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CORRESPONDENCE

PD-L1 importance in malignancies comprehensive insights into the role of PD-L1 in malignancies: from molecular mechanisms to therapeutic opportunities

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Abstract
The phenomenon of upregulated programmed death-ligand 1 (PD-L1) expression is common in numerous human malignancies. The overexpression of PD-L1 significantly contributes to immune evasion because its interaction with the PD-1 receptor on activated T lymphocytes impairs anti-tumour immunity by neutralizing T cell stimulatory signals. Furthermore, beyond its immunological interface, PD-L1 possesses intrinsic capabilities that directly modulate oncogenic processes, fostering cancer cell proliferation and survival. This dual function of PD-L1 challenges the efficacy of immune checkpoint inhibitors and highlights its possible application as a direct target for therapy. Recent discoveries concerning the cancer cell-intrinsic signalling pathways of PD-L1 have significantly enhanced our understanding of the pathological implications linked to its tumour-specific expression. These entail the orchestration of tumour proliferation and viability, maintenance of cancer stem cell-like phenotypes, modulation of immune responses, as well as impacts on DNA repair mechanisms and transcriptional regulation. This review aims to deliver an exhaustive synthesis of PD-L1's molecular underpinnings alongside its clinical implications in a spectrum of cancers, spanning both solid neoplasms and haematological disorders. It underscores the necessity for an integrated understanding of PD-L1 in further refining therapeutic strategies and improving patient outcomes.

Keywords Programmed death ligand-1 · Solid tumour · PD-L1 · Immune checkpoints · Haematological malignancies · Immunotherapy

Introduction

Cancer cells adeptly utilize a variety of mechanisms to circumvent immune recognition and responses, thereby facilitating disease advancement and escalating patient mortality rates [1]. Among these immune-evasion tactics, the manipulation of immune checkpoints represents a critical target for therapeutic innovation. Programmed cell death ligand-1 (PD-L1), also called B7-H1 or CD274, functions as an immune checkpoint ligand, naturally present in tissues including the placenta, lungs, and heart. In contrast, within malignancies, PD-L1 is overexpressed and binds to the PD-1 receptors on immune effector cells, which inhibits their activation and results in the suppression of antitumour immune responses [2]. PD-L1 expression is susceptible to upregulation by pro-inflammatory cytokines, notably Interferon-gamma (IFN-γ), secreted by activated T cells and natural killer (NK) cells. This regulatory process is instrumental in shaping the immune landscape of the tumour microenvironment [3].

In response, various immune checkpoint blockade (ICB) agents (e.g. anti-PD-1 and anti-PD-L1) have received FDA approval and have undergone extensive clinical trials targeting conditions including non-small cell lung cancer (NSCLC), bladder cancer, melanoma, Hodgkin's lymphoma (HL), renal cell carcinoma (RCC), head and neck squamous cell carcinoma (HNSCC), and Merkel cell carcinoma. These

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agents have been utilized both as individual treatments and combined with other therapeutic methods such as immunotherapy and chemotherapy [4–8]. Although there have been significant improvements in clinical outcomes, unfortunately, only a small portion of patients experience long-lasting responses. The therapeutic efficacy in solid tumours is notably restricted due to challenges such as adverse events and drug resistance. Furthermore, the intracellular and molecular roles of PD-L1 remain relatively underexplored.

An in-depth investigation into the mechanisms underpinning resistance to PD-1/PD-L1 inhibitors could catalyse the emergence of novel immunotherapeutic approaches or enhance the effectiveness of existing treatments. This might offer a means to mitigate progression of the disease and secure more enduring survival benefits for patients [9]. In this review, we present an exhaustive analysis of PD-L1, dissecting both its molecular facets and clinical relevance. Initially, we explore its molecular aspects, focussing on its structural characteristics, intracellular signalling pathways, transcription factors, and non-coding RNAs that modulate its expression. Following this, we delve into the clinical impact of PD-L1 across both solid and haematological cancer types.

Molecular structure and signalling pathways of PD-L1 and PD-1

Programmed death ligand-1 (PD-L1)

Programmed death-ligand 1 (PD-L1), designated as B7-H1 or CD-274, was first identified in 1999 as a constituent of the B7 family. In humans, this type I transmembrane protein is encoded by the CD274 gene, which is located on chromosome 9. It is present across a variety of immune cells that are derived from myeloid lineages, such as dendritic cells, macrophages, and myeloid-derived suppressor cells (MDSCs). Moreover, the expression of PD-L1 can be enhanced upon activation by pro-inflammatory cytokines—including IFN-γ and TNF-α—in lymphoid immune cells like T cells, B cells, and NK cells, as well as other cell types such as endothelial and epithelial cells [10].

Widely acknowledged as a counter-receptor for the inhibitory PD-1 receptor on CD8 + T cells and other immune cell types, PD-L1 engages in the transmission of immunosuppressive alerts to tumour-infiltrating lymphocytes (TILs). This interaction significantly hampers antitumour immune responses. Elevated PD-L1 expression has been identified in a multitude of different types of cancer, including lung, cervical, breast, ovarian, and colon cancers, as well as melanoma, which can critically influence patient prognoses [11–14].

The construction of the PD-L1 protein encompasses an IgV-like domain, an IgC-like domain, a transmembrane domain, and a conserved intracellular region noted for its signal transduction capabilities. Within this intracellular segment, three highly conserved sequence motifs are present: "RMLDVEKC", "DTSSK", and "QFEET". The first two motifs play a crucial role in modulating interferon-driven cytotoxic activities [15, 16]. Among the primary signalling cascades initiated downstream of PD-L1 is the mTOR-AKT pathway [16]. Within tumour cells, PD-L1 is known to relay pro-survival cues, facilitating cancer initiation, progression, metastasis, and resistance to drugs. For instance, the "RMLDVEKC" motif acts to impede IFN-mediated cytotoxic actions against tumour cells by obstructing STAT3 phosphorylation and caspase-mediated apoptotic processes [15]. It has been demonstrated that PD-L1 stimulation promote pentose phosphate pathway and fatty acid oxidation in cancer cells which respectively related to their proliferation and survival [17]. One motif of intracellular fraction of PDL1 inhibit STAT3 phosphorylation, which, in turn, halts caspase-mediated apoptosis [16]. Interaction of PD-L1 to T cells PD-1 reduce T cell activation and proliferation by inhibition of T cell receptor (TCR) signalling by dephosphorylating key kinases like Lck and ZAP70.

Additionally, an association between PD-L1 expression and epithelial-mesenchymal transition (EMT) is observed across various solid tumours, notably in gastric, lung, breast, and colon cancers [18]. Activation of PD-L1 stimulates signalling pathways, including the PI3K-Akt-mTORC1, driving cellular proliferation and tumour growth in vivo. Furthermore, cell-autonomous signalling through PD-L1 has been documented to activate the RAS-MAPK pathway [19]. This comprehensive mechanistic understanding of PD-L1 not only highlights its multifaceted role in tumour biology but suggests potential pathways for therapeutic intervention [20]. PD-L1 regulate of the cGAS-STING pathway by directly binding to the STING promoter region, which negatively regulates STING expression. Furthermore, it has been shown that the PD-L1 deficiency promote the activation of the cGAS-STING pathway by increasing DNA damage, which is sensed by cGAS [21, 22]. Conversely, the PD-L1 expression on tumour cell is elevated by activation of the cGAS-STING pathway [23]. Considering that STING pathway lead to the production of type I interferons (IFNs) and pro-inflammatory cytokines like IL-1β and TNF-α which critical for innate immune cell function, PD-L1 can eventually dampen anti-tumour immunity and promote cancer growth.

