Recent Findings in the Regulation of Programmed Death Ligand 1 Expression

Xiangfeng Shen[1], Lihong Zhang[1], Jicheng Li[2], Yulin Li[1]*, Yishu Wang[1]* and Zhi-Xiang Xu[1]*

[1] Key Laboratory of Pathobiology, Ministry of Education, Norman Bethune College of Medicine, Jilin University, Changchun, China, [2] Department of Physiology, College of Basic Medical Sciences, Jilin University, Changchun, China

With the recent approvals for the application of monoclonal antibodies that target the well-characterized immune checkpoints, immune therapy shows great potential against both solid and hematologic tumors. The use of these therapeutic monoclonal antibodies elicits inspiring clinical results with durable objective responses and improvements in overall survival. Agents targeting programmed cell death protein 1 (PD-1; also known as PDCD1) and its ligand (PD-L1) achieve a great success in immune checkpoints therapy. However, the majority of patients fail to respond to PD-1/PD-L1 axis inhibitors. Expression of PD-L1 on the membrane of tumor and immune cells has been shown to be associated with enhanced objective response rates to PD-1/PD-L1 inhibition. Thus, an improved understanding of how PD-L1 expression is regulated will enable us to better define its role as a predictive marker. In this review, we summarize recent findings in the regulation of PD-L1 expression.

Keywords: PD-L1 expression, intrinsic signals, extrinsic signals, anti-PD-1/PD-L1, immune checkpoint therapy

INTRODUCTION

With rapid development of immunotherapy for cancer treatment in decades, immune checkpoint therapy that mediates tumor cell death through the reactivated immune system has become the most attractive strategy for cancer therapy due to their impressive therapeutic efficacy. Immune checkpoints, a cluster of immune inhibitory receptors and their reciprocal ligands that negatively regulate the immune system function, are important for avoiding autoimmunity and for protecting collateral tissue from damage under physiological conditions. On the other hand, cancer cells could also make use of immune checkpoints to inhibit the activity of T cells, leading to the immune escape of tumors.

The role of immune checkpoints in the suppression of T cell activity has led to the development of immune checkpoint inhibitors in the treatment of cancer. Among the immune checkpoints, programmed cell death protein 1 (PD-1) and its ligand PD-L1 have stood out because of their proven value as therapeutic targets in a large number of malignancies. Inhibition of the PD-1/PD-L1 axis contributes to important clinical advances in cancer therapy, including melanoma (1, 2), non-small cell lung cancer (NSCLC) (3–5), renal cell carcinoma (RCC) (6), Hodgkin's lymphoma (7, 8), bladder cancer (9, 10), head and neck squamous cell carcinoma (HNSCC)

(11–13), Merkel-cell carcinoma (14), urothelial carcinoma (15), and microsatellite instable-high (MSI-H) or mismatch repair-deficient (dMMR) solid tumors (16–18). However, despite the considerable improvement in patient outcome that has been achieved with PD-1/PD-L1 blockade, the durable objective responses to the checkpoint therapeutics are various among different tumor types and limited in only a minority of patients. Intra-tumoral PD-L1 expression is generally associated with a better response to PD-1/PD-L1 blockade in patients across multiple cancer types (3, 19–21). Therefore, in order to predict the efficiency and optimize the anti-PD-1/PD-L1 therapy alone or in combination, improving the understanding of the regulatory mechanisms of PD-L1 in cancer should be of utmost importance for not only identifying its role as biomarker but also for designing the synergistic treatment combinations. Here, we focus on the current knowledge of PD-L1 regulation.

