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Optimization of cancer immunotherapy on the basis of programmed death ligand-1 distribution and function

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Abstract

Programmed cell death protein-1 (PD-1)/programmed death ligand-1 (PD-L1) immune checkpoint blockade as a breakthrough in cancer immunotherapy has shown unprecedented positive outcomes in the clinic. However, the overall effectiveness of PD-L1 antibody is less than expected. An increasing number of studies have demonstrated that PD-L1 is widely distributed and expressed not only on the cell membrane but also on the inside of the cells as well as on the extracellular vesicles secreted by tumour cells. Both endogenous and exogenous PD-L1 play significant roles in influencing the therapeutic effect of anti-tumour immunity. Herein, we mainly focused on the distribution and function of PD-L1 and further summarized the potential targeted therapeutic strategies. More importantly, in addition to taking the overall expression abundance of PD-L1 as a predictive indicator for selecting corresponding PD-1/PD-L1 monoclonal antibodies (mAbs), we

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AUTHOR CONTRIBUTIONS

Yin Lu, Zhonghong Wei and Yang Zhao contributed to the conception and design of the review. Wei Zou and Xin Luo reviewed the literature and wrote the draft. Mengyuan Gao, Chang Yu and Xueting Wan collected the data and drew the tables and figures. Suyun Yu, Yuanyuan Wu, Aiyun Wang, William Fenical and Yang Zhao revised the manuscript. All authors have read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

All authors declare that they have no conflict of interest. All authors declare that they have no known competing financial interest or personal relationships that could have appeared to influence the work reported in this paper.

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also proposed that personalized combination therapies based on the different distribution of PD-L1 are worth attention to achieve more efficient and effective therapeutic outcomes in cancer patients.

Keywords

antibodies blockade; combination therapy; PD-L1 distribution; PD-L1 function; pharmacological modulators; predictive biomarkers

1 | INTRODUCTION

It has been widely held that the continuing success of immunotherapy in the clinic has enabled it to be a prime focus in the field of cancer treatment (Zhang & Zhang, 2020). Immune checkpoints have been regarded as the key hub for immune resistance. Tumour cells are capable of activating immune checkpoints to hide from the killing effects of various types of lymphocytes in the immune system, leading to tumour immune escape. Of note, the immune checkpoint blockade therapy targeting **PD-1**/**PD-L1** marks a milestone in tumour immunotherapy.

In fact, antibody drugs that antagonize PD-1/PD-L1 have been used for treating cancer patients for many years, and the existing drugs targeting PD-1/PD-L1 in the clinic are all monoclonal antibodies (mAbs). These PD-1/PD-L1 mAbs exert striking effects to prolong the survival of patients with advanced cancers including melanoma and non-small cell lung cancer (NSCLC), with a majority of patients even being completely cured (Eggermont et al., 2018; Huang et al., 2021; Tang et al., 2018). However, the overall response rate (ORR) for most solid tumours is only approximately 20% (Li & Tian, 2019). Indeed, a growing body of evidence has revealed that PD-L1 is widely distributed inside and outside cells: it is prone to locate not only on the surface of the cell membrane but also on the Golgi apparatus, circulating endosomes and extracellular vesicles (Gao et al., 2020; Tang et al., 2020; Yao et al., 2019). PD-L1 inside the cells tends to promote cancer progression and also can be re-transported to the cell surface through circulating endosomes, thereby restricting anti-tumour immunity. Moreover, exosomes expressing PD-L1 released by tumour cells are able to inhibit systemic immunity. This may be one of the driving forces behind the compromised therapeutic effects of existing antibodies.

In this perspective, investigation of the distribution and function of PD-L1 is beneficial for deepening the understanding of the mechanisms underlying failure of PD-1/PD-L1 mAbs and in guiding the selection of therapeutic regimens. Herein, the PD-L1 distribution and function in the cells have been summarized in detail, and the knowledge about current treatment strategies on the basis of distinct forms of PD-L1 have also been outlined. All of these provide reliable insight into selecting more effective and personalized PD-L1 therapeutic strategies, paving the route for optimizing the tumour immunotherapy.

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2 | DISTRIBUTION AND FUNCTION OF PD-L1

2.1 | Cell membrane PD-L1 (mPD-L1) regulates tumour-specific immune tolerance

It is well established that PD-L1 is a transmembrane protein that is predominantly expressed on the surface of antigen-presenting cells and tumour cells (Keir et al., 2008). mPD-L1 is recognized as the most important form, it can specifically bind to PD-1 and augment the tyrosine phosphorylation of PD-1 at the immunoreceptor tyrosine-based switch motif (ITSM) domain, causing dephosphorylation of the downstream spleen tyrosine kinase (**Syk**) and phosphatidylinositol-3-kinase (PI3K) as well as impeding the activation of downstream protein kinase B (**Akt**), extracellular signal-regulated kinase (ERK) and other signalling pathways (Marasco et al., 2020; Wu, Gu, et al., 2019). In addition, mPD-L1 has profound consequences involving inhibiting the transcription and translation of genes that are required for T cell activation and thus attenuating T cell-mediated killing activity, thereby leading to immune escape for tumour cells (Figure 1). To this end, blocking the interactions between PD-1 and PD-L1 enhances the killing effect of T cells on tumour cells (Dammeijer et al., 2020; Dong et al., 2002). The Food and Drug Administration (FDA) has approved 13 types of PD-1/PD-L1 immune checkpoint inhibitors used for immunotherapy so far (Yi et al., 2022). All approved antagonists are mAbs that are capable of specifically binding to PD-1 or PD-L1. These mAbs have demonstrated very solid and durable responses, abolishing cancer progression in a wealth of patients. Even though PD-1/PD-L1 antibody therapy has achieved considerable success, the overall objective response rates were much less than expected, and drug resistance and severe side effects are frequently observed after long-term use. Interestingly, recent studies have revealed that PD-L1 is widely locates inside and outside cells, and these distributed forms of PD-L1 may influence the effects of cancer immunotherapy mediated by mPD-L1 blockade (Gao et al., 2020; Tang et al., 2020; Yao et al., 2019).

2.2 | Endogenous PD-L1 replenishes PD-L1 on the cell membrane

In addition, it has been demonstrated that cancer patients with cPD-L1 expression displayed shorter disease-free survival than those without cPD-L1 expression (Chen et al., 2016). Qu et al. highlighted that the proliferation and migration of SKOV3 (RRID: CVCL_0532) cells (an ovarian cell line with mPD-L1-negative but cPD-L1-positive expression) were significantly inhibited using a specific siRNA to silence the expression of PD-L1 in the SKOV3 cells, highlighting the critical function of cPD-L1 (Qu et al., 2017). Similarly, a study on circulating tumour cells (CTCs) showed that elevated nPD-L1 expression levels were significantly associated with short survival (Satelli et al., 2016). Interestingly, chemotherapeutic drugs may preferentially boost the expression of mPD-L1 as well as cPD-L1, suggesting that the abnormal expression of nPD-L1 is closely related to augmented cytochemical resistance (Ghebeh et al., 2010).

