doi: 10.13241/j.cnki.pmb.2020.15.021

PD-1、PD-L1 的表达与肺癌临床病理特征及预后的相关性分析 *

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摘要 目的:分析程序性死亡因子 -1(PD-1)、程序性死亡 1- 配体(PD-L1)的表达与肺癌临床病理特征及预后的相关性。**方法:**回顾性分析我院 2015 年 3 月 ~2016 年 6 月收治的 73 例肺癌患者的临床资料，取距离切除肿瘤边缘 3cm 内的非癌组织作为癌旁组织。比较两组 PD-1、PD-L1 的表达,分析其和肺癌患者临床病理特征和预后的关系,采用 COX 比例回归分析肺癌患者预后的影响因素。**结果:**肺癌组织 PD-1、PD-L1 阳性表达率均显著高于癌旁组织(P<0.05)。不同性别、年龄、病理类型、吸烟情况、EGFR 表达、肿瘤大小肺癌患者 PD-1、PD-L1 的阳性表达率比较差异无统计学意义(P>0.05);低分化程度、临床分期 III 及 IV 期、有淋巴结转移肺癌患者 PD-1、PD-L1 阳性表达率分别高于中分化程度、临床分期 III 期、无淋巴结转移患者,差异有统计学意义(P<0.05)。PD-1、PD-L1 阳性表达及阴性表达组无疾病进展生存期比较均有统计学差异(P<0.05)。COX 比例风险回归模型显示分化程度、临床分期、淋巴结转移、PD-1、PD-L1 的表达是影响肺癌患者预后的危险因素(P<0.05)。**结论:**肺癌组织 PD-1、PD-L1 呈高表达,可能参与肺癌的发生发展,有助于病情严重程度的评价和预后预测。

关键词:肺癌;程序性死亡因子 -1;程序性死亡 1- 配体;临床病理特征;预后

中图分类号:R734.2 **文献标识码:**A **文章编号:**1673-6273(2020)15-2904-06

Correlation of PD-1, PD-L1 Expression with the Clinicopathological Characteristics and Prognosis of Lung Cancer*

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ABSTRACT Objective: To analyze the correlation of the expression of programmed death factor -1(PD-1) and programmed death 1-ligand (PD-L1) with the clinicopathological features and prognosis of lung cancer. **Methods:** The clinical data of 73 patients with lung cancer admitted to our hospital from March 2015 to June 2016 were retrospectively analyzed. Non-cancerous tissues within 3cm from the edge of the resected tumor were taken as paracancerous tissues. The expressions of PD-1 and PD-L1 in the two groups were compared, and the relationship between PD-1 and PD-L1 expression and the clinicopathological features and prognosis of lung cancer patients were analyzed. COX proportional regression was used to analyze the influencing factors of prognosis of lung cancer patients. **Results:** The positive expression rates of PD-1 and PD-L1 in lung cancer tissues were significantly higher than those in the adjacent tissues (P<0.05). There was no significant difference in the positive expression rates of PD-1 and PD-L1 between patients with lung cancer of different sex, age, pathological type, smoking status, EGFR expression and tumor size (P>0.05). The positive expression rates of PD-1 and PD-L1 in patients with low differentiation degree, clinical stage III and IV, and lung cancer with lymph node metastasis were higher than those in patients with medium differentiation degree, clinical stage I and II, and without lymph node metastasis (P<0.05). There were significant differences in the disease-free progression survival time between PD-1 and PD-L1 positive and negative expression groups (P<0.05). COX proportional hazards regression model showed that differentiation degree, clinical stage, lymph node metastasis, PD-1, PD-L1 expression were risk factors affecting the prognosis of lung cancer patients (P<0.05). **Conclusion:** PD-1 and PD-L1 are highly expressed in lung cancer tissues, which may participate in the occurrence and development of lung cancer and contribute to the evaluation of disease severity and prognosis prediction.

