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程序性死亡配体-1在鼻咽癌组织中的表达及临床意义

黄庆文¹ 何江² 阙丽琳³ 陈伊¹ 李文¹

(1 玉林市第一人民医院病理科 广西 玉林 537000; 2 玉林市第一人民医院耳鼻喉科 广西 玉林 537000;

3 玉林市第一人民医院肿瘤科 广西 玉林 537000)

摘要 目的:探讨程序性死亡配体-1(PD-L1)在鼻咽癌组织中的表达及临床意义。**方法:**选取2015年7月-2017年6月期间在我院接受治疗的鼻咽癌患者333例,收集其鼻咽癌组织作为观察组标本,另选取同期在我院接受治疗的慢性鼻炎患者102例的鼻咽炎组织作为对照组标本。采用免疫组化法和逆转录-聚合酶链反应(RT-PCR)检测两组患者鼻咽组织中PD-L1蛋白和PD-L1mRNA的表达,并分析观察组患者鼻咽癌组织中PD-L1蛋白和PD-L1mRNA的表达与临床病理参数的关系。**结果:**对照组患者鼻咽炎组织中PD-L1蛋白的阳性率为0.00%(0/102),观察组患者鼻咽癌组织中PD-L1蛋白的阳性率为69.37%(231/333),两组PD-L1蛋白的阳性率比较差异有统计学意义($P<0.05$)。RT-PCR结果显示,对照组患者鼻咽炎组织中未见PD-L1 mRNA表达,观察组患者鼻咽癌组织中PD-L1 mRNA的相对表达水平为 (0.82 ± 0.27) ,差异有统计学意义($P<0.05$)。观察组患者鼻咽癌组织中PD-L1蛋白和PD-L1 mRNA的表达与年龄、性别无关($P>0.05$),而TNM分期为III-IV期、有淋巴结转移、有吸烟史患者鼻咽癌组织中PD-L1蛋白阳性率和PD-L1 mRNA的表达均高于TNM分期I-II期、无淋巴结转移、无吸烟史患者($P<0.05$)。**结论:**在鼻咽癌组织中PD-L1蛋白和PD-L1mRNA呈现高表达,且其表达与TNM分期、淋巴结转移、吸烟史有关。

关键词:程序性死亡配体-1;鼻咽癌;表达;临床意义

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Expression of Programmed Cell Death Ligand -1 in Nasopharyngeal Carcinoma and Its Clinical Significance

HUANG Qing-wen¹, HE Jiang², QUE Li-lin³, CHEN Yi¹, LI Wen¹

(1 Department of Pathology, The First People's Hospital of Yulin, Yulin, Guangxi, 537000, China;

