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·临床研究·

甲状腺滤泡癌组织中PD-L1与dMMR相关蛋白表达的关系及其临床意义

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[摘 要] **目的**:探讨甲状腺滤泡癌组织中PD-L1与dMMR相关蛋白表达的关系及其临床意义。**方法**:收集2015年1月至2020年6月福建医科大学附属第二医院60例甲状腺滤泡癌患者的癌组织蜡块,再次经H-E染色确诊,采用免疫组化法检测癌组织和癌旁组织中PD-L1的表达以及MMR系统4个基因(MLH1、MSH2、MSH6、PMS2)编码的4种同源蛋白表达情况,分析甲状腺滤泡癌组织中PD-L1表达与MMR相关蛋白缺失的关系及其临床意义。**结果**:60例甲状腺滤泡癌组织中,PD-L1表达率显著高于癌旁组织[(63.3%(38/60) *vs* 11.7%(7/60),*P*<0.05)];PD-L1的表达与肿瘤的直径、甲状腺外浸润、血管侵犯、复发与否具有显著相关性(均*P*<0. 05)。60例患者癌组织标本中,24(40.0%)例患者4种MMR相关蛋白均有表达,为pMMR肿瘤;36(60.0%)例出现1种或多种MMR相关蛋白表达缺失,为dMMR肿瘤。dMMR型甲状腺滤泡癌与患者有无淋巴结转移和肿瘤分期有显著相关性(均*P*<0. 05)。PD-L1与dMMR发生率成正相关,前者是肿瘤复发的独立风险因素,后者与患者有更好的预后相关。PD-L1$^+$/pMMR患者与肿瘤更高恶性程度相关,而PD-L1$^+$/dMMR患者与肿瘤病理特征无关,但可能容易从免疫治疗中获益。**结论**:PD-L1阳性表达及dMMR在甲状腺滤泡癌中有较高的发生率,前者与肿瘤侵袭性增加相关,且是肿瘤复发的独立风险因素,而后者是甲状腺滤泡癌发生过程中的早期分子事件,且与患者有更好的预后相关。

[关键词] 甲状腺滤泡癌;程序性死亡配体1;错配修复功能缺陷;侵袭;复发;预后
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Correlation between the expression of PD-L1 and dMMR related proteins in follicular thyroid carcinoma tissues and its clinical significance

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[Abstract] Objective: To investigate the correlation between PD-L1 expression and dMMR related proteins in follicular thyroid carcinoma tissues and its clinical significance. **Methods:** The postoperative paraffin-embedded tissue samples from 60 patients with thyroid follicular carcinoma were collected from the Second Affiliated Hospital of Fujian Medical University during January 2015 and June 2020. The collected samples were re-confirmed as thyroid follicular carcinoma tissues by Hematoxylin-eosin staining. The expression of PD-L1 and four homologous proteins encoded by four genes (MLH1, MSH2, MSH6, PMS2) in MMR system were detected by immunohistochemistry in the cancer and paracancerous tissues. The relationship between the expression of PD-L1 and depletion of MMR related proteins in thyroid follicular carcinoma tissues and its clinical significance were analyzed. **Results:** The positive expression rate of PD-L1 was significantly higher in the follicular thyroid carcinoma tissues than that in paracancerous tissues [63.3%(38/60) *vs* 11.7%(7/60), *P*<0.05]. The expression of PD-L1 was significantly correlated with tumor diameter, extrathyroidal infiltration, vascular invasion and recurrence (all *P*<0.05). In the cancer tissue specimens from 60 patients, 24 (40.0%) had expression of four MMR related proteins, which were pMMR tumors, and 36 (60.0%) had depletion of one or more MMR related proteins, which were dMMR tumors. The dMMR-type thyroid follicular carcinoma was significantly correlated with the status of lymph node metastasis and tumor staging (all *P*<0.05). PD-L1 was positively correlated with the incidence of dMMR, and PD-L1 was an independent risk factor for disease recurrence, while dMMR was associated with a better prognosis. Patients with PD-L1$^+$/pMMR type were associated with higher tumor malignancy, while patients with PD-L1$^+$/dMMR type were not associated with tumor pathological features but may easily benefit from immunotherapy. **Conclusion:** Positive PD-L1 expression and dMMR highly occur in follicular

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thyroid carcinoma. PD-L1 is associated with the increased tumor invasion and is an independent risk factor for disease recurrence, while dMMR is an early molecular event in the development of thyroid follicular carcinoma and is associated with better prognosis of patients.

