Contents lists available at ScienceDirect

Engineering

journal homepage: www.elsevier.com/locate/eng

Views & Comments

DNA损伤反应抑制剂和抗PD-L1治疗前列腺癌——预测性生物标志物的开发

Chuandong Geng , Timothy C. Thompson

Departmentof Genitourinary Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA

1. 引言

尽管雄性激素受体生物合成和信号抑制剂已经显著改善了去势抵抗性前列腺癌（CRPC）患者的预后，但对晚期前列腺癌患者仍然缺乏有效的治疗方案。近年来的研究表明，DNA损伤和DNA损伤反应（DDR）途径的改变可能是前列腺癌向CRPC发展的重要原因。超过25%的转移性CRPC（mCRPC）男性患者在DDR基因中有丰富的生殖系或体细胞改变[1–2]。基于之前的工作（创建了第一批临床应用的综合致死癌症治疗方法的实例之一），最初的临床试验表明，DDR信号和DNA修复基因普遍存在有害缺陷[主要是乳腺癌易感基因2（*BRCA2*）变异]的CRPC患者，对聚（ADP-核糖）聚合酶（PARP）的抑制有明显的反应[3–4]。这项工作引起了人们对PARP抑制剂（PARPis）作为CRPC第一个靶向治疗的密切关注，并促使美国食品和药物管理局（FDA）突破性地指定了三种PARPis（奥拉帕利、鲁卡帕利和尼拉帕利）治疗药物，用于治疗患有特异性*BRCA2*突变的mCRPC患者[5–8]。DDR抑制剂（DDRis）已迅速扩展到包括其他途径的抑制剂，包括共济失调毛细血管扩张症和Rad3相关（ATR）激酶，ATR激酶与共济失调症突变（ATM）一起，作为复制应激反应（RSR）信号的关键调节调控因子[9–11]。

2. DDR靶向治疗诱导前列腺癌细胞的内源性免疫信号

最近PARPis联合免疫检查点治疗（ICT）的临床前研究显示，在*BRCA*突变型和*BRCA1/2*野生型癌症细胞中，PARPis具有潜在的附加效益。这些研究表明，PARPis可以通过各种机制诱导免疫激活，包括通过诱导I型干扰素（IFN）表达和IFN调节因子3活性，激活肿瘤细胞先天免疫途径环磷酸鸟苷–腺苷一磷酸合成酶（cGAS）–干扰素基因刺激因子（STING）信号转导和免疫检查点蛋白程序性细胞死亡配体1（PD-L1）表达[12–17]，以及通过糖原合成酶激酶3β的失活来稳定PD-L1蛋白[18]。最近的一项研究表明，在CRPC临床前模型中，ATR抑制剂（ATRi）激活了cGAS-STING信号通路，并证明ATRi联合抗PD-L1抗体ICT在体内可协同抑制前列腺癌生长[19]。虽然PARPis和ATRis之间已知的免疫激活机制有相似之处，但对这些药物之间作用的具体机制的分析，揭示了肿瘤细胞表达的免疫检查点蛋白的潜在关键作用，如PD-L1在调节I型IFN、肿瘤细胞固有和自分泌信号通路中对DDRis的响应，作为治疗结果的重要调节因子[19]。例如，与PARP抑制相反，ATRis通过激活检查点激酶1–细胞分裂周期25C–周期蛋白依赖性激酶1–斑点型痘病毒和锌指蛋白E3连接酶复合体信号轴诱导PD-L1蛋白下调，从而导致CRPC模型中自分泌的IFN-β-IFN-α受体1介导的凋亡

英文原文：Engineering 2022, 12(5): 12–15
引用本文：Chuandong Geng, Timothy C. Thompson. DNA Damage Response Inhibitor and Anti-PD-L1 Therapy for Prostate Cancer: Development of Predictive Biomarkers. *Engineering*, http://doi.org/10.1016/j.eng.2022.01.002

反应[19]。这项研究和其他研究的结果提出了一个问题：除了PD-L1，其他免疫检查点蛋白B7家族成员（其在功能上受到IFN和干扰素调节因子IRF的调节）的表达是否在前列腺癌和其他恶性肿瘤的DDRi和ICT联合治疗反应中发挥重要作用？