Key words: Lung Cancer; Programmed death factor-1; Programmed death 1-ligand; Clinicopathological features; Prognosis

Chinese Library Classification(CLC): R734.2 Document code: A

Article ID:1673-6273(2020)15-2904-06

前言

肺癌是严重威胁机体生命安全的恶性肿瘤之一,其发生率较高,临床研究证实[1,2]早期肺癌经有效治疗能够获得较好的效

* 基金项目:山东省自然科学基金项目(ZR2015HL130)

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(收稿日期:2020-03-06 接受日期:2020-03-31)

果。但因肺癌早期发病较隐匿,影像学诊断假阳性及公众对肺癌认知的缺乏,肺癌早期的发现率较低[3]。研究报道[4]大部分肺癌患者就诊时已发展至中晚期,错失最佳手术治疗时机。晚期肺癌单纯采用传统化疗无法杀灭存留在机体的癌细胞,且可能伤及正常组织及细胞[5]。近年来,研究表明肺癌发生、发展为多基因、多阶段参与的复杂生物学反应,并提出靶向治疗可作为指导晚期肺癌患者的一线靶向治疗方式,尽管靶向治疗能够在短期内获得明显获益,但仍有部分患者可能出现获得性耐药[6]。肿瘤免疫逃逸在肺癌治疗及预后中有重要作用,可能成为肺癌个体化治疗的重要靶点。

程序性死亡因子 -1(PD-1,programmed death factor-1)为负性协同刺激分子受体,程序性死亡 1- 配体(PD-L1,programmed death 1-ligand)和 PD-1 分子结合后能够传递正向信号,负性调节 T 细胞的功能及活化,导致肿瘤细胞凋亡[7,8]。目前研究表明[8]PD-L1 在多种肿瘤组织类呈异常表达,且和肿瘤转移、进展及预后有一定相关性。Aso M 等[9]研究发现 PD-L1 的表达能够直接抑制 $CD8^+$T 淋巴细胞功能,诱导癌细胞逃避活化 T 淋巴细胞杀伤,减弱机体自身抗肿瘤反应。国外研究报道[10]阻断 PD-1/PD-L1 信号通路在多种恶性晚期癌症治疗中有较好的效果。本研究主要分析了 PD-1、PD-L1 表达和肺癌临床病理特征和预后关系,结果报道如下。

1 材料与方法

1.1 一般资料

73 例肺癌患者入选标准[11]:经活体组织病理检查学证实为原发性肺癌;预计生存时间在 3 个月以上;既往无其他恶性肿瘤;临床资料完整。排除标准:入组前 4 周进行抗肿瘤治疗;全身系统明显病变。73 例肺癌患者中年龄 36~75 岁,平均(57.91±4.33)岁;男 49 例,女 24 例;腺癌 34 例,鳞癌 39 例;49 例有吸烟史,24 例无吸烟史;表皮生长因子受体(Epidermal growth factor receptor,EGFR):野生型 38 例,突变型 35 例;分化程度:中高分化 49 例,低分化 24 例;临床分期:Ⅰ、Ⅱ期 28 例,Ⅲ、Ⅳ期 45 例;肿瘤大小:T_1~$T_2$24 例、T_3~$T_4$49 例;淋巴结转移:有 47 例,无 26 例。取距离切除肿瘤边缘 3 cm 内的非癌组织作为癌旁组织。

1.2 方法

1.2.1 检测方法 手术收集相关病理组织,放置于液氮中并转移至 -80℃低温箱中待用。用免疫组织化学染色法测定 PD-1、PD-L1 表达情况,标本经 10%福尔马林液固定,用石蜡进行包埋,按 4 μm 层厚连续切片,于切皮漂烘温控仪,在 38℃下将连续切片展开。取处理后的载玻片切片,脱蜡。用高温高压修复抗原,免疫组化染色依据 SP 试剂盒说明书进行。

1.2.2 结果判定 在高倍镜(400 倍)随机选择 5 个视野,单个视野观察细胞在 200 个以上,按着色深浅及阳性细胞所占比例判定结果。(1)阳性细胞百分比计分:阳性细胞数在 51%~100%计为 3 分,26%~50%计为 2 分,10%~25%计为 1 分, 低于 10%计为 2 分;(2)着色深浅:棕褐色计为 3 分,棕黄色计为 2 分,浅黄色计为 2 分,无色计为 0 分。二者分数乘积超过 3 分即阳性[12]。

