Am J Cancer Res 2020;10(1):1-11
www.ajcr.us /ISSN:2156-6976/ajcr0106488

Review Article

Regulation of PD-L1 expression in cancer and clinical implications in immunotherapy

Xiaoli Ju[1*], Heng Zhang[2*], Zidi Zhou[1], Qiang Wang[3]

[1]School of Medicine, Jiangsu University, Zhenjiang, P. R. China; [2]Department of General Surgery, Nanjing Lishui District People's Hospital, Zhongda Hospital Lishui Branch, Southeast University, Nanjing, P. R. China; [3]Institute of Life Sciences, Jiangsu University, Zhenjiang, Jiangsu, P. R. China. [*]Equal contributors.

Received December 16, 2019; Accepted December 26, 2019; Epub January 1, 2020; Published January 15, 2020

Abstract: PD-1/PD-L1 immune checkpoint blockade therapy has become an effective method for the treatment of cancers in the clinic. It has great clinical advantages and therapeutic effects in the treatment of various cancers. However, a considerable number of cancer patients currently have relatively low response rates and drug resistance to PD-1/PD-L1 immunotherapy. Therefore, an in-depth understanding of the regulatory mechanism of PD-L1 expression in tumor cells will provide new insights into PD-1/PD-L1 immunotherapy. This review will systematically review the regulatory mechanisms of PD-L1 including genomic amplification, epigenetic regulation, transcriptional regulation, translational regulation and posttranslational modification. We will also discuss PD-L1 expression regulation in clinical applications. Finally, we hope to provide new routes for PD-1/PD-L1 immunotherapy in the clinic.

Keywords: Immune checkpoint blockade therapy, PD-1/PD-L1, gene expression, regulatory mechanism

Introduction

In recent years, immunotherapy has become a new method of cancer treatment. Currently, immune checkpoint blockade therapy is one of the most widely used methods of tumor immunotherapy. The pathway involving programmed death protein 1 (PD-1) and its ligand (PD-L1) is a well-characterized immune checkpoint and has been applied in the clinical treatment of various cancers. Antibodies targeting the PD-1/PD-L1 pathway have been approved for various cancers, including melanoma, non-small cell lung cancer (NSCLC), Hodgkin's lymphoma, bladder cancer, renal cell carcinoma (RCC), head and neck squamous cell carcinoma (HNSCC), breast cancer, Merkel cell carcinoma, hepatocellular carcinoma (HCC) and gastric cancer (GC) [3]. However, these antibodies are only efficacious in a small portion of patients with certain cancers.

At present, the understanding of the resistance mechanism of immune checkpoint blockade therapy and the regulation of PD-L1 expression is quite limited. To develop a more effective and lasting immune checkpoint blocking therapy strategy, it is necessary to gain insights into the multiple roles and complex regulatory mechanisms of PD-L1 in cancers. In this review, we will discuss the molecular mechanisms of PD-L1 expression in cancer cells at the levels of genomic amplification, epigenetic regulation, transcriptional regulation, posttranscriptional regulation, translational regulation, and posttranslational modification. These findings may provide new insights into targeting tumor immune escape after immunotherapy in the clinic.

Classification of PD-L1 expression in tumor cells

The expression of PD-L1 can be divided into constitutive expression and inducible expression depending on the extrinsic or intrinsic stimuli (**Figure 1**). Constitutive expression of PD-L1 in tumor cells is induced by dysregulation of oncogenic or tumor suppressor gene signaling pathways, by activation of abnormal transcription factors, or by genomic aberrations or gene amplifications. Many oncogenic transcrip-

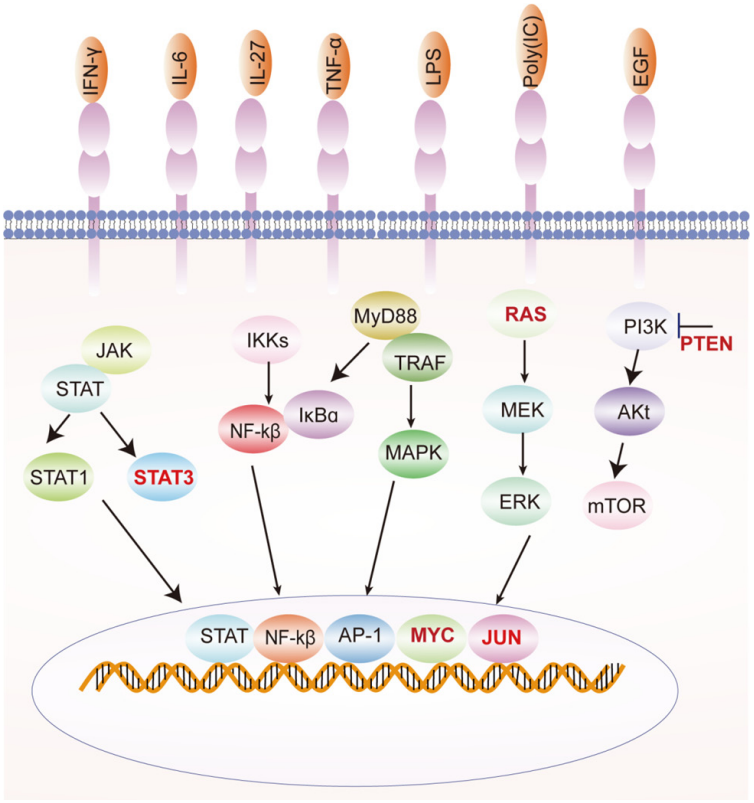

Figure 1. Classification of PD-L1 expression. PD-L1 expression can be divided into constitutive expression and inducible expression. Constitutive expression is induced by dysregulation of signal transduction components in tumor cells. Inducible expression is induced by a number of inflammatory cytokines.

promoter to regulate PD-L1 expression [4, 11] (**Figure 1**).

Inducible expression refers to the expression of PD-L1-controlled inflammatory signals from tumor cells or other immune cells, such as APCs and T cells, in the tumor microenvironment. A number of inflammatory cytokines have been found to induce the expression of PD-L1. These inflammatory factors include IFN-γ, TNF-α, IL-17, IL-27, IL-10, IL-4, IL-2 and IL-10 [12, 13] (**Table 1**).

Regulation of PD-L1 expression by genomic amplification

PD-L1 and PD-L1 are located on chromosome 9p24.1. The amplification of the 9p24.1 region is closely related to an increase in PD-L1 levels in a wide range of cancers [14].

It has been found that copy number alterations (CNAs) of PD-L1 occur in various types of tumors, which lead directly to up-regulation of PD-L1 expression [15].

tion factors have been found to directly regulate PD-L1 expression.

