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·临床研究·

可溶性 PD-L1 作为晚期肢端及黏膜黑色素瘤预后因素的研究

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[摘　要]　**目的：**可溶性 PD-L1（sPD-L1）水平升高与肾细胞癌和多发性骨髓瘤预后相关。然而，sPD-L1 在晚期黑色素瘤中的调节作用和功能尚不完全清楚。本研究旨在评估晚期肢端及黏膜黑色素瘤患者循环系统中 sPD-L1 浓度与预后的关系。**方法：**于 2012 年 1 月至 2015 年 12 月期间在北京大学肿瘤医院招募了未经治疗的晚期肢端及黏膜黑色素瘤患者 102 例，同时收集 40 例健康人外周血，使用酶联免疫吸附法测定受试者循环系统中 sPD-L1 浓度。**结果：**晚期黑色素瘤队列包括 58 名肢端黑色素瘤患者和 44 名黏膜黑色素瘤患者。患者治疗前血清 sPD-L1 平均浓度（2.91±2.23 ng/ml）高于健康献血者（0.59 ng/ml）。102 例患者中 39 例（38.2%）患者血清 sPD-L1 水平显著升高（>2.91 ng/ml），与 LDH 水平和 Tregs 数量增加显著相关，*P* 值分别为 0.021 和 0.017。高浓度和低浓度 sPD-L1 患者的总生存期存在显著差异，分别为 8.5 个月和 11.6 个月（*P*=0.022）。**结论：**晚期肢端或黏膜黑色素瘤患者的 sPD-L1 浓度升高，可能在疗效预测方面发挥重要作用。

[关键词]　可溶性 PD-L1；肢端黑色素瘤；黏膜黑色素瘤；预后
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Soluble PD-L1 as a prognostic factor for advanced acral and mucosal melanoma

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[Abstract] **Objective:** Elevated levels of soluble PD-L1 (sPD-L1) are associated with worse prognosis of renal cell carcinoma and multiple myeloma. However, the regulatory roles and functions of sPD-L1 in advanced melanoma are not fully understood. This study was designed to evaluate the association between circulating sPD-L1 concentrations and prognosis of patients with advanced acral or mucosal melanoma. **Methods:** A total of 102 untreated patients with advanced acral and mucosal melanoma admitted to Peking University Cancer Hospital between January 2012 and December 2015 were enrolled in this study. In the meanwhile, peripheral blood samples were obtained from 40 healthy donors. Circulating sPD-L1 concentrations were determined using an enzyme-linked immunosorbent assay. **Results:** The advanced melanoma cohort included 58 acral melanoma patients and 44 mucosal melanoma patients. The pre-treatment concentration of sPD-L1 (2.91±2.23 ng/ml) in plasma of patients group was elevated as compared with that in healthy donors (0.59 ng/ml). The concentration of sPD-L1 in serum was significantly upregulated in 39/102 (38.2%) patients and significantly associated with increased LDH level (*P*=0.021) and number of Tregs (*P*=0.017). The overall survival rates of patients with high or low concentrations of sPD-L1 were statistically different (8.5 months [high level] *vs* 11.6 months [low level], *P*=0.022). **Conclusion:** sPD-L1 concentration is elevated in patients with advanced acral or mucosal melanoma, which may play an important role in predicting prognosis.

[Key words] soluble PD-L1 (sPD-L1); acral melanoma; mucosal melanoma; prognosis

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PD-1 是 CD28 家族的一种免疫抑制受体，可在 T 细胞表面表达，限制 T 细胞的活化和增殖[1-3]。PD-1 与其配体PD-L1 结合（PD-L1 通常在肿瘤微环境中上调）后可激活免疫检查点通路，进而抑制 T 细胞介导的抗肿瘤活性[4-5]。PD-L1 在多种类型的癌组织中均有表达[6-16]，尽管在黑色素瘤的报道存在矛盾[15]，但 PD-L1 的表达与某些肿瘤类型的临床预

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后较差相关[11, 16]。

可溶性 PD-L1（sPD-L1）存在于癌症和其他慢性疾病（如类风湿关节炎）患者的外周血中[17-18]。外周血中 sPD-L1 可能与 T 细胞上的 PD-1 结合，抑制 T 细胞相关免疫[19-20]。此外，sPD-L1 浓度与黑色素瘤患者的预后相关[21]。然而，sPD-L1 在肢端和黏膜黑色素瘤中的免疫调节作用尚不完全清楚。本研究旨在评估晚期肢端或黏膜黑色素瘤患者的外周血 sPD-L1 的浓度与预后的关系。

