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原发性肝癌中PD-L1表达的调控机制

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原发性肝癌中PD-L1表达的调控机制

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Regulatory Mechanism of PD-L1 Expression in Primary Liver Cancer

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Abstract: The application of immunotherapy has become a hot spot in tumor research currently. In particular, immune checkpoint inhibitors have played an important role in the treatment of advanced unresectable primary liver cancer. However, the efficacy of immune checkpoint inhibitors varies greatly in the treatment of different patients, which has aroused people's attention to the regulatory mechanism of PD-L1 in the immune escape of liver tumors. PD-L1 is regulated by multiple levels and multiple signaling pathways in liver cancer, including gene mutation, epigenetic mechanisms, transcriptional regulation, post-transcriptional regulation and post-translational modification. Studies have also found that the high expression of PD-L1 may be the main factor affecting the immunotherapy of primary liver cancer. Therefore, it can provide more evidence for immunotherapy and immune combination therapy strategies of primary liver cancer by clarifying the regulatory mechanism of PD-L1.

Key words: Primary liver cancer; PD-L1; Immunotherapy; Regulatory mechanism

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摘 要: 免疫疗法的应用是目前肿瘤研究的热点,尤其是免疫检查点抑制剂在晚期不可手术切除原发性肝癌的治疗中发挥了重要的作用。但不同患者免疫检查点抑制剂治疗疗效的差异较大,这引起了行业对PD-L1在肝脏肿瘤免疫逃逸中的调节机制的关注。PD-L1在肝癌中是由多个层次和多个信号通路调控的,包括表观遗传、转录调控、转录后调控和翻译后修饰。有研究发现PD-L1的高表达可能是影响原发性肝癌免疫治疗的主要因素,因此明确原发性肝癌中PD-L1的调控机制,可为原发性肝癌免疫治疗以及免疫联合治疗策略提供更多的依据。

关键词: 原发性肝癌; PD-L1; 免疫治疗; 调控机制

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0 引言

原发性肝癌是全球第三大癌症死亡原因,其中肝细胞癌(hepatocellular carcinoma, HCC)约占原发性肝癌的75%~85%^[1]。几十年来,有效改

善晚期肝癌预后的疗法较少。酪氨酸蛋白激酶抑制剂如索拉非尼、瑞戈非尼和乐伐替尼被认为是最有效的靶向药物,并且是晚期肝癌患者的唯一有效疗法^[2]。然而,最近一项关于索拉非尼在亚太地区晚期肝癌患者中的有效性和安全性临床试验证明,索拉非尼只能将晚期HCC患者的生存期延长3月,并且出现了耐药的问题^[3]。

免疫治疗被誉为肿瘤学的重大突破。最近研究发现靶向程序性细胞死亡受体配体-1(programmed cell death ligand 1, PD-L1)/程序性细胞死亡受体-1(programmed cell death 1, PD-1)的药物在HCC治疗中具有显著的抗肿瘤作用^[4],在HCC肿瘤微环境中,PD-L1主要在肿瘤细胞和宿主免疫细胞中表达。PD-L1表达增加导致抗肿瘤

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T细胞迁移、增殖和细胞毒性分泌的抑制^[5]。因此,明确PD-L1在肝癌中的调控机制对于免疫治疗至关重要。

1 PD-L1在宿主免疫细胞上的表达

1.1 骨髓来源抑制细胞 (myeloid-derived suppressor cells, MDSCs)

骨髓来源的抑制细胞在免疫调节中起重要作用,但MDSCs在肝细胞癌患者中的免疫抑制功能尚未阐明。高表达集落刺激因子1 (colony stimulating factor 1, M-CSF) 和血管内皮生长因子A (vascular endothelial growth factor A, VEGFA) 的肝癌细胞系显著诱导MDSCs PD-L1的表达^[6]。进一步研究发现MDSCs有助于肿瘤免疫抑制微环境形成。HCC患者的肿瘤浸润性CD11b⁺CD33⁺HLA-DR-MDSCs可以有效抑制CD8⁺T细胞的增殖。进一步研究发现肝细胞周期蛋白依赖性激酶 (cyclin dependent kinase, CCRK) 通过激活EZH2/核转录因子- κ B (nuclear transcription factor- κ B, NF- κ B) / IL-6级联反应导致MDSCs积累^[7]。相反,值得注意的是,肿瘤性CCRK耗竭上调了PD-L1表达并增加了肿瘤内CD8⁺T细胞,从而增强了PD-L1抗体治疗肝癌的作用。