2.3 | Exogenous PD-L1 surrounds solid tumours and spreads to the whole body

Notably, PD-1/PD-L1 mAbs were found to be extremely ineffective in the treatment of glioblastoma (Litak et al., 2019; Wang et al., 2019). Further studies revealed that glioblastoma displayed a new mechanism of escaping the immune system, in that tumour cells were able to secrete extracellular vesicles expressing PD-L1 DNA and RNA (Himes et

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al., 2020). Moreover, a large amount of PD-L1 DNA was detected in the blood of 14 patients with glioblastoma, which was much more than that in the blood of healthy people. More interestingly, the content of PD-L1 DNA was positively correlated to tumour size (Cumba Garcia et al., 2019). It has been widely appreciated that exosomal PD-L1 (exoPD-L1) is capable of inhibiting the activity of T cells and spreading directly from tumour tissue to the whole body, thereby profoundly attacking and suppressing the human immune system (Chen et al., 2018; Himes et al., 2020). In addition, exoPD-L1 released from lung tumours also tended to activate noncanonical nuclear factor-kappaB (NF-κB) signalling through modulating toll-like receptors, to influence the metabolic process of macrophages and convert macrophages into an immunosuppressive phenotype, thus providing a favourable microenvironment for tumour metastasis (Morrissey et al., 2021). Therefore, exoPD-L1 is also regarded as an important form of PD-L1, which not only acts directly on antibody drugs and thus produce drug resistance but also regulates tumour microenvironment-favourable cells, contributing to immunosuppression (Poggio et al., 2019). Importantly, exoPD-L1 expression levels appeared to vary on the basis of the stages of an-tumour immunity, suggesting that exoPD-L1 may serve as a biomarker for cancer patients in choosing appropriate anti-PD-L1 therapy.

3 | IMMUNOTHERAPEUTIC STRATEGIES BASED ON PD-L1 DISTRIBUTION

3.1 | mPD-L1 blockade

Blocking the PD-1/PD-L1 signalling pathway can promote the activation of T cells and orchestrate the endogenous anti-tumour immune response to exert therapeutic effects on tumour progression. With great success in clinical trials, the development of PD-1/PD-L1 antibodies has attracted extensive attention. At present, a total of 13 PD-1/PD-L1 immune checkpoint inhibitors have been approved for the treatment of various types of cancer, with ten types of anti-PD-1 mAbs and three types of anti-PD-L1 mAbs (Table 1). In the future, it is predicted that multiple anti-PD-1/PD-L1 mAbs may be approved for marketing. Except for prolgolimab, the basic structure of anti-PD-1 mAb is IgG4, which is able to exchange Fab segments with other IgG4 molecules to initiate and propel “semi molecular exchange” (van der Neut Kolfschoten et al., 2007). Serine at position 228 of the core hinge motif is deemed to be a key element required for “semi molecular exchange”, as validated by the substitution of serine with proline (S228P site) through point mutation to prevent Fab segment exchange of IgG4 (Crescioli et al., 2016; Yang et al., 2015). Therefore, anti-PD-1 mAbs are modified with S228P to stabilize the disulfide bond between chains, preventing Fab segment exchange and overcoming the unpredictable efficacy and toxicity caused by the instability of IgG4 (Dumet et al., 2019). The basic structure of anti-PD-L1 mAb is IgG1, and the proline at position 228 of the core hinge motif is relatively stable and hence no ‘semi molecular exchange’ is observed.

Although PD-1/PD-L1 blockade based therapy has been verified to be a specific and relatively safe anti-cancer strategy, it still encounters a series of issues that need to be addressed. For instance, PD-1/PD-L1 inhibitors are either humanized or completely human mAbs with certain immunogenicity (Lin et al., 2020). Besides, biological macromolecules are prone to trigger a cytokine storm after entering the body, resulting in a strong immune

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response and increased occurrence of adverse reactions (Postow et al., 2018). Previous meta-analysis data showed that patients treated with anti-PD-1 antibodies exhibited significantly increased risk of pneumonia compared with patients treated with chemotherapy or targeted therapy (Abdel-Rahman & Fouad, 2016; Baxi et al., 2018). According to reports from the World Health Organization (WHO), patients treated with PD-1/PD-L1 antibodies are at a risk of fatal fulminant immune-associated myocarditis (Moslehi et al., 2018). It is undeniable that the complicated tumour microenvironment with extensive vascular leakage, solidified collagen and increased hyaluronic acid severely influences the penetration and distribution of mAbs in tissues (Li et al., 2017). In particular, in solid tumours, the penetration capability of PD-1/PD-L1 mAbs appears to be poor, and the effective response may be restricted to some cancer cells adjacent to blood vessels. More importantly, the response rate of mAb drug treatment substantially relies on the expression level of mPD-L1, and has limited impact on the expression of nPD-L1 and cPD-L1, so that antibody drugs only have limited therapeutic efficacy. Moreover, there are concerns affecting anti-PD-L1 mAb drug usage in the clinic that should be considered, including cost, compliance as well as accessibility of the mAbs.

Notably, in comparison with mAbs, PD-L1 small-molecule inhibitors have innate advantages with lower molecular weight, better penetration, weaker immunogenicity, higher patient compliance and lower production cost (Lin et al., 2020; Wu et al., 2021). CA-170 is regarded as the world's first small-molecule PD-L1 inhibitor jointly developed by Aurigene and Curis. It is a small-molecule dual inhibitor for the PD-1/PD-L1 signalling axis and VISTA based on a peptide design derived from PD-1 to rescue T-cell function in vitro (Pan et al., 2021). In addition, BMS-1002 is one of the most effective compounds and has been used as a structural prototype for many structural modifications documented to date (Song et al., 2021). Moreover, Jonathan Rios-Doria and his team from Incyte announced that they have identified a small-molecule inhibitor of PD-L1 named INCB086550, which could block PD-L1-mediated signals, activate immune effector cells, and boost the immune surveillance function to fight against tumours (Koblish et al., 2022). Indeed, small-molecule PD-L1 inhibitors have shown striking therapeutic value in a variety of mouse tumour models and in clinical trials for cancer patients. It is speculated that small-molecule PD-L1 inhibitors block the binding of PD-1 and PD-L1 proteins mainly through two routes. Firstly, some small-molecule inhibitors of PD-L1 tend to bind to two molecules of PD-L1 protein to form a dimer, in which the binding sites of the small-molecule inhibitors and PD-L1 are highly overlapped compared with those of PD-1 (Guzik et al., 2017). Compared with the monomer, the conformation of the dimer is dramatically altered, which curtails its binding ability to PD-1 protein. Secondly, the conformations of the PD-L1 monomer or dimer bound to small-molecule inhibitors are unstable, driving the endocytosis of PD-L1 (Koblish et al., 2022; Park et al., 2021).

Although small-molecule and peptide inhibitors directly targeting PD-1/PD-L1 interactions have been substantially investigated in various preclinical cancer models, no small-molecule inhibitors have been approved for marketing so far. In fact, for the development of PD-L1 small-molecule inhibitors, designing small-molecule compounds with small-molecular weight, good oral bioavailability, excellent pharmacokinetic performance and sufficient

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safety as well as potently blocking the interactions between PD-1 and PD-L1 should be taken into serious consideration (Lin et al., 2020).

3.2 | Regulation of endogenous PD-L1 expression and transportation

In general, endogenous PD-L1 provides continuous opportunities for tumour cells to achieve immune escape. In this perspective, eliminating PD-L1 (down-regulating PD-L1 expression or promoting PD-L1 degradation) is shown to be a reliable target to alleviate the immunosuppressive tumour microenvironment. Intracellular PD-L1 is frequently up-regulated in multiple types of malignant tumours (Sun et al., 2018). Emerging evidence has revealed that a number of potential underlying mechanisms have critical roles in modulating different carcinogenic signalling pathways. Hence, broadening the understanding of PD-L1 upstream and downstream signalling pathways is important to improve the efficacy of the current cancer immunotherapy (Figure 2). More importantly, specific small-molecule inhibitors tend to suppress two key carcinogenic signalling pathways, PD-L1 expression as well as PD-L1 localization and function, paving the way for developing attractive candidate drugs for existing immune checkpoints and targeted therapies.