[Key words] follicular thyroid carcinoma; programmed death-ligand 1(PD-L1); defective DNA mismatch repair (dMMR); invasion; recurrence; prognosis

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甲状腺滤泡癌（follicular thyroid carcinoma，FTC）占甲状腺癌所有类型的10%~15%[1-2]，是分化型甲状腺癌（differentiated thyroid carcinoma，DTC）中预后较差的一个类型，经过标准治疗后仍有约20%的患者出现术后复发和转移[3]。对于这部分患者，传统治疗的疗效往往不尽人意，需寻找更加有效的治疗手段。近年来，使用免疫检查点抑制剂的疗法在多个系统肿瘤中取得快速进展，该疗法能使晚期甲状腺癌患者获益[4]，有望成为这部分患者新的治疗方法。程序性死亡配体1（programmed death-ligand 1，PD-L1）及错配修复功能缺陷（defective DNA mismatch repair，dMMR）/高频微卫星不稳定（microsatellite instability high，MSI-H）是免疫检查点抑制剂发挥效应的的重要指标，dMMR是指其4个重要基因（MLH1、PMS2、MSH2、MSH6）中有1个或多个产生突变，导致它们编码蛋白的缺失表达，为dMMR肿瘤[5]。研究显示[6-7]，对于dMMR/MSI-H实体瘤患者，无论肿瘤起源的组织类型如何，免疫治疗都能使患者获益。因此，检测甲状腺滤泡癌中PD-L1的表达及MMR相关蛋白表达缺失情况对于筛选可能从免疫治疗中获益的患者具有重要临床意义。本研究检测了甲状腺滤泡癌组织中PD-L1与dMMR相关蛋白表达的关系并探讨其临床意义。

1　资料与方法

1.1　临床资料

收集2015年1月至2020年6月福建医科大学附属第二医院病理科存档的60例甲状腺癌滤泡癌组织和癌旁组织的蜡块，再次经H-E染色后由病理科2位以上病理医师确诊。所有患者术前均未接受放、化疗，无合并其他系统恶性肿瘤，经过标准手术后均未进行辅助放、化疗。门诊或电话随访术后复发情况。所有患者均签署知情同意书，研究方案和程序经医院伦理委员会批准。

1.2　主要试剂

浓缩型鼠抗人PD-L1/CD274单克隆抗体（克隆号2B11D11）、MLH1（多克隆抗体）、MSH2（克隆号2H5F5）、MSH6（克隆号2E10B2）、PMS2（克隆号1G4E6）单克隆抗体购自Proteintech公司，抗体稀释浓度为PD-L1（1∶1 600）、MLH1（1∶400）、MSH2（1∶400）、MSH6（1∶1 600）、PMS2（（1∶1 200）。抗体稀释液、鼠/兔通用二抗、PBS缓冲液、DAB染色剂均购自福州迈新公司。

1.3　免疫组化Envision法检测PD-L1及dMMR相关蛋白的表达

所有标本均经4%甲醛固定，石蜡包埋，4μm厚连续切片，切片后烤片、脱蜡及水化，以柠檬酸抗原修复液高压抗原修复，阻断内源性过氧化氢酶活性，滴加一抗（PD-L1、MLH1、MSH2、MSH6、PMS2）常温孵育1.5 h后弃去，二抗常温孵育30 min；DAB常温显色1.5 min，置入去离子水中终止显色，苏木精复染、盐酸酒精分化、梯度酒精脱水，吹风机吹干，中性树脂封固，盖玻片封片后即可显微镜下观察。用已知阳性组织作为阳性对照，以PBS代替一抗作为阴性对照。免疫组化染色阳性评估由2名病理科医生采用双盲法操作。PD-L1蛋白定位于细胞质及细胞膜，阳性染色≥1%为PD-L1阳性[8]。MMR相关蛋白MLH1、MSH2、MSH6、PMS2均定位于细胞核，任一细胞表达阳性即判定免疫组化染色阳性；所有细胞表达阴性即判定为蛋白缺失，4种蛋白中任一蛋白表达缺失为dMMR[9]。

1.4　统计学处理

所有数据采用SPSS 23.0统计学软件进行作图和统计学分析，PD-L1及MMR相关蛋白表达与甲状腺癌滤泡癌病理特征关系采用χ^2或者Fisher精确检验，PD-L1表达与MMR相关蛋白表达的关系采用Pearson相关性分析，生存分析应用Kaplan-Meier生存曲线法，多因素分析采用Logistic回归法，以P<0.05或P<0.01表示差异有统计学意义。