3. B7免疫检查点蛋白家族成员在肿瘤中的表达

如表1所示，B7免疫检查点蛋白家族至少包含10个跨膜或与细胞膜相连的糖基磷脂酰肌醇（GPI）（B7-H4）蛋白成员。所有B7蛋白家族成员都具有细胞外免疫球蛋白V（IgV）-IgC结构域，这些结构域与淋巴细胞上各自的受体结合，通过信号传导活性调节T细胞免疫应答。尽管早期的研究描述了B7蛋白家族成员在免疫细胞中的表达，但最近的研究将B7家族成员的表达模式扩大到各种组织中的多种细胞类型，特别是在恶性肿瘤中[20–34]。重要的是，B7免疫检查点蛋白经过广泛的翻译后修饰，像许多其他膜和分泌蛋白一样，在其细胞外的IgV-IgC结构域被糖基化，这是其功能活动所必需的。有趣的是，虽然细胞表面蛋白的糖基化和糖基结构改变是许多癌细胞的普遍特征，但据报道，癌细胞表达的B7蛋白家族成员的糖基化改变会阻碍其相互作用的免疫细胞识别功能，这可以通过去糖基化而恢复[35–39]。最近的研究发现，肿瘤细胞在转移过程中会利用多种机制途径，包括抑制性免疫检查点来逃避免疫反应。靶向这些免疫检查点蛋白的功能已成为一种可能有效阻止癌症进展的新疗法[40]。在抑制性免疫检查点通路中，PD-L1/程序性细胞死亡蛋白1（PD-1）免疫检查点通路已成为适应性免疫反应的关键调节因子，并已被证明在许多癌症转移过程中促进免疫系统的逃避[41–43]。为此，阻断PD-L1/PD-1相互作用的抑制剂被开发为治疗性抗癌药物，并与其他药物联合使用，以最大化癌症治疗的疗效[44]。

4. 肿瘤细胞表达的PD-L1作为ICT的治疗靶点和预测生物标志物

PD-L1（B7-H1, CD274）属于B7免疫检查点蛋白家族。PD-L1表达于多种细胞的细胞膜表面，包括T细胞、B细胞、树突状细胞、巨噬细胞和非淋巴细胞，如间充质干细胞、上皮细胞、内皮细胞和棕色脂肪细胞。据报道，

表1 B7免疫检查点蛋白家族

B7 family checkpoint protein ligand	Ligand alias	Extracelluar domian structure	Expression in immune cells	Tumor expression	Receptors	Regulating response of T-cell
B7-H1	CD274, PD-L1	IgV–IgC	T cells, B cells, DCs, monocytes	+	PD-1	Inhibition
B7-H2	ICOS-L, GL-50, B7h, B7RP-1	IgV–IgC	T cells, B cells, DCs, macrophages	+	ICOS	Inhibition
B7-H3	CD276	IgV–IgC–IgV–IgC (human) IgV–IgC (mouse)	T cells, B cells, DCs, monocytes	+	TREML2? TLT-2?	Activation/ inhibition
B7-H4	B7S1, B7x, Vtcn1	IgV–IgC	T cells, B cells, NK cells, DCs, monocytes	+	Unknown	Inhibition
B7-H5	VISTA, Platelet receptor GI24, Dies1, PD-1H	IgV–IgC	T cells, DCs, macrophage, neutrophils	−	CD28H	Inhibition
B7-H6	NCR3LG1	IgV–IgC	Unknown	+	NKp30	Activation
B7-H7	HHLA2	IgV–IgC–IgV	T cells, B cells, DCs, monocytes	+	CD28H	Activation/ inhibition
B7-1	CD80	IgV–IgC	T cells, B cells, DCs, monocytes	+	CD28, CTLA-4	Inhibition
B7-2	CD86	IgV–IgC	T cells, B cells, DCs, monocytes	+	CD28, CTLA-4	Inhibition
B7-DC	CD273, PD-L2	IgV–IgC	DCs and monocytes	+	PD-1	Inhibition