3.2.1 | Transcriptional, post-transcriptional and translational regulation of intracellular PD-L1 expression—It has been increasingly recognized that numerous transcription regulators participate in influencing the expression of PD-L1. For example, under stimulation by interferon-gamma (IFN-γ), the **Janus kinase**-signal transducer and activator of transcription (JAK-STAT) signal can activate interferon regulatory factor-1 (IRF-1), which directly binds to the promoter of PD-L1, thereby inducing the transcription of PD-L1 and inhibiting the tumour immune response (Garcia-Diaz et al., 2019; Mandai et al., 2016). **IFN-γ** secreted by tumour-associated macrophages (TAMs) is capable of increasing the expression level of PD-L1 in lung adenocarcinoma (LUAD) cells through the JAK/STAT3 and PI3K/Akt signalling pathways (Zhang et al., 2017). Of note, the expression of PD-L1 is also associated with mutation of the **epidermal growth factor receptor** (EGFR). EGFR up-regulates the expression of PD-L1 in tumour cells through boosting the activation of **ERK1**/2, interleukin 6 (IL-6)/JAK/STAT3, mitogen-activated protein kinases (MAPK) and PI3K/mechanistic target of rapamycin (mTOR) signalling pathways (Chen et al., 2015; Stutvoet et al., 2019; Zhang et al., 2016). Therefore, inhibitors for each component of these signalling pathways are able to reduce the expression of PD-L1 in various types of cancer, which has been validated for triciribine (Akt inhibitor) and rapamycin (mTOR inhibitor) used in NSCLC, for buparlisib and wortmannin (PI3K inhibitor) employed for treating head and neck squamous cell cancer (HNSCC) or breast cancer, and for MK-2206 (Akt inhibitor) in the treatment of glioblastoma. Additionally, TAMs have been found to release several critical pro-inflammatory cytokines including tumour necrosis factor-α (**TNF**-α) and IL-6, thus activating the NF-κB and **STAT3** signalling pathways and further regulating the expression of PD-L1 (Ju et al., 2020). Zhang et al. showed that IL-6 accelerated MAPK signal transduction and activated the JAK-STAT3 signalling pathway, and the expression of PD-L1 mediated by IL-6 was diminished after the treatment with inhibitors for these two signalling pathways (Zhang et al., 2021).

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Intriguingly, it has been documented that multiple transcription factors reinforce PD-L1 expression by directly binding to its promoter region. For example, inhibition of MYC led to decreased mRNA and protein expression levels of PD-L1 (Casey et al., 2016). Han et al. formulated a collection of MYC small-molecule inhibitors, which could down-regulate PD-L1 expression and further increase the infiltration of T cells (Han et al., 2019). Currently, the direct effect of STAT3 on the PD-L1 promoter is controversial. The transcription factor STAT3 has been verified to bind to the promoter of PD-L1 to potentiate the expression of PD-L1 in thyroid cancer and glioma (Tong et al., 2020; Zhang et al., 2021). However, Chromatin immunoprecipitation (ChIP) detection in melanoma cells has elucidated that STAT3 fails to bind to the PD-L1 promoter. Instead, STAT3 has been outlined to be involved in regulation of the PD-L2 promoter induced by IFN (Garcia-Diaz et al., 2019). Furthermore, hypoxia-inducible factor 1 alpha (HIF-1α) interacts with hypoxia response element (HRE) in the proximal promoter of PD-L1 and thus augments PD-L1 expression in tumour cells and myeloid suppressor cells (MDSCs) (Koh et al., 2019; Noman et al., 2014; Zou et al., 2018). In addition, the transcription factor activator protein-1 (AP-1) is a heterodimer complex composed of c-Jun, Fos or activating transcription factor (ATF). The PD-L1 enhancer has preference to bind to the AP-1 component c-Jun to enhance the activity of the PD-L1 promoter in an AP-1-dependent manner and therefore restrict the T-cell-mediated response (Green et al., 2012). Similarly, an NF-κB binding site is also located in the promoter region of the PD-L1 gene. Indeed, it has been documented that MYC and NF-κB p65 are recruited to the PD-L1 promoter to initiate the transcription of PD-L1 in gastric cancer (GC), NSCLC and triple negative breast cancer (TNBC) (Bouillez et al., 2017; Maeda et al., 2018). Furthermore, the NF-κB signalling pathway is able to interact with a set of other signalling pathways, such as the STAT3, MAPK and PI3K signalling pathways, to trigger the expression of PD-L1. Further, IRF-1 is regarded as a fundamental positive regulator of PD-L1 expression. Two IRF-1 response elements, IRE1 and IRE2, are found in the upstream region of the PD-L1 promoter (Yan et al., 2020). IRF-1 is able to bind to the PD-L1 promoter under stimulation by IFN-γ (Garcia-Diaz et al., 2019). Smithy et al. emphasized that IRF-1 could be utilized as an indicator for PD-L1 expression (Smithy et al., 2017). Interestingly, it has been reported that yes-associated protein 1 (YAP)/transcriptional co-activator with PDZ-binding motif (TAZ) complex also tends to bind to the PD-L1 promoter through the transcriptional enhanced associate domain (TEAD), thereby strengthening the activity of the PD-L1 promoter and further intensifying the expression level of PD-L1 in NSCLC and breast cancer, leading to immune escape of tumour cells (Janse van Rensburg et al., 2018; Kim et al., 2018; Miao et al., 2017). However, the relationship between TAZ and PD-L1 is not conserved in multiple mouse cell lines, which probably results from differences between human and mouse PD-L1 promoter sequences. Du et al. showed that WNT ligand and activated EGFR induced the β-catenin/T cell factor 1 (TCF)/lymphoid enhancer factor (LEF) complex to bind to the PD-L1 promoter region and increased the expression of PD-L1 (Du et al., 2020). Notably, in NSCLC, resveratrol (RSV) enhanced the binding of β-catenin/ T cell factor 1 (TCF) to the PD-L1 promoter through increasing the stability of SNAIL protein and promoting the transcription of PD-L1 (Yang, Li, et al., 2021). Recently, Chen and Liu et al. revealed that blocking the adenosine **A_1 receptor**-cyclic adenosine monophosphate (cAMP) signalling axis could cause the expression of ATF3 and further up-regulate PD-L1 expression in melanoma cells

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(Sun et al., 2018). Moreover, in TNBC, nuclear phosphoprotein (NPM1) has been shown to specifically bind to the PD-L1 promoter and thus initiate the transcription of PD-L1, thereby antagonizing the activity of T cells. Nevertheless, poly adenosine diphosphate-ribose polymerase (**PARP1**) can markedly inhibit the transcription of PD-L1 by interacting with the nucleic acid-binding domain of NPM1 (Chen et al., 2016). Additionally, cancer fork protein P3 (C-FOXP3) has been postulated to directly activate PD-L1 and inhibit the activity of CD8+ T cells, and is a core transcription factor mediating the immune escape of pancreatic ductal adenocarcinoma (PDAC) (Zhang et al., 2017). Furthermore, the nuclear receptor **NR4A1**/SP1 complex is able to bind to the proximal germinal centre-enriched region of the PD-L1 gene and hence maintain the expression level of PD-L1. In this regard, the expression of PD-L1 mRNA in tumour cells was reduced after treatment with Cl-OCH3, a bis-indole derived NR4A1 antagonist (Mandai et al., 2016).