Programmed death-1 (PD-1)

PD-1, which was discovered in 1992, is part of the B7-CD28 immunoglobulin superfamily and in the human genome is encoded by the PDCD1 gene located on chromosome 2 [24, 25]. The structural composition of PD-1 includes

an extracellular IgV-like domain, a stalk region, a transmembrane domain, and a cytoplasmic tail distinguish by two distinct tyrosine-based signalling motifs: namely, the immunoreceptor tyrosine-based inhibitory motif (ITIM) and the immunoreceptor tyrosine-based switch motif (ITSM). With regards to amino acid sequence homology, PD-1 shares approximately 20% similarity with CTLA-4 and about 15% with CD-28, respectively [26]. Various factors, such as the nuclear factor of activated T cells (NFAT), interferon regulatory factor 9 (IRF9), and Forkhead box (FOX) proteins, are recognized as modulators of PD-1 expression. PD-1, as an inhibitory receptor on activated T cells and several other immune cells, plays a crucial role in establishing and maintaining immune tolerance towards self-antigens [27]. It primarily interacts with two ligands: PD-L1 (B7-H1, CD274) as well as PD-L2 (B7-DC, CD273). The interaction with these ligands results in the recruitment of the SHP-2 tyrosine phosphatase to the ITIM and ITSM motifs, which subsequently undergo activation and initiate dephosphorylation of critical T cell receptor (TCR) signalling proteins. This process encompasses the attenuation of pathways such as the phosphoinositide 3-kinase (PI3K)-phosphoinositide-dependent kinase 1 (PDK1)-AKT-mTOR pathway, the Janus kinases (JAKs)-signal transducers and activators of transcription (STAT) pathway, as well as the RAS-RAF-MEK-extracellular-signal-regulated kinase (ERK) pathway [28–30](Fig. 1).

Transcriptional regulation of PD-L1

The expression of PD-L1 is intricately controlled by numerous transcription factors, among which MYC, STAT family members, nuclear factor kappa-B (NF-κB), hypoxia-inducible factor 1-alpha (HIF-1α), and cyclin-dependent kinase 5 (CDK5) are prominent. MYC is known to associate with the PD-L1 promoter region, effectively modulating its transcriptional activity. Casey et al. illustrated that either the inactivation or knockdown of MYC results in a notable decline in PD-L1 levels [31]. The cytokine IFN-γ facilitates PD-L1 expression via the activation of the JAK-STAT signalling cascade, specifically with STAT3 attaching itself directly to the PD-L1 promoter to drive transcriptional engagement. PD-L1 overexpression can, in turn, influence STAT signalling pathways and promote the secretion of pro-angiogenic factors, thereby accelerating tumourigenic processes [32–35] (Fig. 2).

In melanoma cells, NF-κB activation by IFN-γ has been implicated in enhancing PD-L1 expression (29). In prostate cancer, RelB—a crucial NF-κB family member —elevates PD-L1 expression principally by binding to an NF-κB responsive element in its promoter region. Additionally, the upregulation of PD-L1 in cancer cells is influenced by downstream NF-κB signals, including those triggered by stress, oncogenic stimuli, and inflammatory cytokines. This nuanced regulation underlines the complexity of PD-L1's

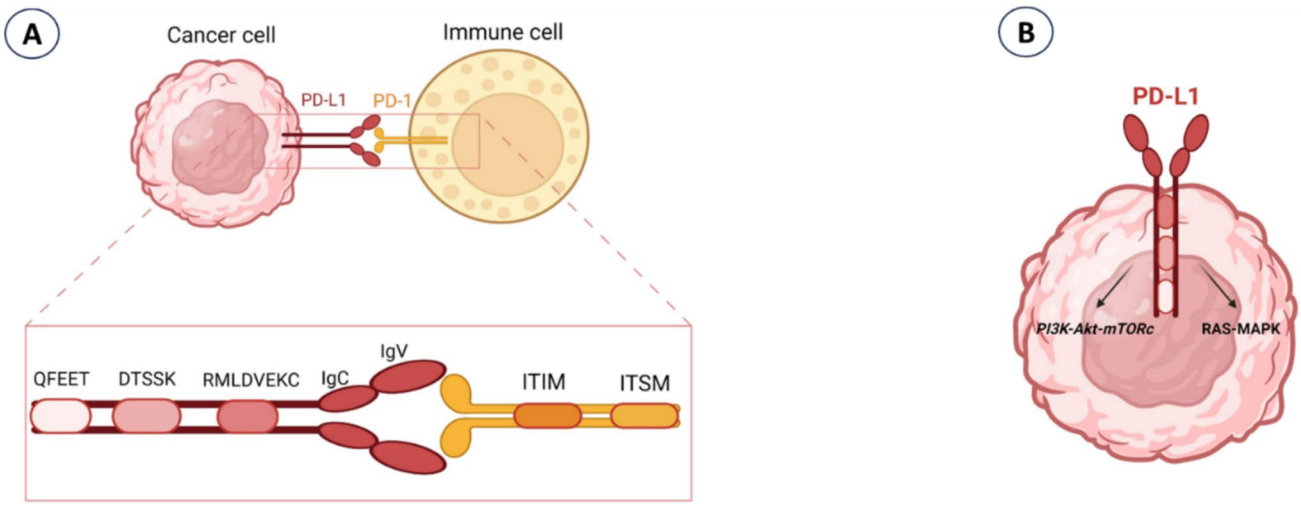

Fig. 1 Molecular configurations and signalling pathways of PD-L1 and PD-1: **A** Tumour cells exhibit PD-L1, encompassing various structural domains, notably the IgV and IgC domains on the extracellular segment, alongside intracellular signalling domains marked by the sequences RMLDVEKC, DTSSK, and QFEET. PD-1 is located on certain immune cells, such as T cells and NK cells, particularly during the exhaustion phase, and features signalling domains characterized by ITIM and ITSM motifs. **B** PD-L1 is known to initiate multiple signalling cascades, such as PI3K/Akt/mTORC and RAS/MAPK. These pathways play pivotal roles in cell proliferation and survival, influencing tumour progression and the immune evasion strategies employed by cancer cells. Enhanced understanding of these molecular interactions provides critical insights for the development of targeted therapies to disrupt this signalling nexus and improve treatment efficacy