2 Department of Otolaryngology, The First People's Hospital of Yulin, Yulin, Guangxi, 537000, China;

3 Department of Oncology, The First People's Hospital of Yulin, Yulin, Guangxi, 537000, China)

ABSTRACT Objective: To investigate the expression and clinical significance of programmed cell death ligand -1 (PD-L1) in nasopharyngeal carcinoma (NPC). **Methods:** A total of 333 patients with nasopharyngeal carcinoma, who were treated in the First People's Hospital of Yulin from July 2015 to June 2017, were collected; the nasopharyngeal carcinoma tissues were collected as observation group, 102 cases of chronic pharyngitis during the same period were taken as control group. Immunohistochemical staining and reverse transcription polymerase chain reaction (RT-PCR) were used to detect the expression of PD-L1 and PD-L1mRNA in the nasopharynx tissues of two groups. The relationship between the expression of PD-L1 protein and PD-L1mRNA and the clinicopathological parameters in the patients with nasopharyngeal carcinoma were analyzed. **Results:** The positive rate of PD-L1 protein in the nasal pharyngitis tissue of the control group was 0.00% (0/102), the positive rate of PD-L1 protein in the nasopharyngeal carcinoma tissues of the observation group was 69.37% (231/333); the positive rates of PD-L1 protein in the two groups were statistically significant ($P<0.05$). The results of RT-PCR showed that there were no expressions of PD-L1 and mRNA in the control group, the relative expression of PD-L1 and mRNA in the nasopharyngeal carcinoma tissues of the observation group was (0.82 ± 0.27) , the difference was statistically significant ($P<0.05$). The expressions of PD-L1 protein and PD-L1 mRNA in the nasopharyngeal carcinoma tissues of the observation group were not related to age and sex ($P>0.05$). The positive rate of PD-L1 protein and the expression of PD-L1 and mRNA in nasopharyngeal carcinoma tissues in patients with TNM stage III-IV, lymph node metastasis and history of smoking were higher than those in patients with TNM stage I-II, no lymph node metastasis, and no smoking history ($P<0.05$). **Conclusion:** The expression of PD-L1 protein and PD-L1mRNA is highly expressed in nasopharyngeal carcinoma, and its expression is related to TNM staging, lymph node metastasis and smoking history.

Key words: Programmed cell death ligand -1; Nasopharyngeal carcinoma; Expression; Clinical significance

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作者简介:黄庆文(1979-),男,硕士,主治医师,从事头颈部肿瘤方面的研究,E-mail:uwegie@163.com

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前言

鼻咽癌是一种在鼻咽腔顶部以及侧壁发生的恶性肿瘤,是我国高发恶性肿瘤之一,其发病率在所有耳鼻咽喉类的恶性肿瘤中排首位^[1,2]。鼻咽癌患者临床表现为鼻塞、涕中带血、听力受损、复视及头疼等,其发病率主要与疾病家属史、种族、环境、易感基因、病毒感染有关^[3,4]。鼻咽癌患者对放化疗较为敏感,虽然大部分患者经过放化疗后近期疗效较好,但整体的生存时间仍然不理想,其主要原因是部分患者在治疗后出现了局部复发和转移,这部分患者的中位生存期仅为 19-21 个月^[5,6]。鼻咽癌患者在通过放化疗治疗后,杀灭了绝大部分的肿瘤细胞,然而部分残留的肿瘤细胞可通过各种免疫抑制机制来逃避活化免疫细胞的杀伤,进行分裂增殖,进而出现局部复发和转移,在这个过程中,共刺激分子对肿瘤细胞的免疫抑制起到了重要的作用^[7,8]。程序性死亡配体-1(PD-L1)是 B7 家族的一员,可通过与其受体 PD-1 相结合对 T 细胞的活化及增殖产生抑制作用,进而降低对肿瘤细胞的杀伤,多项研究表明,PD-L1 与肺癌、肝癌、胃癌、卵巢癌等多种恶性肿瘤有关^[9-11]。本研究通过对鼻咽癌组织进行免疫组化和逆转录-聚合酶链反应(RT-PCR)检测,旨在探讨 PD-L1 蛋白和 PD-L1 mRNA 在鼻咽癌组织中的表达及临床意义,现将研究结果报道如下。

1 资料与方法

1.1 一般资料

选取 2015 年 7 月-2017 年 6 月期间在我院接受治疗的鼻咽癌患者 333 例,收集其鼻咽癌组织作为观察组标本,纳入标准:①所有标本均经病理学检测确诊为鼻咽癌组织;②患者尚未接受过放化疗处理;③患者及其家属对本研究知情同意。排除标准:①患者临床资料不全者;②患有其他恶性肿瘤者;③合并有严重器质性疾病者。333 例患者中,男性 212 例,女性 121 例,年龄 36-69 岁,平均年龄(58.6±8.4)岁。TNM 分期:I-II 期 196 例,III-IV 期 137 例;淋巴结转移:187 例有淋巴结转移,146 例无淋巴结转移;吸烟史:164 例有吸烟史,169 例无吸烟史。另