An increasing number of studies have implicated stabilization of PD-L1 mRNA as contributing to PD-L1 overexpression in cancer. Indeed, microRNAs are thought to attenuate the expression of PD-L1 mRNA by directly targeting the 3'-UTR of PD-L1 (Pichler & Calin, 2015). In malignant pleural mesothelioma, microRNAs including miR-15b, miR-16, miR-193a-3p, miR-195 and miR-200c have been found to target the 3'-UTR of PD-L1, leading to the down-regulation of PD-L1 mRNA and protein levels (Kao et al., 2017). For instance, miR-142–5p reduces the mRNA expression of PD-L1 by binding to the 3'-UTR of PD-L1 in mouse pancreatic cancer cells (Jia et al., 2017). miR-873 also directly interacts with the 3′- UTR of PD-L1 to inhibit PD-L1 expression in breast cancer cells (Gao et al., 2019). Also, it has been reported that the potent binding of miR-17–5p to the 3'-UTR of PD-L1 mRNA leads to down-regulation of PD-L1 post-transcriptional expression in melanoma cells (Audrito et al., 2017). In cervical cancer cells, miR-140/142/340/383 has been shown to serve as a direct inhibitor of PD-L1 (Dong et al., 2018). In addition, microRNAs may also play indirect roles in modulating PD-1/PD-L1 expression via curbing related signalling pathways, such as the IFN-γ/STAT/PI3K/Akt/MEK/ERK signalling cascade. A study has shown that IRF1 expression could be regulated by miR-23b and miR-383, and overexpression of miR-23b significantly diminished the mRNA expression level of IRF1 (Li et al., 2015). Furthermore, miR-197 has been elucidated to act on the CKS1B-STAT3 signalling cascade to inhibit PD-L1 expression in NSCLC (Fujita et al., 2015). miR-18a exerts striking effects to increase PD-L1 expression levels by targeting PTEN, WNK2 and SOX6, activating the PI3K/Akt, MEK/ERK and Wnt/β-catenin signalling pathways, inhibiting the p53 pathway and impairing the expression of the tumour suppressor BTG3 (Dong et al., 2018). Moreover, it has been highlighted that miR-100 can retard the growth and metastasis of bladder cancer cells via targeting mTOR (Xu et al., 2013).

3.2.2 | Regulation of PD-L1 translocation by post-translational modification

N-linked glycosylation of PD-L1: Surprisingly, it has been revealed that glycosylated PD-L1 is present in various types of cancer cell. Li and colleagues demonstrated that four asparagine residues in the extracellular domain of PD-L1 including N35, N192, N200 and N219 acted as the main sites of PD-L1 glycosylation using LC-MS/MS analysis, and when they were replaced with glutamine, the glycosylation level of PD-L1 was markedly decreased (Li et al., 2016). Glycosylation played a significant role in stabilizing PD-L1

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protein, and the half-life of glycosylated PD-L1 was longer than that of non-glycosylated PD-L1 when the tumour cells were treated with cycloheximide, a protein synthesis inhibitor (Li et al., 2016). Additionally, the degree of ubiquitination of non-glycosylated PD-L1 was higher than glycosylated PD-L1 in the presence of the proteasome inhibitor MG132. More intriguingly, Sigma1 and FKBP51 chaperones were found to promote the folding of glycosylated PD-L1 and the stability of endoplasmic reticulum (ER) cavity, whereas ER-related degradation (ERAD) occurred in abnormal PD-L1 glycosylation (D'Arrigo et al., 2017; Maher et al., 2018). Hung et al. found that activation of EGF signalling prevented GSK3β/β-TrCP-mediated ubiquitination and degradation, thus maintaining PD-L1 glycosylation and stability (Li et al., 2016). In this perspective, suppression of EGF signalling with thr small-molecule inhibitor gefitinib conferred impaired PD-L1 stability. Furthermore, Hsu et al. reported that epithelial-mesenchymal transition (EMT) could trigger the expression of N-glycosyltransferase STT3 through orchestrating the transcription of β-catenin in cancer stem cell-like cells, maintaining the stability of glycosylated PD-L1 and eventually driving cancer immune escape (Hsu et al., 2018). Given that etoposide inhibited EMT process, treatment with etoposide diminished the expression of glycosylated PD-L1 and PD-1 binding capability in the mouse models of breast cancer and colon cancer, and played a synergistic role with T cell immunoglobulin mucin-3 (Tim-3) blocking therapy. Furthermore, PD-L1 glycosylation has been shown to regulate the interactions between PD-1 and PD-L1. Li and coworkers took advantage of N-glycosidase F to remove N-linked oligosaccharides from polypeptides, and the binding of PD-L1/PD-1, PD-L1/B7–1 and PD-L2/PD-1 was completely abolished (Hsu et al., 2018). Up-regulation of N-glucosyltransferase B3GNT3 via the EGF/EGFR signalling was able to promote PD-1/PD-L1 interactions. These results suggest that antibodies specifically targeting PD-L1 glycosylation may improve the outcomes of immunotherapy in clinic. In fact, Hung et al. have already successfully isolated a PD-L1 antibody (STM108) that can specifically recognize the B3GNT3-mediated poly-LacNAc moiety on N192 and N200 glycosylation sites of PD-L1, and have proved it can facilitate PD-L1 internalization and degradation (Li, Lim, et al., 2018). The regulation of PD-L1 upon glycosylation was also reflected by the membrane localization (Verdura et al., 2020). When RSV was given to in cancer cells, the mPD-L1 signalling was weakened, accompanied by the accumulation of PD-L1 in a perinuclear compartment, indicating that glycosylation influences the stability and transportation of PD-L1 (Cha et al., 2018).

Serine/threonine/tyrosine phosphorylation of PD-L1: As mentioned above, GSK3β directly binds to the C-terminus of non-glycosylated PD-L1, phosphorylating T180 and S184 sites on PD-L1, and PD-L1 subsequently binds to E3 ligase β-TrCP to augment the polyubiquitination and degradation of PD-L1 in the cytoplasm (Li et al., 2016). AMP-activated protein kinase (**AMPK**) phosphorylates PD-L1 at the S195 site, leading to the abnormal glycosylation of PD-L1. The transportation of PD-L1 from the endoplasmic reticulum to the Golgi apparatus is prevented, and PD-L1 protein is translocated to the cytoplasm, where it rapidly inhibits the ERAD signalling pathway (Cha et al., 2018). Of note, Chan et al. demonstrated that IL-6 activated JAK1 to phosphorylate PD-L1 at the Y112 site and recruited endoplasmic reticulum-related N-glycosyltransferase STT3A to catalyse the glycosylation of PD-L1, maintaining the stability of PD-L1 and enhancing

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tumour immune escape (Chan et al., 2019). In addition, EGF is able to boost the tyrosine phosphorylation of PD-L1 (Horita et al., 2017), however, whether it has significant impacts on the physiological function of PD-L1 or its interactions with target receptor proteins such as PD-1 warrants further investigation.