1.3 随访

所有肺癌患者均以电话、门诊等方式进行 3 年随访,以入组日期即为随访起始日期,至随访结束、失访或者死亡为截止日期,计算疾病无进展生存期:随机化至患者出现肿瘤进展或者死亡时间。

1.4 统计学分析

数据处理选用 SPSS18.0 进行,用($\bar{x}\pm s$)表示计量资料,组间比较选用独立样本 t 检验进行,用[(例)%]表示计数资料,组间比较用 x^2 检验, 采用 Log-rank 检验分析并比较疾病无进展生存期,以 Cox 风险比例模型分析预后影响因素,以 P<0.05 为差异有统计学意义。

2 结果

2.1 肺癌组织及癌旁组织 PD-1、PD-L1 的表达比较

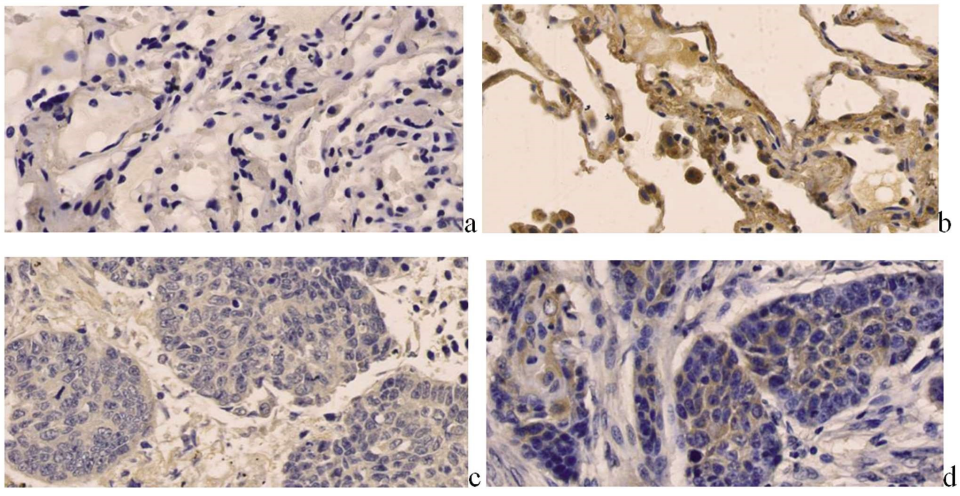

图 1 PD-1 的免疫组织化学染色法结果

Fig. 1 The results of immunohistochemical staining of PD-1

注:PD-1 以细胞膜或细胞质显示黄至棕褐色颗粒为阳性显色,a、b 分别为 PD-1 在癌旁组织呈阴性、阳性表达;c、d 分别为 PD-1 在肺癌组织呈阴性、阳性表达

Note: PD-1 is positive with yellow to tan granules on cell membrane or cytoplasm, and a and b are negative and positive expressions of PD-1 in adjacent tissues; c and d are PD-1 which are negative and positive expression in lung cancer tissue.