1　资料与方法

1.1　临床资料

2012 年 1 月至 2015 年 12 月期间，在北京大学肿瘤医院招募了 102 名未经治疗的晚期肢端或黏膜黑色素瘤患者。入组标准：病理确诊的Ⅲ~Ⅳ期不可切除、原发肢端或黏膜的黑色素瘤，未接受进展期抗肿瘤系统治疗，自愿签署知情同意，并愿意接受定期访视。收集的信息包括性别、诊断年龄、ECOG 评分以及肿瘤的组织病理学特征等。所有患者均经组织学证实为肢端或黏膜黑色素瘤。根据美国癌症联合委员会（AJCC）（第 7 版）指南中临床评估和组织病理学分析进行分期。采用 RECIST 1.1 标准在影像水平对肿瘤反应进行评估。

1.2　随　访

通过电话或门诊对患者进行随访。患者随访至 2018 年 6 月 1 日。随访详细信息，包括是否存活和死因。分析 102 例患者的临床特征、治疗方法和预后。本研究通过了北京大学肿瘤医院伦理委员会的批准，所有患者均签署知情同意书。

1.3　ELISA 分析患者外周血样本中的 sPD-L1 水平

检测样本采集于晚期黑色瘤接受系统治疗前。血液样本通过离心（3 000×*g*，10 min）获得血清，在 –80 ℃ 条件下储存。使用 ELISA 试剂盒（购自 USCN Life Science 公司）检测 102 例患者的血清样本中的 sPD-L1。将含有不同浓度标准品和血清样本的 96 孔板在 37 ℃ 下培养 2 h。加入生物素抗体孵育，多次洗涤后加入 HRP 偶联的链霉亲和素，37 ℃ 下避光孵育 15 ~ 25 min。加入底物溶液后发生酶促反应，溶液变蓝。根据标准曲线计算蛋白质水平。

1.4　统计学处理

采用 SPSS17.0 软件进行统计分析。呈正态分布的计量数据以 $\bar{x}\pm s$ 表示。生存时间是从诊断的日期到最后一次随访日期或死亡日期。用 Kaplan-Meier 法计算无进展生存期（PFS）和总生存期（OS），用 Log-rank 法评估变量或因素对 PFS 和 OS 的影响的统计学意义，采用 Cox 回归模型评价预后因素，计算危险比（HR）和 95% 置信区间（CI），用 Log-rank 比较生存曲线。以 $P<0.05$ 或 $P<0.01$ 表示差异具有统计学意义。

2　结　果

2.1　患者基本特征

本研究包括 58 名晚期肢端黑色素瘤和 44 名黏膜黑色素瘤患者，年龄 15~77 岁（平均 52.3±13.7 岁；中位年龄 54.0 岁）。男女比例为 1∶1.04。在诊断为晚期黑色素瘤时，肺是最常见的转移部位。在该队列中，CKIT（v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog）是最常见的突变（13.7%）（表 1）。

表 1　患者的特征 [*n*(%)]

Tab.1　Patients' characteristics [*n*(%)]

Feature	Total number of patients
Gender	
Male	50 (49.0%)
Female	52 (51.0%)
Subtype	
Mucosal	44 (43.1%)
Acral	58 (56.9%)
Metastatic	
Liver	31 (30.4%)
Lung	56 (54.9%)
Brain	6 (5.9%)
None	9 (8.8%)
Mutations	
c-KIT	14 (13.7%)
NRAS	11 (10.8%)
BRAF	11 (10.8%)
None	66 (64.7%)
Serum LDH level	
>ULN	34 (33.3%)
≤ULN	64 (62.7%)
NA	4 (3.9%)
$CD4^+CD25^{hi}$(Treg) level	
Increase	19 (18.6%)
Normal	79 (77.5%)
NA	4 (3.9%)
$CD8^+CD28^+$ (Tc) level	
Decrease	26 (25.5%)
Normal	72 (70.6%)
NA	4 (3.9%)
Baseline tumor size (*d*/mm)*	
>40	36 (35.3%)
≤40	36 (35.3%)
NA	30 (29.4%)

Tc: cytotoxic T cell; Treg: Regulatory cells; ULN: upper limit of normal. * The sum of the longest diameter (the short diameter of the lymph node) of the lesion