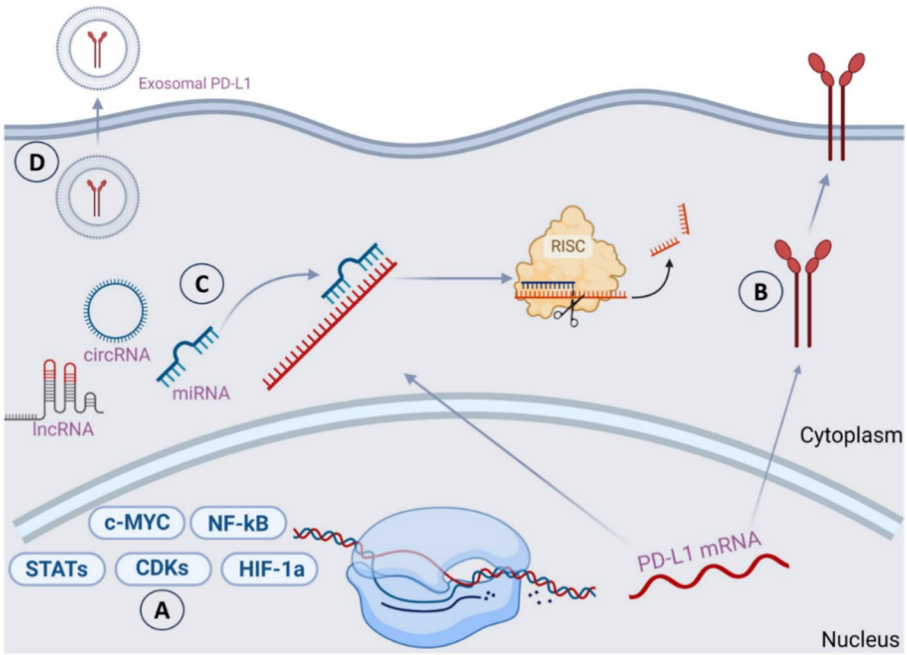

Fig. 2 Varied forms and expression profiles of PD-L1. **A** A range of transcription factors are directly involved in the modulation of PD-L1 expression, impacting its upregulation in differing cellular contexts. **B** Once synthesized, PD-L1 mRNA translocates to the cytoplasm where it undergoes translation into protein, subsequently being presented on the surface of cancer cells. This expression facilitates interactions critical to immune evasion mechanisms. **C** Non-coding RNAs, such as miRNAs, circRNAs, and lncRNAs, play a significant role in inducing PD-L1 degradation. These ncRNAs modulate the levels of PD-L1, thus diminishing its overall expression through various mechanistic pathways. **D** PD-L1 is also encapsulated within extracellular vesicles, particularly displayed in the form of exosomes, which mediate cell–cell communication and influence tumour dynamics. This encapsulation pathway is instrumental in advancing the tumour's immune escape tactics by facilitating systemic dissemination of immunosuppressive signals

role in cancer biology, underscoring potential therapeutic targets within these pathways [33, 34].

Exosomal and soluble PD-L1

Exosomes are small extracellular vesicles, measuring 30 to 150 nm in diameter, that originate from cells and are surrounded by a lipid bilayer. Tumour-derived exosomes possess a myriad of biomolecules, such as non-coding RNAs, microRNAs, signalling proteins, enzymes, mRNAs, and immune checkpoint proteins [36]. Notably, exosomal PD-L1 (exoPD-L1) functions in a manner akin to cell surface PD-L1 on tumour cells, engaging directly with PD-1 receptors on lymphocytes and thereby attenuating their activity [37]. ExoPD-L1 can impede T cell functions, including their activation, cytotoxic effects, and cytokine secretion, through a dose-dependent mechanism that suppresses NF-κB activation and ERK phosphorylation pathways. Additionally, it can inhibit dendritic cell function by preventing their differentiation, instigating apoptosis, and augmenting regulatory T cell (Treg) proportions [38, 39]. In vitro co-culture of exosomes containing high level of PD-L1 with T cells effectively dampened T cell activation and diminished the expression of CD69 on CD8 + T cells [40]. The synthesis and release of exoPD-L1 can be upregulated by IFN-γ exposure via activation of the JAK/STAT pathway and subsequent induction of IRF-1, culminating in increased exoPD-L1 production [41]. Environmental conditions within the tumour microenvironment can also modulate exoPD-L1 levels. Hypoxic circumstances, in particular, amplify exoPD-L1 production through hypoxia-inducible factor (HIF)-STAT3 pathways [42](Fig. 2).

ExoPD-L1 is emerging as a vital prognostic biomarker, significantly associated with tumour advancement, including increased tumour size, metastatic spread, and decreased overall survival in various cancers. These include HNSCC, melanoma, NSCLC, osteosarcoma, and diffuse large B-cell lymphoma (DLBCL) [43–47]. Exosomal form PD-L1 can also have therapeutic value as Poggio et al. have found that the deficiency of exoPD-L1 not only restrain local tumour growth but also can block the ability of wild-type tumour cells to attack the other flank. It is indicating a potent anti-tumour memory response [38].

Proteolytic cleavage of membrane-bound PD-L1 by endogenous matrix metalloproteinases (MMPs) or alternative splicing after its transcription, produce soluble form of PD-L1 (sPD-L1) [48]. Multiple PD-L1 + tumour cell lines

produce high levels of sPD-L1 in their supernatants. Both myeloid cells and activated T lymphocytes exhibit increased levels of mPD-L1 however only myeloid cells can produce sPD-L1. sPD-L1 like mPD-L1, binds to PD-1 and transmit negative regulatory signals. It can also induce apoptosis of T cells and impair their function [49].

Non-coding RNAs: miRNAs, lncRNAs and circRNAs

MicroRNAs (miRNAs) are concise non-coding RNA sequences, consisting of 20–22 nucleotides, involved in critical biological functions, including development, differentiation, cell proliferation, and apoptosis [50]. They associate with complementary miRNAs, leading to their subsequent degradation via the recruitment of the RNA-induced silencing complex (RISC). Several miRNAs have been identified as playing significant roles in regulating PD-L1 expression, either through direct interaction or via indirect pathways (see Table 1). Non-coding RNAs (ncRNAs), such as long non-coding RNAs (lncRNAs), circular RNAs (circRNAs), and miRNAs, are key regulatory molecules that influence gene expression at different stages [51]. Research indicates ncRNAs are pivotal in regulating the biogenesis of PD-L1 [52–54]. Moreover, the implementation of immune checkpoint inhibitors targeting PD-L1 has been observed to influence ncRNA expression profiles [55]. Within gene regulation, miRNAs often bind to the 3′-untranslated region (3′-UTR) of their target gene. Current evidence suggests that dysregulated expression of ncRNAs can modify tumour PD-L1 expression, shifting the tumour microenvironment towards either a pro-inflammatory or an immunosuppressive phenotype and impacting cellular proliferation, tumour migration, chemosensitivity, and apoptosis (refer to Table 1). Furthermore, competitive endogenous RNA (ceRNA) networks have unveiled novel mechanisms through which ncRNAs regulate each other's expression (56). LncRNAs and circRNAs can indirectly modulate PD-L1 expression by sequestering miRNAs, thereby influencing gene regulatory networks (Table 1 and Fig. 2).

