmed cell death 1 ligand 1; interferon-α

系统性红斑狼疮(systemic lupus erythematosus，SLE)是一种以体内高滴度的自身抗体为特征的自身免疫慢性炎症性疾病。T淋巴细胞、B淋巴细胞异常活化和免疫功能紊乱是导致病理性自身抗体产生的主要原因[1]。SLE患者T淋巴细胞异常主要表现为细胞抗原分子表达失调、信号转道和基因转录发生错误，而这些异常是体外病原体以及外周循环微环境共同作用的结果[2]。循环微环境包括各种负向共刺激分子和细胞因子，例如程序性凋亡受体1(programmed cell death 1，PD-1)/程序性凋亡受体配体1(programmed cell death 1 ligand 1，PD-L1)、干扰素(interferon，INF)等炎症因子。$CD3^+CD4^+$和$CD3^+CD8^+$T淋巴细胞在行使免疫功能的时扮演重要角色，$CD4^+/CD8^+$比值异常在SLE患者中较常见，但其具体原因尚不明确。本研究检测并比较分析$CD4^+/CD8^+$倒置、$CD4^+/CD8^+$升高、$CD4^+/CD8^+$正常SLE患者和健康对照组可溶性血清PD-L1和IFN-α水平，分析各组血清PD-L1和IFN-α水平与抗dsDNA抗体滴度的相关性，旨在探讨PD-L1和IFN-α与SLE患者$CD4^+/CD8^+$比值异常的关系。

1 对象与方法

1.1 对象

选取2016年1月至2017年12月在萍乡市人民医院风湿免疫科就诊的SLE患者73例，均为女性，年龄(40.8±16.5)岁。患者均符合美国类风湿病学会1997年修订的SLE诊断标准[3]，活动性判定以SLE疾病活动度评分(SLE disease activity index，SLEDAI)-2000为标准[4]。根据SLE患者T淋巴亚群检测结果，以$CD4^+/CD8^+$比值参考范围(1.5~2.5)为标准，73例SLE患者分为$CD4^+/CD8^+$倒置组(29例)，$CD4^+/CD8^+$正常组(27例)，$CD4^+/CD8^+$升高组(17例)。同时选取20位健康人作为健康对照组，为萍乡市人民医院体检中心体检人员，均为女性，年龄(35±5.2)岁，均无既往病史。收集SLE患者补体C3，C4，C-反应蛋白(C-reactive protein，CRP)，病毒DNA和细菌培

养等实验室检查结果。本研究经萍乡市人民医院医学伦理委员会审核批准，患者均签署知情同意书。

1.2 方法

分别用乙二胺四乙酸(EDTA)抗凝管和普通生化管采集SLE患者及正常对照组外周静脉血2 mL。普通生化管血液标本经离心，分离获取血清，−80 ℃保存备检。EDTA抗凝全血标本抽完后立即做T淋巴细胞亚群检测。取50 μL全血，分别加入5 μL CD3-PC5，CD4-PE，CD8-ECD和CD45-FITC单克隆抗体，震荡混匀后常温避光孵育20 min，加300 μL红细胞裂解液，孵育10 min，加入1.5 mL磷酸缓冲盐溶液(phosphate buffer saline，PBS)洗涤1次，1 000 r/min，离心5 min，弃上清，加入500 μL PBS，震荡混匀后上机，上机前，用标准荧光微球对仪器进行校准。采用贝克曼库尔特Cytomics™ FC 500五色流式细胞仪检测分析，试剂均购自美国贝克曼库尔特公司。PD-L1和IFN-α采用ELISA法，试剂购自R&D System China公司。抗dsDNA抗体采用ELISA法，试剂购自欧蒙医学诊断(中国)有限公司。操作均严格按照说明书进行。

1.3 统计学处理

计量资料以均数±标准差($\bar{x}\pm s$)表示，用GraphPad prism5.0软件进行t检验和Spearman相关性分析，P<0.05为差异有统计学意义。

2 结果

2.1 SLE 患者血清疾病活动性指标的检测

CD4+/CD8+倒置和升高组SLE患者补体C3，C4水平显著低于其余2组(均P<0.01)；CD4+/CD8+倒置组CRP水平显著高于健康组(P<0.01)，但显著低于CD4+/CD8+升高组(P<0.01)，CD4+/CD8+升高组CRP水平显著高于其余3组(均P<0.01)；CD4+/CD8+倒置及CD4+/CD8+升高组抗dsDNA抗体滴度、SLEDAI明显高于健康组和CD4+/CD8+正常组(均P<0.01，表1)。