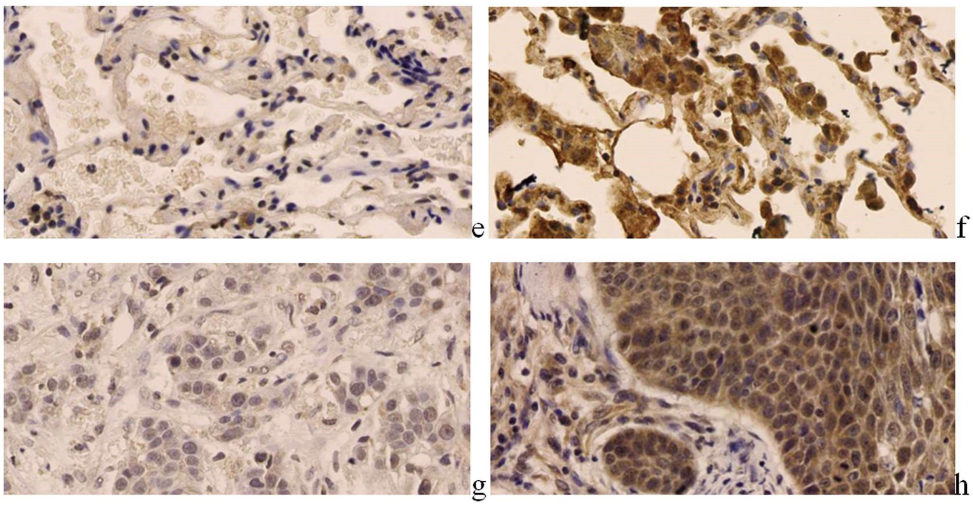

图 2 PD-L1 的免疫组织化学染色法结果

Fig. 2 The results of immunohistochemical staining of PD-L1

注：PD-L1 以细胞膜或细胞浆显示黄至棕褐色颗粒为阳性显色，

e、f 分别为 PD-L1 在癌旁组织呈阴性、阳性表达；g、h 分别为 PD-L1 在肺癌组织呈阴性、阳性表达。

Note: PD-L1 is positively colored by yellow to tan granules on cell membrane or cell plasma, and e and f are PD-L1 negative and positive expression in adjacent tissues; g and h are PD-L1 negative and positive expressions in lung cancer tissues.

肺癌组织 PD-1、PD-L1 阳性率分别为 65.75%，72.6%，均显著高于癌旁组织(5.48%，8.22%)，差异有统计学意义(P<0.05)，见表 1。

表 1 肺癌组织及癌旁组织 PD-1、PD-L1 的表达比较[例(%)]

Table 1 Comparison of the Expression of PD-1 and PD-L1 between lung cancer tissues and adjacent normal lung tissues [n(%)]

Groups	n	PD-1		PD-L1	
		Positive	Negative	Positive	Negative
Lung cancer tissue	73	48(65.75)	25(34.25)	53(72.60)	20(23.40)
Paracancerous tissue	73	4(5.48)	69(94.52)#	6(8.22)	67(91.78)#

Note: Compared with the lung cancer tissue #P<0.05.

2.2 肺癌患者 PD-1、PD-L1 表达和临床病理特征的关系

不同性别、年龄、病理类型、吸烟情况、EGFR 表达、肿瘤大小肺癌患者 PD-1、PD-L1 阳性表达率比较无统计学差异(P>0.05)；低分化程度、临床分期 III 及 IV 期、有淋巴结转移肺癌患者 PD-1、PD-L1 阳性表达率分别高于中分化程度、临床分期 III 期、无淋巴结转移患者，差异有统计学意义(P<0.05)，见表 2。

2.3 肺癌患者 PD-1、PD-L1 表达和生存期的关系

73 例肺癌患者 3 年内死亡 24 例，其中 PD-1 阳性表达死亡 21 例，阴性表达死亡 3 例；PD-1 阳性表达死亡 22 例，阴性表达死亡 2 例，PD-1、PD-L1 阳性表达者无进展生存期分别短于 PD-1、PD-L1 阴性表达者，差异有统计学意义(P<0.05)，见表 3。

2.4 肺癌患者预后的相关因素分析

以随访结束时患者是否死亡作为因变量，将分化程度、临床分期、淋巴结转移、PD-1、PD-L1 作为自变量纳入 COX 比例风险回归模型显示，分化程度、临床分期、淋巴结转移、PD-1、PD-L1 是影响患者预后的危险因素(P<0.05)，见表 4。