Epigenetic regulation of PD-L1

Epigenetic regulations include histone acetylation, methylation and phosphorylation are critical regulators in PD-L1 expression (57). Lysine residue acetylation in histone tails can neutralize positive charges and reduce the affinity of histones for DNA. Histone H3 acetylation in the PD-L1 promoter increase the expression of PD-L1 in various drug-resistant cancer cells like some of lung cancer, breast cancer and hepatocellular carcinoma [58]. Histone deacetylase-3 (HDAC3) is one of HDAC isoform that is responsible for regulating PD-L1 transcription in tumours. It has been shown that inhibition of HDAC-3 can increase IFN-γ production and therefore PD-L1 transcription and activating in tumour cells and also elevate the levels of PD-L1 in dendritic cells in the tumour microenvironment [59]. It can also upregulate PD-L1 expression by intervening in the STAT3 signalling pathway. Additionally, histone acetylase-1 (HAT-1) activation enhance PD-L1 transcription and is associated with poor prognosis [60]. Histone methylation on arginine and lysine residues regulate gene expression however its exact role PD-L1 expression is less well-defined compared to acetylation. Histone phosphorylation is also a modification during mitosis of tumour cells, and its occurrence have a great impact on the structure and function of modified proteins. Wang et al. found that epidermal growth factor (EGF) induces phosphorylation of pyruvate kinase isoform M2 (PKM2) and its translocation to the nucleus. It eventually phosphorylates histone H3 at Thr11 to induce PD-L1 expression (61).

PD-L1 importance in cancer

The expression of PD-L1 holds substantial clinical relevance across various malignancies, serving as a key biomarker from prognostic evaluation to therapeutic decision-making. Within the vast classification of cancers, delineated by tissue or organ of origin, haematological malignancies are categorically distinct from solid tumours and thus necessitate unique management strategies. In this context, PD-L1's role is highlighted across a spectrum of cancers, encompassing solid tumours, haematological malignancies, and lymphomas. Understanding the nuances of PD-L1 expression in these cancer types informs the refinement of therapeutic approaches and enhances the precision of treatment alignment with individual tumour characteristics. Consequently, exploring PD-L1's involvement across these diverse cancer groups provides deeper insights into its potential as a universal target in oncological therapies, facilitating more tailored and potentially effective treatment paradigms (Fig. 3).

PD-L1 and solid tumours

Solid tumours are characterized as abnormal conglomerates of malignant cells, typically lacking cystic or fluid-filled regions. Although substantial research has been conducted over several decades, the exact molecular bases of solid tumours remain incompletely elucidated. Presently, treatments such as surgery, radiotherapy, chemotherapy, and immunotherapy can manage numerous solid tumours; however, securing a complete cure remains a formidable challenge. Tumour cells often express diverse ligands for

Table 1 Non-coding RNAs that control PD-L1 expression: miRNAs, lncRNAs and circRNA

miRNA	Target	Cell line	Species	Sample	Function	Disease type	References
miRNA-561-3p	ZEB1, HIF1A, and MYC	Cell line: MCF-7, MDA-MB-231, and BT-549	Human	biopsy from ($n=45$) patients	The overexpression of miR-561-3p resulted in a reduction in PD-L1 expression and breast cancer cell proliferation, while also inducing apoptosis and cell cycle arrest through the downregulation of specific oncogenes. Additionally, the inhibition of these candidate oncogenes by miR-561-3p led to a decrease in PD-L1 levels at both the mRNA and protein stages	Breast cancer	[54]
miR-138-5p	PD-L1	The human CRC cell lines HCT116, SW620, SW480 and HT29 and human normal colonic epithelium cell lines NCM460 and CCD841CoN	Human	biopsy from ($n=21$) breast cancer patients	miR-138-5p acts as a tumour suppressor in colorectal cancer, with its tumour-suppressive effects being partially mediated through the downregulation of PD-L1	colorectal cancer	[106]
miR-217	PD-L1 and AEG-1	Hep2	Human/Mouse	($n=10$) mice and ($n=29$) laryngeal cancer patients	miR-217 significantly inhibited various metastatic characteristics, including cell migration, invasion, proliferation, apoptosis, epithelial-mesenchymal transition (EMT), and angiogenesis. These inhibitory effects were mediated through the downregulation of its target genes, AEG-1 and PD-L1	Laryngeal cancer	[107]
miR-200	ZEB1	393P, 393LN 344P, 344SQ, 531LN2, 531LN3, B16, KPC, MC38, LLC-JSP, H157, HCC827, H322, H1299, H441, H157, H1155, HCC827 and H460	Human/Mouse	In addition to use of set of samples analysed by the cancer genome atlas project, ($n=250$) patients enrolled The Profiling of Resistance patterns and Oncogenic Signalling Pathways in Evaluation of Cancers of the Thorax (PROSPECT) trial were used	This study showed miR-200 suppresses EMT and metastasis by targeting PD-L1. Furthermore, ZEB1, an activator of EMT and a transcriptional repressor of miR-200, alleviates the miR-200-mediated suppression of PD-L1 on tumour cells, thereby facilitating CD8 + T-cell immunosuppression and promoting metastasis	Lung cancer	[108]

Table 1 (continued)

miRNA	Target	Cell line	Species	Sample	Function	Disease type	References
miR-197	PD-L1	–	Human	A total of ($n=68$) cases of OSCC tissues were collected from patients	This study showed negative correlation and prognostic effects between miR-197 and PD-L1 expression in OSCC	OSCC	[75]
miR-148a-3p	PD-L1	SW837 and HCT116	Human	A total of ($n=395$) cases of colorectal cancer tissues were collected from patients	Elevated expression of miR-148a-3p inhibited IFNγ-induced PD-L1 expression in tumour cells, thereby reducing T-cell apoptosis within a coculture model comprising IL2-activated T cells and IFNγ-treated tumour cells	Colorectal cancer	[109]
miR-142-5p	PD-L1	Panc02	Mouse	NA	Overexpression of miR-142-5p in tumour cells suppresses PD-L1 expression, leading to an elevation in CD4 + and CD8 + T lymphocyte populations, a reduction in PD-1 + T lymphocytes, and an increase in the levels of IFN-γ and TNF-α	Pancreatic cancer	[110]
miR-15b-5p	PD-L1	CT26, MC38, FHC, NCM460, HT29, SW1116, SW480, SW620, and F12K	Human/Mouse	($n=101$) tissue samples for microarray were purchased. Furthermore, ($n=21$) pairs of MSS colorectal tumours and adjacent colon tissues, ($n=27$) cases of colitis cancer tissues, and tissue samples from ($n=160$) cases of colorectal tumours were obtained	This study showed that miR-15b-5p was observed to reduce PD-L1 expression at the protein level, suppress tumourigenesis, and increase sensitivity to anti-PD-1 therapy in colorectal cancer models	Colorectal cancer	[111]