CD: cluster of differentiation; ICOS-L, B7h: inducible costimulatory ligand; B7RP1: B7-related protein 1; B7S1: B7 superfamily member 1; B7x: B7 homolog x; Vtcn1: v-set domain containing T cell activation inhibitor 1; VISTA: v-domain immunoglobulin-containing suppressor of T cell activation; Dies1: differentiation of embryonic stem cells 1; PD-1H: PD-1 homolog; NCR3LG1: natural killer cell cytotoxicity receptor 3 ligand 1; HHLA2: human endogenous retrovirus subfamily H long terminal repeat associating protein 2; CTLA-4: cytotoxic T lymphocyte-associated antigen 4; TREML2, TLT-2: triggering receptor expressed on myeloid cells like transcript 2; CD-28H: CD28 homolog; NKp30: NK-activating receptor; DCs: dendritic cells.

PD-L1也在不同来源的肿瘤细胞中表达。PD-L1是其受体PD-1的配体，PD-1是表达在活化的T细胞和B细胞表面的免疫细胞抑制性受体[41,45]。PD-1通过与PD-L1结合而被激活，抑制组织和肿瘤内效应T细胞的活性，从而促进表达PD-L1的肿瘤细胞的存活和转移。有趣的是，除了在细胞膜上呈现PD-L1蛋白（膜PD-L1、mPD-L1）外，据报道，PD-L1可以分泌到细胞外空间或血清中，并且PD-L1的分泌形式（sPD-L1）包含一个不同于mPD-L1的C端。sPD-L1由选择性剪接的PD-L1 mRNA产生，或者作为膜结合的PD-L1的胞外肽片段结构域，通过基质金属蛋白酶（MMP）或去整合素金属蛋白酶（ADAM）的活性脱落[46–49]。最近，研究发现，PD-L1可以存在于细胞质（细胞质PD-L1、cPD-L1）中，并且通过K263的乙酰化，可以转位到细胞核（细胞核PD-L1、nPD-L1）并被募集到染色质中，对一系列基因包括致癌/致畸基因的mRNA转录进行功能调节。特别是，PD-L1可以调节关键参与调节免疫反应的基因网络的mRNA转录，如B7家族的其他检查点蛋白成员和细胞毒性T淋巴细胞相关抗原4（CTLA-4）[50–51]。正如表2中所总结的那样[46–53]，与“经典”的mPD-L1一样，这些非膜结合的PD-L1是用免疫印迹（IB）、免疫组化（IHC）和酶联免疫吸附试验（ELISA）在免疫和癌症/肿瘤细胞中用特异性抗PD-L1抗体进行检测的。重要的是，通过这些方法检测PD-L1可以大大影响治疗决策，涉及抗PD-L1/抗PD-1的选择性临床使用和治疗后PD-L1检测结果的解释。综上所述，这些研究结果表明，肿瘤细胞和免疫细胞表达的PD-L1在肿瘤免疫逃避和肿瘤发生中起着至关重要的作用，并有可能作为对ICT应答的早期预测性生物标志物。

FDA批准的许多临床试验已经测试了免疫组化检测的肿瘤细胞和肿瘤微环境（TME）细胞表达的PD-L1，作为某些癌症患者的ICT反应的预测标志物，包括黑色素瘤、三阴性乳腺癌和非小细胞肺癌[54–58]。这些研究显示了抗PD-L1免疫染色作为对免疫治疗药物反应的预测性生物标志物的价值。然而，随着越来越多的临床前和临床研究将PD-L1表达作为预测性生物标志物进行测试，关于这一标志物的生物学和临床意义及效用的重要问题也随之产生。关于抗PD-L1 ICT在前列腺癌中的总体疗效和使用，以及PD-L1在前列腺癌组织中检测水平相对较低的问题，提出了一个具有挑战性的方案。理解和使用抗PD-L1 ICT治疗CRPC的努力，以及最近测试抗PD-L1作为单一药物和新组合的临床前研究和临床试验，已经产生了越来越有希望的结果[19,59–60]。总的来说，PD-L1作为许多癌症中基于PD-L1的ICT的预测生物标志物的发展仍然面临着巨大的挑战。要克服这些障碍还有很多工作要做，特别是对CRPC而言。