Polyubiquitylation of PD-L1: The protein expression of PD-L1 is usually governed by the ubiquitin (Ub)-mediated proteasome degradation pathway (Burr et al., 2017; Lim et al., 2016). EGF modulates PD-L1 protein level by inducing PD-L1 monoubiquitin and polyubiquitin (Horita et al., 2017). TNF-α secreted by M2-type macrophages activates COP9 signalling complex subunit 5 (CSN5) by mediating IKKβ and NF-κB p65 signalling and inhibits the ubiquitination and degradation of PD-L1, thereby avoiding immune killing by T-cells (Lim et al., 2016). Under the conditions of chronic inflammation, CSN5 can also be utilized as a de-ubiquitination enzyme to catalyse the de-ubiquitination of PD-L1 to stabilize its protein level. Curcumin has been reported to retard the growth of tumour by repressing the activities of CSN5-related kinases in cancer cells (Lim et al., 2016). The interactions between the cyclin D-CDK4 complex and cullin3-SPOP ubiquitin E3 ligase accelerate the degradation of PD-L1 through proteasomes (Zhang et al., 2018). In a tumour-bearing mouse model, a CDK4/6 inhibitor in combination with anti-PD-1 immunotherapy enhanced tumour regression. In addition, Burr and Mezzadra demonstrated that CMTM6 is located on the cell surface, as well as bound to the PD-L1 protein to stabilize its expression and protect PD-L1 from ubiquitination (Burr et al., 2017; Mezzadra et al., 2017). Consistently, CMTM4 also displayed a similar function. Importantly, the co-expression of CMTM6 and PD-L1 has been utilized to predict the poor prognosis of various types of cancer (Liu, Zhang, Chao, et al., 2021; Peng et al., 2021).

Palmitoylation of PD-L1: Lipid-modified PD-L1 has emerged as a new post-translational modification form to encrypt its expression. Yao and colleagues identified a palmitoylation site of PD-L1, Cys272, to block the ubiquitination of PD-L1 via DHHC3 palmitoyl transferase to stabilize PD-L1 and prevent the transportation of PD-L1 to multivesicular bodies (MVB) via components of the endosomal sorting complex required for transport (ESCRT) and degradation by lysosomes (Yao et al., 2019). In addition, Yang and coworkers uncovered that inhibition of ZDHHC9 sensitized tumour cells to T-cell-mediated killing and limited tumour growth. These data imply that palmitoylation of PD-L1 serves as a new route to enhance the anti-tumour response of immunotherapy (Yang et al., 2019). Xu and colleagues formulated PD-LYSO, a novel competitive inhibitor of PD-L1 palmitoylation to diminish the expression of PD-L1 in the tumour cells (Yao et al., 2019).

Acetylation of PD-L1: It has been held that PD-L1 possesses an acetylation site at position 263 of its cytoplasmic domain. PD-L1 on the cytoplasmic membrane can be deacetylated by **HDAC2**, internalized via endocytosis based on the interactions of HIP1R and clathrin, transported by the vimentin cytoskeleton protein and eventually translocated to the nucleus through importin α1 (Gao et al., 2020). nPD-L1 is prone to bind to DNA and modulates multiple pro-inflammatory, immune checkpoint-related and immune response-related genes, thus sensitizing them to immune checkpoint blockade therapy. Furthermore, HDAC2 inhibitors exert striking effects to block the nuclear translocation of PD-L1, and the

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combination therapy of HDAC2 inhibitors and a PD-1 antibody can enhance the infiltration of CD8 + T cells into tumours and reduce the level of TNF-α, thereby boosting the immune response (Gao et al., 2020; Hu et al., 2021).

3.3 | Inhibition of exogenous PD-L1

Surprisingly, tumour-derived exoPD-L1 is also able to markedly drive tumour cells to evade the surveillance of immune cells. Hence, hampering exoPD-L1 has been thought as a route to open up a new way for improving the effectiveness of immunotherapy (Table 2). Interestingly, knockdown or deletion of critical proteins that are involved in the exosome biogenesis, such as RAB27A, NSMASE2, ESCRT, ALIX and YKT6, has been revealed to hinder the secretion of tumour-derived exosomes (TEXs) and exoPD-L1. Moreover, a classical exosome inhibitor named GW4869 has been found to show profound clinical significance in retarding the growth of tumour (Poggio et al., 2019). Either GW4869 treatment or silencing of RAB27A was shown to enhance the anti-PD-L1 therapy (Shimizu et al., 2021). To impede the formation and release of exosomes, knockout of PD-L1 or exosome secretion-associated genes (NSMase2 and RAB27A) could reverse the resistance to PD-L1 inhibitors (Chen et al., 2018; Poggio et al., 2019; Yang et al., 2018). Moreover, when the mice were injected with exosome defective tumour cells, they were unable to develop tumours because these tumour cells failed to secrete exosomes. The ESCRT was found to be involved in MVB and intralumenal vesicle (ILV) biogenesis (Schmidt & Teis, 2012). ALIX depletion resulted in prolonged and enhanced stimulus-mediated EGFR activity, defective PD-L1 trafficking through the MVB, diminished exosomal secretion, as well as PD-L1 redistribution to the cell surface (Monypenny et al., 2018). Besides, exosome biomarkers including CD9 and CD63 were observed to be expressed on the surface of TEXs. The combined blockade of CD63 and PD-L1 demonstrated better therapeutic efficacy in the B16F10 (RRID:CVCL_0159) melanoma model (Mathieu et al., 2021; Nishida-Aoki et al., 2017). In addition, ablation of circ-CPA4 in NSCLC cells promoted the activation of CD8 + T cells in the tumour microenvironment through down-regulation of secreted PD-L1 (Hong et al., 2020).

Notably, exoPD-L1 is also involved in regulating cancer immunotherapy by influencing macrophages, which can be regarded as an entry point for cancer treatment. Golgi membrane protein 1 (GOLM1) increases CD8 + T cell suppression in hepatocellular carcinoma by promoting the transportation of exoD-L1 into TAMs (Chen et al., 2021). Oral squamous cells carcinoma (OSCC) cell-secreted exosomal CMTM6 skews the polarization of macrophages into the M2 type to aggravate malignant progression (Pang et al., 2021). As such, targeting PD-L1 + TAMs may be a novel therapeutic strategy to enhance the efficacy of anti-PD-L1. Moreover, inhibition of xCT by sulfasalazine blunts the effectiveness of anti-PD-1/PD-L1 via exoPD-L1-mediated M2 macrophage polarization and eventually provokes anti-PD-1/PD-L1 therapy resistance (Liu, Zhang, Yin, et al., 2021). In addition, it has been documented that both miR-23a-3p (Liu et al., 2019) and hY4 (Haderk et al., 2017) trigger M2 phenotype polarization and confer up-regulation of PD-L1 in macrophages: administration of miR-23a-3p inhibitors or destruction of hY4 complete structure can hinder the immune escape of tumour cells.

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Current immunotherapies predominantly focus on blocking mPD-L1, but an increasing body of evidence has implicated that exoPD-L1 can also be employed as a target for a systemic anti-tumour response. In fact, it is reasonable to directly target exoPD-L1 to achieve immunotherapy because it shares the same topology and biological activity as mPD-L1. Lee et al. demonstrated that suppression of tumour-derived exoPD-L1 with the FDA-approved oral drug macitentan led to a dramatically improved anti-tumour immune response of CD8 + T cells (Lee et al., 2022). Of note, exoPD-L1 blockade was found to inhibit tumour growth even in mouse models resistant to anti-PD-L1 mAbs. All of these facts imply an independent role for exoPD-L1 blockade, which can increase the effects of anti-PD-L1 antibodies, rather than being redundant. In addition, other relevant functional components targeting TEXs, such as transforming growth factor β1 (TGF-β1), FasL, TRAIL and MIC, help to reduce the immunosuppressive microenvironment and reinforce the cytotoxicity of T cells and NK cells (Rossowska et al., 2019). Moreover, the overexpression of PD-L1 in various types of cells can be provoked by a series of non-coding RNAs from TEXs including PCED1B-AS1 (Fan et al., 2021), miR-1468–5p (Zhou et al., 2022), miR-92 (Dou et al., 2020), miR-23a-3p (Liu et al., 2019) and hY4 (Haderk et al., 2017), which are able to harness immunosuppression in the tumour microenvironment. Therefore, targeting these pivotal non-coding RNAs has significant therapeutic potential in cancer therapy.