ANTI-PD-1/PD-L1 INHIBITORS AS IMMUNE CHECKPOINT THERAPY

Although the immune system of our body should eliminate cancer cells as "foreign," the interactions between the immune system and cancer cells are complex. A natural balance called tolerance may be reached between immune response and cancer, where cancer cells are seen as "self." Furthermore, tumor cells may evade immune destruction by suppressing immunity through multiple mechanisms, thus called immune escape. T cell immunity, especially activation of cytotoxic T lymphocyte (CTL) determines the ultimate amplitude and quality of antitumor immune response. Signals from T cell receptor, which recognizes antigen along with the major histocompatibility complex (also known as human leukocyte antigen) presented on the surface of antigen-presenting cell (APC), and additional co-stimulatory signals provided by the engagement of CD28 on the T cell surface with B7 molecules (CD80 and CD86) on the APC, are required for T cell activation (22, 23). Activated T cells attack and eventually destroy tumor cells that express tumor-specific antigens as "foreign."

In addition to initiating proliferation and functional differentiation, T cell activation also induces the stimulation of inhibitory pathways (also known as checkpoint pathways), which eventually attenuate and terminate T cell responses (24–26). Many types of solid tumors generate an immunosuppressive microenvironment to avoid the destiny of being lysed by CTL through the inhibitory ligand called PD-L1 that is expressed on the surface of tumor cells (27, 28). PD-1 (CD279), which belongs to the CD28 family, is encoded by the PDCD1 gene located on chromosome 2q37.3 and is mainly expressed on activated T cells (29). It has two ligands, PD-L1 (CD274, B7-H1) and PD-L2 (CD273, B7-DC), with different expression patterns, which are, respectively, encoded by the *CD274* and *PDCD1LG2* genes located on chromosome 9p24.1. PD-L1 is expressed abundantly on immune cells (e.g., T cells, B cells, dendritic cells (DCs), and macrophages) and parenchymal tissue cells (mesenchymal stem cells, epithelial, endothelial cells,

and brown adipocytes), as well as tumor cells. The expression of PD-L2 is considered to be mainly restricted to activated DCs and macrophages (30–33). Studies have shown that PD-1/PD-L1 axis can be hijacked by tumors as a co-inhibitory pathway to compromise the immune response toward cancer via blocking proliferation, induction of apoptosis by CTL, and promotion of regulatory T cell differentiation, which eventually induces an immunosuppressive microenvironment in tumor (25, 26). Considering that PD-L1 overexpression is a situation that is commonly seen in tumors and usually confers a poor prognosis, the therapeutic intervention targeting this co-inhibitory axis is substantially enticing to researchers and patients (34–37). Antibodies blocking the interaction between PD-1 and PD-L1 by either targeting PD-1 (pembrolizumab, nivolumab, and cemiplimab) or PD-L1 (atezolizumab, avelumab, and durvalumab) (**Table 1**) both induce durable objective responses in patients with melanoma (1, 2), NSCLC (3–5) and RCC (6), and other malignancies (7–15). Although the immune checkpoint therapy targeting either PD-1 or PD-L1 has been usually recognized as the same subclass in the field of tumor immunotherapy at present, PD-1 and PD-L1 blockades may differ in the mechanism of action due to the complicated subtle interactions among the immune checkpoint system. For example, in addition to PD-1, studies have reported that co-stimulatory molecule CD80 (B7-1) can also serve as a receptor for PD-L1, and the binding affinity of CD80 to PD-L1 is comparable to its affinity for CD28 (38). More importantly, the binding of PD-L1 to CD80 functionally inhibits the proliferation of T cells and promotes the apoptosis of activated CD8$^+$ T cells (38, 39). Similarly, in addition to PD-L1, PD-1 also binds to its ligand PD-L2, which is expressed on solid tumor cells and hematological malignancies (40–45) and bears an impact on the anti-PD-1 therapy (41, 42, 46). Furthermore, PD-L2 has even been characterized as a novel potential therapeutic target for cancer treatment (45). Therefore, more evidence is needed to underpin the unique characteristics of PD-1 and PD-L1 inhibitors in order to achieve a better understanding of their differences.

PD-L1 REGULATION IN CANCER

Expression of PD-L1 is complicated and various in different tumor types. It can be regulated by various intrinsic and extrinsic signals, such as chromosomal alterations, epigenetic modifications, aberrant oncogenic and tumor suppressor signals, inflammatory cytokines, and other factors at the genetic, transcriptional, post-transcriptional, translational, and post-translational levels.