The oncogenic transcription factor MYC is abnormally expressed in many cancer patients [1, 2]. Inhibition of MYC gene expression in mouse or human tumor cells can reduce the expression of PD-L1 at both the gene and protein levels [3-6]. Further studies showed that MYC could bind to the promoter region of PD-L1 and regulate the expression of PD-L1 [3]. Approximately 41% of NSCLC patients show overexpression of MYC [7]. Immunostaining of NSCLC tissues revealed that MYC expression significantly correlated with PD-L1 expression in non-small cell lung cancer [8]. PD-L1 expression was up-regulated by a KRAS mutation and through p-ERK signaling in lung adenocarcinoma [9]. Other studies have shown that oncogenic RAS signaling can drive PD-L1 expression through the RAS-MEK signaling pathway [10]. STAT3 has also been found to act on the PD-L1

The highest frequency of CNAs of PD-L1 has been found in primary mediastinal B-cell lymphoma (PMBCL), classical Hodgkin lymphoma (cHL), and triple-negative breast cancer (TNBC), at 63% [16], 40% [17] and 29% [18], respectively. However, in GC, small cell lung cancers, NSCLCs and diffuse large B-cell lymphoma (DLBCL), the CNAs were much lower, with frequencies of 15% [19], 1.9% [20], 5.3% [21] and 3% [22], respectively. In general, the increase in CNAs is positively correlated with PD-L1 protein levels [23] (**Figure 2**).

Epigenetic regulation of PD-L1 expression

Epigenetic modifications, such as microRNAs (miRNAs), promoter DNA methylation and histone modifications, can regulate the recognition and binding of transcription factors to DNA elements without affecting DNA sequences, thereby altering chromatin structure and regulating PD-L1 expression [24] (**Figure 2**).

Table 1. Classification of PD-L1 expression

Type	Inducer	Type of cancers	Ref
Constitutive expression	MYC	NSCLC, lymphoma, HCC, melanoma	[3-5, 8]
	KRAS	NSCLC, lung cancer	[9, 10, 35, 71]
	STAT3	HNSC, lymphoma, melanoma	[4, 11, 72, 73]
	JUN	Lymphoma, melanoma, medulloblastoma	[53, 72, 74]
	PTEN	Glioma, colorectal cancer, melanoma, breast cancer	[72, 75-78]
	EGFR	Head and neck cancer, breast cancer, NSCLC	[10, 61, 79]
	MEK-ERK	Melanoma, lymphoma, multiple myeloma	[67, 80, 81]
Inducible expression	IFN-γ	Pancreatic cancer, colon cancer, HCC, melanoma, lung cancer, gastric cancers	[82-86]
	IL-6	HCC, lung cancer, prostate cancer	[87-89]
	IL-27	Lung cancer, epithelial ovarian cancer	[88, 90]
	TNF-α	Breast cancer, HCC, prostate and colon cancer cells	[52, 83, 91]
	LPS	Gastric cancers	[92]
	EGF	NSCLC, breast cancer	[10, 61, 71, 93]
	IL-8	Gastric cancers, NSCLC, melanoma	[94, 95]

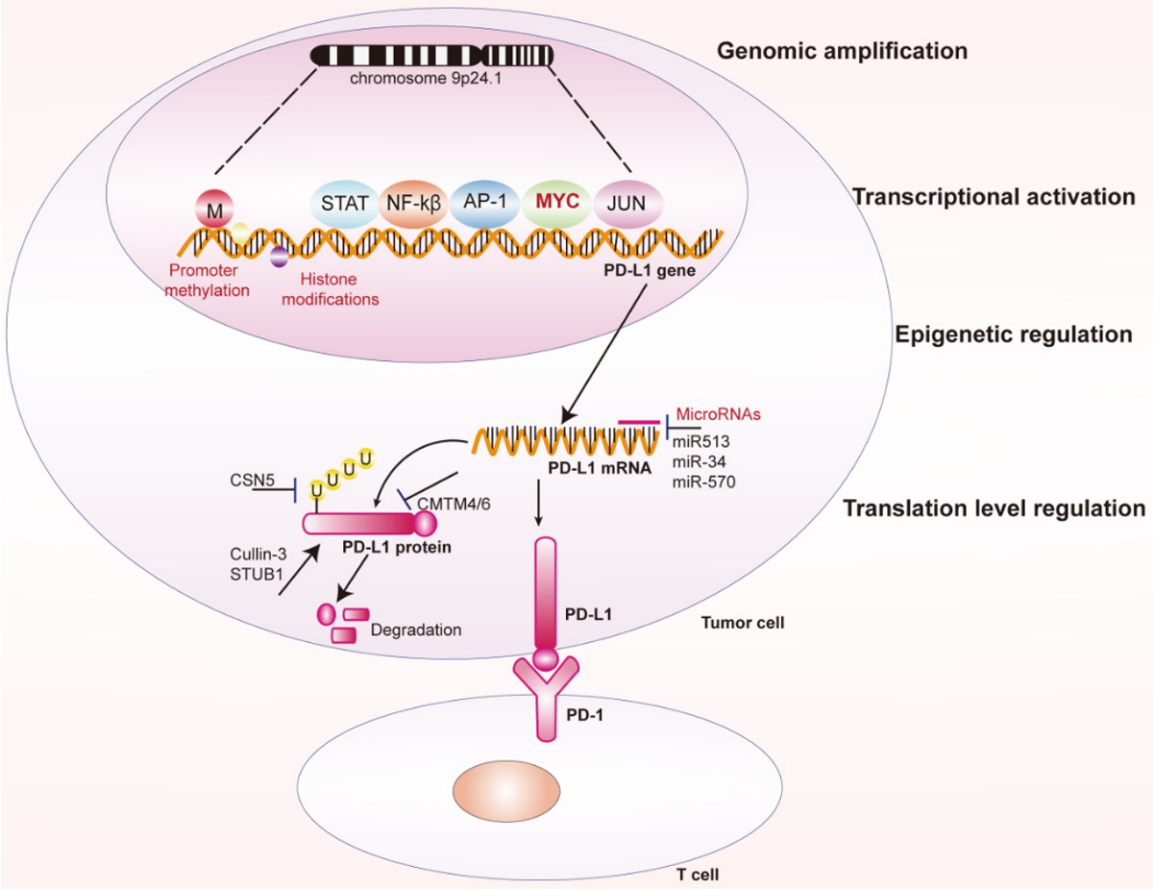

Figure 2. Regulation of PD-L1 expression in cancer cells at different levels. PD-L1 expression can be regulated by genomic amplification, transcriptional regulation, epigenetic regulation and transcriptional regulation.

miRNAs are a class of non-coding single-stranded RNAs that contain 22-24 nucleotides. miRNAs inhibit translation or degradation of target mRNA by binding to the 3'untranslated region (3'UTR) of the target mRNA. A number of miRNAs have been found to regulate PD-L1

expression in different types of cancers [24]. They can regulate PD-L1 expression directly or indirectly.

Direct effectors regulate PD-L1 expression primarily by binding to PD-L1 mRNA. miRNAs that directly regulate PD-L1 expression include miR513 [25], miR-34 [26], miR-570 [27, 28], miR-152 [29], miR-200 [30], miR-138 [31], miR-142-5p [32], miR-424 [33], miR-193a [34] and miR-140/142/340/383 [35]. Indirect effects mainly occur through affecting the expression of other PD-L1 regulators. miRNAs that indirectly regulate PD-L1 expression include miR-20b, miR-21, miR-130b [36], and miR-197 [37].