2.2 循环系统中 sPD-L1 的浓度

晚期黑色素瘤患者治疗前血清中 sPD-L1 浓度（2.91±2.23 ng/ml）较报道的健康献血者（0.59 ng/ml）升高[22]。102 例患者中 39 例（38.2%）血清中 sPD-L1 浓度高度上调（>2.91 ng/ml），并与乳酸脱氢酶（LDH）浓度显著相关 [（LDH 正常患者 sPD-L1 浓度为（2.46±1.50）ng/ml *vs* LDH 升高患者 sPD-L1 为（3.78±3.10）ng/ml，*P*=0.021]（表 2）。调节性 T 细胞（Tregs）数量增加（>10%）与高 sPD-L1 浓度相关 [（4.22±2.37）*vs*（2.60±1.82）ng/ml，*P*=0.017]（表 2）。

2.3 患者对治疗的反应和生存期

将患者分为以下治疗队列：（1）队列 A，替莫唑胺/达卡巴嗪组（*n*=73），客观有效率（ORR）为 5.5%，无进展生存期（PFS）为 2.43 个月；（2）队列 B，紫杉醇治疗组（*n*=14），ORR 为 0，PFS 为 2.5 个月；（3）队列 C，靶向治疗组（*n*=6），分别接受伊马替尼（3 例）或维罗非尼（3 例）靶向治疗，总体 ORR 为 50%，PFS 分别为 1.46 个月和 15.36 个月。sPD-L1 浓度在总人群及各治疗队列中与客观有效率和无进展生存期均无显著相关性。sPD-L1≤2.91 ng/ml 组 PFS 为 2.4 个月 *vs* sPD-L1>2.91 ng/ml 组 PFS 为 2.9 个月，*P*=0.414。

在 2018 年 1 月的最后一次数据收集中，97/102（95.1%）的患者死于黑色素瘤。随访时间的中位数为 10.4 个月（2.0~80.6 个月）。转移患者的中位 OS 为 11.0 个月（95%*CI*：8.405~13.452）。

单变量风险分析提示，黑色素瘤预后变量的影响因素包括年龄（≥65 岁）、LDH 浓度（高于正常范围的上限）和肝转移（表 3）。sPD-L1 高、低浓度患者的 OS 分别为 8.5 和 11.6 个月，存在显著性差异（*P*=0.022）。多变量分析显示除肝转移与 OS 具有显著的相关性（*P*=0.009）外，sPD-L1 浓度与 OS 之间亦有显著相关性（表 3）。

表 2 血清 sPD-L1 水平与患者临床特征的相关性

Tab.2 Correlations between serum sPD-L1 concentration and patients' clinical characteristics

Characteristics	Expression of sPD-L1		*P*
	Low	High	
Gender			1.000
Male	31 (62.0%)	19 (38.0%)	
Female	32 (61.5%)	20 (38.5%)	
Age(*t*/a)			0.624
<65	51 (63.0%)	30 (37.0%)	
≥65	12 (57.1%)	9 (42.9%)	
Subtype			0.193
Mucosal	30 (68.2%)	14 (31.8%)	
Acral	33 (56.9%)	25 (43.1%)	
Metastatic			
Liver	16 (51.6%)	15 (48.4%)	0.188
Lung	30 (53.6%)	26 (46.4%)	0.069
BRAF			1.000
Wide type	53 (63.9%)	30 (36.1%)	
Mutant	10 (52.6%)	9 (474%)	
Lactate dehydrogenase level			0.021
Normal	44 (68.8%)	20 (31.3%)	
Elevated (>100%ULN)	17 (50.0%)	17 (50.0%)	
Baseline tumor size			0.627
≤Median (≤40 mm)	24 (66.7%)	12 (33.3%)	
>Median (>40 mm)	21 (58.3%)	15 (41.7%)	
Increase $CD4^+CD25^{hi}$ (Treg)	7 (36.8%)	12 (63.2%)	0.017
Decrease $CD8^+CD28^+$ (Tc)	14 (53.8%)	12 (46.2%)	0.349

表 3 总生存期 OS 的预后因子的单参数和多参数分析

Tab.3 Univariate and multivariate analyses of prognostic factors for OS

Variable	Univariate			Multivariate		
	HR	95%*CI*	*P*	*HR*	95%*CI*	*P*
Gender (Male/Female)	0.90	0.60−1.34	0.595			
Age (≥65 *vs* <65 years)	1.66	1.00−2.77	0.047	1.40	0.80−2.47	0.238
BRAF mutations (Yes *vs* No)	1.11	0.58−2.10	0.757			
Subtype (Acral *vs* Mucosal)	0.90	0.70−1.16	0.846			
Liver Metastatic (Yes vs No)	0.54	0.35−0.84	0.006	0.48	0.28−0.83	0.009
LDH (Elevated *vs* Normal)	2.04	1.32−3.16	0.001	1.00	0.99−1.00	0.305
Baseline tumor size (>40 *vs* ≤40 mm)	1.23	0.76−1.99	0.393			
sPD-L1 (High expression *vs* Low)	1.64	1.07−2.51	0.022	1.67	1.07−2.60	0.025