5. 肿瘤细胞表达的PD-L1作为前列腺癌ICT的治疗靶点和预测生物标志物的进展

首先，由于前列腺癌的极端异质性，采样偏差可能是准确评估前列腺癌活检中PD-L1表达的最大障碍之一。由于肿瘤活检往往包含有限数量的可评估的肿瘤细胞，而且样本处理是可变的，免疫染色分析可能是次优的，不能代表前列腺癌病变。因此，除了免疫组化检测外，还应该评估和考虑其他检测方案和方法，如反转录实时定量DNA聚合酶链反应、IB或ELISA，用于PD-L1分析。其次，正如我们前面所讨论的，肿瘤表达的PD-L1可以位于血清、细胞外基质、细胞膜表面、细胞质或细胞核中。重要的是，PD-L1的不同翻译后修饰已被确定与这些不同的隔室有关。虽然PD-L1的糖基化是膜和细胞外基质的定位、分泌和配体功能所必需的，但这些修饰可能阻止或减少PD-L1抗体识别的PD-L1肽抗原的暴露。此外，PD-L1的糖基化有可能在癌细胞中发生改变，这可能会进一步影响通过特定的PD-L1抗体检测癌细胞表达的PD-L1。最近的一份报告显示，体外酶促去除*N*-连接糖基化后，可通过几种方法（包括IB、免疫荧光、ELISA和免疫组化）明显增强PD-L1的检测[61]。然而，由于蛋白质糖基化的改变在癌细胞中是一种普遍的观察，这种方法的适用性和实用性需要在临床样本中进行密集的验证，特别是在极不均匀的肿瘤中，如前列腺癌。需要开发识别PD-L1不同翻译后修饰形式的抗体及其广泛的表征（包括细胞分布）。再次，不同形式PD-L1的细胞类型特异性功能分析应被优先

表2 PD-L1蛋白的区间定位

Cellular compartment	Source	Detection	References
Membrane; extracelluar vescle	PD-L1 mRNA translated full length protein	IB, IHC	[52–53]
Cytoplasma and nucleus	PD-L1 mRNA translated full length protein	IB, IHC	[50–51]
Extracellular and serum	Alternative spliced PD-L1 mRNA translated full length protein; extracellar domain (peptides fragment) of mPD-L1 shed by MMP13, ADAM10, or ADAM17	ELISA	[46–49]

用于未来的转化研究。尽管通常用免疫组化对肿瘤和免疫细胞（包括巨噬细胞和淋巴细胞）的PD-L1表达进行独立评分，但关于PD-L1在这些癌症离散细胞类型中的功能意义的信息很少，包括肿瘤对抗PD-L1治疗的反应。此外，更好的定量分析及计算生物学方法的开发和应用可能会在短期内提高这些临床生物标志物研究的实用性。

总之，肿瘤细胞和免疫细胞表达的PD-L1在包括前列腺癌在内的多种癌症中的表达模式是复杂的。此外，肿瘤中的各种PD-L1翻译后修饰难以通过免疫组化方法检测，并可能会混淆PD-L1蛋白表达在高度异质性前列腺癌肿瘤样本中的解释。因此，需要开发能够识别不同翻译后修饰的PD-L1分子的PD-L1抗体，并对其进行广泛的表征（包括细胞分布）。此外，必须优先考虑对PD-L1在前列腺癌细胞和肿瘤相关的巨噬细胞和淋巴细胞中可能存在的不同、分区的功能进行基础和转化研究，以解决关于PD-L1 IHC的临床意义的知识缺口。这些研究工作可能需要开发更多的定量分析方法，使用计算生物学，以及特定的生化和蛋白质工程方法。总之，增加这些领域的研究可以更准确地识别和管理前列腺癌患者，使其可以从抗PD-L1 ICT中受益。

Acknowledgements

We acknowledge the editorial assistance of Sarah E. Townsend. We also acknowledge the support from MD Anderson National Cancer Institute (NCI) Prostate Cancer SPORE (P50 CA140388) and the NCI Cancer Center Support (P30 CA16672).