Recently, it was found that the promoter methylation of PD-L1 was negatively correlated with PD-L1 expression in a number of cancers [38-42]. PD-L1 promoter methylation has been found in many cancers, including acute myeloid leukemia [38], HNSCC [43-45], glioblastoma [41], glioma [42, 43], colorectal cancer [40], and prostate cancer [46]. Analysis of PD-L1 promoter methylation has clinical significance for predicting the outcome of PD-1/PD-L1 immune checkpoint blockade therapies. In PD-1/PD-L1 targeted drug-treated patients, increased PD-L1 promoter methylation is associated with overall patient survival and recurrence-free survival [40].

In addition, histone modifications, including methylation, acetylation, phosphorylation, adenylation, ubiquitination, and ADP ribosylation, can also regulate PD-L1 gene expression [24]. The histone acetylation of the promoter region of the PD-L1 gene is essential for the expression of PD-L1 [24].

Transcriptional activation of PD-L1 expression

A number of transcription factors have been found to regulate PD-L1 transcriptional activation. These transcription factors include MYC, STAT3, NF-kβ, AP1, and HIF-1 (**Figure 2**).

The oncogene MYC is a transcription factor that is overexpressed and activated in a variety of tumors and involved in tumorigenesis [47]. However, there is controversy about the regulation of PD-L1 expression by MYC. Casey et al. found that inhibition of MYC in tumor cells resulted in a decrease in PD-L1 mRNA and protein expression. MYC can bind directly to the promoters of PD-L1 and enhance the anti-tumor immune response [3]. In contrast, Hogg and Durand-Panteix et al. reported that MYC transcriptional levels inhibited PD-L1 mRNA expression [48, 49]. Future research is also needed to clarify these discrepancies.

STAT3 is another reported transcription factor that is involved in the regulation of PD-L1 expression. In chimeric nucleophosmin (NPM)/ALK-carrying T cell lymphoma, STAT3 upregulates PD-L1 expression by binding to the PD-L1 promoter. This effect can be suppressed by silencing STAT3 with siRNA [49]. It was also reported that latent membrane protein-1 (LMP1) of the Epstein–Barr virus can induce PD-L1 expression through inducing the phosphorylation of STAT3 [50].

NF-kβ is a nuclear transcription factor that also regulates PD-L1 expression. However, the mechanism of regulation is still unclear. In natural killer/T-cell lymphoma (NKTCL), inhibition of the NF-kβ signaling pathway reduces PD-L1 expression [51]. Recently, Lim et al. found that the inflammatory factor TNF-α activates the NF-kβ signaling pathway and activates COP9 signalosome 5 (CSN5) to inhibit ubiquitination and degradation of PD-L1 protein [52].

The transcription factor AP-1 is a dimeric complex composed of c-Jun, FOS, MAF, or ATF. Expression of PD-L1 in Hodgkin's lymphoma is induced by AP1 via binding to the enhancer region of the first intron of the PD-L1 gene [53].

Hypoxia-inducible factor 1α (HIF-1α) is another important carcinogenic factor and has clinical significance in regulating the expression of PD-L1 in tumor cells [54]. Binding of HIF-1α to the PD-L1 proximal promoter stimulates transcription of PD-L1. Overexpression of HIF-1α induces an increase in PD-L1 levels [54, 55].

Translation-level regulation of PD-L1

It has been found that ubiquitination, deubiquitination, glycosylation and phosphorylation can affect the stability of PD-L1 protein in cancer cells, thereby regulating the expression of PD-L1 protein (**Figure 2**).

Several proteins were reported to regulate the stability of the PD-L1 protein through ubiquitination. CSN5 is the fifth component of the CSN complex, which contains a conserved JAMM

motif. CSN5 has deubiquitination activity through the JAMM motif and plays an important role during tumorigenesis. Lim et al. found that macrophages secrete TNF-α to activate NF-kβ and then induce transactivation of CSN5. Activation of CSN5 results in deubiquitination of PD-L1 in breast cancer cells and enhances the stability of PD-L1 [52]. Cyclin-dependent kinase 4/6 is a key regulator of the cell cycle. Cyclin D-CDK4 induces ubiquitination degradation of PD-L1 via cullin 3-SPOP to control therapeutic efficacy in human cancers [56]. CMTM6 was a recently identified type 3 transmembrane protein involved in regulating PD-L1 expression [57, 58]. A genome-wide CRISPR-Cas9 screening technology revealed that CMTM6 inhibits ubiquitination and inhibits lysosomal-mediated degradation of PD-L1 by interacting with PD-L1 on the surface of tumor cells [57]. In addition to CMTM6, its closest family member, CMTM4, has similar functions [58]. Epidermal growth factor (EGF) treatment also induces ubiquitination of PD-L1 and regulates PD-L1 protein expression [59].

Glycosylation is an important posttranslational modification of proteins. N-linked glycosylation is a key protein modification that determines the structure and function of proteins and plays an important role in regulating membrane proteins. N-linked glycosylation of PD-L1 was shown to stabilize the PD-L1 protein and prevent degradation by the 26S proteasome [60, 61]. In triple-negative breast cancer, β-1,3-N-acetylglucosaminyl transferase (B3GNT3) was required for the interaction between PD-L1 and PD-1 [60].

Clinical application of PD-L1 expression regulation

Due to tumor heterogeneity and genetic differences between individuals, there are significant defects in the therapeutic effects of targeting the PD-1/PD-L1 pathway alone. Recent studies have found that combining PD-L1/PD1 immunotherapy with targeted therapy significantly improves therapeutic effects by regulating PD-L1 at a very low level [62]. This strategy inhibits PD-L1 expression by regulating key proteins in the signaling pathway, and it combines with the immunotherapy of PD-L1 or PD-1 antibody to achieve a greater therapeutic effect.

In NSCLC, EGFR mutations can induce PD-L1 expression. The combination of osimertinib and durvalumab in the treatment of NSCLC patients with EGFR mutations showed significant efficacy and an overall response rate (ORR) of up to 70% [63-65]. Patients with advanced NSCLC treated with nivolumab in combination with erlotinib for EGFR mutations showed a durable clinical benefit [66]. The use of the KRAS/MEK inhibitor trametinib in combination with anti-PD-1 antibodies also significantly reduced PD-L1 expression and showed better therapeutic effects than individual treatments in NSCLC [67, 68].

On the other hand, the expression of PD-L1 is also regulated by MAPK and PI3K/Akt signaling pathways, and inhibition of these pathways also reduces PD-L1 expression [69]. Inhibition of these signaling pathways can inhibit cell proliferation and regulate PD-L1 expression. Clinical studies have found that receptor tyrosine kinase inhibitors have a better therapeutic effect in lung cancers with high PD-L1 expression [70].