选取同期在我院接受治疗的慢性鼻咽炎患者 102 例的鼻咽炎组织作为对照组标本,其中男性 68 例,女性 34 例;年龄 33-71 岁,平均年龄(58.4±7.8)岁。两组患者的性别比例以及年龄的比较无统计学差异($P>0.05$),可行组间对比。本研究符合我院伦理委员会的相关规定,并已获得委员会批准。

1.2 免疫组化法

取经过石蜡包埋的病理组织切片,二甲苯脱蜡处理,梯度酒精脱水,PBS 缓冲液冲洗 3 min,重复两次,滴加 3%过氧化氢 50 μ L,在室温下孵育 5 min,PBS 缓冲液冲洗 3 min,重复两次,甩去 PBS,进行 EDTA 高压热修复,自然冷却 30 min,蒸馏水大量冲洗,PBS 缓冲液冲洗 3 min,重复两次,甩去 PBS。滴加兔抗人 PD-L1 抗体(广州安必平医药科技有限公司),4℃过夜处理,PBS 缓冲液冲洗 3 min,重复两次,甩去 PBS。滴加即用型 Max Vision 试剂(广州安必平医药科技有限公司)50 μ L,在室温下孵育 15 min,PBS 缓冲液冲洗 3 min,重复两次,甩去 PBS。滴加 DAB 溶液(广州安必平医药科技有限公司)100 μ L 进行显色,3-5 min 后使用自来水冲洗,将组织标本浸入苏木素溶液中复染 10 min 左右,梯度酒精脱水干燥,二甲苯透明处理,滴加少量中性树胶,封片晾干。选取高倍镜(400×)下的 5 个视野,观察 PD-L1 阳性细胞占比情况。细胞膜或细胞质呈现棕黄色为 PD-L1 阳性,计算阳性细胞数与细胞总数的比值,最终结果为 5 个视野的均值。阳性细胞率<10%为(-),10%≤阳性细胞率≤25%为(+),25%<阳性细胞率≤75%为(++),阳性细胞率>75%为(+++),(+),(++),(+++)例数相加即为阳性总例数。

1.3 RT-PCR

采用 Trizol 法提取总 RNA,测定总 RNA 浓度及纯度。逆转录合成 cDNA 第一链产物。PD-L1 的引物序列由上海生工生物工程公司合成,以 β -actin 作为内参。PD-L1 和 β -actin 的引物序列和长度见表 1。PCR 扩增:(1)变性:反应条件为 94℃,45 s;(2)退火:58℃,1 min;(3)延伸:72℃,1 min;共进行 35 个循环。将扩增产物置于 1.5%琼脂糖中进行凝胶电泳,应用凝胶成像系统扫描电泳条带,并进行分析。PD-L1 的相对表达水平用 PD-L1/ β -actin 的比值表示。

表 1 PD-L1 和 β -actin 的引物序列和长度

Table 1 Primer sequences and lengths of PD-L1 and β -actin

Genes	Upstream and downstream primers	Primer sequences	Lengths
PD-L1	Upstream primers	5'-AAACAATTAGACCTGGCTG-3'	399 bp
	Downstream primers	5'-TCTTACCACTCAGGACTTG-3'	
β -actin	Upstream primers	5'-CCAGCCATGTACGTTGCTATC-3'	150 bp
	Downstream primers	5'-CAGGTCCAGACGACGAGGATGGC-3'	

1.4 观察指标

比较两组患者鼻咽组织中 PD-L1 蛋白的阳性率和 PD-L1 mRNA 的相对表达水平,并分析观察组患者鼻咽癌组织中临床病理参数与 PD-L1 蛋白的阳性率和 PD-L1 mRNA 的相对表达水平的关系。