Genetic Basis of PD-L1 Expression in Cancer

The genetic aberrations of the chromosome 9p24.1, on which *CD274* resides, represent a key mechanism affecting PD-L1 expression. Copy number alterations (CNAs) in chromosome 9p involving *PD-L1* were recently detected in 22 cancer types (47). It revealed that gains of copy numbers in chromosome

TABLE 1 | Characteristics of current FDA-approved PD-1/PD-L1 checkpoint blockades.

Drug	Brand name	Target	Company	Time approved	FDA approved indications
Pembrolizumab	Keytruda	PD-1	Merck	09/04/2014	Metastatic NSCLC
				12/18/2015	Unresectable or metastatic melanoma
				08/05/2016	Recurrent of metastatic HNSCC
				03/15/2017	Refractory cHL
				05/18/2017	Advanced or metastatic urothelial carcinoma
				05/10/2017	Untreated metastatic non-squamous NSCLC (combined with pemetrexed and carboplatin)
				05/23/2017	Unresectable or metastatic MSI-H or dMMR solid tumors
				09/22/2017	Advanced gastric cancer
				06/12/2018	Recurrent or metastatic cervical cancer
				06/13/2018	Refractory PMBCL
Nivolumab	Opdivo	PD-1	Bristo-Myers Squibb	12/22/2014	Unresectable or metastatic melanoma
				03/04/2015	Metastatic squamous NSCLC
				10/09/2015	Metastatic NSCLC
				11/23/2015	Untreated advanced renal cell carcinoma
				05/17/2016	Relapsed cHL
				11/10/2016	Recurrent or metastatic HNSCC
				02/02/2017	Advanced or metastatic urothelial carcinoma
				08/01/2017	MSI-H or dMMR metastatic CRC
				09/22/2017	HCC previously treated with sorafenib
				12/20/2017	Resectable or metastatic melanoma
				07/10/2018	Advanced RCC (Combined with ipilimumab)
Cemiplimab	Libtayo	PD-1	Sanofi/Regeneron	09/28/2018	Metastatic CSCC
Atezolizumab	Tecentriq	PD-L1	Genetech/Roche	05/18/2016	Advanced or metastatic urothelial carcinoma
				10/18/2016	Metastatic NSCLC
Avelumab	Bavencio	PD-L1	EMD Serono	03/23/2017	Metastatic MCC
				05/09/2017	Advanced or metastatic urothelial carcinoma
Durvalumab	Imfinzi	PD-L1	AstraZeneca	05/01/2017	Advanced or metastatic urothelial carcinoma (UK Limited)
				02/16/2018	Unresectable stage III NSCLC

FDA, US Food and Drug Administration; PD-1, programmed death protein 1; PD-L1, programmed death ligand-1; NSCLC, non-small cell lung cancer; HNSCC, head and neck squamous cell carcinomas; cHL, classical Hodgkin lymphoma; MSI-H, microsatellite instability-high; dMMR, mismatch repair-deficient; PMBCL, primary mediastinal large B-cell lymphoma; CRC, colorectal cancer; HCC, hepatocellular carcinoma; RCC, renal cell carcinoma; CSCC, cutaneous squamous cell carcinoma; MCC, Merkel cell carcinoma.

9p occur frequently in bladder, breast, cervical, colorectal, head and neck, and ovarian carcinomas, but are a rare event in pancreatic, renal cell, and papillary thyroid carcinoma. On the other hand, *PD-L1* gene deletions were found to be more frequent than *PD-L1* gains in cancers, especially in melanoma and NSCLC (>50%). Generally, overexpression of PD-L1 frequently occurs in tumors coupled with copy number gains, especially amplification of the *PD-L1* gene. Other studies also revealed high CNAs in classical Hodgkin lymphoma (cHL) and primary mediastinal B-cell lymphoma (48, 49). A recent study showed that the CNAs of *PD-L1* are also prevalent in soft-tissue sarcomas (21.1%), with higher frequency in myxofibrosarcoma (35%) and undifferentiated pleomorphic sarcoma (34%) (50). In contrast, absence or low frequency of CNAs has been reported in lung cancer (51–53) and diffuse large B-cell lymphoma (DLBCL) (54).