Conclusions and future challenges

Immunotherapies are a new direction in cancer therapy and have many advantages over traditional treatments. Currently, immunotherapy that targets the PD-1/PD-L1 axis has been clinically approved in many countries for the treatment of various human cancers. It has shown unprecedented efficacy in the treatment of a wide range of human cancers. However, only a small proportion of patients show an effect with PD-1/PD-L1 immune checkpoint blockade therapy. The expression of PD-L1 varies greatly in tumor tissues. At present, methods to detect PD-L1 expression in tumor tissues include immunostaining, Western blotting, qPCR and microarray. However, these methods for detecting the expression of PD-L1 vary greatly. An in-depth understanding of the regulatory mechanism of PD-L1 expression has been very helpful for PD-1/PD-L1 immunotherapy in the clinic. Although the regulatory mechanism of PD-L1 expression has been investigated to some extent, there are still many questions that need to be solved. For example, new mechanisms that regulate PD-L1 expression need to be investigated in future studies.

The expression of PD-L1 can be regulated at different levels; however, it is necessary to study which regulatory mechanism plays a critical role in certain types of cancer. A number of

transcription factors that regulate the expression of PD-L1 regulate it by binding to the PD-L1 promoter, but the transcription factors that play key roles in certain types of cancer also need to be identified. In addition, the expression of PD-L1 varies greatly in different stages of tumor development, such as in primary cancer and metastatic cancer. In addition to antibody drugs, it is also necessary to develop a small molecule inhibitor of PD-L1 for treatment of cancer patients. Finally, these studies will provide new ideas for immunological checkpoint blocking therapy.

The understanding of the regulatory mechanism of PD-L1 expression will continue to deepen and will finally provide more choices and more effective methods for tumor immunotherapy of the PD-1/PD-L1 pathway.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (81502621 and 81502088), the China Postdoctoral Science Special Foundation (2017M5654), medical clinical science and technology development fund of Jiangsu University (JLY20180033).

Disclosure of conflict of interest

None.

Address correspondence to: Qiang Wang, Institute of Life Sciences, Jiangsu University, Zhenjiang, Jiangsu, P. R. China. E-mail: wangqiang@ujs.edu.cn

References

[1] Hsieh AL, Walton ZE, Altman BJ, Stine ZE and Dang CV. MYC and metabolism on the path to cancer. Semin Cell Dev Biol 2015; 43: 11-21.

[2] Dang CV. MYC on the path to cancer. Cell 2012; 149: 22-35.

[3] Casey SC, Tong L, Li Y, Do R, Walz S, Fitzgerald KN, Gouw AM, Baylot V, Gütgemann I, Eilers M and Felsher DW. MYC regulates the antitumor immune response through CD47 and PD-L1. Science 2016; 352: 227-231.

[4] Atsaves V, Tsesmetzis N, Chioureas D, Kis L, Leventaki V, Drakos E, Panaretakis T, Grander D, Medeiros LJ, Young KH and Rassidakis GZ. PD-L1 is commonly expressed and transcriptionally regulated by STAT3 and MYC in ALK-negative anaplastic large-cell lymphoma. Leukemia 2017; 31: 1633-1637.

[5] Wang J, Jia Y, Zhao S, Zhang X, Wang X, Han X, Wang Y, Ma M, Shi J and Liu L. BIN1 reverses PD-L1-mediated immune escape by inactivating the c-MYC and EGFR/MAPK signaling pathways in non-small cell lung cancer. Oncogene 2017; 36: 6235-6243.

[6] Casey SC, Baylot V and Felsher DW. MYC: master regulator of immune privilege. Trends Immunol 2017; 38: 298-305.

[7] Lorenz J, Friedberg T, Paulus R, Oesch F and Ferlinz R. Oncogene overexpression in non-small-cell lung cancer tissue: prevalence and clinicopathological significance. Clin Investig 1994; 72: 156-163.

[8] Kim EY, Kim A, Kim SK and Chang YS. MYC expression correlates with PD-L1 expression in non-small cell lung cancer. Lung Cancer 2017; 110: 63-67.

[9] Chen N, Fang W, Lin Z, Peng P, Wang J, Zhan J, Hong S, Huang J, Liu L, Sheng J, Zhou T, Chen Y, Zhang H and Zhang L. KRAS mutation-induced upregulation of PD-L1 mediates immune escape in human lung adenocarcinoma. Cancer Immunol Immunother 2017; 66: 1175-1187.

[10] Coelho MA, de Carné Trécesson S, Rana S, Zecchin D, Moore C, Molina-Arcas M, East P, Spencer-Dene B, Nye E, Barnouin K, Snijders AP, Lai WS, Blackshear PJ and Downward J. Oncogenic RAS signaling promotes tumor immunoresistance by stabilizing PD-L1 mRNA. Immunity 2017; 47: 1083-1099, e6.

[11] Marzec M, Zhang Q, Goradia A, Raghunath PN, Liu X, Paessler M, Wang HY, Wysocka M, Cheng M, Ruggeri BA and Wasik MA. Oncogenic kinase NPM/ALK induces through STAT3 expression of immunosuppressive protein CD274 (PD-L1, B7-H1). Proc Natl Acad Sci U S A 2008; 105: 20852-20857.

[12] Sun C, Mezzadra R and Schumacher TN. Regulation and function of the PD-L1 checkpoint. Immunity 2018; 48: 434-452.

[13] Shi Y. Regulatory mechanisms of PD-L1 expression in cancer cells. Cancer Immunol Immunother 2018; 67: 1481-1489.

[14] Wang X, Teng F, Kong L and Yu J. PD-L1 expression in human cancers and its association with clinical outcomes. Onco Targets Ther 2016; 9: 5023-5039.

[15] Budczies J, Bockmayr M, Denkert C, Klauschen F, Gröschel S, Darb-Esfahani S, Pfarr N, Leichsenring J, Onozato ML, Lennerz JK, Dietel M, Fröhling S, Schirmacher P, Iafrate AJ, Weichert W and Stenzinger A. Pan-cancer analysis of copy number changes in programmed death-ligand 1 (PD-L1, CD274)-associations with gene expression, mutational load, and survival. Genes Chromosomes Cancer 2016; 55: 626-639.

[16] Green MR, Monti S, Rodig SJ, Juszczynski P, Currie T, O'Donnell E, Chapuy B, Takeyama K, Neuberg D, Golub TR, Kutok JL and Shipp MA. Integrative analysis reveals selective 9p24.1 amplification, increased PD-1 ligand expression, and further induction via JAK2 in nodular sclerosing Hodgkin lymphoma and primary mediastinal large B-cell lymphoma. Blood 2010; 116: 3268-3277.

[17] Ansell SM, Lesokhin AM, Borrello I, Halwani A, Scott EC, Gutierrez M, Schuster SJ, Millenson MM, Cattry D, Freeman GJ, Rodig SJ, Chapuy B, Ligon AH, Zhu L, Grosso JF, Kim SY, Timmerman JM, Shipp MA and Armand P. PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. N Engl J Med 2015; 372: 311-319.

[18] Barrett MT, Anderson KS, Lenkiewicz E, Andreozzi M, Cunliffe HE, Klassen CL, Dueck AC, McCullough AE, Reddy SK, Ramanathan RK, Northfelt DW and Pockaj BA. Genomic amplification of 9p24.1 targeting JAK2, PD-L1, and PD-L2 is enriched in high-risk triple negative breast cancer. Oncotarget 2015; 6: 26483-26493.

[19] Cancer Genome Atlas Research Network. Comprehensive molecular characterization of gastric adenocarcinoma. Nature 2014; 513: 202-209.