Table 1 (continued)

miRNA	Target	Cell line	Species	Sample	Function	Disease type	References
miR-155	PD-L1	Farage cells, DB, B95–8, A20	Human/Mouse	In addition to ($n=60$) patients for Training cohort, ($n=140$) patents were evaluated for validation cohort	This study showed a functional interaction between tumour cells and CD8 + T cells through miR155-PD-L1 regulatory axis. miR-155 upregulated PD-L1 expression in lymphoma cells, facilitated the recruitment of CD8 + T cells through PD-1/PD-L1 interactions, and suppressed CD8 + T cell function by dephosphorylating AKT and ERK. Furthermore, miR155 induced Fas-mediated apoptosis of CD8 + T cells	DLBCL	[112]
LncRNA							
MALAT1	miR-195	OCI-Ly10	Human	A total of ($n=37$) cases of DLBCL tissues were collected from patients	This study showed that MALAT1 possesses the ability to sponge miR-195, thereby modulating the expression of PD-L1. Inhibition of MALAT1 by decreasing PD-L1 prevented the proliferation, migration, and immune escape capabilities of OCI-Ly10 cells, while increasing their apoptosis ratio. Moreover, this inhibition promoted proliferation and inhibited apoptosis of CD8 + T cells	DLBCL	[53]
MALAT1	miR-200a-3p	A549 and CAL-12T	Human	A total of ($n=113$) cases of NSCLC tissues were collected from patients	This study showed that MALAT1 enhanced the proliferation, mobility, migration, and invasion of NSCLC cells through targeting of miR-200a-3p. PD-L1 was identified as a target of miR-200a-3p and was indirectly influenced by MALAT1	NSCLC	[113]

Table 1 (continued)

miRNA	Target	Cell line	Species	Sample	Function	Disease type	References
HOTTIP	c-Jun	293 T, SKOV3, OVCAR3, and Hy-A8	Human/Mouse	A total of ($n=53$) cases of ovarian cancer tissues were collected from patients. Furthermore, ($n=25$) normal fallopian tube fimbriae tissues were obtained as a control group	This study showed that HOTTIP is capable of inducing IL-6 secretion and promoting PD-L1 expression in neutrophils. Furthermore, they found upregulation of HOTTIP restrains T cell proliferation and T cell-mediated tumour immunotherapy	Ovarian cancer	[114]
MEG3	miR-216a	HEC-50, HEC-1, HOUA-I, HEC-1, SPAC-1-L, and immortalized human endometrial epithelial cell line (EM)	Human	A total of ($n=65$) human primary endometrial cancer tissues and 18 normal endometrium samples were obtained	This study illustrated that MEG3 represses the expression of miR-216a. This results in increase in PD-L1 expression. Interestingly, PD-L1 showed the anti-tumour effects by downregulating MCL-1 expression and cell proliferation	Endometrial cancer	[115]
lncAMPC	miR-637	J82, T24, 786-O and ACHN	Human/Mouse	Total paired tissues (tumour and normal para tumour) were collected ($n=65$). In total, 32 primary prostate cancer tissues from patients undergoing radical prostatectomy and 157 urine samples from patients with positive prostate biopsy were collected	This study showed upregulation of lncAMPC in patients promotes LIFR transcription by sponging miR-637 as well as decoying histone H1.2 away from the upstream sequence of LIFR gene. This leads to activation of Jak1-STAT3 signalling pathway to increase PD-L1 protein stability and metastasis-associated gene expression	prostate cancer	[116]
HOXA-AS2	miR-519	SUNE1, SUNE2, and NP69	Human	Total paired tissues (tumour and normal para tumour) were collected ($n=15$)	This study investigated the role of HOXA-AS2 in NPC patients. HOXA-AS2 by sponging miR-519 increases HIF-1α and PD-L1 as targets of miR-519. This result in elevated proliferation, migration and invasion of tumour cells	NPC	[117]
CircRNA							

Table 1 (continued)

miRNA	Target	Cell line	Species	Sample	Function	Disease type	References
CircFOXK2	miR-485-5p				This study investigated the role of CircFOXK2 in NSCLC cancer cell. They found CircFOXK2 by sponging miR-485-5p increases PD-L1 expression. This result in a decrease in cytotoxicity in CD8 + T-cell and increase of tumourigenesis	NSCLC	[118]
CircCHST15	miR-155-5p/ miR-194-5p	16HBE, H1299, H23, H1359, H1435, H358, PC-9 and CMT-167	Human/Mouse	Total paired tissues (tumour and normal para tumour) were collected ($n = 90$)	This study showed Circ-CHST15 sponge miR-155-5p and miR-194-5p. Then they observed cancer cell viability and proliferation were increased by miR-155-5p and inhibited by miR-194-5p	Lung cancer	[119]
circ_0000284	miR-377-3p	MRC-5, A549, and H82	Human	Total paired tissues (tumour and normal para tumour) were collected ($n = 60$)	This study showed miR-377-3p could be sponged by circ_0000284, and PD-L1 expression was directly inhibited by miR-377-3p. This result in tumourigenesis and lower survival in patients	NSCLC	
circ_0003288	miR-145	HepG2, Huh7, SMMC-7721, Bel-7402, and L02	Human	Total paired tissues (tumour and normal para tumour) were collected ($n = 40$)	This study found circ_0003288 is elevated in patients and functioned as a ceRNA by regulating miR-145. This result in promoting EMT and invasion by regulating PD-L1	HCC	[120]
circ-CPA4	let-7	A549, H1299, SK-MES-1, Calu-3, and human normal bronchial epithelial cell line	Human	Total paired tissues (tumour and normal para tumour) were collected ($n = 50$)	In this study by overexpression of circ-CPA4, they found the intracellular PD-L1 as well as extracellular ones expressions is promoted due to acting as RNA sponges for let-7 miRNA	NSCLC	[121]

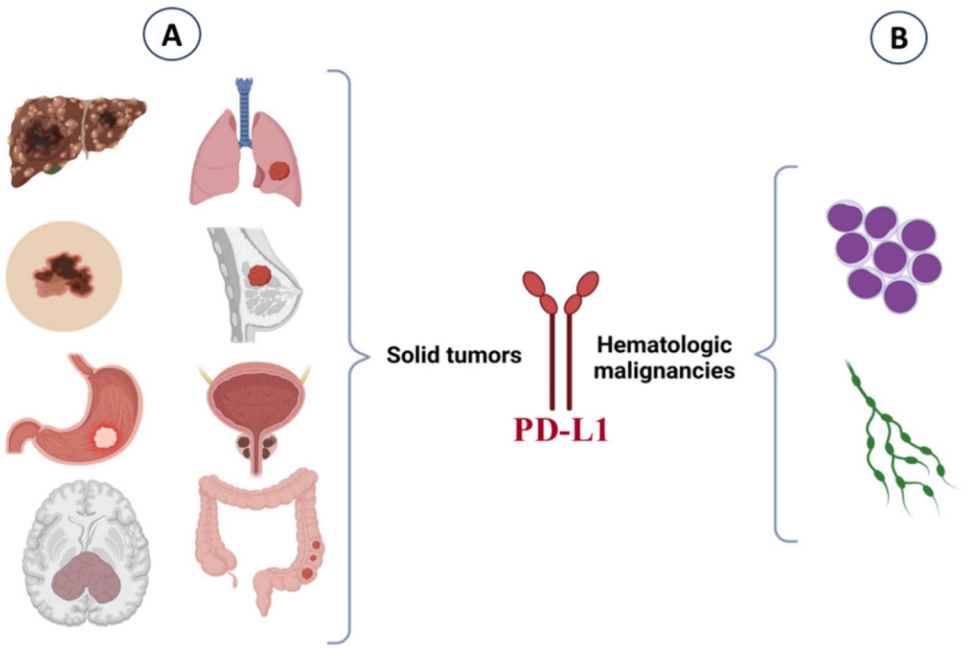

Fig. 3 The role of PD-L1 in cancer progression. **A** Solid Tumours: PD-L1 is a critical molecule for prognosis and therapeutic targeting in a variety of solid cancers, including but not limited to non-small cell lung cancer, breast cancer, prostate cancer, colorectal cancer, hepatocellular carcinoma, melanoma, gastric cancer, and brain tumours. **B** Haematological Malignancies: In haematological cancers such as leukaemia and lymphoma, PD-L1 maintains its significance as a therapeutic target