In addition to the CNAs, a previous study confirmed that a somatic mutation at a naturally occurring polymorphism locus, rs4143815, in the 3′ untranslated region (3′-UTR) of *PD-L1* gene is correlated with elevated PD-L1 protein expression in gastric cancer (55, 56). Another polymorphism

in the promoter region of *PD-L1* was verified to upregulate *PD-L1* mRNA and protein expression by offering a binding site for transcriptional factor SP1 in gastric cancer (57). The disruption of *PD-L1* 3′-UTR was further confirmed to invariably lead to a marked elevation of aberrant *PD-L1* transcripts. Using whole-genome sequencing, Kataoka et al. (58) identified a novel genetic mechanism termed structural variants for PD-L1 overexpression in adult T cell leukemia/lymphoma (ATL), DLBCL, and gastric adenocarcinoma. These structural variants invariably generate *PD-L1* transcripts with aberrant 3′-UTR, leading to a delayed clearance of the transcripts and elevated PD-L1 expression. Furthermore, expression of 3′-UTR-truncated *PD-L1* transcripts in EG7-OVA cells contributes to tumor immune evasion in a mouse model, which is effectively inhibited by PD-1/PD-L1 blockade. Kogure and Kataoka (59) also reported that structural variants induce PD-L1 overexpression in ATL. More recently, a study in gastric cancer has revealed that *PD-L1* rs2297136 AA+AG genotype, a new polymorphism in 3′-UTR of *PD-L1*, is also correlated with the positive protein expression of PD-L1 (60).

Epigenetic Regulation of PD-L1 Expression in Cancer

DNA methylation and post-translational histone modifications, the most foundational epigenetic events, are central mechanisms in cancer development and progression (61, 62). Both of them contribute to immunosuppressive environment within tumors by manipulating the expression of genes associated with the process of antigen presentation, immune evasion, and T-cell exhaustion (63, 64). Hypomethylating agents and histone deacetylase inhibitors enhance the processing and presentation of tumor-associated antigens and promote the expression of additional immune-related genes, chemokines, and co-stimulatory molecules (65, 66), hence reversing the immune suppression. It suggests that the efficacy of epigenetic agents is dependent, at least in part, on adaptive immune responses. Interestingly, recent studies on the role of epigenetics in immune evasion have identified a role for epigenetic modulators in the upregulation of immune checkpoint. Yang et al. (67) reported that application of hypomethylating agents elevates PD-L1, which is responsible for the resistance of patients to the original treatment. As a corollary, a blockade of the PD-1/PD-L1 axis may be an option to help overcome the resistance. On the other hand, sufficient expression of PD-L1 within tumor microenvironment is the basis for anti-PD-1/PD-L1 therapy. Deficiency of PD-L1 could contribute to "target missing" resistance (68). Treatments leading to the upregulation of PD-L1 within a tumor may sensitize PD-1/PD-L1 checkpoint therapy. Therefore, it is possible that combined application of epigenetic therapies with PD-1/PD-L1 inhibitors will exhibit a synergy antitumor effect through the altered expression of PD-L1, as well as the host immune response.