[20] George J, Saito M, Tsuta K, Iwakawa R, Shiraishi K, Scheel AH, Uchida S, Watanabe SI, Nishikawa R, Noguchi M, Peifer M, Jang SJ, Petersen I, Büttner R, Harris CC, Yokota J, Thomas RK and Kohno T. Genomic amplification of CD274 (PD-L1) in small-cell lung cancer. Clin Cancer Res 2017; 23: 1220-1226.

[21] Ikeda S, Okamoto T, Okano S, Umemoto Y, Tagawa T, Morodomi Y, Kohno M, Shimamatsu S, Kitahara H, Suzuki Y, Fujishita T and Maehara Y. PD-L1 is upregulated by simultaneous amplification of the PD-L1 and JAK2 genes in non-small cell lung cancer. J Thorac Oncol 2016; 11: 62-71.

[22] Georgiou K, Chen L, Berglund M, Ren W, de Miranda NF, Lisboa S, Fangazio M, Zhu S, Hou Y, Wu K, Fang W, Wang X, Meng B, Zhang L, Zeng Y, Bhagat G, Nordenskjöld M, Sundström C, Enblad G, Dalla-Favera R, Zhang H, Teixeira MR, Pasqualucci L, Peng R and Pan-Hammarström Q. Genetic basis of PD-L1 overexpression in diffuse large B-cell lymphomas. Blood 2016; 127: 3026-3034.

[23] Zerdes I, Matikas A, Bergh J, Rassidakis GZ and Foukakis T. Genetic, transcriptional and post-translational regulation of the programmed death protein ligand 1 in cancer: biology and clinical correlations. Oncogene 2018; 37: 4639-4661.

[24] Kumar S and Sharawat SK. Epigenetic regulators of programmed death-ligand 1 expression in human cancers. Transl Res 2018; 202: 129-145.

[25] Gong AY, Zhou R, Hu G, Li X, Splinter PL, O'Hara SP, LaRusso NF, Soukup GA, Dong H and Chen XM. MicroRNA-513 regulates B7-H1 translation and is involved in IFN-gamma-induced B7-H1 expression in cholangiocytes. J Immunol 2009; 182: 1325-1333.

[26] Wang X, Li J, Dong K, Lin F, Long M, Ouyang Y, Wei J, Chen X, Weng Y, He T and Zhang H. Tumor suppressor miR-34a targets PD-L1 and functions as a potential immunotherapeutic target in acute myeloid leukemia. Cell Signal 2015; 27: 443-452.

[27] Wang W, Li F, Mao Y, Zhou H, Sun J, Li R, Liu C, Chen W, Hua D and Zhang X. A miR-570 binding site polymorphism in the B7-H1 gene is associated with the risk of gastric adenocarcinoma. Hum Genet 2013; 132: 641-648.

[28] Wu L, Chen Z, Zhang J and Xing Y. Effect of miR-513a-5p on etoposide-stimulating B7-H1 expression in retinoblastoma cells. J Huazhong Univ Sci Technolog Med Sci 2012; 32: 601-606.

[29] Xie G, Li W, Li R, Wu K, Zhao E, Zhang Y, Zhang P, Shi L, Wang D, Yin Y, Deng R and Tao K. Helicobacter pylori promote B7-H1 expression by suppressing miR-152 and miR-200b in gastric cancer cells. PLoS One 2017; 12: e0168822.

[30] Chen L, Gibbons DL, Goswami S, Cortez MA, Ahn YH, Byers LA, Zhang X, Yi X, Dwyer D, Lin W, Diao L, Wang J, Roybal J, Patel M, Ungewiss C, Peng D, Antonia S, Mediavilla-Varela M, Robertson G, Suraokar M, Welsh JW, Erez B, Wistuba II, Chen L, Peng D, Wang S, Ullrich SE, Heymach JV, Kurie JM and Qin FX. Metastasis is regulated via microRNA-200/ZEB1 axis control of tumour cell PD-L1 expression and intratumoral immunosuppression. Nat Commun 2014; 5: 5241.

[31] Zhang XL, Xu LL and Wang F. Hsa_circ_0020397 regulates colorectal cancer cell viability, apoptosis and invasion by promoting the expression of the miR-138 targets TERT and PD-L1. Cell Biol Int 2017; 41: 1056-1064.

[32] Jia L, Xi Q, Wang H, Zhang Z, Liu H, Cheng Y, Guo X, Zhang J, Zhang Q, Zhang L, Xue Z, Li Y, Da Y, Zhao P and Zhang R. miR-142-5p regulates tumor cell PD-L1 expression and enhances anti-tumor immunity. Biochem Biophys Res Commun 2017; 488: 425-431.

[33] Xu S, Tao Z, Hai B, Liang H, Shi Y, Wang T, Song W, Chen Y, OuYang J, Chen J, Kong F, Dong Y, Jiang SW, Li W, Wang P, Yuan Z, Wan X, Wang C, Li W, Zhang X and Chen K. miR-424(322) reverses chemoresistance via T-cell immune response activation by blocking the PD-L1 immune checkpoint. Nat Commun 2016; 7: 11406.

[34] Kao SC, Cheng YY, Williams M, Kirschner MB, Madore J, Lum T, Sarun KH, Linton A, McCaughan B, Klebe S, van Zandwijk N, Scolyer RA, Boyer MJ, Cooper WA and Reid G. Tumor suppressor microRNAs contribute to the regulation of PD-L1 expression in malignant pleural mesothelioma. J Thorac Oncol 2017; 12: 1421-1433.

[35] Dong P, Xiong Y, Yu J, Chen L, Tao T, Yi S, Hanley SJB, Yue J, Watari H and Sakuragi N. Control of PD-L1 expression by miR-140/142/340/383 and oncogenic activation of the OCT4-miR-18a pathway in cervical cancer. Oncogene 2018; 37: 5257-5268.

[36] Zhu J, Chen L, Zou L, Yang P, Wu R, Mao Y, Zhou H, Li R, Wang K, Wang W, Hua D and Zhang X. MiR-20b, -21, and -130b inhibit PTEN expression resulting in B7-H1 over-expression in advanced colorectal cancer. Hum Immunol 2014; 75: 348-353.

[37] Fujita Y, Yagishita S, Hagiwara K, Yoshioka Y, Kosaka N, Takeshita F, Fujiwara T, Tsuta K, Nokihara H, Tamura T, Asamura H, Kawaishi M, Kuwano K and Ochiya T. The clinical relevance of the miR-197/CKS1B/STAT3-mediated PD-L1 network in chemoresistant non-small-cell lung cancer. Mol Ther 2015; 23: 717-727.

[38] Goltz D, Gevensleben H, Grunen S, Dietrich J, Kristiansen G, Landsberg J and Dietrich D. PD-L1 (CD274) promoter methylation predicts survival in patients with acute myeloid leukemia. Leukemia 2017; 31: 738-743.