3 讨论

近年来研究表明[15]肿瘤发生发展和机体免疫功能密切相关，免疫逃逸在恶性肿瘤发生中有重要作用，可能成为癌症个体化治疗的新靶点。免疫检查点疗法并不直接作用于癌细胞，且不针对肿瘤表层的特定物质，可系统性增强全身抗肿瘤免疫效应。机体免疫系统对突变细胞有监视及清除能力，T 细胞调节的肿瘤抗原识别、提呈和活化在肿瘤免疫应答反应中有重要作用，免疫抑制是肿瘤细胞发生及进展的主要原因[16]。最新研究认为[17]肿瘤能够经异常调节共刺激分子表达、表面抗原封闭等多种机制逃避机体免疫监视及杀伤，导致机体无法产生有效的抗肿瘤免疫应答，从而导致肿瘤细胞发生免疫逃逸。肿瘤细胞能够免疫检查点分子表达上调，和 T 细胞表面受体结合，抑制 T 细胞识别活化及清除反应。协同刺激分子作为一种免疫检查点分子能够为 T 细胞活化提供信号，在肿瘤细胞免疫逃逸中有重要作用[18]。机体正常状态下，负性共刺激分子与共刺激分子之间相对平衡，从而保持淋巴细胞的免疫效应，既避免自体免疫损伤又可保持正常免疫监视及杀伤功能[19]。但肿瘤细胞能够刺激部分负性共刺激分子及相关配体表达，较正性协同分子更具优势，破坏正常正负信号的平衡，抑制 T 细胞免疫活性，参与肿瘤发生发展[20]。阻断肿瘤负性共刺激分子和配体的结合能

表 2 肺癌患者 PD-1、PD-L1 表达和临床病理特征的相关性

Table 2 Relationship between PD-1, PD-L1 Expression and Clinicopathological

Clinicopathological features	n	PD-1		PD-L1	
		Positive(n=48)	Negative(n=25)	Positive(n=53)	Negative(n=20)
Gender					
male	49	32(65.31)	17(34.69)	34(69.39)	15(30.61)
female	24	16(66.67)	8(33.33)	19(79.17)	5(20.83)
Age (years)					
<65	46	31(67.39)	15(32.61)	32(69.57)	14(30.43)
≥ 65	27	17(62.96)	10(37.04)	21(77.78)	6(22.22)
Pathological type					
Adenocarcinoma	34	22(64.71)	12(35.29)	26(76.47)	8(23.53)
Squamous cell carcinoma	39	26(66.67)	13(33.33)	27(69.23)	12(30.77)
Smoking history					
Yes	49	31(63.27)	18(36.73)	38(77.55)	11(22.45)
No	24	17(70.833)	7(29.17)	15(62.50)	9(37.50)
EGFR					
Wild type	38	23(60.53)	15(39.47)	25(65.79)	13(34.21)
mutant	35	25(71.42)	10(28.57)	28(80.00)	7(20.00)
Degree of differentiation					
Medium-high differentiation	49	26(53.06)	23(46.94)	30(61.22)	19(38.78)
poorly differentiated	24	22(91.67)	2(8.33)[a]	23(95.83)	1(4.17)[a]
Clinical staging					
Phase I and II	28	10(35.71)	18(64.29)	12(42.86)	16(57.14)
Phases III and IV	45	38(84.44)	7(15.56)[a]	41(91.11)	4(8.89)[a]
Tumor size					
T_1~T_2	24	14(58.33)	10(41.67)	16(66.67)	8(33.33)
T_3~T_4	49	34(69.39)	15(30.61)	37(75.51)	12(24.49)
Lymph node metastasis					
Yes	47	42(89.36)	5(10.64)	43(91.49)	4(8.51)
No	26	6(23.08)	20(76.92)[a]	10(38.46)	16(61.54)[a]

Note: [a]P<0.05.

表 3 肺癌患者 PD-1、PD-L1 表达和生存期的关系

Table 3 Relationship between PD-1, PD-L1 Expression and Survival Time of Lung Cancer Patients

Indicators	n	Disease progression-free survival (months)	x^2	P
PD-1				
Positive	48	30.3	6.318	0.012
Negative	25	34.1		
PD-L1				
Positive	53	29.9	5.939	0.015
Negative	20	34.9		

表 4 肺癌患者预后的相关因素分析

Table 4 Analysis of the Prognostic Factors of Lung Cancer Patients

Independent variable	β	*S.E*	*Wald*	*OR*	*95%CI*	*P*
Degree of differentiation	0.411	0.207	5.597	1.142	1.020~1.562	0.032
Clinical staging	0.593	0.280	4.849	1.809	1.045~3.132	0.028
Lymph node metastasis	0.846	0.268	6.284	2.330	1.378~3.940	0.012
PD-1	1.152	0.299	14.873	3.614	1.762~5.682	0.000
PD-L1	1.322	0.399	10.988	3.753	1.717~8.202	0.001