DNA Methylation

Recent studies suggested that the DNA methylation status of the *PD-L1* promoter can serve as a prognostic biomarker in various malignancies (69–72). There are robust data to support that DNA methylation plays a fundamental role within the dynamic expression of the PD-L1. In melanoma, both the changes in global methylation and the DNA methylation of CpG loci in the *PD-L1* promoter are involved in regulating the expression of PD-L1 (72, 73). Consistently, hypomethylation of the *PD-L1* promoter was found to be inversely correlated with both mRNA and protein expression in HNSCC (74). In glioma, the cancer genome atlas (TCGA) data showed that cytosolic $NADP^+$-dependent isocitrate dehydrogenase 1 (IDH1) mutation tumors represent an attenuated level of PD-L1 expression accompanied by higher *PD-L1* gene promoter methylation (75, 76). Supportively, the addition of 2-hydroxyglutarate, key production of IDH1 mutation, transiently showed efficacy to elevate the DNA methylation in CpG site within *PD-L1* and diminish the expression of PD-L1 (76). Moreover, it was reported that transforming growth factor β1 (TGFβ1) induces decreased expression of DNA methyltransferase 1 (DNMT1) and *PD-L1* promoter demethylation, which subsequently results in PD-L1 overexpression in lung cancer cells undergoing epithelial-mesenchymal transition (EMT) (77). These results spark significant interest in detecting the effect of hypomethylating agents on PD-L1 expression and the combination efficiency of this epigenetic therapy and anti-PD-1/PD-L1 inhibitors. As expected, decitabine, which induces the inhibition of global methylation, upregulates the transcript and protein of PD-L1 in NSCLC cell lines (78). In a study in myelodysplastic syndrome, a high level of PD-L1, PD-L2, PD-1 and cytotoxic T lymphocyte associated antigen 4 (CTLA4) expression was observed in patients treated with decitabine (67). Furthermore, the supplement of decitabine to anti-PD-1 therapy improves the efficiency of antitumor immunity (79, 80). Of note, anti-PD-1 therapy enhanced *PD-L1* promoter methylation was identified to be involved in the resistance to immune checkpoint inhibitor in NSCLC (80).

Histone Modifications

Histone deacetylases (HDACs) have pleiotropic efficiency in regulating immune response (81). HDAC inhibitors have been evaluated as anticancer drugs over the past two decades (82). The role of HDACs in immunotherapies has recently been investigated (65, 83–86). In melanoma, inhibition of HDAC8, a class I histone deacetylase, was proven to elevate the expression of PD-L1 via increasing the activity of a fragment of the *PD-L1* promoter (87). Another study also demonstrated the durable upregulation effect of three class I histone deacetylase inhibitors on PD-L1 due to enhanced histone acetylation of the *PD-L1* gene in melanoma (88). In contrast, Lienlaf et al. (89) have described a negative effect of HDAC6 (a class IIb histone deacetylase) inhibition or depletion on PD-L1 expression, which is mediated by activated signal transducer and activator of transcription 3 (STAT3). Both HDAC6 and STAT3 are recruited to the *PD-L1* gene promoter in melanoma. Consistently, in a study in multiple myeloma, ACY241 (an HDAC6 selective inhibitor) significantly decreases PD-L1 expression on $CD138^+$ myeloma cells in patients (90). In a recent study by Booth et al. (86), two pan-HDAC inhibitors were found to decrease the expression of PD-L1 both *in vitro* and *in vivo*. The authors argued that knockdown of HDAC1 and HDAC2, members of the class I histone deacetylase family, contributes to the reduced expression of PD-L1, but not HDAC6 and HDAC10, which belong to the class IIb histone deacetylase family (86). Discrepancy of HDACs inhibitors in regulating PD-L1 expression was also reported in lung cancer (65, 83, 91).

In addition to HDACs, in a screening for epigenetic mechanisms that regulate PD-L1 expression in pancreatic cancer, histone methylation (H3K4me3) is evident to be enriched in the proximal *CD274* promoter region both *in vitro* and *in vivo*. Chromatin immunoprecipitation (ChIP) analysis revealed that MLL1, one of the H3K4 methylation-specific histone methyltransferases, is directly associated with the *CD274* promoter region. Silencing MLL1 expression dramatically decreases the H3K4me3 level in the *CD274* promoter region, leading to a decreased *PD-L1* mRNA in both human and mouse pancreatic cancer cells (92).