1.2 肿瘤相关巨噬细胞

巨噬细胞分化与肝细胞癌的发生密切相关。巨噬细胞分化相关基因 (macrophage differentiation-associated genes, MDGs) 中的CDC42与M2巨噬细胞标志物和免疫检查点呈正相关, CDC42的表达与Wnt信号通路密切相关。研究表明CDC42是肝癌中重要的MDGs, 并且被证明是研究肝癌中巨噬细胞分化的新基因^[8]。类赖氨酰氧化酶4 (lysyl oxidase like 4, LOXL4) 是一种胺氧化酶, 主要参与细胞外基质重塑, 并在肝细胞癌组织中高表达, 但其在介导肝癌发生中的功能未知。LOXL4对巨噬细胞的免疫抑制功能主要依赖于IFN介导的STATs依赖性PD-L1活化, 从而进一步抑制CD8⁺T细胞的功能^[9]。

研究发现肝癌外周血单核细胞中的肿瘤浸润性T细胞的O型蛋白酪氨酸磷酸酶受体 (protein tyrosine phosphatase receptor type o, PTPRO) 显著降低, 并且PTPRO与肝癌外周血单核细胞和肿瘤相关巨噬细胞中PD-L1表达的增加有关。血清IL-6通过激活STAT3/c-MYC/miR-25-3p轴, 降低PTPRO的表达, 引起PD-L1诱导的免疫抑制来促进肿瘤生长^[10]。HCC细胞发生内质网应激, 并以释放外泌

体的形式促进免疫抑制的形成, 外泌体通过miR-23a-PTEN-AKT途径上调巨噬细胞中PD-L1的表达, 巨噬细胞进一步抑制T细胞功能^[11]。这些研究为深入了解肿瘤细胞的肿瘤免疫逃避机制提供了依据。

1.3 单核细胞

活化单核细胞释放的自分泌肿瘤坏死因子- α (tumor necrosis factor- α , TNF- α) 和IL-10刺激单核细胞自身PD-L1的表达。PD-L1阳性单核细胞可有效抑制肿瘤特异性T细胞免疫, 并促进人体内肿瘤的生长。肿瘤来源的可溶性因子透明质酸片段诱导了肿瘤相关的单核细胞中关键糖酵解酶PFKFB3的上调, 该酶通过激活细胞中的NF- κ B信号促进PD-L1的表达^[12]。该机制揭示了细胞代谢可以调节肿瘤微环境中单核细胞的促肿瘤功能。

在肿瘤微环境中, 免疫逃逸的关键驱动因素肿瘤细胞内源性骨桥蛋白 (osteopontin, OPN) 具有致癌活性, 肝癌组织中OPN和PD-L1表达以及肿瘤相关巨噬细胞 (tumor-associated macrophage, TAM) 浸润之间存在正相关。OPN促进了巨噬细胞趋化性迁移和替代激活, 并通过激活巨噬细胞中的CSF1-CSF1R途径促进肿瘤细胞中PD-L1的表达^[13], 阻断该途径可防止TAM转运, 从而增强免疫检查点抑制剂治疗HCC的疗效。

M1型巨噬细胞被认为具有杀伤肿瘤作用, 但一些研究报道了其促进肿瘤的作用。CD68⁺HLA-DR⁺M1型巨噬细胞的浸润与HCC细胞中PD-L1表达水平有关, M1型巨噬细胞分泌IL-1 β 可诱导肿瘤细胞NF- κ B p65和转录调节因子-1 (interferon regulatory factor-1, IRF-1) 的表达, 促进PD-L1表达^[14]。

PD-L1水平的升高代表了肿瘤细胞响应内源性抗肿瘤活性而产生的适应性免疫抵抗机制, 肿瘤细胞PD-L1的上调主要是由肿瘤微环境中存在的活化CD8⁺T细胞诱导的, 它是HCC有利的预后因素^[15]。也有研究认为PD-L1能下调肿瘤微环境中T细胞活化相关的基因。高表达PD-L1的小鼠肝癌细胞系BNL-MEA与CD8⁺T细胞共培养可降低T细胞增殖以及细胞因子IFN- γ 和TNF- α 的表达^[16]。虽然表达PD-L1的肿瘤显示出对抗PD-1治疗更好的反应, 但是CD8⁺T细胞的耗竭消除了抗PD-1的抗肿瘤效果。

2 PD-L1的表现遗传调控

果蝇zeste基因增强子的人类同源物2 (enhancer of zeste homolog 2, EZH2) 以IFN- γ 依赖性方式

负调控肝癌细胞系PD-L1的表达。EZH2可以通过上调CD274启动子上的组蛋白H3的N端第27位赖氨酸三甲基化水平(编码PD-L1)和干扰素调节因子1(IRF1)来抑制PD-L1表达^[17], EZH2是免疫联合治疗HCC的潜在治疗靶点。

3 PD-L1转录调控

3.1 STAT3信号通路

研究发现信号转导与转录激活因子3(signal transducer and activator of transcription 3, STAT3)与PD-L1启动子结合, 转录调控PD-L1表达^[18]。