immune checkpoints, including PD-L1, that impede the activity of immune cells and simultaneously support cancer cell proliferation, survival, and resistance to pharmaceuticals [62, 63].

This discourse underscores the critical role of PD-L1 expression in several commonly occurring solid tumours. Numerous cancer types, including NSCLC, melanoma, bladder cancer, renal carcinoma, prostate cancer, breast cancer, head and neck cancers (squamous cell carcinomas), oesophageal cancer (squamous cell carcinoma), gastric cancer (adenocarcinoma), colorectal cancer, and cervical cancer, display an upregulation of PD-L1. This overexpression correlates with immunotherapy strategies aimed at targeting PD-L1, facilitating the cancer cells' evasion of immune detection (Table 2).

The PD-L1 immunohistochemistry (IHC) test has an important role in the planning of treatment approaches for many tumour categories and is used as a companion diagnostic biomarker [64]. In a meta-analysis conducted by Wu et al., the prognostic significance of PD-L1 in human solid tumours was evaluated. Their findings indicate that, generally, PD-L1 expression correlates with inferior survival outcomes in solid tumours, though the association between PD-L1 levels and prognosis can differ by tumour type [65]. Specifically, in NSCLC, high PD-L1 expression is strongly related to increased tumour proliferation, aggressiveness, and decreased patient survival rates [66].

The prognostic significance of PD-L1 expression remains a contentious subject within oncological research. However, its expression has been linked to enhanced responsiveness to immune checkpoint inhibitors targeting the PD1/PD-L1 axis, underscoring its potential utility as a pivotal biomarker in directing immunotherapeutic interventions. In patients with advanced NSCLC who have elevated PD-L1 levels, the effectiveness of PD-L1 blockade notably surpasses that of conventional chemotherapy, particularly in cases of previously untreated metastatic squamous NSCLC [67].

In melanoma, PD-L1 is often observed on both malignant melanocytes and resident immune cells. Its presence in biopsy specimens collected prior to treatment has shown potential in augmenting antitumour responses in melanoma patients [68]. Within bladder cancer, PD-L1 acts as an essential biomarker, associating with tumour grade and contributing to the trajectory of disease progression. Notably, heightened PD-L1 expression is more prevalent in higher-grade bladder cancers in contrast to their lower-grade counterparts [69].

In prostate cancer, PD-L1 expression varies significantly among patients, with higher levels observed in cases of metastatic castration-resistant prostate cancer (mCRPC) compared to primary tumour sites [70]. Elevated PD-L1 is particularly pronounced in high-risk patient profiles and is often regarded as an unfavourable prognostic marker for those receiving adjuvant hormonal therapy subsequent to surgical intervention [71]. Literature further suggests that PD-L1 is generally more upregulated in prostate cancer tissues compared to normative tissue samples [72].

In breast cancer, PD-L1 expression is notably linked with high-risk clinicopathological features, contributing to a poorer prognosis in patients with primary breast cancer (PBC). Elevated PD-L1 expression is linked to increased tumour size, higher histological grading, enhanced Ki-67 proliferation indices, negativity for oestrogen receptor (ER) and progesterone receptor (PR), the triple-negative breast

Table 2 PD-L1 in different cancers

Type of cancer	State of PD-L1 expression	Importance in severity and prognosis	Importance in immunotherapy	References
Solid tumours				
NSCLC	Overexpression	Increase in tumour proliferation and aggressiveness. Decrease in survival	Better response to immune checkpoint therapies based on PD1/PDL1	[66, 67]
Melanoma	Overexpression on malignant and immune cells	–	Better antitumour response after immunotherapy	[68]
BC	Overexpression in high grades	As a biomarker related to the pathological grading	–	[69]
Prostate cancer & mCRPC	Variable but Overexpression in mCRPC	Unfavourable prognostic biomarker for predicting high-risk patients	–	[70, 71]
Breast cancer	Overexpression	Large tumour size, histologic grade, Ki-67 high level, ER and PR negative, TNBC subtype and shorter survival time	Can be a potential treatment target	[73, 74]
GC	Overexpression and its expression are scored using the CPS scoring system	–	Better the therapeutic response to anti–PD-1/PD-L1 agents (pembrolizumab)	[75, 76]
CRC	Expression on tumour cells and also several tumour-infiltrating immune cells- such as T and B lymphocytes, dendritic cells, macrophages	Its overexpression is prevalent in liver and lung metastatic foci compared to the primary tumour	–	[78, 79]
HCC	Overexpression	Controversial Associated with poor survival	Better overall response rate (ORR) patients treated with anti-PD-1/PD-L1-based therapies	[80, 81]
Glioblastomas	Overexpression	Controversial	Controversial	[82–84]
Haematologic malignancies				
Myeloid leukemias	Overexpression in AML and CML	Negatively correlated with disease outcome and poorer OS	–	[17, 86–89]
Lymphoid leukemias	Overexpression in B-ALL and CLL	Controversial	Controversial	[92–94]
Lymphomas				
B-cell malignant lymphomas	Overexpression	Negatively correlated with treatment time	–	[97]

NSCLC (non-small cell lung cancer), *BC* (Bladder cancer), *mCRPC* (Metastatic Castration-Resistant Prostate Cancer), *CPS* (combined positive score), *CRC* (colorectal cancer), *HCC* (hepatocellular carcinoma), *OS* (overall survival)

cancer (TNBC) phenotype, and diminished survival rates, as highlighted in a meta-analysis [73]. Nevertheless, targeting PD-L1, especially within cancer stem cells, emerges as a potentially promising therapeutic avenue [74].

For gastric cancer (GC), PD-L1 expression is typically measured utilizing the combined positive score (CPS). This method evaluates the extent of PD-L1 staining in tumour cells, lymphocytes, and macrophages compared to the total number of viable tumour cells, with the result scaled by a factor of 100. This scoring method offers an enhanced overview of PD-L1 levels within the tumour microenvironment, thus refining predictions regarding therapeutic responses to anti–PD-1/PD-L1 therapies [75]. The efficacy and patient response rates to pembrolizumab are closely tied to PD-L1 expression, with the overall response rate (ORR) being markedly higher in PD-L1-positive gastric cancer compared to PD-L1-negative cases [76].