References

[1] Pritchard CC, Mateo J, Walsh MF, de Sarkar N, Abida W, Beltran H, et al. Inherited DNA-repair gene mutations in men with metastatic prostate cancer. N Engl J Med 2016;375(5):443–53.
[2] Robinson D, van Allen EM, Wu YM, Schultz N, Lonigro RJ, Mosquera JM, et al. Integrative clinical genomics of advanced prostate cancer. Cell 2015;161 (5):1215–28. Erratum in: Cell 2015;162(2):454.
[3] Lord CJ, Ashworth A. Targeted therapy for cancer using PARP inhibitors. Curr Opin Pharmacol 2008;8(4):363–9.
[4] Mateo J, Carreira S, Sandhu S, Miranda S, Mossop H, Perez-Lopez R, et al. DNA-repair defects and olaparib in metastatic prostate cancer. N Engl J Med 2015;373(18):1697–708.
[5] Mateo J, Porta N, Bianchini D, McGovern U, Elliott T, Jones R, et al. Olaparib in patients with metastatic castration-resistant prostate cancer with DNA repair gene aberrations (TOPARP-B): a multicentre, open-label, randomised, phase 2 trial. Lancet Oncol 2020;21(1):162–74.
[6] Abida W, Campbell D, Patnaik A, Shapiro JD, Sautois B, Vogelzang NJ, et al. Non-BRCA DNA damage repair gene alterations and response to the PARP inhibitor rucaparib in metastatic castration-resistant prostate cancer: analysis from the phase II TRITON2 study. Clin Cancer Res 2020;26(11):2487–96.
[7] Antonarakis ES, Gomella LG, Petrylak DP. When and how to use PARP inhibitors in prostate cancer: a systematic review of the literature with an update on on-going trials. Eur Urol Oncol 2020;3(5):594–611.
[8] De Bono J, Mateo J, Fizazi K, Saad F, Shore N, Sandhu S, et al. Olaparib for metastatic castration-resistant prostate cancer. N Engl J Med 2020; 382 (22): 2091–102.
[9] Pilié PG, Tang C, Mills GB, Yap TA. State-of-the-art strategies for targeting the DNA damage response in cancer. Nat Rev Clin Oncol 2019;16(2):81–104.
[10] Wengner AM, Siemeister G, Lücking U, Lefranc J, Wortmann L, Lienau P, et al. The novel ATR inhibitor BAY 1895344 is efficacious as monotherapy and combined with DNA damage-inducing or repair-compromising therapies in preclinical cancer models. Mol Cancer Ther 2020;19(1):26–38.
[11] Yap TA, O'Carrigan B, Penney MS, Lim JS, Brown JS, de Miguel Luken MJ, et al. Phase I trial of first-in-class ATR inhibitor M6620 (VX-970) as monotherapy or in combination with carboplatin in patients with advanced solid tumors. J Clin Oncol 2020;38(27):3195–204.
[12] Karzai F, VanderWeele D, Madan RA, Owens H, Cordes LM, Hankin A, et al. Activity of durvalumab plus olaparib in metastatic castration-resistant prostate cancer in men with and without DNA damage repair mutations. J Immunother Cancer 2018;6(1):141.
[13] Sen T, Rodriguez BL, Chen L, Corte CMD, Morikawa N, Fujimoto J, et al. Targeting DNA damage response promotes antitumor immunity through STING-mediated T-cell activation in small cell lung cancer. Cancer Discov 2019;9(5):646–61.