STAT3活性降低, 则降低IFN- γ 诱导的PD-L1表达, 并恢复T细胞杀伤肿瘤细胞功能^[19]。另外, STAT3上游分子通路对STAT3的磷酸化和糖基化修饰, 也影响PD-L1的表达。D蛋白酪氨酸磷酸酶受体(protein tyrosine phosphatase receptor type D, PTPRD)是一种重要的肿瘤抑制基因, 可通过抑制STAT3磷酸化, 抑制PD-L1的表达^[20]。高尔基膜蛋白1(Golgi membrane protein 1, GOLM1)作为一种致癌基因, 通过选择性地与EGFR结合促进肝癌的生长和转移。另外, 研究还发现GOLM1通过增强EGFR的水平来促进STAT3的磷酸化, 而上调PD-L1的转录表达^[21]。Toll样受体9(Toll-like receptors 9, TLR9)负调节PARP1表达, 从而介导STAT3多聚ADP核糖基化修饰(Poly(ADP-ribosyl)ation, PARylation)的减少和STAT3 Tyr705磷酸化的增加, 促进PD-L1转录^[22]。

3.2 MAPK信号通路

有丝分裂原活化蛋白激酶(mitogen-activated protein kinase, MAPK)信号通路与肝癌中PD-L1基因的表达有关。表皮生长因子(epidermal growth factor, EGF)或IFN- γ 的刺激可增加PD-L1转录和蛋白水平的表达。表皮生长因子受体、丝裂原活化蛋白激酶激酶1和丝裂原活化蛋白激酶激酶2阻断, 可抑制EGF和IFN- γ 诱导的PD-L1转录和蛋白表达水平上调。IFN- γ 增加了PD-L1的转录活性, 而MAPK信号转导增加了PD-L1 mRNA的稳定性^[23]。另外MAPK还受到其他信号通路的调控, 受体酪氨酸激酶C-MET与肝细胞生长因子(hepatocyte growth factor, HGF)结合形成二聚体, 导致C-MET羧基末端酪氨酸磷酸化, 进而导致MAPK和PI3K活化。HGF诱导的C-MET活化发生在PD-1/PD-L1信号通路的活化过程中, 因此在HCC中C-MET调节PD-L1的表达^[24]。

3.3 IFN- γ 信号通路

肿瘤浸润性T细胞释放IFN- γ 诱导PD-L1表达^[25]。IFN- γ 通过上调小鼠和人HCC细胞中IRF-1的表达诱导PD-L1转录和蛋白水平表达^[26]。研究也发现人肝癌细胞系中IFN- γ 主要依赖JAK/STAT1/IRF1途径诱导PD-L1表达^[27]。转录因子IRF-1和IRF-2信号通路均调节HCC细胞中的PD-L1的表达。IRF-2过表达可以抑制IFN- γ 诱导的PD-L1启动子活性和蛋白水平。而IRF-1拮抗IRF-2与PD-L1中的IRE启动子结合, 为HCC免疫检查点抑制剂治疗中PD-1/PD-L1途径的调控提供了新的启示。研究发现TNF- α 通过上调IFN- γ 受体的表达来增强IFN- γ 信号转导。另外, 研究发现IFN刺激基因12a(IFN stimulates gene 12a, ISG12a)通过抑制Axin泛素化降解来促进 β -catenin蛋白酶体降解, 从而抑制了经典的Wnt/ β -catenin信号转导途径^[28]。 β -catenin被鉴定为PD-L1的转录因子。ISG12a抑制Wnt/ β -catenin信号转导可抑制免疫检查点PD-L1的表达, 从而使NK细胞对癌细胞杀伤敏感, 这项研究揭示了IFN抗癌作用的潜在机制。

3.4 雄激素受体(androgen receptor, AR)信号通路

雄激素受体作为PD-L1的转录抑制因子负调控PD-L1^[29]。体外实验发现肝癌细胞中AR的过表达增强了CD8⁺ T的功能, AR低表达的肿瘤对PD-L1抑制剂的反应较好。因此, AR抑制PD-L1的表达可能与HCC中的性别差异有关。另外有研究发现, 羟类固醇17- β 脱氢酶6(hydroxysteroid 17- β dehydrogenase 6, HSD17B6)是参与合成二氢睾酮的关键蛋白, 在HCC的发生和发展中发挥重要的作用。HSD17B6可通过产生双氢睾酮(dihydrotestosterone, DHT)抑制TGF- β 1和PD-L1的表达^[30]。