[39] Franzen A, Vogt TJ, Muller T, Dietrich J, Schröck A, Golletz C, Brossart P, Bootz F, Landsberg J, Kristiansen G and Dietrich D. PD-L1 (CD274) and PD-L2 (PDCD1LG2) promoter methylation is associated with HPV infection and transcriptional repression in head and neck squamous cell carcinomas. Oncotarget 2018; 9: 641-650.

[40] Goltz D, Gevensleben H, Dietrich J and Dietrich D. PD-L1 (CD274) promoter methylation predicts survival in colorectal cancer patients. Oncoimmunology 2017; 6: e1257454.

[41] Heiland DH, Haaker G, Delev D, Mercas B, Masalha W, Heynckes S, Gäbelein A, Pfeifer D, Carro MS, Weyerbrock A, Prinz M and Schnell O. Comprehensive analysis of PD-L1 expression in glioblastoma multiforme. Oncotarget 2017; 8: 42214-42225.

[42] Rover LK, Gevensleben H, Dietrich J, Bootz F, Landsberg J, Goltz D and Dietrich D. PD-1 (PDCD1) promoter methylation is a prognostic factor in patients with diffuse lower-grade gliomas harboring isocitrate dehydrogenase (IDH) mutations. EBioMedicine 2018; 28: 97-104.

[43] Marwitz S, Scheufele S, Perner S, Reck M, Ammerpohl O and Goldmann T. Epigenetic modifications of the immune-checkpoint genes CTLA4 and PDCD1 in non-small cell lung cancer results in increased expression. Clin Epigenetics 2017; 9: 51.

[44] Zhang Y, Xiang C, Wang Y, Duan Y, Liu C and Zhang Y. PD-L1 promoter methylation mediates the resistance response to anti-PD-1 therapy in NSCLC patients with EGFR-TKI resistance. Oncotarget 2017; 8: 101535-101544.

[45] Goltz D, Gevensleben H, Dietrich J, Schroeck F, de Vos L, Droege F, Kristiansen G, Schroeck A, Landsberg J, Bootz F and Dietrich D. PDCD1 (PD-1) promoter methylation predicts outcome in head and neck squamous cell carcinoma patients. Oncotarget 2017; 8: 41011-41020.

[46] Gevensleben H, Holmes EE, Goltz D, Dietrich J, Sailer V, Ellinger J, Dietrich D and Kristiansen G. PD-L1 promoter methylation is a prognostic biomarker for biochemical recurrence-free survival in prostate cancer patients following radical prostatectomy. Oncotarget 2016; 7: 79943-79955.

[47] Lancho O and Herranz D. The MYC enhancerome: long-range transcriptional regulation of MYC in cancer. Trends Cancer 2018; 4: 810-822.

[48] Hogg SJ, Vervoort SJ, Deswal S, Ott CJ, Li J, Cluse LA, Beavis PA, Darcy PK, Martin BP, Spencer A, Traunbauer AK, Sadovnik I, Bauer K, Valent P, Bradner JE, Zuber J, Shortt J and Johnstone RW. BET-bromodomain inhibitors engage the host immune system and regulate expression of the immune checkpoint ligand PD-L1. Cell Rep 2017; 18: 2162-2174.

[49] Durand-Panteix S, Farhat M, Youlyouz-Marfak I, Rouaud P, Ouk-Martin C, David A, Faumont N, Feuillard J and Jayat-Vignoles C. B7-H1, which represses EBV-immortalized B cell killing by autologous T and NK cells, is oppositely regulated by c-Myc and EBV latency III program at both mRNA and secretory lysosome levels. J Immunol 2012; 189: 181-190.

[50] Fang W, Zhang J, Hong S, Zhan J, Chen N, Qin T, Tang Y, Zhang Y, Kang S, Zhou T, Wu X, Liang W, Hu Z, Ma Y, Zhao Y, Tian Y, Yang Y, Xue C, Yan Y, Hou X, Huang P, Huang Y, Zhao H and Zhang L. EBV-driven LMP1 and IFN-gamma upregulate PD-L1 in nasopharyngeal carcinoma: implications for oncotargeted therapy. Oncotarget 2014; 5: 12189-12202.

[51] Bi XW, Wang H, Zhang WW, Wang JH, Liu WJ, Xia ZJ, Huang HQ, Jiang WQ, Zhang YJ and Wang L. PD-L1 is upregulated by EBV-driven LMP1 through NF-kappaB pathway and correlates with poor prognosis in natural killer/T-cell lymphoma. J Hematol Oncol 2016; 9: 109.

[52] Lim SO, Li CW, Xia W, Cha JH, Chan LC, Wu Y, Chang SS, Lin WC, Hsu JM, Hsu YH, Kim T,

Chang WC, Hsu JL, Yamaguchi H, Ding Q, Wang Y, Yang Y, Chen CH, Sahin AA, Yu D, Hortobagyi GN and Hung MC. Deubiquitination and stabilization of PD-L1 by CSN5. Cancer Cell 2016; 30: 925-939.

[53] Green MR, Rodig S, Juszczynski P, Ouyang J, Sinha P, O'Donnell E, Neuberg D and Shipp MA. Constitutive AP-1 activity and EBV infection induce PD-L1 in Hodgkin lymphomas and posttransplant lymphoproliferative disorders: implications for targeted therapy. Clin Cancer Res 2012; 18: 1611-1618.

[54] Noman MZ, Desantis G, Janji B, Hasmim M, Karray S, Dessen P, Bronte V and Chouaib S. PD-L1 is a novel direct target of HIF-1alpha, and its blockade under hypoxia enhanced MDSC-mediated T cell activation. J Exp Med 2014; 211: 781-790.

[55] Shehade H, Oldenhove G and Moser M. Hypoxia in the intestine or solid tumors: a beneficial or deleterious alarm signal? Eur J Immunol 2014; 44: 2550-2557.

[56] Zhang J, Bu X, Wang H, Zhu Y, Geng Y, Nihira NT, Tan Y, Ci Y, Wu F, Dai X, Guo J, Huang YH, Fan C, Ren S, Sun Y, Freeman GJ, Sicinski P and Wei W. Cyclin D-CDK4 kinase destabilizes PD-L1 via cullin 3-SPOP to control cancer immune surveillance. Nature 2018; 553: 91-95.

[57] Burr ML, Sparbier CE, Chan YC, Williamson JC, Woods K, Beavis PA, Lam EYN, Henderson MA, Bell CC, Stolzenburg S, Gilan O, Bloor S, Noori T, Morgens DW, Bassik MC, Neeson PJ, Behren A, Darcy PK, Dawson SJ, Voskoboinik I, Trapani JA, Cebon J, Lehner PJ and Dawson MA. CMTM6 maintains the expression of PD-L1 and regulates anti-tumour immunity. Nature 2017; 549: 101-105.

[58] Mezzadra R, Sun C, Jae LT, Gomez-Eerland R, de Vries E, Wu W, Logtenberg MEW, Slagter M, Rozeman EA, Hofland I, Broeks A, Horlings HM, Wessels LFA, Blank CU, Xiao Y, Heck AJR, Borst J, Brummelkamp TR and Schumacher TNM. Identification of CMTM6 and CMTM4 as PD-L1 protein regulators. Nature 2017; 549: 106-110.