[14] Shen J, Zhao W, Ju Z, Wang L, Peng Y, Labrie M, et al. PARPi triggers the STING-dependent immune response and enhances the therapeutic efficacy of immune checkpoint blockade independent of BRCAness. Cancer Res 2019; 79(2):311–9.
[15] Ding L, Kim HJ, Wang Q, Kearns M, Jiang T, Ohlson CE, et al. PARP inhibition elicits STING-dependent antitumor immunity in brca1-deficient ovarian cancer. Cell Rep 2018;25(11). 2972–80.e5.
[16] Pantelidou C, Sonzogni O, de Oliveria Taveira M, Mehta AK, Kothari A, Wang D, et al. PARP inhibitor efficacy depends on $CD8^+$ T-cell recruitment via intratumoral STING pathway activation in BRCA-deficient models of triplenegative breast cancer. Cancer Discov 2019;9(6):722–37.
[17] Pilié PG, Gay CM, Byers LA, O'Connor MJ, Yap TA. PARP inhibitors: extending benefit beyond BRCA-mutant cancers. Clin Cancer Res 2019;25(13): 3759–71.
[18] Jiao S, Xia W, Yamaguchi H, Wei Y, Chen MK, Hsu JM, et al. PARP inhibitor upregulates PD-L1 expression and enhances cancer-associated immunosuppression. Clin Cancer Res 2017;23(14):3711–20.
[19] Tang Z, Pilié PG, Geng C, Manyam GC, Yang G, Park S, et al. ATR inhibition induces CDK1-SPOP signaling and enhances anti-PD-L1 cytotoxicity in prostate cancer. Clin Cancer Res 2021;27(17):4898–909.
[20] Carvajal-Hausdorf D, Altan M, Velcheti V, Gettinger SN, Herbst RS, Rimm DL, et al. Expression and clinical significance of PD-L1, B7–H3, B7–H4 and TILs in human small cell lung cancer (SCLC). J Immunother Cancer 2019; 7(1):65.
[21] Xu Z, Shen J, Wang MH, Yi T, Yu Y, Zhu Y, et al. Comprehensive molecular profiling of the B7 family of immune-regulatory ligands in breast cancer. OncoImmunology 2016;5(8):e1207841.
[22] Bachawal SV, Jensen KC, Wilson KE, Tian Lu, Lutz AM, Willmann JK. Breast cancer detection by B7-H3-targeted ultrasound molecular imaging. Cancer Res 2015;75(12):2501–9.
[23] Boorjian SA, Sheinin Y, Crispen PL, Farmer SA, Lohse CM, Kuntz SM, et al. T-cell coregulatory molecule expression in urothelial cell carcinoma: clinicopathologic correlations and association with survival. Clin Cancer Res 2008;14(15):4800–8.
[24] Ghebeh H, Tulbah A, Mohammed S, ElKum N, Amer SMB, Al-Tweigeri T, et al. Expression of B7-H1 in breast cancer patients is strongly associated with high proliferative Ki-67-expressing tumor cells. Int J Cancer 2007;121(4): 751–8.
[25] Flies DB, Chen L. The new B7s: playing a pivotal role in tumor immunity. J Immunother 2007;30(3):251–60.
[26] Nomi T, Sho M, Akahori T, Hamada K, Kubo A, Kanehiro H, et al. Clinical significance and therapeutic potential of the programmed death-1 ligand/ programmed death-1 pathway in human pancreatic cancer. Clin Cancer Res 2007;13(7):2151–7.
[27] Thompson RH, Dong H, Kwon ED. Implications of B7-H1 expression in clear cell carcinoma of the kidney for prognostication and therapy. Clin Cancer Res 2007;13(2):709s–15s.
[28] Nakanishi J, Wada Y, Matsumoto K, Azuma M, Kikuchi K, Ueda S.