1.5 统计学方法

所有数据均用 SPSS19.0 进行统计分析,计数资料以率(%)的形式表示,采用卡方检验,计量资料以($\bar{x} \pm s$)的形式表

示。以 $P<0.05$ 为差异有统计学意义。

2 结果

2.1 两组鼻咽组织中 PD-L1 蛋白的阳性率和 PD-L1 mRNA 的相对表达水平比较

对照组患者鼻咽炎组织中未见棕黄色颗粒,PD-L1 蛋白的阳性率为 0.00%(0/102);观察组患者鼻咽癌组织中存在部分棕黄色颗粒,多位于肿瘤的细胞质和细胞膜上,PD-L1 蛋白的阳

性率为 69.37%(231/333),两组 PD-L1 蛋白的阳性率比较差异有统计学意义($P<0.05$)。RT-PCR 结果显示,对照组患者鼻咽炎组织中未见 PD-L1 mRNA 表达,观察组患者鼻咽癌中 PD-L1 mRNA 的相对表达水平为 (0.82 ± 0.27), 差异有统计学意义 ($P<0.05$)。

2.2 鼻咽癌组织中 PD-L1 蛋白和 PD-L1 mRNA 的表达与临床

病理参数的关系

鼻咽癌组织中 PD-L1 蛋白和 PD-L1 mRNA 的表达与年龄、性别无关($P>0.05$),TNM 分期为 III-IV 期、有淋巴结转移、有吸烟史患者鼻咽癌组织中 PD-L1 蛋白阳性率和 PD-L1 mRNA 的表达均高于 TNM 分期 I-II 期、无淋巴结转移、无吸烟史患者($P<0.05$),详见表 2。

表 2 鼻咽癌组织中 PD-L1 蛋白和 PD-L1 mRNA 的表达与临床病理参数的关系

Table 2 Expression of PD-L1 protein and PD-L1 mRNA in nasopharyngeal carcinoma tissues and its relationship with clinicopathological parameters

Pathological parameters	n	PD-L1 protein		χ^2	P	PD-L1 mRNA	t	P
		+	-					
Age	<60 years old	183	124(67.76)	59(32.24)	0.495	0.81± 0.31	0.647	0.518
	60 years old	150	107(71.33)	43(28.67)		0.83± 0.24		
Gender	Male	212	148(69.81)	64(30.19)	0.054	0.81± 0.22	0.813	0.417
	Female	121	83(68.60)	38(31.40)		0.84± 0.37		
TNM stage	I-II stage	196	118(60.20)	78(39.80)	18.834	0.74± 0.31	4.606	0.000
	III-IV stage	137	113(82.48)	24(17.52)		0.91± 0.36		
Lymph node metastasis	Yes	187	152(81.28)	35(18.72)	28.492	0.73± 0.27	5.890	0.000
	No	146	79(54.11)	67(45.89)		0.94± 0.38		
Smoking history	Yes	164	126(76.83)	38(23.17)	8.463	0.86± 0.38	2.635	0.009
	No	169	105(62.13)	64(37.87)		0.76± 0.31		

3 讨论

鼻咽癌是一种在我国南方及东南亚区域高发的恶性肿瘤,其中广东省发病率高达 25-30/10 万,因此又被称为 "广东瘤"^[12,13]。鼻咽癌具有早期远处转移以及局部转移的特点,虽然目前以放射治疗技术为主的放疗综合治疗可以显著提高鼻咽癌患者的临床缓解率,但仍有部分鼻咽癌患者治疗后出现转移、复发,严重威胁患者生命安全,因此寻找新的治疗方法以降低鼻咽癌患者的转移、复发率具有重要的临床意义^[14,15]。近年来,免疫治疗成为肿瘤领域的研究热点,免疫治疗是指通过自身的免疫系统来识别和杀死肿瘤细胞,但其难点在于肿瘤细胞经常有逃避免疫系统的能力,在正常人体内机体的细胞免疫机制可对肿瘤细胞进行识别和清除,但在肿瘤微环境中存在着多种机制帮助肿瘤细胞逃避机体免疫系统识别和攻击^[16]。PD-L1 是活化 T 细胞表面 PD-1 的配体,其可以通过与 PD-1 结合抑制 T 细胞的活性,肿瘤细胞的免疫逃逸与 PD-1/PD-L1 信号通路密切相关^[17-19]。相关研究发现^[20-22],通过利用抗 PD-1、PD-L1 的单克隆抗体阻断 PD-1/PD-L1 信号通路,可明显恢复 T 细胞对肿瘤细胞的识别杀伤功能,这进一步说明 PD-1/PD-L1 信号通路对免疫系统存在抑制作用。