3.5 其他特异性转录调控

氧化应激反应1(oxidative stress response 1, OXSR1)与部分肿瘤的恶性进展密切相关。OXSR1在肝癌组织中上调, 促进肿瘤细胞的增殖、迁移和侵袭。此外, OXSR1的表达水平与HCC中肿瘤浸润免疫细胞的浸润水平和PD-L1表达呈正相关^[31]。MYC原癌基因上调淋巴瘤中PD-L1的表达, HCC细胞中敲低MYC, 增加了PD-L1 mRNA和蛋白质水平的表达^[32]。MYC抑制信号转导及转录激活子-1(signal transducer and activator of transcription 1, STAT1)的表达, STAT1是IFN- γ 信号通路的重要组成部分, IFN- γ 刺激HCC细胞促进PD-L1表达。Hippo信号通路在多种癌症类型中失活, 导致定位在细胞质当中的Yes1相关转录

调节因子 (Yes-associated transcriptional regulator, YAP1) 进入细胞核, 调控下游相关基因的转录。研究发现, YAP1抑制剂可以降低肝癌组织PD-L1的表达, 破坏肿瘤的免疫抑制微环境, 从而改善HCC的治疗效果^[33]。

4 转录后调控PD-L1的表达

4.1 MicroRNAs对PD-L1的调节

MicroRNA-1 (miR-1) 是一种肿瘤抑制性microRNA, 直接调控PD-L1表达。miR-1的缺失促进对索拉非尼耐药的肝癌细胞中PD-L1的表达^[34]。癌基因转录因子核因子E2相关因子2 (Nuclear factor, erythroid 2 like 2, NRF-2) 可抑制miR-1的表达, NRF-2/miR-1/PD-L1调控轴有助于索拉非尼耐药肝癌细胞耐药性的维持和发展, 并为克服HCC中索拉非尼耐药性提供了潜在的治疗靶点。另外研究发现miR-155-5p和miR-194-5p可通过X失活的特异性转录本 (X inactive specific transcript, XIST) 上调PD-L1的表达^[35]。

4.2 LncRNAs对PD-L1的调节

在HCC中, 长链非编码RNA PCED1B-AS1 (PCED1B antisense RNA 1, PCED1B-AS1) 和hsa-miR-194-5p表达上调。PCED1B-AS1与PD-Ls正相关, 而与hsa-miR-194-5p负相关。PCED1B-AS1与抑制PD-Ls表达的hsa-miR-194-5p相互作用, 增强PD-Ls的表达^[36]。癌症易感性候选物11 (cancer susceptibility 11, CASC11) 募集真核翻译起始因子4A3 (eukaryotic translation initiation factor 4A3, EIF4A3), 并增强E2F1 mRNA的稳定性, 促进NF- κ B信号和PI3K/AKT/mTOR通路的激活, 调节PD-L1的表达^[37]。研究还表明, 肝癌中长链非编码RNA MIAT的表达与PD-1、PD-L1和CTLA4等免疫检查点分子的表达呈正相关^[38]。

LINC00657在HCC组织和细胞系中过表达, 与预后不良有关。LINC00657通过降低miR-42调节PD-L1的表达, PD-L1的3'UTR与miR-424高度保守, miR-424可显著抑制PD-L1的mRNA和蛋白表达水平^[39]。长链非编码RNA KCNQ1重叠转录本1 (KCNQ1 overlapping transcript 1, KCNQ1OT1) 已被证明与部分肿瘤细胞的耐药性有关。KCNQ1OT1充当miR-506的竞争性内源RNA, 并在索拉非尼耐药的肝癌细胞中促进PD-L1的表达^[40]。

5 翻译后修饰对PD-L1的调控作用

EGF刺激促进了HCC细胞中PD-L1 mRNA

和蛋白的表达。EGF处理导致PD-L1启动子处的H3-Thr11磷酸化增强, 抑制表皮生长因子受体可以逆转EGF诱导的PD-L1 mRNA和蛋白的表达。抑制丙酮酸激酶同工型M2 (pyruvate kinase M2, PKM2) 则显著阻止EGF诱导的PD-L1表达和H3-Thr11的磷酸化^[41]。肝癌患者的肿瘤组织样本中观察到聚腺苷酸二磷酸核糖转移酶-1 (poly(ADP-ribose)polymerase-1, PARP-1) 和磷酸化的糖原合成酶激酶3 β (p-glycogen synthase kinase 3 beta, p-GSK3 β) 或PD-L1表达之间呈负相关, 抑制PARP1活性可以增强GSK3 β 磷酸化, 上调PD-L1表达, 并最终抑制T细胞浸润^[42]。