2.2 SLE 患者血清可溶性 PD-L1 和 IFN-α 的检测

CD4+/CD8+倒置、升高组血清PD-L1水平分别为(2.71±0.87) ng/mL和(2.66±0.89) ng/mL，均显著高于正常组[(1.19±0.30) ng/mL]和健康组[(0.36±0.15) ng/mL；均P<0.05]，CD4+/CD8+正常组显著高于健康组(P<0.05)，而CD4+/CD8+倒置组和升高组之间差异无统计学意义(P>0.05，图1A)。CD4+/CD8+倒置组血清IFN-α水平[(5.04±1.52) pg/mL]显著高于CD4+/CD8+正常组[(2.77±0.89) pg/mL]和健康组[(0.87±0.30) pg/mL；均P<0.05]，且CD4+/CD8+倒置组血清IFN-α水平显著高于CD4+/CD8+升高组[(2.64±0.87) pg/mL；P<0.05]，正常组[(2.77±0.89) pg/mL]显著高于健康组[(0.87±0.30) pg/mL；P<0.05，图1B]。

2.3 各组PD-L1和IFN-α与抗dsDNA抗体的相关性

在CD4+/CD8+倒置和升高组中，血清PD-L1和IFN-α均与抗dsDNA抗体滴度呈正相关(均P<0.01，图2A，2B)。在CD4+/CD8+正常组中，血清PD-L1与抗dsDNA抗体滴度呈正相关(P<0.05)，IFN-α与抗dsDNA抗体无相关性(图2C)。在健康组中，PD-L1和IFN-α与抗dsDNA抗体均无相关性(图2D)。

表1 各组SLE患者疾病活动性指标水平

Table 1 Serum level in disease activity index of SLE patients of each group

组别	C3/(g·L^{-1})	C4/(g·L^{-1})	CRP/(mg·dL^{-1})	Anti-dsDNA/(IU·mL^{-1})	SLEDAI
CD4+/CD8+倒置组	0.65 ± 0.22*	0.11 ± 0.05*	13.23 ± 4.57*	82.55 ± 22.52*	15.2 ± 3.8*
CD4+/CD8+升高组	0.69 ± 0.39*	0.10 ± 0.07*	45.34 ± 24.03*	63.12 ± 28.47*	14.8 ± 3.4*
CD4+/CD8+正常组	0.97 ± 0.34	0.17 ± 0.08	10.17 ± 4.26	34.77 ± 26.03	5.1 ± 2.1
健康对照组	1.33 ± 0.19	0.26 ± 0.09	2.71 ± 2.06	9.99 ± 2.57	—

与CD4+/CD8+正常组和健康对照组相比，*P<0.05。

Compared with the CD4+/CD8+ normal and healthy control group, *P<0.05.

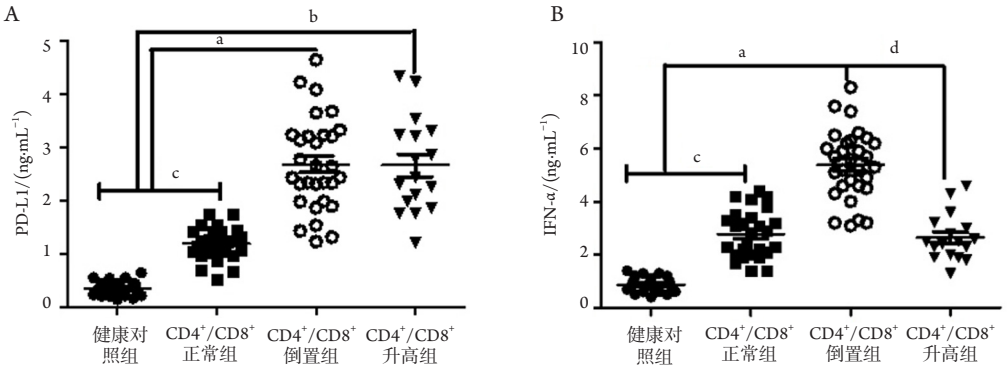

图1 各组SLE患者及健康对照组血清PD-L1和IFN-α水平

Figure 1 Serum PD-L1 and IFN- α levels in SLE patients and healthy controls

(A)各组SLE患者及健康对照组血清PD-L1水平；(B)各组SLE患者及健康对照组血清IFN-α水平。$CD4^+/CD8^+$倒置组与健康对照组和$CD4^+/CD8^+$正常组相比，$^aP<0.05$；$CD4^+/CD8^+$升高组与健康对照组和$CD4^+/CD8^+$正常组相比，$^bP<0.05$；$CD4^+/CD8^+$正常组与健康对照组相比，$^cP<0.05$；$CD4^+/CD8^+$倒置组与$CD4^+/CD8^+$升高组相比，$^dP<0.05$。