Overexpression of B7-H1 (PD-L1) significantly associates with tumor grade and postoperative prognosis in human urothelial cancers. Cancer Immunol Immunother 2007;56(8):1173–82.
[29] Krambeck AE, Thompson RH, Dong H, Lohse CM, Park ES, Kuntz SM, et al. B7-H4 expression in renal cell carcinoma and tumor vasculature: associations with cancer progression and survival. Proc Natl Acad Sci USA 2006; 103(27): 10391–6.
[30] Blank C, Kuball J, Voelkl S, Wiendl H, Becker B, Walter B, et al. Blockade of PDL1 (B7-H1) augments human tumor-specific T cell responses *in vitro*. Int J Cancer 2006;119(2):317–27.
[31] Castriconi R, Dondero A, Augugliaro R, Cantoni C, Carnemolla B, Sementa AR, et al. Identification of 4Ig-B7-H3 as a neuroblastoma-associated molecule that exerts a protective role from an NK cell-mediated lysis. Proc Natl Acad Sci USA 2004;101(34):12640–5.
[32] Chen L. Co-inhibitory molecules of the B7-CD28 family in the control of T-cell immunity. Nat Rev Immunol 2004;4(5):336–47.
[33] Sica GL, Choi IH, Zhu G, Tamada K, Wang SD, Tamura H, et al. B7-H4, a molecule of the B7 family, negatively regulates T cell immunity. Immunity 2003;18(6):849–61.
[34] Yamazaki T, Akiba H, Iwai H, Matsuda H, Aoki M, Tanno Y, et al. Expression of programmed death 1 ligands by murine T cells and APC. J Immunol 2002; 169 (10):5538–45.
[35] Kim B, Sun R, Oh W, Kim AMJ, Schwarz JR, Lim SO. Saccharide analog, 2-deoxy-D-glucose enhances 4-1BB-mediated antitumor immunity via PD-L1 deglycosylation. Mol Carcinog 2020;59(7):691–700.
[36] Chester C, Sanmamed MF, Wang J, Melero I. Immunotherapy targeting 4-1BB: mechanistic rationale, clinical results, and future strategies. Blood 2018;131(1): 49–57.
[37] Cabral J, Hanley SA, Gerlach JQ, O'Leary N, Cunningham S, Ritter T, et al. Distinctive surface glycosylation patterns associated with mouse and human $CD4^+$ regulatory T cells and their suppressive function. Front Immunol 2017; 8:987.
[38] Beatson R, Tajadura-Ortega V, Achkova D, Picco G, Tsourouktsoglou TD, Klausing S, et al. The mucin MUC1 modulates the tumor immunological microenvironment through engagement of the lectin Siglec-9. Nat Immunol 2016;17(11):1273–81.
[39] Varki A, Kannagi R, Toole B, Stanley P. Glycosylation changes in cancer. In: Varki A, Cummings RD, Esko JD, Stanley P, Hart GW, Aebi M, editors. Essentials of glycobiology. New York: Cold Spring Harbor; 2015. p. 597–609.
[40] Safarzadeh A, Alizadeh M, Beyranvand F, Falavand Jozaaee R, Hajiasgharzadeh K, Baghbanzadeh A, et al. Varied functions of immune checkpoints during cancer metastasis. Cancer Immunol Immunother 2021; 70(3):569–88.
[41] Sun C, Mezzadra R, Schumacher TN. Regulation and function of the PD-L1 checkpoint. Immunity 2018;48(3):434–52.
[42] Black M, Barsoum IB, Truesdell P, Cotechini T, Macdonald-Goodfellow SK, Petroff M, et al. Activation of the PD-1/PD-L1 immune checkpoint confers tumor cell chemoresistance associated with increased metastasis. Oncotarget 2016;7(9):10557–67.
[43] Iwai Y, Ishida M, Tanaka Y, Okazaki T, Honjo T, Minato N. Involvement of PD-L1 on tumor cells in the escape from host immune system and tumor immunotherapy by PD-L1 blockade. Proc Natl Acad Sci USA 2002; 99(19): 12293–7.
[44] Oliveira LJC, Gongora ABL, Jardim DLF. Spectrum and clinical activity of PD-1/PD-L1 inhibitors: regulatory approval and under development. Curr Oncol Rep 2020;22(7):70.