够提高机体抗肿瘤免疫应答效应,控制肿瘤进展[21]。

PD-1、PD-L1 为目前临床常见的免疫检查点分子,PD-1 常表达于活化的树突状细胞、自然杀伤细胞、B 细胞及 T 细胞和活化单核细胞表面,能够缩短 T 细胞和抗原呈递细胞的接触时间[22]。PD-1 与其配体 PD-L1 共同组成信号通路,参与机体病毒感染、细菌感染等过程,负性调节正常机体的免疫反应[23]。PD-L1 为协同刺激分子,在活化 T 细胞、胸腺皮质细胞、胎盘滋养层、心肌内皮细胞等表达,也可高表达于大部分肿瘤细胞[24]。PD-1 和 PD-L1 结合能够形成共刺激分子,激活 PD-1/PD-L1 通路可抑制免疫淋巴细胞活化,诱导其凋亡,使肿瘤产生免疫逃逸,为肿瘤生长提供有利环境[25]。PD-L1 在肿瘤细胞上的表达能够影响特异性 T 细胞应答,抑制 T 淋巴细胞的增殖分化。另外血管内皮生长、白介素 -10 等细胞因子又可促进 PD-L1 表达,从而影响 T 细胞的抗肿瘤免疫应答能力[26]。

近年来,随着临床对肿瘤免疫逃逸机制研究的不断深入,研究表明阻断 PD-1/PD-L1 通路能够恢复 T 淋巴细胞的抗肿瘤免疫应答反应,抑制局部肿瘤生长速度,发挥抗肿瘤作用,使癌症患者获得更长的生存期 [27]。临床研究显示 [28] 肿瘤细胞的 PD-L1 表达和治疗敏感性有关。Lisberg A 等[29]研究发现 PD-L1 阳性者接受抗 PD-L1 单克隆抗体治疗有效率相对较高,PD-L1 阴性者则对治疗无明显反应。临床研究证实抗 PD-1 及抗 PD-L1 药物和常规化疗能够改善患者预后,为抗 PD-1 单抗治疗恶性肿瘤提供了理论基础。PD-L1 主要在肿瘤细胞区域分布,癌旁组织及良性组织 PD-L1 阳性细胞较少见。本研究结果也显示肺癌组织中 PD-1、PD-L1 阳性表达率高于癌旁组织。本研究结果显示 PD-1、PD-L1 阳性表达和肿瘤细胞分化程度、临床分期、淋巴结转移有关,考虑与 PD-L1 表达和肺癌的肿瘤负荷及累积范围有关,肿瘤细胞异常高表达的 PD-1、PD-L1 可影响 T 细胞杀伤功能,躲避免疫监视,为肿瘤细胞存活创造有利条件,并利于肿瘤细胞的远处转移,因此分期更晚。

相关研究认为 PD-L1 表达为恶性肿瘤患者预后不良的危险因素,PD-L1 高表达者预后较不表达或低表达 PD-L1 者差。对宫颈癌长期随访的研究显示 PD-L1 高表达者均出现肿瘤进展,且有较高的死亡风险,较 PD-L1 低表达者,高表达者的生存期显著缩短,推测 PD-L1 检测对宫颈癌的预后判断有重要作用。随访结果显示 PD-1、PD-L1 低表达者无疾病进展生存期相对较好,进一步的 COX 分析发现 PD-1、PD-L1 为影响肺癌患者预后的独立危险因素,可能原因为 PD-1 和 PD-L1 结合后能够抑制 T 细胞活化,导致免疫细胞无法有效清除肿瘤细胞,逃避免疫系统的攻击,使疾病进一步发展,患者预后相对较差。

综上所述,肺癌组织 PD-1、PD-L1 呈高表达,可能参与肺癌的发生发展,有助于病情严重程度的评价和预后预测。但本研究样本量较少,且样本选择缺乏广泛性,结果可能存在一定偏差,结论仍有待更多大规模、多中心的研究证实。

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