3 讨 论

PD-L1 在抗原提呈细胞表面表达，且在人肿瘤细胞表面表达，进而抑制抗肿瘤免疫[23]。sPD-L1 可能从 PD-L1 阳性肿瘤或免疫细胞中释放[24]。这一理论被旨在确定 sPD-L1 在实体瘤患者中预后价值的

研究所证实[25-27]。本研究提供了血清 sPD-L1 浓度在晚期肢端和黏膜黑色素瘤的预后预测作用的证据，即与健康对照组相比，晚期肢端或黏膜黑色素瘤患者的血清中 sPD-L1 浓度升高，与先前在皮肤黑色素瘤中的研究结果一致[21]。

黑色素瘤患者 sPD-L1 的来源尚不清楚。患者血清中的循环 sPD-L1 可能由多种来源产生，如通过肿瘤细胞固有的剪接活性或抗肿瘤免疫反应产生。异常的选择性剪接活性发生在多种癌症中，影响转录因子、细胞信号因子和膜蛋白的表达[28]。此外，这些剪接蛋白的功能改变促进肿瘤的发生、增殖和转移[28-30]。例如，在黑色素瘤细胞表面表达的 PD-L1 与分泌的 sPD-L1 对细胞因子的反应相似[21]。

本研究发现，在晚期肢端和黏膜黑色素瘤患者血清中 sPD-L1 的浓度与 LDH 水平显著相关，而与肿瘤负荷无关。这证实了治疗前 sPD-L1 增加是由肿瘤细胞的异常剪接活性引起的，而不是由与高肿瘤负荷相关。LDH 是公认的癌症预后因子，先前的研究[31] 也报道了 sPD-L1 浓度与全身炎症反应相关（高水平的可溶性程序性死亡配体（sPD-L1）肝细胞癌患者预后差的）。本研究中，sPD-L1 水平升高与 LDH 水平升高相关，提示 sPD-L1 可能与机体状况恶化有关。

患者治疗前高浓度的 sPD-L1 水平可能反映出某些患者已存在抗肿瘤免疫反应或耗尽的抗肿瘤免疫反应。本研究中发现，Treg 的增加与高浓度的 sPD-L1 相关。已发表的研究[32] 发现，$CD3^+$ T 细胞浸润水平高的胰腺癌患者血清 sPD-L1 浓度明显升高。此外，黑色素瘤患者的髓系 DC 分泌 sPD-L1[21]，而且髓系 DC 表达高水平的 PD-L1，抑制 T 细胞活化[33]。因此，推测高浓度的 sPD-L1 水平代表了晚期黑色素瘤的免疫抑制状态。

对细胞系的研究[34] 发现，sPD-L1 可以通过捕获抗 PD-L1 抗体来干扰 PD-L1 的阻断，并可能导致对 PD-L1 阻断治疗产生耐药性。本研究中检测到的治疗前的 sPD-L1 浓度的差异可能代表了影响治疗反应的有利或不利因素。例如，免疫检查点治疗后，sPD-L1 浓度的长期或延迟增加的黑色素瘤患者倾向于在检查点阻断治疗中临床获益[21]。然而，纳武利尤单抗对肢端或黏膜黑色素瘤的 ORR 低于 20%，远低于皮肤黑色素瘤[35]。因此，需要进一步的研究以确定 sPD-L1 的表达差异是否可作为免疫检查点抑制剂治疗肢端或黏膜黑色素瘤患者临床获益的标志物。

荟萃分析[36] 发现，与低浓度 sPD-L1 相比，高浓度 sPD-L1 的实体瘤患者的总生存期 OS 较短。我们发现治疗前高浓度的 sPD-L1 对 OS 有持续的负面影响，提示高浓度的 sPD-L1 可能是预测预后较差的生物标志物之一。

综上，晚期肢端或黏膜黑色素瘤患者的 sPD-L1 浓度升高，可能在预测患者预后方面发挥重要作用，但尚有待扩大样本量时进一步明确。未来的研究应该尝试评估 sPD-L1 作为免疫治疗的生物标志物。

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