[45] Shen X, Zhang L, Li J, Li Y, Wang Y, Xu ZX. Recent findings in the regulation of programmed death ligand 1 expression. Front Immunol 2019;10:1337.
[46] Orme JJ, Jazieh KA, Xie T, Harrington S, Liu X, Ball M, et al. ADAM10 and ADAM17 cleave PD-L1 to mediate PD-(L)1 inhibitor resistance. OncoImmunology 2020;9(1):1744980.
[47] Mahoney KM, Shukla SA, Patsoukis N, Chaudhri A, Browne EP, Arazi A, et al. A secreted PD-L1 splice variant that covalently dimerizes and mediates immunosuppression. Cancer Immunol Immunother 2019;68(3):421–32.
[48] Hira-Miyazawa M, Nakamura H, Hirai M, Kobayashi Y, Kitahara H, Bou-Gharios G, et al. Regulation of programmed-death ligand in the human head and neck squamous cell carcinoma microenvironment is mediated through matrix metalloproteinase-mediated proteolytic cleavage. Int J Oncol 2018;52(2): 379–88.
[49] Zhou J, Mahoney KM, Giobbie-Hurder A, Zhao F, Lee S, Liao X, et al. Soluble PDL1 as a biomarker in malignant melanoma treated with checkpoint blockade. Cancer Immunol Res 2017;5(6):480–92.
[50] Gao Y, Nihira NT, Bu X, Chu C, Zhang J, Kolodziejczyk A, et al. Acetylationdependent regulation of PD-L1 nuclear translocation dictates the efficacy of anti-PD-1 immunotherapy. Nat Cell Biol 2020;22(9):1064–75.
[51] Yu J, Qin B, Moyer AM, Nowsheen S, Tu X, Dong H, et al. Regulation of sister chromatid cohesion by nuclear PD-L1. Cell Res 2020;30(7):590–601. Erratum in: Cell Res 2020;30(9):823.
[52] Burr ML, Sparbier CE, Chan YC, Williamson JC, Woods K, Beavis PA, et al. CMTM6 maintains the expression of PD-L1 and regulates anti-tumour immunity. Nature 2017;549(7670):101–5.
[53] Mezzadra R, Sun C, Jae LT, Gomez-Eerland R, de Vries E, Wu W, et al. Identification of CMTM6 and CMTM4 as PD-L1 protein regulators. Nature 2017;549(7670):106–10.
[54] Schmid P, Adams S, Rugo HS, Schneeweiss A, Barrios CH, Iwata H, et al. Atezolizumab and nab-paclitaxel in advanced triple-negative breast cancer. N Engl J Med 2018;379(22):2108–21.
[55] Daud AI, Wolchok JD, Robert C, Hwu WJ, Weber JS, Ribas A, et al. Programmed death-ligand 1 expression and response to the antiprogrammed death 1 antibody pembrolizumab in melanoma. J Clin Oncol 2016;34(34): 4102–9.
[56] Garon EB, Rizvi NA, Hui R, Leighl N, Balmanoukian AS, Eder JP, et al. Pembrolizumab for the treatment of non-small-cell lung cancer. N Engl J Med 2015;372(21):2018–28.
[57] Herbst RS, Soria JC, Kowanetz M, Fine GD, Hamid O, Gordon MS, et al. Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients. Nature 2014;515(7528):563–7.
[58] Taube JM, Klein A, Brahmer JR, Xu H, Pan X, Kim JH, et al. Association of PD-1, PD-1 ligands, and other features of the tumor immune microenvironment with response to anti-PD-1 therapy. Clin Cancer Res 2014;20(19):5064–74.
[59] Petrylak DP, Loriot Y, Shaffer DR, Braiteh F, Powderly J, Harshman LC, et al. Safety and clinical activity of atezolizumab in patients with metastatic castration-resistant prostate cancer: a phase I study. Clin Cancer Res 2021;27(12):3360–9.
[60] Sharma P, Pachynski RK, Narayan V, Fléchon A, Gravis G, Galsky MD, et al. Nivolumab plus ipilimumab for metastatic castration-resistant prostate cancer: preliminary analysis of patients in the checkmate 650 trial. Cancer Cell 2020; 38(4). 489–99.e3.
[61] Lee HH, Wang YN, Xia W, Chen CH, Rau KM, Ye L, et al. Removal of N-linked glycosylation enhances PD-L1 detection and predicts anti-PD-1/PD-L1 therapeutic efficacy. Cancer Cell 2019;36(2). 168–78.e4.