[59] Horita H, Law A, Hong S and Middleton K. Identifying regulatory posttranslational modifications of PD-L1: a focus on monoubiquitinaton. Neoplasia 2017; 19: 346-353.

[60] Li CW, Lim SO, Chung EM, Kim YS, Park AH, Yao J, Cha JH, Xia W, Chan LC, Kim T, Chang SS, Lee HH, Chou CK, Liu YL, Yeh HC, Perillo EP, Dunn AK, Kuo CW, Khoo KH, Hsu JL, Wu Y, Hsu JM, Yamaguchi H, Huang TH, Sahin AA, Hortobagyi GN, Yoo SS and Hung MC. Eradication of triple-negative breast cancer cells by targeting glycosylated PD-L1. Cancer Cell 2018; 33: 187-201, e10.

[61] Li CW, Lim SO, Xia W, Lee HH, Chan LC, Kuo CW, Khoo KH, Chang SS, Cha JH, Kim T, Hsu JL, Wu Y, Hsu JM, Yamaguchi H, Ding Q, Wang Y, Yao J, Lee CC, Wu HJ, Sahin AA, Allison JP, Yu D, Hortobagyi GN and Hung MC. Glycosylation and stabilization of programmed death ligand-1 suppresses T-cell activity. Nat Commun 2016; 7: 12632.

[62] Moya-Horno I, Viteri S, Karachaliou N and Rosell R. Combination of immunotherapy with targeted therapies in advanced non-small cell lung cancer (NSCLC). Ther Adv Med Oncol 2018; 10: 1758834017745012.

[63] Li X, Lian Z, Wang S, Xing L and Yu J. Interactions between EGFR and PD-1/PD-L1 pathway: implications for treatment of NSCLC. Cancer Lett 2018; 418: 1-9.

[64] Chih-Hsin Yang J, Shepherd FA, Kim DW, Lee GW, Lee JS, Chang GC, Lee SS, Wei YF, Lee YG, Laus G, Collins B, Pisetzky F and Horn L. Osimertinib plus durvalumab versus osimertinib monotherapy in EGFR T790M-positive NSCLC following previous EGFR TKI therapy: CAURAL brief report. J Thorac Oncol 2019; 14: 933-939.

[65] Ahn MJ. Combination of osimertinib with durvalumab in epidermal growth factor receptor-mutant non-small cell lung cancer: is there room for reinvestigation? J Thorac Oncol 2019; 14: 766-767.

[66] Neoadjuvant PD-1 Blockade in Resectable Lung Cancer; Nivolumab and Ipilimumab in Advanced Melanoma; Overall Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma; Prolonged Survival in Stage III Melanoma with Ipilimumab Adjuvant Therapy; Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma; Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma; Nivolumab and Ipilimumab versus Ipilimumab in Untreated Melanoma; Rapid Eradication of a Bulky Melanoma Mass with One Dose of Immunotherapy; Genetic Basis for Clinical Response to CTLA-4 Blockade; Genetic Basis for Clinical Response to CTLA-4 Blockade in Melanoma; Nivolumab plus Ipilimumab in Advanced Melanoma; Safety and Tumor Responses with Lambrolizumab (Anti-PD-1) in Melanoma; Hepatotoxicity with Combination of Vemurafenib and Ipilimumab. N Engl J Med 2018; 379: 2185.

[67] Liu L, Mayes PA, Eastman S, Shi H, Yadavilli S, Zhang T, Yang J, Seestaller-Wehr L, Zhang SY, Hopson C, Tsvetkov L, Jing J, Zhang S, Smothers J and Hoos A. The BRAF and MEK inhibitors dabrafenib and trametinib: effects on immune function and in combination with immunomodulatory antibodies targeting PD-1, PD-L1, and CTLA-4. Clin Cancer Res 2015; 21: 1639-1651.

[68] Gettinger S, Hellmann MD, Chow LQM, Borghaei H, Antonia S, Brahmer JR, Goldman

JW, Gerber DE, Juergens RA, Shepherd FA, Laurie SA, Young TC, Li X, Geese WJ and Rizvi N. Nivolumab plus erlotinib in patients with EGFR-mutant advanced NSCLC. J Thorac Oncol 2018; 13: 1363-1372.

[69] Lastwika KJ, Wilson W 3rd, Li QK, Norris J, Xu H, Ghazarian SR, Kitagawa H, Kawabata S, Taube JM, Yao S, Liu LN, Gills JJ and Dennis PA. Control of PD-L1 expression by oncogenic activation of the AKT-mTOR pathway in non-small cell lung cancer. Cancer Res 2016; 76: 227-238.

[70] Lin C, Chen X, Li M, Liu J, Qi X, Yang W, Zhang H, Cai Z, Dai Y and Ouyang X. Programmed death-ligand 1 expression predicts tyrosine kinase inhibitor response and better prognosis in a cohort of patients with epidermal growth factor receptor mutation-positive lung adenocarcinoma. Clin Lung Cancer 2015; 16: e25-35.

[71] Lastwika KJ, Wilson W 3rd, Li QK, Norris J, Xu H, Ghazarian SR, Kitagawa H, Kawabata S, Taube JM, Yao S, Liu LN, Gills JJ and Dennis PA. Control of PD-L1 expression by oncogenic activation of the AKT-mTOR pathway in non-small cell lung cancer. Cancer Res 2016; 76: 227-238.

[72] Jiang X, Zhou J, Giobbie-Hurder A, Wargo J and Hodi FS. The activation of MAPK in melanoma cells resistant to BRAF inhibition promotes PD-L1 expression that is reversible by MEK and PI3K inhibition. Clin Cancer Res 2013; 19: 598-609.

[73] Bu LL, Yu GT, Wu L, Mao L, Deng WW, Liu JF, Kulkarni AB, Zhang WF, Zhang L and Sun ZJ. STAT3 induces immunosuppression by upregulating PD-1/PD-L1 in HNSCC. J Dent Res 2017; 96: 1027-1034.

[74] Dorand RD, Nthale J, Myers JT, Barkauskas DS, Avril S, Chirieleison SM, Pareek TK, Abbott DW, Stearns DS, Letterio JJ, Huang AY and Petrosiute A. Cdk5 disruption attenuates tumor PD-L1 expression and promotes antitumor immunity. Science 2016; 353: 399-403.

[75] Parsa AT, Waldron JS, Panner A, Crane CA, Parney IF, Barry JJ, Cachola KE, Murray JC, Tihan T, Jensen MC, Mischel PS, Stokoe D and Pieper RO. Loss of tumor suppressor PTEN function increases B7-H1 expression and immunoresistance in glioma. Nat Med 2007; 13: 84-88.

[76] Song M, Chen D, Lu B, Wang C, Zhang J, Huang L, Wang X, Timmons CL, Hu J, Liu B, Wu X, Wang L, Wang J and Liu H. PTEN loss increases PD-L1 protein expression and affects the correlation between PD-L1 expression and clinical parameters in colorectal cancer. PLoS One 2013; 8: e65821.