In colorectal cancer (CRC), PD-L1 is commonly found to be expressed not only on tumour cells themselves but also on several tumour-infiltrating immune cells, which include T and B lymphocytes, dendritic cells, macrophages, other innate immune cells that are derived from the bone marrow, along with vascular endothelial cells. Such a distribution pattern offers strategic possibilities for developing innovative immune-based therapeutic strategies designed to target these expressions effectively [77]. Recent investigations have revealed that PD-L1 expression tends to be more prevalent in observed in metastatic sites, like those found in liver and lung, compared to primary tumours [78, 79].

In hepatocellular carcinoma (HCC), a higher expression level of PD-L1 has been linked, in an independent and significant manner, with decreased survival rates, substantiating the view of the PD-1/PD-L1 axis as a plausible target for immunotherapy interventions in HCC [80]. Conversely, a systematic review and meta-analysis conducted by Yang et al. has highlighted that the presence of positive PD-L1 expression is associated with an improved overall response rate (ORR) among individuals with advanced HCC who have undergone therapies targeting PD-1/PD-L1. This finding suggests that assessing PD-L1 expression levels might help in identifying those HCC patients who could potentially receive greater benefit from these immunotherapeutic approaches [81].

In contrast, the prognostic significance of PD-L1 expression in gliomas, particularly glioblastomas, remains a contentious issue despite extensive investigations. Two recent meta-analyses focussing on the prognosis of glioblastoma multiforme (GBM) patients highlighted a notable link between PD-L1 expression and decreased overall survival, suggesting its role as a negative prognostic marker in GBM cases [82–84]. Conversely, Masood et al. have posited that blood-based measurements of PD-L1 within GBM can serve as an important prognostic indicator and therapeutic target, offering a swift and relatively non-invasive screening tool suitable for routine clinical application [85]. (See Table 2).

PD-L1 and haematologic malignancies

Haematologic malignancies comprise a diverse collection of disorders originating from the genetic transformation of haematopoietic cells, with prevalent types including leukaemias and lymphomas. The role of immune checkpoint expressions and their ligands is crucial in both the prognosis and treatment approaches for these diseases. In this context, the expression of PD-L1 is particularly significant, warranting close attention (Table 2). Understanding PD-L1's expression patterns can provide vital insights into disease progression and therapeutic response, ultimately informing more effective patient-specific treatment strategies.

Myeloid leukaemia

Leukaemias are categorized based on cell differentiation and the dominant cell type, resulting in classifications such as acute versus chronic and myelocytic versus lymphocytic leukaemias. Acute myeloid leukaemia (AML) and chronic myelogenous leukaemia (CML) are notable examples of myelocytic leukaemias. PD-L1 expression on CD34 + myeloid blasts is known to attenuate anti-leukaemic immune responses by engaging PD-1, as well as increasing the malignancy potential of leukemic cells. Interferon-gamma (IFN-γ) raises PD-L1 levels on myeloid precursor cells, which fosters the expansion of regulatory T cells [86]. In AML, increased PD-L1 expression on leukemic cells correlates negatively with patient prognoses [87]. Recent investigations show that elevated PD-1, and PD-L1 expression is linked to poorer overall survival and clinical outcomes in AML patients [88]. PD-L1 also influences the metabolic reprogramming of AML cells by enhancing pathways such as fatty acid oxidation, the pentose phosphate pathway, and glycolysis, promoting the survival and proliferation of AML cells [62, 89].

In CML, PD-L1 presence on leukemic cells allows them to bind PD-1, which is commonly overexpressed on cytotoxic T lymphocytes (CTLs), thereby hampering their cytotoxic function and contributing to disease progression [90]. In multiple myeloma (MM), PD-L1 is present on tumour cells while T cells often display elevated PD-1 levels. The interaction between PD-L1 and PD-1 disrupts immune functionality, facilitating immune evasion by hindering the activation and function of tumour-reactive T cells. This interaction effectively shields tumour cells from MM-specific T cell-mediated killing, protection that can potentially be reversed using anti-PD-1 or PD-L1 antibodies [91, 92].

Lymphoid leukaemia

Acute lymphoblastic leukaemia (ALL) is the predominant leukaemia type diagnosed in paediatric cohorts, comprising approximately 80% of all childhood leukaemia cases. In contrast, among adults, chronic lymphocytic leukaemia (CLL) is the most frequently occurring form, accounting for an estimated 40% of all leukaemia cases in this demographic. In cases of newly diagnosed B-acute lymphoblastic leukaemia (B-ALL), expression of PD-L1 is commonly observed. This expression is not confined solely to instances that have relapsed but is prevalent in initial diagnoses as well. Although less frequent, PD-L2 expression tends to coincide with PD-L1 expression when it does occur. Those patients who test positive for PD-L1 expression might be suitable candidates for therapies utilising PD-1/PD-L1 immune checkpoint inhibitors [93].

The debate surrounding the prognostic significance of PD-L1 expression in lymphoid leukaemia persists within the scientific community. The expression form, either at the mRNA or protein level, may have differing implications. Yang et al. demonstrated that patients with elevated levels of CD47 and PD-L1 mRNA expression tend to exhibit improved one-year survival rates compared to those with lower expression levels. Conversely, the elevated expression of CD47 and PD-L1 protein correlated with poorer one-year survival in comparison to low protein expression (93).

In CLL, interactions mediated by CD84 among cells lead to an increased level of PD-L1 on CLL cells through activation of the Akt-mTOR pathway, which exacerbates T-cell exhaustion. Reducing CD84 expression can potentially reverse this exhaustion [94]. Additionally, the BTK inhibitor Ibrutinib has shown potential in enhancing tumour-specific immune responses by targeting and inhibiting the STAT3-induced selective and sustained downregulation of PD-L1 on CLL cells and PD-1 on CD4 + and CD8 + T cells. Research has revealed that early blockade of PD-L1 can efficiently rectify the immune dysfunction induced by leukaemia and inhibit the development of CLL in mouse models [95, 96].

Lymphomas

Malignant lymphoma stands as the most prevalent form of haematologic disease, encompassing both Hodgkin lymphoma (HL) and the several subtypes of non-Hodgkin lymphoma (NHL). According to research carried out by Yang et al., there is a notable overexpression of PD-L1 in B-cell malignant lymphomas, which inversely correlates with the duration of treatment. This makes PD-L1 a biomarker with high diagnostic precision for identifying B-cell lymphoma and underscores its utility as a possible target for immunotherapy in treating this disease [97].

Recent studies focussing on classical Hodgkin lymphoma (CHL) have revealed a strong correlation between PD-L1 expression and various immunological markers. Specifically, PD-L1 expression is linked with the expression of Major Histocompatibility Complex class II (MHC-II) in CHL, facilitating the recruitment of T-helper (TH) cells and the accumulation of TH1 regulatory cells [98]. This relationship underscores the potential of PD-L1 not only as a biomarker for the disease but also as a strategic target for therapeutic interventions in CHL. By exploring the nuanced roles that PD-L1 plays within these mechanisms, researchers can better leverage it to enhance diagnostic and treatment approaches.