2　结　果

2.1　甲状腺滤泡癌患者的临床资料和病理特征

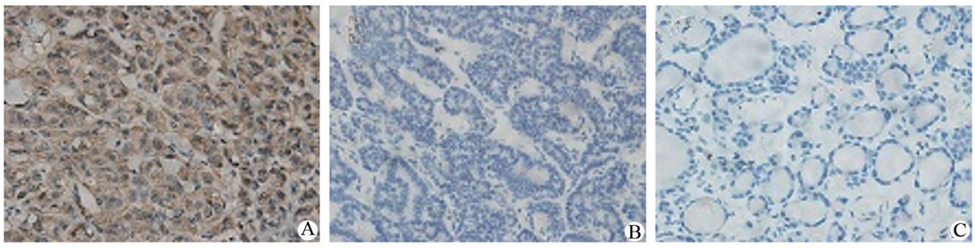
60例甲状腺滤泡癌患者中，男性18例、女性42例；年龄20～83岁，平均（45.3±14.72）岁，中位年龄31岁；术后病理确诊有癌细胞转移病灶多于1个的占36.67%，淋巴结转移的占15.00%，病理分期为Ⅰ-Ⅱ期的占83.33%。以结构复发为诊断标准，对所有患者进行随访，随访中位数时间是28.5个月，共有11例患者发生复发。

2.2 甲状腺滤泡癌组织中PD-L1的表达及其与病理特征的关系

PD-L1表达阳性定位于细胞膜和细胞质，阳性染色为棕褐色。60例甲状腺滤泡癌组织中PD-L1表达率为63.3%(38/60)、癌旁组织表达率为11.7%(7/60)，PD-L1在癌组织中的表达率显著高于癌旁组织(P<0.05，图1)。PD-L1的表达与肿瘤的直径、甲状腺外浸润、血管侵犯、复发转移具有显著相关性(均P<0.05)，与患者的年龄、性别、肿瘤病灶数、淋巴结转移以及TNM分期无显著相关性(表1)。

2.3 甲状腺滤泡癌组织中dMMR相关蛋白的表达及其与病理特征的关系

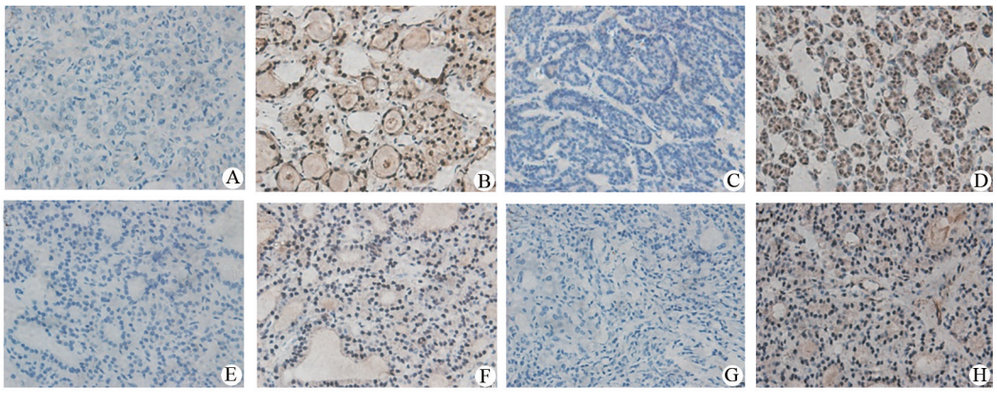
dMMR系统中的4个蛋白MLH1、MSH2、MSH6、PMS2表达均定位于细胞核，阳性染色为棕褐色。60例甲状腺滤泡癌组织中，24(40.0%)例患者4种相关蛋白均有表达，为错配修复功能正常(proficient DNA mismatch repair，pMMR)型肿瘤；36(60.0%)例出现1种或多种MMR相关蛋白表达缺失，为dMMR型肿瘤(图2)。1/2/3/4种蛋白缺失分别有10(16.7%)/20(33.3%)/4(6.7%)/2(3.3%)例，其中1种蛋白缺失的5(8.3%)例为MLH1缺失、5(8.3%)例为PMS2缺失，2种蛋白缺失的9(15%)例为MLH1/PMS2联合缺失、5例(8.3%)为MSH2/MSH6联合缺失、6例(10.0%)为其他类型组合，3种蛋白联合缺失的2例为MLH1/MSH2/MSH6联合缺失、1例为MLH1/PMS2/MSH6联合缺失、1例为PMS2/MSH2/MSH6联合缺失。dMMR型甲状腺滤泡癌与患者的年龄、性别、病灶直径、病灶多灶性、甲状腺外浸润、血管侵犯、复发与否无显著相关性，而与患者有无淋巴结转移和肿瘤分期(AJCC第8版甲状腺癌分期标准[10])有显著相关性，肿瘤分期为Ⅰ-Ⅱ期dMMR发生率显著高于肿瘤分期为Ⅲ-Ⅳ期(34/50 *vs* 2/10，P<0.05)、无淋巴结转移发生率显著高于有淋巴结转移的患者(34/51 *vs* 2/9，P<0.05)(表1)。