6 免疫检查点抑制剂的临床应用

肿瘤免疫治疗的特点在于激发特异性免疫反应。国产卡瑞利珠单抗单药用于晚期肝癌的治疗, 客观缓解率14.7%, 6月生存率74.4%, 12月生存率55.9%, 中位生存期13.8月^[43]。替雷利珠单抗单药治疗晚期二线肝细胞癌患者的ORR高达18.8%, DCR达56.3%, 在同类药物中处于领先水平^[44]。另外, PD-L1单抗在肝胆肿瘤治疗中也开展了很多临床试验。一项关于阿替利珠单抗联合贝伐单抗一线治疗晚期肝细胞肝癌患者的研究结果显示, 索拉非尼组mOS为13.2月, 联合组可使死亡风险降低42%; 联合组的mPFS为6.8月, 索拉非尼组为4.3月, 疾病进展风险降低41%。此外, 在中国患者中带来更大获益, 降低了56%的死亡风险^[45]。该联合方案不仅被NCCN指南纳入肝癌患者的一线治疗, 也被FDA批准为肝癌史上首个免疫联合的一线治疗方案。2020 CSCO指南将阿替利珠单抗联合贝伐单抗组合纳入晚期肝癌一线治疗的I级推荐。

7 总结与展望

综上所述, 肝癌免疫微环境中PD-L1在多种细胞上表达, 包括巨噬细胞、单核细胞和肿瘤细胞等。PD-L1的表达可明显抑制效应T细胞的抗肿瘤作用。目前针对PD-L1的研究主要集中在免疫治疗方面, 但也有研究发现, PD-L1也可不依赖PD-1/PD-L1途径, 发挥促进肿瘤生长的作用。另外PD-L1表达的调控受到多种因素的调控, 包括转录、转录后翻译和翻译后修饰等多层面的调控, 而且不同层次和信号通路之间交叉调控, 机制复杂, 见表1。PD-L1阳性的患者可在免疫检查点抑制剂的治疗中获益, 但是PD-L1阳性的患者并未

表1 肝癌PD-L1的调控机制

Table 1 Regulatory mechanism of PD-L1 in liver cancer

Types of regulation	Key molecule	Regulatory mechanism	Change of PD-L1	Type of cells
Regulation of signaling pathways	M-CSF, VEGFA	M-CSF and VEGFA were expressed in tumor cells ^[6]	Up-regulated	Bone marrow derived suppressor cells
	CCRK	The depletion of CCRK upregulated PD-L1 expression ^[7]	Down-regulated	Tumor cells
	LOXL4	It relied on STATs-dependent PD-L1 activation mediated by IFN ^[9]	Up-regulated	Macrophage
	PTPRO	IL-6 activated the STAT3/c-MYC /miR-25-3paxis ^[10]	Down-regulated	Monocyte Macrophages
	miR-23a	Exosomes upregulated the expression of PD-L1 in macrophages through miR-23a-PTEN-AKT pathway ^[11]	Up-regulated	Macrophage
	PFKFB3	PFKFB3 mediated PD-L1 expression by activating NF-κB signals in cells ^[12]	Up-regulated	Monocyte
	OPN	Promoting PD-L1 expression in tumor cells via activating CSF1-CSF1R pathway in macrophages ^[13]	Up-regulated	Tumor cells
Epigenetic regulation	IL-1 β	M1-type cells secreting IL-1β induced the expression of NF-κB p65 and IRF-1 in tumor cells ^[14]	Up-regulated	Tumor cells
	EZH2	EZH2 inhibited PD-L1 expression by upregulating the N-terminal lysine 27 trimethylation level of histone H3 on CD274 promoter and IRF1 expression ^[17]	Down-regulated	Tumor cells
Transcriptional regulation	STAT3	STAT3 bound to the PD-L1 promoter and transcriptionally regulated PD-L1 expression ^[18-19]	Up-regulated	Tumor cells
	PTPRD	PTPRD inhibited the expression of PD-L1 by inhibiting STAT3 phosphorylation ^[20]	Down-regulated	Tumor cells
	GOLM1	GOLM1 promoted STAT3 phosphorylation by enhancing the level of EGFR, and up-regulated the transcription level of PD-L1 ^[21]	Up-regulated	Tumor cells
	TLR9	TLR9 mediated a reduction in ribosylation of STAT3 poly ADP and an increase in phosphorylation of STAT3 Tyr705, promoting PD-L1 transcription ^[22]	Up-regulated	Tumor cells