Whilst the regulation of DNA methylation and histone modifications in PD-L1 expression has been explored, a novel epigenetic drug, JQ1, a selective bromodomain inhibitor (BETi), was corroborated to suppress PD-L1 expression in ovarian cancer

to restore cytotoxic T cell responses (93). Another study reported by Hogg et al. (94), corroborated that both constitutive and inducible expression of PD-L1 can be directly repressed at transcriptional level in different tumor cell lines and primary patient samples via decreasing the occupancy of bromodomain and extraterminal protein at the *CD274* locus. Downregulation of PD-L1 plays a crucial role in JQ1 mediated anti-cancer therapy since ectopic expression of PD-L1 blunted the therapeutic effect of JQ1. The role of BET inhibition in modulating PD-L1 expression was further confirmed by Cioffi et al. revealing that OTX015 (a BETi) diminishes the expression of *CD274* via upregulating miR-93 and miR-106b (95). Furthermore, JQ1 in combination with anti-PD-1 antibody enhances antitumor responses in mice bearing Myc-driven lymphomas and KRAS-driven NSCLC (94).

Non-coding RNAs

MicroRNAs (miRs) are a group of small non-coding RNAs known to regulate target genes at the post-transcriptional level (96). Adding to the growing body of evidence, the role of miRs in regulating PD-L1 expression via several mechanisms has been demonstrated. In general, most miRs are negatively correlated with PD-L1 through inducing the degradation or translational repression of *PD-L1* mRNA by direct binding to *PD-L1* 3′-UTR, whereas several miRs are found to be positively connected with PD-L1 expression. For example, MiR-3127-5p and miR-135 are associated with elevated levels of PD-L1 in NSCLC by targeting STAT3 and TRIM16/JAK/STAT, respectively (97, 98). MiR-20b, miR-21, miR-130b, and miR-142-5P induce PD-L1 overexpression via inhibiting phosphatase and tensin homolog (PTEN) (99, 100). The detailed information for miR-mediated PD-L1 regulation is delineated in **Table 2** (95, 97–128).

Moreover, the profiled miRs in serum from NSCLC patients uncover seven miRs (miR-215-5p, miR-411-3p, miR- 493-5p, miR-494-3p, miR-495-3p, miR-548j-5p, miR-93-3p) strongly associated with overall survival after treatment with the immune checkpoint inhibitor, nivolumab (129). In addition, a study in CRC highlights the role of circular RNA in accommodating PD-L1 expression, revealing that circular RNA has_circ_0020397 promotes the expression of PD-L1 by inhibiting miR-138 activity (130). More importantly, a very recent study has identified miR-146a as a comparable immune checkpoint molecule in melanoma, and a miR-146a antagomiR combined with anti-PD-1 enhances the anti-tumor effect of anti-PD-1 therapy, suggesting that miRNAs may be a novel combination target for immune checkpoint therapy (131).

Extrinsic Control of PD-L1 Expression
Virus Infection and Inflammatory Signaling

Although a generalized conclusion for PD-L1 expression in virus infection remains uncertain as comparable levels of PD-L1 were detected in individuals with or without infection (74, 132–134), escalated PD-L1 levels were shown to be connected with specific viruses, such as Epstein-Barr virus (EBV) (135–139), hepatitis B viral (HBV) (114, 140, 141), hepatitis C virus (HCV) (142–146), human immunodeficiency virus (HIV) (132, 147–150), human papilloma virus (HPV) (135, 151–155), Merkel