Positive(A)/negative(B) expression of PD-L1 proteins in follicular thyroid carcinoma and negative(C) in paracancerous tissues

图1 甲状腺滤泡癌组织(A/B)和癌旁组织(C)中PD-L1的表达(×200)

Fig.1 The expression of PD-L1 in follicular thyroid carcinoma tissues (A/B) and paracancerous tissues (C)(×200)



Negative expression of MLH1(A)/PMS2(C)/MSH2(E)/MSH6(G) proteins in follicular thyroid carcinoma tissues and positive expression of MLH1(B)/PMS2(D)/MSH2(F)/MSH6(H) proteins in follicular thyroid carcinoma tissues

图2 甲状腺滤泡癌中dMMR相关蛋白的表达(×200)

Fig.2 The expression of dMMR related proteins in follicular thyroid carcinoma tissues(×200)

2.4 PD-L1表达与dMMR相关蛋白表达的关系

PD-L1表达与dMMR相关蛋白表达的关系采用Sperson相关性分析，结果显示dMMR患者PD-L1表达率显著增高，dMMR及pMMR的PD-L1表达率为71.1% *vs* 40.9%(P<0.05)。虽然结果显示MLH1/PMS2及MSH2缺失的患者中PD-L1的表达率较高(77.3%

vs 55. 3%，*P*>0. 05）及（79. 0% *vs* 56. 1%, *P*>0. 05），但差异无统计学意义（表2）。同时对PD-L1$^+$/pMMR及PD-L1$^+$/dMMR型肿瘤与其他类型肿瘤的临床病理特征进行对比，结果显示，前者更容易发生淋巴结转移、病理分期更晚（均*P*<0. 05），而后者与患者的临床病理特征均无显著性关系（*P*>0. 05）（表1）。

表1 甲状腺滤泡癌组织中PD-L1及dMMR相关蛋白表达与病理特征的关系

Tab.1 The correlation between the expression of PD-L1 and dMMR related proteins in follicular carcinoma tissues with clinicopathology features

Feature	*N*	PD-L1				MMR				PD-L1$^+$/pMMR				PD-L1$^+$/dMMR			
		+	-	χ^2	*P*	pMMR	dMMR	χ^2	*P*	Yes	No	χ^2	*P*	Yes	No	χ^2	*P*
Age (*t*/a)																	
＜55	46	29	17	0.007	1.000	16	30	2.236	0.212	8	38	0.117	1.000	21	25	0.034	1.000
≥55	14	9	5			8	6			3	11			6	8		
Gender																	
Male	42	27	15	0.6	0.500	18	24	0.476	0.573	9	33	0.896	0.478	17	25	1.158	0.397
Female	18	11	7			6	12			2	16			10	8		
Sites(*d*/cm)																	
≤4	32	16	16	5.249	0.032	14	18	0.402	0.603	5	27	0.336	0.740	13	19	0.530	0.604
＞4	28	22	6			10	18			6	22			14	14		
Multifocal																	
Positive	22	17	5	2.907	0.104	10	12	0.431	0.589	7	15	4.219	0.080	11	11	0.351	0.599
Negative	38	21	17			14	24			4	34			16	22		
Extrathyroid infiltration																	
Positive	12	11	1	5.185	0.041	5	7	0.017	1.000	4	8	2.254	0.206	6	6	0.152	0.754
Negative	48	27	21			19	29			7	41			21	27		
LN metastasis																	
Positive	9	7	2	0.951	0.464	7	2	6.296	0.023	5	4	9.798	0.002	5	4	0.477	0.781
Negative	51	31	20			17	34			6	56			22	29		
Vascular invasion																	
Positive	36	27	9	5.275	0.030	14	22	0.046	1.000	9	27	2.672	0.173	16	20	0.011	1.000
Negative	24	11	13			10	14			2	22			11	13		
TNM stage[a]																	
Ⅰ-Ⅱ	50	31	19	0.230	0.732	16	34	8.000	0.010	6	44	8.037	0.005	22	28	0.121	1.000
Ⅲ-Ⅳ	10	7	3			8	2			5	5			5	5		
Recurrence																	
Yes	11	10	1	4.411	0.043	5	6	0.167	0.467	4	7	2.925	0.189	4	7	0.306	0.739
No	49	28	21			19	30			7	42			23	26		