	EGF, IFN-γ	EGF and IFN-γ up-regulated the transcription and protein levels of PD-L1. IFN-γ increased the transcriptional activity of PD-L1, while MAPK signal transduction increased the stability of PD-L1 mRNA ^[23]	Up-regulated	Tumor cells
	C-MET	C-MET bound to hepatocyte growth factor (HGF) to form a dimer that led to phosphorylation of the carboxy-terminal tyrosine of C-MET, which led to the activation of MAPK and PI3K ^[24]	Up-regulated	Tumor cells
	IFN-γ	IFN-γ mainly induced PD-L1 expression through the JAK/STAT1/IRF1 pathway ^[27]	Up-regulated	Tumor cells
	TNF-α	TNF-α enhanced IFN-γ signal transduction by upregulating IFN-γ receptor expression. The expression of PD-L1 cooperatively induced by TNF-α and IFN-γ promoted tumor growth <i>in vivo</i> ^[27]	Up-regulated	Tumor cells
	ISG12a	ISG12a suppressed immune checkpoint PD-L1 expression by inhibiting Wnt/β-catenin signal transduction ^[28]	Down-regulated	Tumor cells
	AR	Androgen receptors negatively regulated PD-L1 by acting as a transcriptional inhibiting factor of PD-L1 ^[29]	Down-regulated	Tumor cells
	HSD17B6	HSD17B6 inhibited the expression of TGF-β1 and PD-L1 by producing DHT ^[30]	Down-regulated	Tumor cells
	YAP1	Studies found that YAP1 inhibitors reduced PD-L1 expression in liver cancer ^[33]	Up-regulated	Tumor cells
	NRF-2	NRF-2 inhibited miR-1 expression and promoted PD-L1 expression through the NRF-2/miR-1/PD-L1 regulatory axis in sorafenib-resistant HCC cells ^[34]	Up-regulated	Tumor cells
	miR-155-5p	miR-194-5p up-regulated PD-L1 expression through XIST ^[35]	Up-regulated	Tumor cells
	PCED1B-AS1	PCED1B-AS1 interacted with hsa-miR-194-5p, which inhibited PD-Ls expression, and enhanced PD-Ls expression ^[36]	Up-regulated	Tumor cells
	CASC11	CASC11 recruited EIF4A3, enhanced the stability of E2F1 mRNA, promoted the activation of NF-κB signaling and PI3K/Akt/mTOR pathway, and regulated PD-L1 expression ^[37]	Up-regulated	Tumor cells
	LINC00657	LINC00657 regulated PD-L1 expression by decreasing miR-42, and miR-424 significantly inhibited the mRNA and protein levels of PD-L1 ^[39]	Up-regulated	Tumor cells
	KCNQ10T1	KCNQ10T1 acted as a competitive endogenous RNA of miR-506 and promoted PD-L1 expression in sorafenib-resistant HCC cells ^[40]	Up-regulated	Tumor cells
Posttranslational modification	PKM2	Inhibition of PKM2 significantly inhibited EGF-induced PD-L1 expression and H3-Thr11 phosphorylation ^[41]	Up-regulated	Tumor cells