PD-L1 importance in suppressive immune cells in TME

PD-L1 have a critical role in TME by affecting of the suppressor immune cells like tumour associated macrophages, myeloid-derived suppressor cells (MDSCs) and Treg cells. Expression of PD-L1 on tumour associated macrophages (TAMs) can either stimulate or suppress immune responses. Although in most cancers PD-L1 expressed on TAMs mediate immune suppression by inhibition of T cell activity, Wang et al. found that PD-L1$^+$ TAMs are more activated and can promote CD8$^+$ T cells proliferation and cytotoxic capacity [99]. Tumour-infiltrating MDSCs highly express PD-L1 but the exact role of PD-L1 on MDSCs in T cell suppression needs to be investigated. Treg cells were also shown to increase PD-L1 expression on MDSCs [100]. PD-L1 is also expressed on iTreg and promotes their differentiation by downregulating the Akt-mTOR signalling pathway and upregulating PTEN [101].

PD-L1 as therapeutic targets

Monoclonal antibodies

Anti-PD-L1 monoclonal antibodies have demonstrated significant potential both as standalone therapies and when conjugated with pharmacologically active agents, including anti-cancer drugs, enzymes, hormones, toxins (predominantly derived from plants or bacteria), and radionuclides. This strategy enables the targeted delivery of cytotoxic agents to a broad spectrum of cancers that exhibit PD-L1 expression, a feature commonly observed in numerous solid tumours. Among the most widely recognized anti-PD-L1 antibodies are Atezolizumab, Durvalumab, and Avelumab. Furthermore, ongoing research is exploring the efficacy of additional anti-PD-L1 antibodies, including the anti-PD-L1 mAb clone 10F.9G2 (IgG2b), as well as gold nanoparticles

(AuNPs) incorporating murine or human anti-PD-L1 mAb [102].

Small molecules

Despite significant advancements in improving survival rates and even achieving complete remission in many cancer patients through the use of monoclonal antibodies, certain limitations persist. Studies have highlighted that monoclonal antibody drugs often struggle to penetrate deeply into tumour tissues, failing to reach all regions of the tumour and accumulate at therapeutic concentrations. Additionally, the immunogenicity of antibody-based therapies can trigger the production of anti-antibodies within the body, potentially diminishing their therapeutic efficacy [103]. Small molecule inhibitors, however, offer a promising alternative by addressing these challenges. A variety of small molecules targeting PD-L1 have been identified, each employing distinct mechanisms of action, with the majority currently undergoing preclinical investigation. These molecules can inhibit PD-L1 expression (e.g. JQ1, Osimertinib, and eFT508), enhance its degradation (e.g. PD-LYLSO, Curcumin, and Metformin), or disrupt its interaction with PD-1 (e.g. AUNP-12, BMS-202, TPP-1, and CA-170) [104].

Combination therapies with PD-L1 blockade

To enhance the effectiveness of PD-L1 blockade therapy, it can be combined with other therapies that exhibit synergistic effects. These include conventional treatments such as chemotherapy, radiotherapy, and angiogenesis inhibitors, which have been shown to complement the action of anti-PD-L1 antibodies. Additionally, combining anti-PD-L1 antibodies with other immune checkpoint inhibitors (e.g. anti-CTLA-4 agents), or with co-stimulatory pathway activators, has emerged as a promising strategy. Furthermore, PD-L1 blockers can be co-administered with targeted therapies, including epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs), Ras-targeted therapies, and others. Early clinical trials investigating these combinations have yielded encouraging outcomes, although research in this area remains ongoing to fully optimize and validate these strategies [105]. (Fig. 4).

Summary and conclusion

The excessive expression of PD-L1 in cancer cells plays a significant role in promoting tumour growth and survival, all the while dampening anti-tumour immunity through its interaction with PD-1. A thorough understanding of PD-L1, encompassing both its molecular mechanisms and clinical implications, is essential for developing more effective and targeted therapeutic approaches. Targeting PD-L1 as a therapeutic approach presents a substantial opportunity to improve the efficacy of cancer therapies and achieve better patient outcomes. However, future research needs to explore the molecular and clinical dimensions of PD-L1 more deeply. Future studies should aim to uncover additional intracellular effects of PD-L1, such as its influence on metabolic processes and downstream signalling pathways, as well as the design and evaluation of novel small molecules

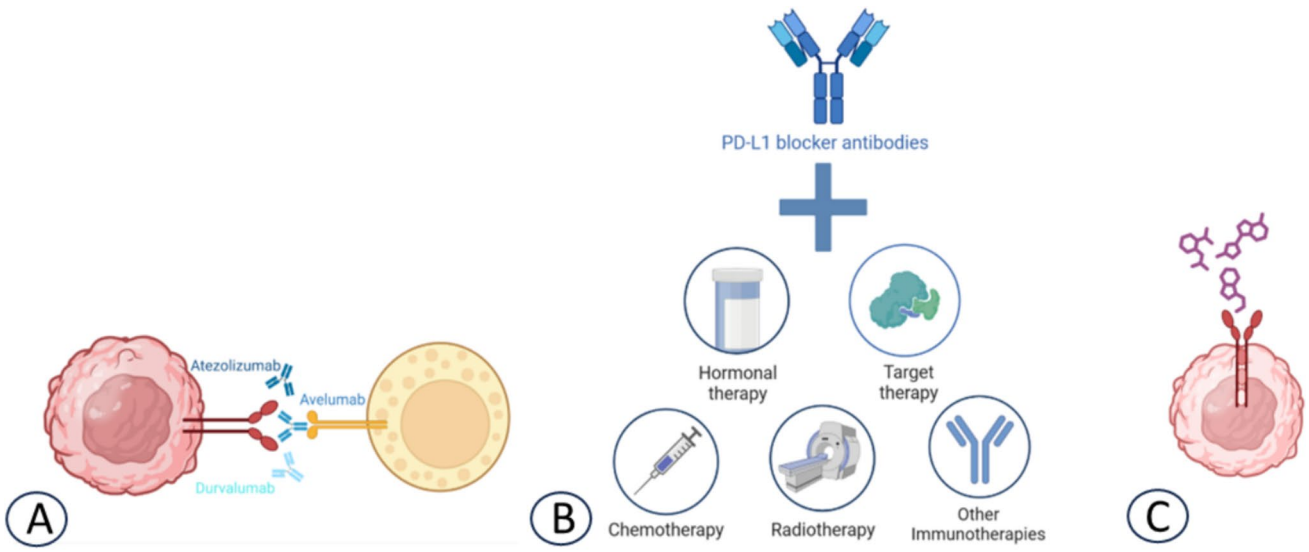

Fig. 4 Therapeutic approaches based on PD-L1. **A** FDA-approved monoclonal antibodies including Atezolizumab, Avelumab and Durvalumab (Right: immune cells specially T cell, left: tumour cell), **B** Combinational therapies including chemotherapy, radiotherapy, other immunotherapies and etc. along with PD-L1 blockers. **C** Small molecules against PD-L1

targeting PD-L1. Investigating their therapeutic potential, both as standalone treatments and combined with other therapies, represents an interesting direction for advancing cancer treatment strategies.

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