[77] Atefi M, Avramis E, Lassen A, Wong DJ, Robert L, Foulad D, Cerniglia M, Titz B, Chodon T, Graeber TG, Comin-Anduix B and Ribas A. Effects of MAPK and PI3K pathways on PD-L1 expression in melanoma. Clin Cancer Res 2014; 20: 3446-3457.

[78] Mittendorf EA, Philips AV, Meric-Bernstam F, Qiao N, Wu Y, Harrington S, Su X, Wang Y, Gonzalez-Angulo AM, Akcakanat A, Chawla A, Curran M, Hwu P, Sharma P, Litton JK, Molldrem JJ and Alatrash G. PD-L1 expression in triple-negative breast cancer. Cancer Immunol Res 2014; 2: 361-370.

[79] Concha-Benavente F, Srivastava RM, Trivedi S, Lei Y, Chandran U, Seethala RR, Freeman GJ and Ferris RL. Identification of the cell-intrinsic and -extrinsic pathways downstream of EGFR and IFNgamma that induce PD-L1 expression in head and neck cancer. Cancer Res 2016; 76: 1031-1043.

[80] Liu J, Hamrouni A, Wolowiec D, Coiteux V, Kuliczkowski K, Hetuin D, Saudemont A and Quesnel B. Plasma cells from multiple myeloma patients express B7-H1 (PD-L1) and increase expression after stimulation with IFN-γ and TLR ligands via a MyD88-, TRAF6-, and MEK-dependent pathway. Blood 2007; 110: 296-304.

[81] Yamamoto R, Nishikori M, Tashima M, Sakai T, Ichinohe T, Takaori-Kondo A, Ohmori K and Uchiyama T. B7-H1 expression is regulated by MEK/ERK signaling pathway in anaplastic large cell lymphoma and Hodgkin lymphoma. Cancer Sci 2009; 100: 2093-2100.

[82] Imai D, Yoshizumi T, Okano S, Itoh S, Ikegami T, Harada N, Aishima S, Oda Y and Maehara Y. IFN-γ promotes epithelial-mesenchymal transition and the expression of PD-L1 in pancreatic cancer. J Surg Res 2019; 240: 115-123.

[83] Li N, Wang J, Zhang N, Zhuang M, Zong Z, Zou J, Li G, Wang X, Zhou H, Zhang L and Shi Y. Cross-talk between TNF-alpha and IFN-gamma signaling in induction of B7-H1 expression in hepatocellular carcinoma cells. Cancer Immunol Immunother 2018; 67: 271-283.

[84] Garcia-Diaz A, Shin DS, Moreno BH, Saco J, Escuin-Ordinas H, Rodriguez GA, Zaretsky JM, Sun L, Hugo W, Wang X, Parisi G, Saus CP, Torrejon DY, Graeber TG, Comin-Anduix B, Hu-Lieskovan S, Damoiseaux R, Lo RS and Ribas A. Interferon receptor signaling pathways regulating PD-L1 and PD-L2 expression. Cell Rep 2017; 19: 1189-1201.

[85] Zhang X, Zeng Y, Qu Q, Zhu J, Liu Z, Ning W, Zeng H, Zhang N, Du W, Chen C and Huang JA. PD-L1 induced by IFN-gamma from tumor-associated macrophages via the JAK/STAT3 and PI3K/AKT signaling pathways promoted progression of lung cancer. Int J Clin Oncol 2017; 22: 1026-1033.

[86] Moon JW, Kong SK, Kim BS, Kim HJ, Lim H, Noh K, Kim Y, Choi JW, Lee JH and Kim YS. IFNgamma induces PD-L1 overexpression by JAK2/STAT1/IRF-1 signaling in EBV-positive gastric carcinoma. Sci Rep 2017; 7: 17810.

[87] Chan LC, Li CW, Xia W, Hsu JM, Lee HH, Cha JH, Wang HL, Yang WH, Yen EY, Chang WC, Zha Z, Lim SO, Lai YJ, Liu C, Liu J, Dong Q, Yang Y, Sun L, Wei Y, Nie L, Hsu JL, Li H, Ye Q, Hassan MM, Amin HM, Kaseb AO, Lin X, Wang SC and Hung MC. IL-6/JAK1 pathway drives PD-L1 Y112 phosphorylation to promote cancer immune evasion. J Clin Invest 2019; 129: 3324-3338.

[88] Carbotti G, Nikpoor AR, Vacca P, Gangemi R, Giordano C, Campelli F, Ferrini S and Fabbi M. IL-27 mediates HLA class I up-regulation, which can be inhibited by the IL-6 pathway, in HLA-deficient Small Cell Lung Cancer cells. J Exp Clin Cancer Res 2017; 36: 140.

[89] Xu L, Chen X, Shen M, Yang DR, Fang L, Weng G, Tsai Y, Keng PC, Chen Y and Lee SO. Inhibition of IL-6-JAK/Stat3 signaling in castration-resistant prostate cancer cells enhances the NK cell-mediated cytotoxicity via alteration of PD-L1/NKG2D ligand levels. Mol Oncol 2018; 12: 269-286.

[90] Carbotti G, Barisione G, Airoldi I, Mezzanzanica D, Bagnoli M, Ferrero S, Petretto A, Fabbi M and Ferrini S. IL-27 induces the expression of IDO and PD-L1 in human cancer cells. Oncotarget 2015; 6: 43267-43280.

[91] Wang X, Yang L, Huang F, Zhang Q, Liu S, Ma L and You Z. Inflammatory cytokines IL-17 and TNF-alpha up-regulate PD-L1 expression in human prostate and colon cancer cells. Immunol Lett 2017; 184: 7-14.

[92] Li H, Xia JQ, Zhu FS, Xi ZH, Pan CY, Gu LM and Tian YZ. LPS promotes the expression of PD-L1 in gastric cancer cells through NF-kappaB activation. J Cell Biochem 2018; 119: 9997-10004.

[93] Chen N, Fang W, Zhan J, Hong S, Tang Y, Kang S, Zhang Y, He X, Zhou T, Qin T, Huang Y, Yi X and Zhang L. Upregulation of PD-L1 by EGFR activation mediates the immune escape in EGFR-driven NSCLC: implication for optional immune targeted therapy for NSCLC patients with EGFR mutation. J Thorac Oncol 2015; 10: 910-923.

[94] Sun L, Wang Q, Chen B, Zhao Y, Shen B, Wang H, Xu J, Zhu M, Zhao X, Xu C, Chen Z, Wang M, Xu W and Zhu W. Gastric cancer mesenchymal stem cells derived IL-8 induces PD-L1 expression in gastric cancer cells via STAT3/mTOR-c-Myc signal axis. Cell Death Dis 2018; 9: 928.

[95] Sanmamed MF, Perez-Gracia JL, Schalper KA, Fusco JP, Gonzalez A, Rodriguez-Ruiz ME, Oñate C, Perez G, Alfaro C, Martín-Algarra S, Andueza MP, Gurpide A, Morgado M, Wang J, Bacchiocchi A, Halaban R, Kluger H, Chen L, Sznol M and Melero I. Changes in serum interleukin-8 (IL-8) levels reflect and predict response to anti-PD-1 treatment in melanoma and non-small-cell lung cancer patients. Ann Oncol 2017; 28: 1988-1995.