4 | CLINICAL PERSPECTIVE OF PD-L1 DISTRIBUTION-BASED CANCER IMMUNOTHERAPY

4.1 | Molecular basis and limitations of clinical application of PD-1/PD-L1 blocking drugs

PD-L1 expression is an important biomarker associated with tumour progression and is one of the FDA-approved biomarkers for assessing the effectiveness of immune checkpoint inhibitors (Zouein et al., 2021). Although PD-L1 positive expression is a logical prerequisite for PD-L1 antibody therapy, it is not always coincident with PD-L1 positivity and objective response rates of cancer patients. Besides, lasting responses are observed in patients with low or no PD-L1 expression, which may be at least partially due to the heterogeneous dynamics and expression of PD-L1. Notably, PD-L1 expression as a biomarker for immunotherapy possesses some other limitations. For example, each PD-1/PD-L1 antibody drug has its own supporting immunohistochemical (IHC) staining method. As such, the detection of PD-L1 relies on the usage of different antibody clones and thus presents different affinities, specificities and clinical decision thresholds (Lu et al., 2019). The subjective interpretation by pathologists also determines the varieties of IHC staining results. In addition, due to tumour heterogeneity, the expression of PD-L1 is uneven with the phenomenon of PD-L1 expression varying with tumour location (Patel & Kurzrock, 2015). Further, the distribution of PD-L1 is a hurdle for precisely exploring the location of PD-L1 expression.

In addition, tumour mutation load (TMB) is emerging as a key biomarker for PD-1/PD-L1 inhibitor response and shows great promise in various types of tumour (Samstein et al., 2019). TMB can be detected in circulating tumour DNA by clinically available techniques, such as targeted next-generation sequencing, integrated genomics, and blood-based assays. However, TMB is not routinely utilized in clinical practice because it is still at the research

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stage and the detection costs are high. Taken together, PD-L1 remains to be the only prospectively testing biomarker though it still has some unsolved limitations.

4.2 | Personalized PD-L1 combination therapy

With the in-depth understanding of PD-L1 distribution, not only mPD-L1 but also intracellular PD-L1 and exogenous PD-L1 have been validated to have impacts on the antibody response. When intracellular PD-L1 is translocated to the cell membrane or secreted outside the cells, antibody blockade benefits the ORR of the PD-L1 positive cohort. When mPD-L1 is internalized into cells with the form of cPD-L1, antibody blockade alone leads to reduced ORR of the PD-L1 positive cohort (Wu, Chen, et al., 2019). More frequent administration and higher dosages of antibody drugs may be required, but the risks are incalculable.

Herein, we go above and beyond the usage of the overall expression abundance of PD-L1 as a criterion to select PD-1/PD-L1 mAbs for cancer treatment, and comprehensively take the form of PD-L1 into consideration in immunotherapy. In terms of cancers with high mPD-L1 expression, such as melanoma and NSCLC, the ideal therapeutic strategy is on the basis of antibody blockade in combination with other strategies, including radiotherapy, chemotherapy and intratumoural therapy, thereby facilitating T cells infiltration into the tumours to improve antigen presentation or reactivating the immune system through complementary/synergistic mechanisms (Galon & Bruni, 2019). For cancers with elevated intracellular PD-L1 expression and innate immune resistance, modulation of relevant signals with chemical inhibitors has been validated to markedly inhibit the production and function of intracellular PD-L1, thereby potentiating the efficacy of anti-PD-L1 (Yamaguchi et al., 2022). To this end, blood levels of exoPD-L1 can also be taken into consideration as the target for immunotherapy (Xiong et al., 2021). In fact, exoPD-L1 as a predictive marker for immunotherapy response is less invasive and more accurate compared with traditional biopsy. However, the interactions between exoPD-L1 and existing therapies still remain unclear. It may be that PD-L1 expression on the surface of exosomes is not responsive to current immunotherapies, or that the expression level of exoPD-L1 is high enough to compete for binding sites on immune cells with antibodies. It is also possible that exosomes are able to expose targets that are hidden upon antibody treatment. As such, in patients, high levels of immune checkpoint molecules before immunotherapy may be associated with exosomes elimination, which should be taken into consideration. Collectively, figuring out the answers to these concerns will facilitate rapid development and optimization of exoPD-L1 as a screening tool for clinical prediction.

5 | CONCLUSION AND DISCUSSION

The clinical application of immune checkpoint inhibitors has opened up a new era for cancer therapy. Although PD-1/PD-L1 antibody therapies have achieved striking efficacy, the low ORR of cancer patients is still a predominant clinical concern. Existing antibody drugs can bind to and further block PD-L1 that is expressed on the surface of tumour cells, suggesting that they mainly target mPD-L1. The lack of comprehensive consideration of other forms of PD-L1, in particular intracellular or extracellular PD-L1, seems to be an important reason

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why these antibody drugs display only limited efficacy. Blocking the circulating localization of endogenous PD-L1 and helping T cells to escape the restriction of exogenous PD-L1 surrounding tumour cells may be a key breakthrough to improve the efficacy of treating solid tumours. With the development of PD-L1-based drugs, a strategic combination of antibody blockade, gene silencing and drug modulation, taking into account the distribution of PD-L1 in cancer patients, will help to further improve the clinical outcomes of PD-L1-based treatments.

Interestingly, the latest trend in cancer therapy is towards combination immunotherapy (Zhu et al., 2021). Nonetheless, only combinations of anti-PD-1/PD-L1 with chemotherapeutic agents, angiogenesis inhibitors, or anti-CTLA-4 antibodies have been approved by the FDA or National Medical Products Administration (NMPA) (Meric-Bernstam et al., 2021). Identifying an appropriate preclinical assessment model is a major challenge in verifying the effectiveness of combined regimens. Of note, combination therapy potentially increases the risk of immune-related adverse events (irAE) (Darnell et al., 2020). Inappropriate combination therapy has the tendency to expose cancer patients to high toxicity. How to rationalize the dosing schedule, including dose amount, timing and sequence appears to be another challenge in the advancement of combination therapy. We believe that all these concerns will be addressed one by one in the near future to optimize immunotherapy for cancer patients.

In conclusion, tumour cells not only enable PD-L1 to be expressed on the cell membrane but also release a large number of PD-L1-expressing exosomes, resulting in systemic immunosuppression in cancer patients. PD-L1 located inside the cell has remarkable cancer-promoting functions and also circulates to the cell surface to renew and replenish PD-L1 on the cell membrane. A better understanding of these underlying mechanisms will be conducive to the continuous development and optimization of tumour immunotherapy, leading to the generation of more accurate and effective diagnostic and therapeutic regimens.

5.1 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, and are permanently archived in the Concise Guide to PHARMACOLOGY 2021/22 (Alexander, Christopoulos, et al., 2021; Alexander, Cidlowski, et al., 2021; Alexander, Fabbro, et al., 2021; Alexander, Kelly, et al., 2021).

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DECLARATION OF TRANSPARENCY AND SCIENTIFIC RIGOUR

This Declaration acknowledges that this paper adheres to the principles for transparent reporting and scientific rigour of preclinical research as stated in the *BJP* guidelines for Design and Analysis, and as recommended by funding agencies, publishers and other organizations engaged with supporting research.