(A) Serum PD-L1 and IFN-α levels in SLE patients; (B) Serum PD-L1 and IFN-α levels in healthy controls. $CD4^+/CD8^+$ inversion group vs healthy control and $CD4^+/CD8^+$normal group, $^aP<0.05$; $CD4^+/CD8^+$ uprise group vs healthy control and $CD4^+/CD8^+$normal group, $^bP<0.05$; $CD4^+/CD8^+$normal group vs healthy control, $^cP<0.05$; $CD4^+/CD8^+$ inversion group vs $CD4^+/CD8^+$ uprise group, $^dP<0.05$.

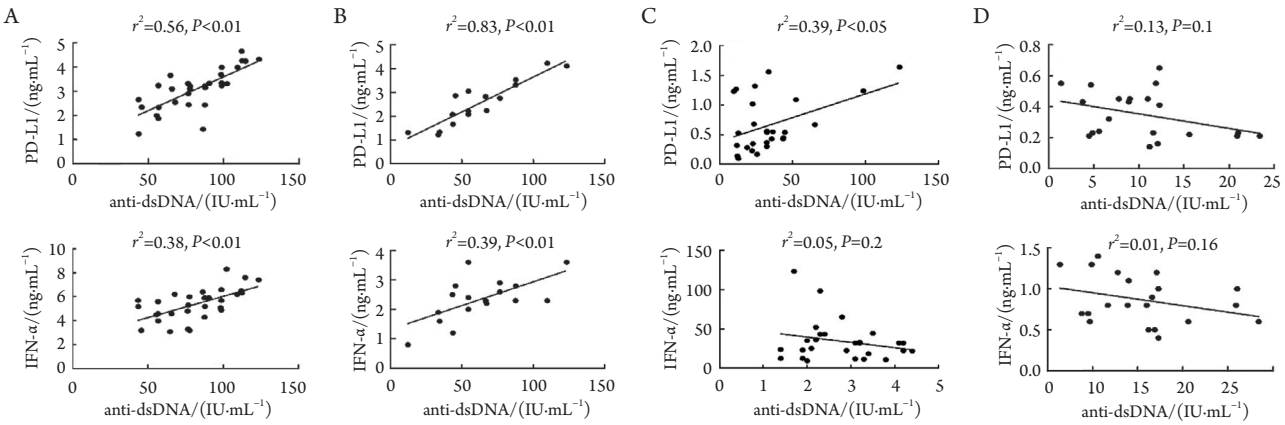

图2 观察组和健康组PD-L1和IFN-α与抗dsDNA抗体的相关性

Figure 2 Correlation between PD-L1, IFN-α and anti dsDNA antibody in observation group and healthy group

(A)$CD4^+/CD8^+$倒置组PD-L1和IFN-α与抗dsDNA抗体的相关性分析；(B)$CD4^+/CD8^+$升高组PD-L1和IFN-α与抗dsDNA抗体的相关性分析；(C)$CD4^+/CD8^+$正常组PD-L1和IFN-α与抗dsDNA抗体的相关性分析；(D)健康对照组PD-L1和IFN-α与抗dsDNA抗体的相关性分析。

(A) Correlation between PD-L1, IFN-α and anti-dsDNA antibody in $CD4^+/CD8^+$ inversion group; (B) Correlation between PD-L1, IFN-α and anti-dsDNA antibody in $CD4^+/CD8^+$ uprising group; (C) Correlation between PD-L1, IFN-α and anti-dsDNA antibody in $CD4^+/CD8^+$ normal group; (D) Correlation between PD-L1, IFN-α and anti-dsDNA antibody in the healthy control.