cell polyomavirus (MCPyV) (156), bovine leukemia virus (BLV) (157), and Kaposi sarcoma-associated herpes virus (KSHV) (158). The pathobiological mechanisms by which viruses trigger the expression of PD-L1 were revealed. Pathogen associated molecular patterns (PAMPs) stemming from a pathogen (for example virus, bacteria, and fungi) activate toll like receptors (TLRs) to initiate the immune response and protect the host against pathogens infection. TLR agonists-induced synthesis of PD-L1 has been observed in a variety of cell types (159–164). PAMPs from EBV was reported to induce PD-L1 upregulation in a TLR-dependent manner (136, 165, 166). Similarly, HIV stimulates PD-L1 expression on APC via TLR signaling or in an indirect manner by increasing the production of cytokines (149, 150). Several downstream signaling pathways activated by virus infection, such as JAK/STAT, MAPK, and NF-κB signaling, are involved in both TLR agonists- and virus infection-mediated regulation of PD-L1 (114, 137, 138, 159, 161, 166), further supporting the notion that TLR signaling serves as an effector for the induction of PD-L1 upon virus infection. TLRs-independent induction of PD-L1 in virus infection was also uncovered (114, 139, 148). For an example, amplification of *PD-L1* gene, a major cause of PD-L1 overexpression, was observed in EBV-positive gastric tumors (139).

Persistent infections of pathogens lead to chronic inflammation via promoting the secretion of inflammatory cytokines. Pro-inflammatory molecules or cytokines, such as IFN-γ, IFN-α, IFN-β, TNF-α, EGF, IL-17, IL-4, and IL-27 have been reported to induce PD-L1 expression in tumors (167–175). Among them, IFN-γ is the most potent inducer of PD-L1. Upregulation of PD-L1 by IFN-γ has been extensively described in diverse cell types (31, 168, 176–179). PD-L1, largely induced locally at the tumor by tumor-infiltrating lymphocytes (TILs)-derived IFN-γ, which are termed adaptive immune resistant, was first reported in melanomas by Taube et al. (180) and Abiko et al. (181). JAK/STAT and NF-κB pathways are the main downstream signals in the inflammation for IFN-γ-induced PD-L1 expression (170, 182–184). Another transcriptional mechanism is used for controlling the expression of PD-L1 by IFN-γ in melanoma and medulloblastoma, in which activation of JAK/STAT signal increases the expression of a series of transcription factors named the interferon-responsive factors (IRFs) (182, 185). Likewise, TNF-α, another pro-inflammatory cytokine, upregulates PD-L1 expression via TNF-α-NF-κB pathway (167, 170, 172, 186). Furthermore, TNF-α was reported to synergistically act with IFN-γ to induce PD-L1 expression at both mRNA and protein levels and enhance the adaptive immune resistance mediated by IFN-γ-induced PD-L1 in hepatocellular carcinoma cells via upregulating the expression of IFN-γ receptors (187).

Transforming Growth Factor β (TGF-β)

TGF-β, which is generally considered as an anti-inflammatory cytokine, plays a paradox role in cancer. High levels of TGF-β render tumor cells capable of escaping immune surveillance (188–190). It was recently reported that TGF-β elevated PD-L1 expression. In lung cancer, TGF-β-mediated EMT facilitates PD-L1 expression through an epigenetic mechanism (77, 191, 192). Consistently, TGF-β-induced EMT

TABLE 2 | microRNAs regulate PD-L1 expression.