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Abbreviations:

ADA	anti-drug antibodies
AP-1	activator protein-1
ATF	activating transcription factor
C-FOXP3	cancer fork protein P3
ChIP	chromatin immunoprecipitation
CMTM6	CKLF-like MARVEL transmembrane domain-containing 6
cPD-L1	cytoplasm PD-L1
CSN5	complex subunit 5
EMT	epithelial-mesenchymal transition
ER	endoplasmic reticulum
ERAD	ER-related degradation
ESCRT	endosomal sorting complex required for transport
exoPD-L1	exosomal PD-L1
GOLM1	Golgi membrane protein 1
HIF-1α	hypoxia-inducible factor one alpha
HNSCC	head and neck squamous cell cancer
HRE	hypoxia response element
ILV	intralumenal vesicles
IRF-1	interferon regulatory factor-1
ITSM	immunoreceptor tyrosine-based switch motif
LEF	lymphoid enhancer factor
LUAD	lung adenocarcinoma
mAbs	monoclonal antibodies
MDSCs	myeloid suppressor cells
mPD-L1	membrane PD-L1
mTOR	mechanistic target of rapamycin
MVB	multivesicular bodies
nPD-L1	nuclear PD-L1

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NSCLC	non-small cell lung cancer
ORR	overall response rate
OSCC	oral squamous cells carcinoma
PDAC	pancreatic ductal adenocarcinoma
PI3K	phosphatidylinositol-3-kinase
RSV	resveratrol
TAMs	tumour-associated macrophages
TAZ	transcriptional co-activator with PDZ-binding motif
TEAD	transcriptional enhanced associate domain
TEXs	tumour-derived exosomes
Tim-3	T cell immunoglobulin mucin-3
TMB	tumour mutation load
TNBC	triple negative breast cancer
Ub	ubiquitin
YAP	yes-associated protein.

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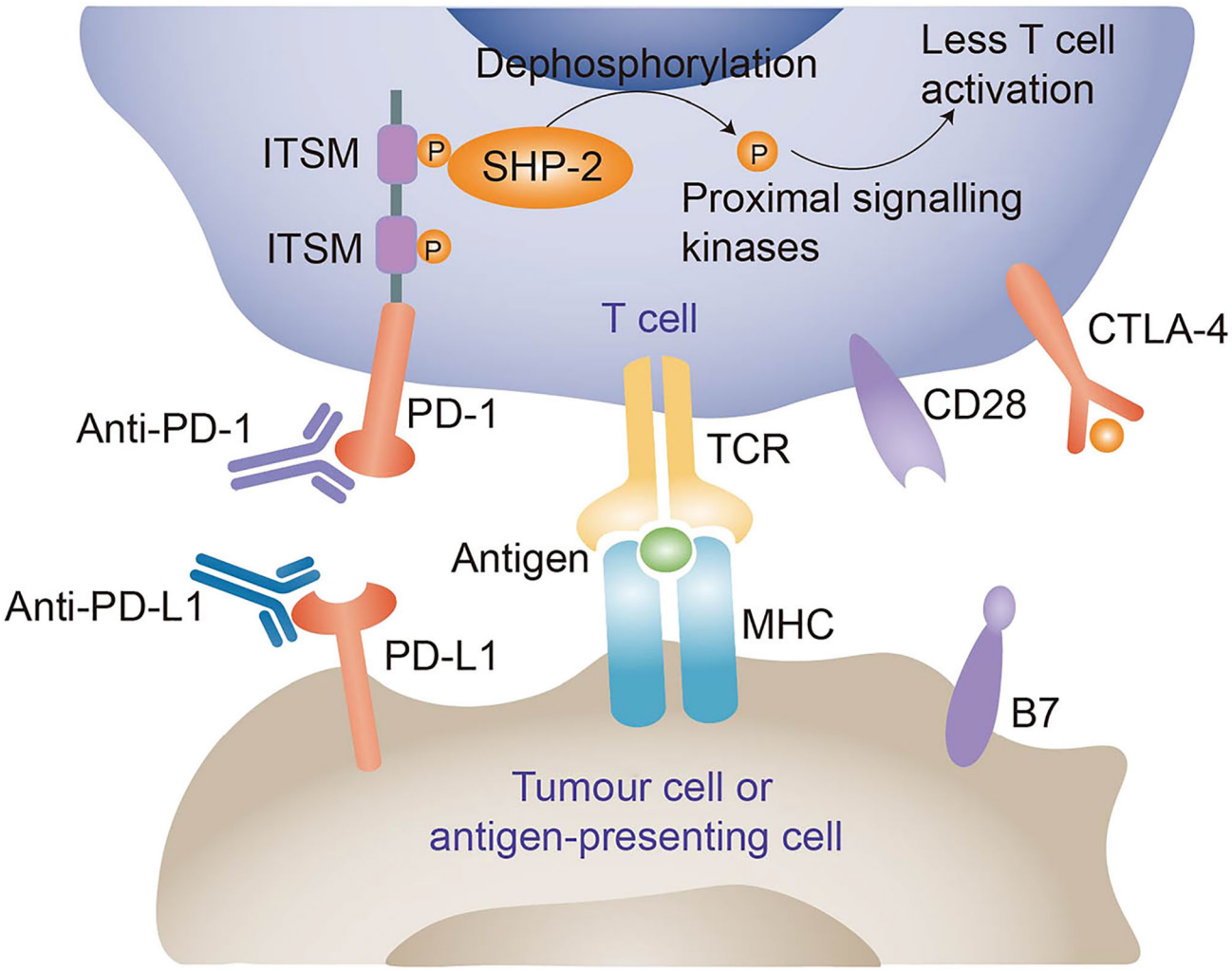

FIGURE 1.
Molecular mechanisms of immune escape mediated by PD-1/PD-L1 immune checkpoints.

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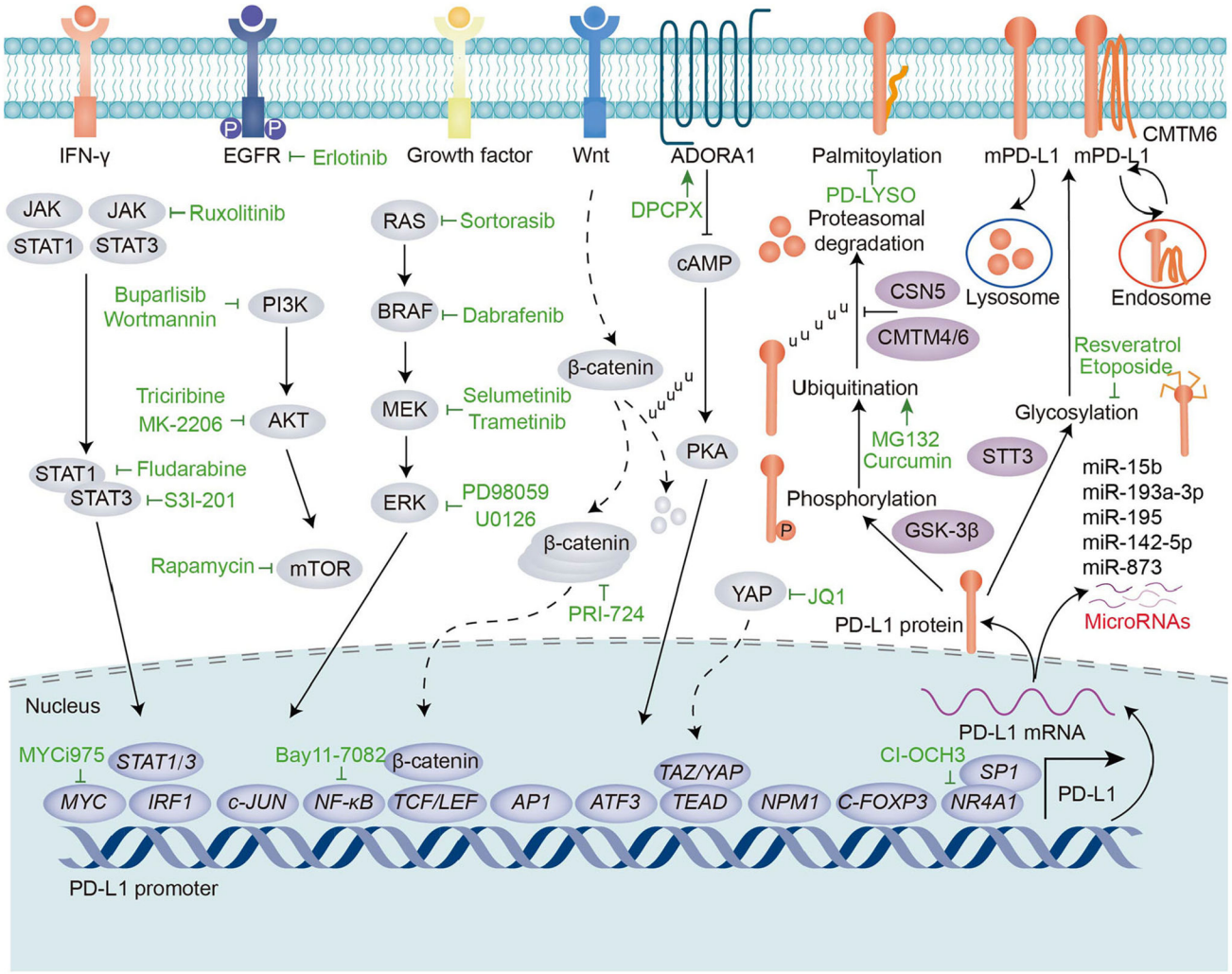