a: According to the AJCC staging criteria (English edition) for thyroid cancer

表2 PD-L1与dMMR相关蛋白表达的关系

Tab.2 The correlation between the expression of PD-L1 and dMMR related proteins

Index	PD-L1		*r*	*P*
	+	-		
MMR				
dMMR	27	9	0.297	0.021
pMMR	11	13		
MLH1				
+	21	17	0.220	0.091
-	17	5		
PMS2				
+	21	17	0.220	0.091
-	17	5		
MSH2				
+	23	18	0.221	0.090
-	15	4		
MSH6				
+	27	18	0.120	0.362
-	11	4		

2.5　PD-L1与dMMR相关蛋白表达对患者生存和预后的影响

通过绘制Kaplan-Meier曲线进行患者生存期分析显示，PD-L1表达与患者的无进展生存期（PFS）及总生存期（OS）无显著相关性，而dMMR相比于pMMR肿瘤有更好的PFS及OS，差异有统计学意义（*P*<0. 05）（图3）。

将所有患者分为复发和非复发组，通过多因素Logistic回归分析PD-L1及dMMR与疾病复发的关系，发现PD-L1是疾病复发的独立风险因素（*P*<0. 05），而dMMR不是复发的独立风险因素（*P*>0. 05）（表3）。

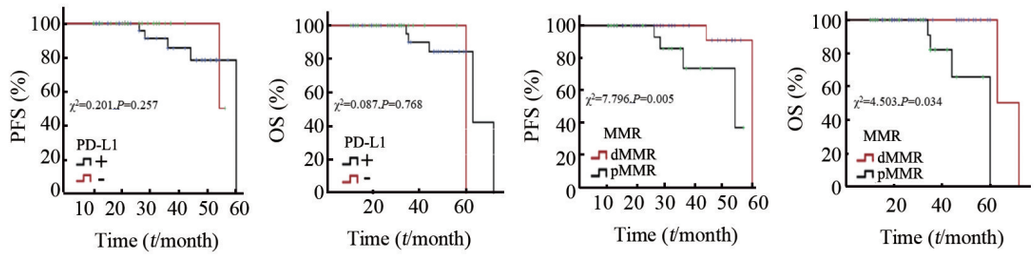


图3 Kaplan-Meier法分析PD-L1与dMMR相关蛋白表达与患者PFS及OS的关系

Fig.3 Correlation of PFS and OS with the expression of PD-L1 and dMMR related proteins analyzed by Kaplan-Meier curve

表3 甲状腺滤泡癌PD-L1及dMMR与患者预后的多因素分析

Tab.3 Multivariate analysis of the expression of PD-L1 and dMMR with prognosis of follicular thyroid carcinoma patients

Variable	Regression coefficient	SE	Wald	*P*	EXP(B)
PD-L1	2.307	1.130	4.165	0.041	10.044
dMMR	-0.837	0.739	1.280	0.258	0.433