在治疗中完全有效。相反,PD-L1阴性的患者也可以在免疫检查点抑制剂治疗中获益。免疫检查点抑制剂治疗失败的原因可能是肿瘤细胞免疫原性的突变、肿瘤细胞上多种免疫检查点的配体的表达以及T细胞的浸润缺陷。因此,免疫检查点抑制剂的联合治疗策略,为免疫检查点抑制剂的应用拓展了新空间,同时也显现出非常显著的治疗效果,最终将为患者带来更多的选择,延长患者生存期。

参考文献:

- [1] Sung H, Ferlay J, Siegel RL, *et al.* Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries[J]. CA Cancer J Clin, 2021, 71(3): 209-249.
- [2] El-Khoueiry AB, Sangro B, Yau T, *et al.* Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial[J]. Lancet, 2017, 389(10088): 2492-2502.
- [3] Cheng AL, Kang YK, Chen Z, *et al.* Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial[J]. Lancet Oncol, 2009, 10(1): 25-34.
- [4] Qin S, Ren Z, Meng Z, *et al.* Camrelizumab in patients with previously treated advanced hepatocellular carcinoma: a multicentre, open-label, parallel-group, randomised, phase 2 trial[J]. Lancet Oncol, 2020, 21(4): 571-580.
- [5] Makarova-Rusher OV, Medina-Echeverez J, Duffy AG, *et al.* The yin and yang of evasion and immune activation in HCC[J]. J Hepatol, 2015, 62(6): 1420-1429.
- [6] Iwata T, Kondo Y, Kimura O, *et al.* PD-L1(+) MDSCs are increased in HCC patients and induced by soluble factor in the tumor microenvironment[J]. Sci Rep, 2016, 6: 39296.
- [7] Zhou J, Liu M, Sun H, *et al.* Hepatoma-intrinsic CCRK inhibition diminishes myeloid-derived suppressor cell immunosuppression and enhances immune-checkpoint blockade efficacy[J]. Gut, 2018, 67(5): 931-944.
- [8] Cao J, Zhang C, Jiang GQ, *et al.* Identification of hepatocellular carcinoma-related genes associated with macrophage differentiation based on bioinformatics analyses[J]. Bioengineered, 2021, 12(1): 296-309.
- [9] Tan HY, Wang N, Zhang C, *et al.* Lysyl Oxidase-Like 4 Fosters an Immunosuppressive Microenvironment During Hepatocarcinogenesis[J]. Hepatology, 2021, 73(6): 2326-2341.
- [10] Zhang W, Liu Y, Yan Z, *et al.* IL-6 promotes PD-L1 expression in monocytes and macrophages by decreasing protein tyrosine phosphatase receptor type O expression in human hepatocellular carcinoma[J]. J Immunother Cancer, 2020, 8(1): e000285.
- [11] Liu J, Fan L, Yu H, *et al.* Endoplasmic Reticulum Stress Causes Liver Cancer Cells to Release Exosomal miR-23a-3p and Up-regulate Programmed Death Ligand 1 Expression in Macrophages[J]. Hepatology, 2019, 70(1): 241-258.
- [12] Chen DP, Ning WR, Jiang ZZ, *et al.* Glycolytic activation of peritumoral monocytes fosters immune privilege via the PFKFB3-PD-L1 axis in human hepatocellular carcinoma[J]. J Hepatol, 2019, 71(2): 333-343.
- [13] Zhu Y, Yang J, Xu D, *et al.* Disruption of tumour-associated macrophage trafficking by the osteopontin-induced colony-stimulating factor-1 signalling sensitises hepatocellular carcinoma to anti-PD-L1 blockade[J]. Gut, 2019, 68(9): 1653-1666.
- [14] Zong Z, Zou J, Mao R, *et al.* M1 Macrophages Induce PD-L1 Expression in Hepatocellular Carcinoma Cells Through IL-1 β Signaling[J]. Front Immunol, 2019, 10: 1643.
- [15] Xie QK, Zhao YJ, Pan T, *et al.* Programmed death ligand 1 as an indicator of pre-existing adaptive immune responses in human hepatocellular carcinoma[J]. Oncoimmunology, 2016, 5(7): e1181252.
- [16] Ou DL, Lin YY, Hsu CL, *et al.* Development of a PD-L1-Expressing Orthotopic Liver Cancer Model: Implications for Immunotherapy for Hepatocellular Carcinoma[J]. Liver Cancer, 2019, 8(3): 155-171.
- [17] Xiao G, Jin LL, Liu CQ, *et al.* EZH2 negatively regulates PD-L1 expression in hepatocellular carcinoma[J]. J Immunother Cancer, 2019, 7(1): 300.
- [18] Ding L, Chen X, Xu X, *et al.* PARP1 Suppresses the Transcription of PD-L1 by Poly (ADP-Ribosyl) ating STAT3[J]. Cancer Immunol Res, 2019, 7(1): 136-149.
- [19] Ke M, Zhang Z, Xu B, *et al.* Baicalein and baicalin promote antitumor immunity by suppressing PD-L1 expression in hepatocellular carcinoma cells[J]. Int Immunopharmacol, 2019, 75: 105824.
- [20] Huang X, Qin F, Meng Q, *et al.* Protein tyrosine phosphatase receptor type D (PTPRD)-mediated signaling pathways for the potential treatment of hepatocellular carcinoma: a narrative review[J]. Ann Transl Med, 2020, 8(18): 1192.
- [21] Yan J, Zhou B, Guo L, *et al.* GOLM1 upregulates expression of PD-L1 through EGFR/STAT3 pathway in hepatocellular carcinoma[J]. Am J Cancer Res, 2020, 10(11): 3705-3720.
- [22] Zhou B, Yan J, Guo L, *et al.* Hepatoma cell-intrinsic TLR9 activation induces immune escape through PD-L1 upregulation in hepatocellular carcinoma[J]. Theranostics, 2020, 10(14): 6530-6543.
- [23] Xing S, Chen S, Yang X, *et al.* Role of MAPK activity in PD-L1 expression in hepatocellular carcinoma cells[J]. J BUON, 2020, 25(4): 1875-1882.
- [24] Chun HW, Hong R. Significance of PD-L1 clones and C-MET expression in hepatocellular carcinoma[J]. Oncol Lett, 2019, 17(6): 5487-5498.
- [25] Itoh S, Yugawa K, Shimokawa M, *et al.* Prognostic significance of inflammatory biomarkers in hepatocellular carcinoma following hepatic resection[J]. BJS Open, 2019, 3(4): 500-508.