FIGURE 2.
Molecular regulation of PD-L1 in tumour cells.

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TABLE 1

Basic information and characteristics of anti-PD-1/PD-L1 monoclonal antibodies.

Drugs	Approval	Targets	Type	Binding domain	Cancer type	ADA (%)
Nivolumab	2014-US 2015-EU 2018-PRC	PD-1	lgG4	N, FG and BC loops	SC, NSCLC, SCLC, RCC, HL, HNC, UC, CRC, HCC, ESC, MPM,GC and GEJC	8.5
Pembrolizumab	2014-US 2015-EU 2018-PRC	PD-1	lgG4	C'D loop	SC, NSCLC, SCLC, RCC, HL, HNC, UC, CRC, HCC, ESC, GC, GEJC, TNBC, BC, CC and EC	0.8
Cemiplimab	2018-US 2019-EU	PD-1	lgG4	BC, N, FG and DE loops	SC and NSCLC	1.3
Toripalimab	2018-PRC	PD-1	lgG4	FG loop	SC, HNC and UC	18
Sintilimab	2018-PRC	PD-1	lgG4	FG loop	NSCLC, HL and HCC	0.5
Camrelizumab	2019-PRC	PD-1	lgG4	CC' and FG loops	NSCLC, HL, HNC, HCC and ESC	14.5
Tislelizumab	2019-PRC	PD-1	lgG4	CC' loop	NSCLC, HL and UC	18.7
Zimberelimab	2021-PRC	PD-1	lgG4	C strand, FG loop and G strand	HL	--
Prolgolimab	2020-RU	PD-1	lgG1	--	SC	--
Dostarlimab	2021-US 2021-EU	PD-1	lgG4	BC, C'D and FG loops	EC	2.5
Atezolizumab	2016-US 2017-EU 2020-PRC	PD-L1	lgG1	BC, CC', C'CC" and FG loops	SC, NSCLC, SCLC, UC, HCC and TNBC	31.7–41.9
Avelumab	2017-US 2017-EU	PD-L1	lgG1	C strand, C′ strand, F strand, G strand and CC' loop	NSCLC, SCLC and BC	3.5
Durvalumab	2017-US 2018-EU 2019-PRC	PD-L1	lgG1	C strand, F strand, G strand, CC' loop and N-terminal region	SC, RCC and UC	3.3–4.3

Abbreviations: ADA, anti-drug antibodies; BC, bladder cancer; CC, cervical cancer; CRC, colorectal cancer; EC, endometrial cancer; ESC, oesophageal carcinoma; EU, European Union; GC, gastric cancer; GEJC, gastroesophageal junction cancer; HCC, hepatocellular carcinoma; HL, Hodgkin lymphoma; HNC, head and neck cancer; MPM, malignant pleural mesothelioma; NSCLC, non-small cell lung cancer; PRC, People's Republic of China; RCC, renal cell carcinoma; SC, skin cancer; TNBC, triple negative breast cancer; UC, urothelial carcinoma.

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TABLE 2

Potential intervention targets modulating TEXs in the PD-1/PD-L1 signalling axis.

Target name	Function of the target	Intervention strategy	Reference
RAB27A	RAB27A mediates exosome release	Knock-down of gene expression	(Chen et al., 2018; Poggio et al., 2019; Yang et al., 2018)
NSMASE2	NSMASE2 participates in the biogenesis of exosomes	Knock-down of gene expression or application of inhibitor GW4869	(Poggio et al., 2019; Yang et al., 2018)
ESCRT	ESCRT mediates the recognition and sorting of exosomal cargos	Knockdown of the ESCRT subunit HRS	(Larios et al., 2020; Schmidt & Teis, 2012)
ALIX	ALIX transports PD-L1 located at tumour cell membrane to exosome	Knock-down of gene expression	(Larios et al., 2020; Monypenny et al., 2018)
YKT6	YKT6 participates in the regulation of exosome production and release	MiR-134 and miR-135b or knock-down of gene expression	(Morrissey et al., 2021; Ruiz-Martinez et al., 2016; Yang, Yan, et al., 2021)
CD9 and CD63	CD9 and CD63 are biomarkers located at the surface of TEXs	Application of antibodies	(Mathieu et al., 2021; Nishida-Aoki et al., 2017)
Circ-CPA4	Circ-CPA4 up-regulates exoPD-L1 expressions	Knock-down of gene expression	(Hong et al., 2020)
GOLM1	GOLM1 increases exoPD-L1 transport into tumour-associated macrophages and promotes PD-L1 stabilization	Knock-down of gene expression	(Chen et al., 2021)
CMTM6	Exosomal CMTM6 induces M2 phenotype polarization and up-regulation of PD-L1	Knock-down of gene expression	(Pang et al., 2021)
xCT	XCT reduces the efficacy of anti-PD-1/PD-L1 via exoPD-L1-induced macrophage M2 polarization	Application of sulfasalazine	(Liu, Zhang, Yin, et al., 2021)
PCED1B-AS1	PCED1B-AS1 enhances the expression of PD-L1 and PD-L2 via sponging hsa-miR-194–5p	Application of PCED1B-AS1 inhibitor	(Fan et al., 2021)
miR-1468–5p	Exosomal miR-1468–5p promotes PD-L1 up-regulation and impairs T cell immunity	Application of miR-1468–5p inhibitor	(Zhou et al., 2022)
miR-92	Exosomal miR-92 enhances YAP1 nuclear translocation and PD-L1 transcription activity	Application of miR-92 inhibitor	(Dou et al., 2020)
miR-23a-3p	MiR-23a-3p induces M2 phenotype polarization and up-regulation of PD-L1 in macrophages	Application of miR-23a-3p inhibitor	(Liu et al., 2019)
hY4	HY4 acts as a driver of TLR7 signalling to induce M2 phenotype polarization and up-regulation of PD-L1 in macrophages	Destruction of its complete structure	(Haderk et al., 2017)