2.4 SLE 患者感染情况回顾性分析

27例$CD4^+/CD8^+$倒置SLE患者中，20例巨细胞病毒DNA检测阳性，4例EB病毒DNA检测阳性，1例全血细菌培养阳性。17例$CD4^+/CD8^+$升高SLE患者中，5例全血细菌培养阳性。27例$CD4^+/CD8^+$正常SLE患者中，1例巨细胞病毒DNA检测阳性，2例全血细菌培养阳性。$CD4^+/CD8^+$倒置组病毒感染率(82.8%)显著高于其他组(均$P<0.01$)，$CD4^+/CD8^+$升高组细菌感染率(29.4%)显著高于其他组(均$P<0.05$，表2)。

表2 SLE患者病原体感染分布情况

Table 2 Distribution of pathogen infection in SLE patients

组别	病毒感染/%	细菌感染/%	支原体感染/%
CD4+/CD8+倒置组	82.8*	3.4	3.4
CD4+/CD8+升高组	0	29.4*	0
CD4+/CD8+正常组	5	7.4	0
健康对照组	—	—	—

与其余3组相比，*P<0.05。

Compared with the other 3 groups, *P<0.05.

3 讨论

SLE是一种自身免疫性疾病，体内T淋巴细胞、B淋巴细胞异常活化，表现为免疫过度激活[5]。SLE的发病机制主要包括体外环境的诱导和体内免疫功能的调节异常，但其具体机理尚不明确。正常人CD4+T细胞和CD8+T细胞比例正常，比值通常为1.5~2.5，将当机体受到病原体侵犯时，比值将出现异常。SLE作为自身免疫性疾病，免疫功能出现紊乱，CD4+/CD8+比值异常较普遍，但其具体机制不明。

共刺激分子PD1/PD-L1在维持免疫细胞的激活和功能方面有至关重要的作用[6-7]。PD1/PD-L1信号途径被认为与移植排斥反应、自身免疫性疾病、慢性病毒和肿瘤免疫逃逸等疾病密切相关[8]。付文哲[9]研究发现：SLE患者可溶性血清PD-L1能够封闭PD-1/PD-L1相互作用，降低PD-1获得抑制信号的强度，导致T细胞因缺乏负性调控信号而过度活化、增殖，产生自身组织的免疫损伤。本研究结果显示：CD4+/CD8+倒置和升高组SLE患者血清PD-L1显著高于正常组和健康对照组，且与抗dsDNA抗体滴度呈正相关，与上述报道[6-9]相符。说明SLE患者免疫功能紊乱时，PD-L1在血清中表达增强，参与调节T细胞的活性和疾病的发展。IFN-α作为Toll样受体(Toll-like receptor，TLR)通路和干扰素刺激通路(STING pathway)的最终产物，能够反向调节T淋巴细胞，使活化的T淋巴细胞生存期延长，还能促进记忆性T淋巴细胞的分化[10-11]。IFN-α还能诱导B淋巴细胞刺激因子的产生，B淋巴细胞通过细胞受体和免疫球蛋白的结合而活化和分化，最终产生致病的自身抗体[12]。本研究发现：CD4+/CD8+倒置和升高组SLE患者血清IFN-α水平均高于健康对照组，且与抗dsDNA抗体滴度呈正相关，与上述报道[10-12]一致。说明SLE患者免疫功能紊乱时，IFN-α能反向调节T淋巴细胞、B淋巴细胞活性，参与疾病的发展。此外，本研究还发现：CD4+/CD8+倒置组IFN-α水平显著高于升高组，而CRP水平与CD4+/CD8+正常组相比差异无统计学意义，这可能与SLE患者病毒感染有关[13]。本研究对各组SLE患者病原体感染分布回顾性分析发现：CD4+/CD8+倒置组病毒感染率显著高于其他组，且以巨细胞病毒为主，而CD4+/CD8+升高组细菌感染率显著高于其余组。CD4+/CD8+倒置组和升高组补体C3，C4水平显著低于其余组，这与本研究组的前期研究[14]结论一致。升高组CRP水平要显著高于其余组，这可能与升高组SLE患者细菌感染相关。CD4+/CD8+倒置和升高组抗dsDNA抗体滴度和SLEDAI显著高于正常组和健康对照组，说明病原体感染是CD4+/CD8+异常的直接诱因，且加剧SLE患者的活动度。

综上所述，病原体感染是SLE患者免疫功能紊乱的诱因，当机体处于感染状态时，血清PD-L1能调节免疫细胞，而IFN-α作为体内及体外清除细胞碎片各种信号转道通路的最终产物也能反向调节免疫细胞，一同参与SLE患者免疫功能的调节。

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