本次研究结果显示,对照组患者鼻咽炎组织中 PD-L1 蛋白的阳性率为 0.00%,观察组患者鼻咽癌组织中 PD-L1 蛋白的阳性率为 69.37%。对照组患者鼻咽炎组织中未见 PD-L1 mRNA 表达,观察组患者鼻咽癌组织中 PD-L1 mRNA 的相对表达水平为 (0.82 ± 0.27) ($P<0.05$)。这说明 PD-L1 蛋白和 PD-L1 mRNA 在鼻咽癌组织中呈现高表达,但在鼻咽炎组织中不表达,提

示 PD-L1 与鼻咽癌肿瘤的发生、发展可能存在一定的相关性。本研究结果还显示,鼻咽癌组织中 PD-L1 蛋白和 PD-L1 mRNA 的表达与年龄、性别无关($P>0.05$),TNM 分期为 III-IV 期、有淋巴结转移、有吸烟史患者鼻咽癌组织中 PD-L1 蛋白阳性率和 PD-L1 mRNA 的表达均高于 TNM 分期为 I-II 期、无淋巴结转移、无吸烟史患者($P<0.05$),这说明 PD-L1 蛋白和 mRNA 的高表达可能对肿瘤的发展具有一定的促进作用。目前关于 PD-L1 在肿瘤细胞发生免疫逃逸中的具体作用机制尚无统一说法。Chen BJ 等人研究发现^[23-25],PD-L1 只在病毒和免疫缺陷相关的恶性肿瘤中表达,其对 18 例鼻咽癌组织进行检验发现 PD-L1 蛋白的阳性表达高达 88.89%(16/18),与本研究结果类似。PD-L1 通过与其受体 PD-1 结合,可以启动 G_q/G_i 的检查点,从而导致大部分细胞停留在细胞增殖周期时相,降低了进入细胞周期的细胞数量^[26-28]。PD-1/PD-L1 途径既可以对 T 细胞增殖产生抑制作用,同时也可以减少白介素 2、干扰素等细胞因子的分泌,这些作用对机体免疫功能下调起到了一定的作用^[29,30]。同时,在机体出现癌变时,上调了细胞表面的 PD-L1 表达,其通过与 T 细胞表面的 PD-1 相结合,对 T 细胞的活化、增殖产生抑制作用,进而降低免疫反应,减少对肿瘤的杀伤。由于 PD-L1 表达上调对免疫功能有抑制作用,因此其将会促进病情的发展,本研中 TNM 分期越高、有淋巴结转移、有吸烟史患者其 PD-L1 蛋白和 mRNA 表达更高,这也说明 PD-L1 与鼻咽癌的发展有一定的关系。目前,关于 PD-L1 的研究尚处于初级阶段,关于抗 PD-1/PD-L1 途径的免疫治疗已是研究热点,后续可进一步分析 PD-1/PD-L1 途径的具体作用机制,以为临床治疗鼻咽癌提供新的思路。

综上所述,在鼻咽癌组织中 PD-L1 蛋白和 PD-L1 mRNA 呈现高表达,且其表达与 TNM 分期、淋巴结转移、吸烟史有关,PD-L1 可能参与了鼻咽癌的发生与发展,抗 PD-L1 治疗可能成为临床上治疗鼻咽癌的新靶点。

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