3 讨 论

癌细胞试图通过抑制肿瘤特异性免疫T细胞和NK细胞、诱导抑制性T细胞表达等多种机制逃避免疫系统的识别和清除[11]。PD-1是一种免疫共抑制分子，PD-L1是其发挥免疫效应的主要配体[12]。PD-L1与T细胞表面的PD-1结合，可激活下游信号转导途径并抑制T细胞增殖及细胞因子的分泌，发挥负性免疫调节作用，从而促使肿瘤细胞免疫逃逸[13-14]。因此PD-L1的高表达与肿瘤的恶性度增加和不良预后相关，可能可以成为肿瘤预后指标之一。另外，PD-L1的表达水平是预估免疫治疗疗效的重要指标之一。AHN等[15]探索甲状腺癌组织中PD-L1表达，发现仅有7.6%的FTC表达PD-L1，且与肿瘤病理特征无显著相关性。然而ZHOU等[16]的研究显示，FTC患者PD-L1表达率为67%，且与临床病理特征如肿瘤大小、T分期、TNM分期、转移等相关，抑制PD-L1信号可以延缓肿瘤在体内的生长和转移，推测免疫检查点抑制剂可能对FTC患者有效。本实验结果显示，PD-L1在FTC组织中的表达率为63.3%（38/60），PD-L1高表达的肿瘤直径更大和更容易发生甲状腺外浸润、血管侵犯、复发转移，说明PD-L1的表达与肿瘤侵袭性增加相关，与ZHOU等[16]的实验结果相似。

研究[6, 17-18]表明，dMMR/MSI-H肿瘤具有高突变的特征，该类型患者能够从免疫检查点抑制剂中获益，而与具体的组织来源和癌种无关；2017年FDA批准帕博丽珠单抗用于经治无效且无其他替换方案dMMR/MSI晚期实体瘤的治疗。因此，免疫治疗可能成为经治无效的晚期dMMR/MSI-H甲状腺滤泡癌患者一种新的治疗方式。目前患者的dMMR/MSI状态可以通过免疫组化法及PCR来检测，两种的检测方法符合率可达到93.4%[19]。因免疫组化法的成本低，2018年ESMO指南专家共识推荐先行免疫组化法检测[20-21]。dMMR/MSI在FTC中的发生率为2%~75%，可能与抗体的选择、实验方法、结果判读标准不同及肿瘤异质性有关。SANTOS[22]等研究显示，dMMR/MSI在FFC中的发生率为75%，MSI不是甲状腺肿瘤发生的早期事件，该机制参与了肿瘤的进展，与肿瘤的恶性度和病理因素有关，且预示着不良的预后，该结果与MITMAKER等[22-23]的研究结果相似。然而，DOBOSZ等[24]的研究却显示，MSI主要发生于肿瘤的早期阶段。GENUTIS[25]等对484例甲状腺癌患者（包括156例FTC患者）进行了dMMR/MSI检测，结果发现，在FTC中仅有4例表现为MSI-H（2.5%）。本研究60例甲状腺滤泡癌患者中，40%的患者为pMMR型肿瘤，60%为dMMR型肿瘤。dMMR型甲状腺滤泡癌较少发生淋巴结转移且分期较早，说明dMMR/MSI-H可能是甲状腺癌滤泡癌的早期事件，与DOBOSZ等[24]的研究结果一致。

ESMO指南[26]指出，在多个癌种中dMMR/MSI发生率和PD-L1表达具有相关性，dMMR/MSI患者中具有更高的PD-L1表达，而PD-L1高表达是免疫检查点抑制剂发挥疗效的一种重要指标，这也许可以解释dMMR/MSI肿瘤对免疫治疗有良好的反应。本研究结果显示，dMMR肿瘤PD-L1表达率显著增高，提示甲状腺滤泡癌组织中PD-L1及dMMR相关蛋白的表达可能存在相互调控的机制。PD-L1^{+}/pMMR型的肿瘤对比其他类型的肿瘤更容易发生淋巴结转移且分期较晚，亦提示了两者的蛋白表达可能存在相互促进作用；而PD-L1^{+}/dMMR型与患者的临床病理特征均无显著性关系，但可能更容易从免疫治疗中获益。另外，生存期及预后分析发现，dMMR相比于pMMR肿瘤有更好的PFS及OS，然而PD-L1高表达与患者的PFS、OS无显著相关性。其可能原因是随访时间较短，甲状腺滤泡癌患者大部分在10年内发生复发，本研究的中位随访时间仅为28.5个月，尚未达到临床终点，故而未能发现PD-L1表达与PFS/OS的相关性。

综上所述，PD-L1阳性、dMMR在甲状腺滤泡癌组织中有较高的发生率，免疫治疗可能对晚期甲状腺滤泡癌患者有效，改善这部分患者的预后。PD-L1、MMR蛋白的联合检测有望更加准确地筛选可能从免疫治疗中获益的患者，对指导临床治疗具有重要意义。但甲状腺滤泡癌组织中PD-L1及dMMR相关蛋白表达的临床意义及其对免疫治疗的反应，仍需要通过更多大样本、前瞻性临床研究进一步验证。

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