- [26] Yan Y, Zheng L, Du Q, *et al.* Interferon regulatory factor 1 (IRF-1) and IRF-2 regulate PD-L1 expression in hepatocellular carcinoma (HCC) cells[J]. *Cancer Immunol Immunother*, 2020, 69(9): 1891-1903.
- [27] Li N, Wang J, Zhang N, *et al.* Cross-talk between TNF- α and IFN- γ signaling in induction of B7-H1 expression in hepatocellular carcinoma cells[J]. *Cancer Immunol Immunother*, 2018, 67(2): 271-283.
- [28] Deng H, Kan A, Lyu N, *et al.* Dual Vascular Endothelial Growth Factor Receptor and Fibroblast Growth Factor Receptor Inhibition Elicits Antitumor Immunity and Enhances Programmed Cell Death-1 Checkpoint Blockade in Hepatocellular Carcinoma[J]. *Liver Cancer*, 2020, 9(3): 338-357.
- [29] Jiang G, Shi L, Zheng X, *et al.* Androgen receptor affects the response to immune checkpoint therapy by suppressing PD-L1 in hepatocellular carcinoma[J]. *Aging (Albany NY)*, 2020, 12(12): 11466-11484.
- [30] Lv L, Zhao Y, Wei Q, *et al.* Downexpression of HSD17B6 correlates with clinical prognosis and tumor immune infiltrates in hepatocellular carcinoma[J]. *Cancer Cell Int*, 2020, 20: 210.
- [31] Chen J, Zhou J, Fu H, *et al.* Upregulation of oxidative stress-responsive 1(OXSR1) predicts poor prognosis and promotes hepatocellular carcinoma progression[J]. *Bioengineered*, 2020, 11(1): 958-971.
- [32] Zou J, Zhuang M, Yu X, *et al.* MYC inhibition increases PD-L1 expression induced by IFN- γ in hepatocellular carcinoma cells[J]. *Mol Immunol*, 2018, 101: 203-209.
- [33] Li S, Ji J, Zhang Z, *et al.* Cisplatin promotes the expression level of PD-L1 in the microenvironment of hepatocellular carcinoma through YAP1[J]. *Mol Cell Biochem*, 2020, 475(1-2): 79-91.
- [34] Li D, Sun FF, Wang D, *et al.* Programmed Death Ligand-1 (PD-L1) Regulated by NRF-2/MicroRNA-1 Regulatory Axis Enhances Drug Resistance and Promotes Tumorigenic Properties in Sorafenib-Resistant Hepatoma Cells[J]. *Oncol Res*, 2020, 28(5): 467-481.
- [35] Atwa SM, Handoussa H, Hosny KM, *et al.* Pivotal role of long non-coding ribonucleic acid-X-inactive specific transcript in regulating immune checkpoint programmed death ligand 1 through a shared pathway between miR-194-5p and miR-155-5p in hepatocellular carcinoma[J]. *World J Hepatol*, 2020, 12(12): 1211-1227.
- [36] Fan F, Chen K, Lu X, *et al.* Dual targeting of PD-L1 and PD-L2 by PCED1B-AS1 via sponging hsa-miR-194-5p induces immunosuppression in hepatocellular carcinoma[J]. *Hepatol Int*, 2021, 15(2): 444-458.
- [37] Song H, Liu Y, Li X, *et al.* Long noncoding RNA CASC11 promotes hepatocarcinogenesis and HCC progression through EIF4A3-mediated E2F1 activation[J]. *Clin Transl Med*, 2020, 10(7): e220.
- [38] Peng L, Chen Y, Ou Q, *et al.* LncRNA MIAT correlates with immune infiltrates and drug reactions in hepatocellular carcinoma[J]. *Int Immunopharmacol*, 2020, 89(Pt A): 107071.
- [39] Cao X, Zhang G, Li T, *et al.* LINC00657 knockdown suppresses hepatocellular carcinoma progression by sponging miR-424 to regulate PD-L1 expression[J]. *Genes Genomics*, 2020, 42(11): 1361-1368.
- [40] Zhang J, Zhao X, Ma X, *et al.* KCNQ1OT1 contributes to sorafenib resistance and programmed death-ligand-1-mediated immune escape via sponging miR-506 in hepatocellular carcinoma cells[J]. *Int J Mol Med*, 2020, 46(5): 1794-1804.
- [41] Wang X, Liang C, Yao X, *et al.* PKM2-Induced the Phosphorylation of Histone H3 Contributes to EGF-Mediated PD-L1 Transcription in HCC[J]. *Front Pharmacol*, 2020, 11: 577108.
- [42] Zhou B, Guo L, Zhang B, *et al.* Disulfiram combined with copper induces immunosuppression via PD-L1 stabilization in hepatocellular carcinoma[J]. *Am J Cancer Res*, 2019, 9(11): 2442-2455.
- [43] Qin S, Ren Z, Meng Z, *et al.* Camrelizumab in patients with previously treated advanced hepatocellular carcinoma: a multicentre, open-label, parallel-group, randomised, phase 2 trial[J]. *Lancet Oncol*, 2020, 21(4): 571-580.
- [44] Finn RS, Ryoo BY, Merle P, *et al.* Pembrolizumab As Second-Line Therapy in Patients With Advanced Hepatocellular Carcinoma in KEYNOTE-240: A Randomized, Double-Blind, Phase III Trial[J]. *J Clin Oncol*, 2020, 38(3): 193-202.
- [45] Finn RS, Qin S, Ikeda M, *et al.* Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma[J]. *N Engl J Med*, 2020, 382(20): 1894-1905.

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