miR	Cell types	Regulation of PD-L1	Targets	References
miR-106b	PDAC	−	−	(95)
miR-130b	CRC	+	PTEN	(99)
miR-135	NSCLC	+	TRIM16/JAK/STAT	(98)
miR-138-5p	CRC	−	3′-UTR	(101)
miR-140	NSCLC	−	3′-UTR	(102)
miR-140	Osteosarcoma	−	3′-UTR	(103)
miR-140	Cervical cancer	−	3′-UTR	(104)
miR-142	Cervical cancer	−	3′-UTR	(104)
miR-142-3p	Macrophage, DC	+	−	(105)
miR-142-5p	PDAC	−	3′-UTR	(106)
miR-142-5p	NSCLC	−	PTEN/Pl3K/Akt	(100)
miR-15a	MPM	−	3′-UTR	(107)
miR-155	HDLEC & DF	−	3′-UTR	(108)
miR-16	MPM	−	3′-UTR	(107)
miR-16	Macrophage	−	3′-UTR	(109)
miR-17-5p	Melanoma	−	3′-UTR	(110)
miR-18a	Cervical cancer	+	PI3K/AKT MEK/ERK Wnt/β-catenin/STAT3 P53/miR-34a	(104)
miR-193a-3p	MPM	−	3′-UTR	(107)
miR-195	DLBCL	−	3′-UTR	(111)
miR-197	OSCC	−	−	(112)
miR-197	NSCLC	−	STAT3	(113)
miR-20b	CRC	+	PTEN	(99)
miR-200c	HCC	−	3′-UTR	(114)
miR-200c	AML	−	3′-UTR	(115)
miR-200c	NSCLC	−	3′-UTR	(116)
miR-21	Macrophage	−	JAK2/STAT1	(117)
miR-21	CRC	+	PTEN	(99)
miR-217	Laryngeal cancer	−	Translation	(118)
miR-24	Macrophage, DC	+	−	(105)
miR-30b	Macrophage, DC	+	−	(105)
miR-3127-5p	NSCLC	+	STAT3	(97)
miR-33a	LA	−	3′-UTR	(119)
miR-34	NSCLC	−	3′-UTR	(120)
miR-34a	Glioma	−	3′-UTR	(121)
miR-34a	AML	−	3′-UTR	(115, 122)
miR-340	Cervical cancer	−	3′-UTR	(104)
miR-375	HNSCC	−	JAK2/STAT1	(123)
miR-383	Cervical cancer	−	3′-UTR	(104)
miR-424(322)	Ovarian	−	3′-UTR	(124)
miR-513	Cholangiocytes	−	3′-UTR	(125, 126)
miR-513a-5p	Retinoblastoma	−	3′-UTR	(127)
miR-574-3p	Chordoma	−	−	(128)
miR-93	PDAC	−	−	(101)

−, negative; +, positive; PDAC, pancreatic ductal adenocarcinoma; CRC, colorectal cancer; NSCLC, non-small cell lung cancer; DC, dendritic cell; MPM, malignant pleural mesothelioma; HDLEC, human dermal lymphatic endothelial cell; DF, dermal fibroblasts; DLBCL, diffuse large B-cell lymphoma; OSCC, oral squamous cell carcinoma; HCC, hepatocellular carcinoma; AML, acute myeloid leukemia; LA, lung adenocarcinoma; HNSCC, head and neck squamous cell carcinomas; PTEN, phosphatase and tensin homolog; TRIM16, tripartite-motif 16; JAK, Janus kinase; STAT, signal transducer and activator of transcription; 3′-UTR, 3′ untranslated region; PI3K, phosphatidylinositol 3 kinase; AKT, protein kinase B; MEK, MAPK/ERK kinase; ERK, extracellular regulated protein kinases; P53, protein 53.

was recently revealed to promote PD-L1 expression by post-translational modification. EMT transcriptionally upregulates N-glycosyltransferase STT3 through β-catenin, and STT3 further glycosylates and stabilizes PD-L1 (193). In the mouse model of pancreatic islet transplantation, TGF-β was found to be necessary for the sustained expression of PD-L1 on CD8$^+$ T cells via autocrine (194). These findings highlight that the role of TGF-β in the regulation of PD-L1 may possibly account for the link between TGF-β and immune evasion.

In addition, TGF-β shapes the tumor microenvironment to restrain antitumor immunity by restricting T cell infiltration and attenuating the efficacy of PD-L1 blockade antibody. TGF-β inhibitor and PD-L1 blockade together provoke vigorous antitumor immune response and tumor regression (189, 190). M7824, a novel bifunctional anti-PD-L1/TGF-β with a soluble extracellular domain of TGF-β receptor II, elicits potent and superior antitumor activity in preclinical and clinical studies (195–197).

Hypoxia

Hypoxia, an inevitable outcome due to the abnormal vasculature and a huge mass of tumor, is represented as a hallmark of a tumor microenvironment. Under the hypoxic environment, tumor cells survive themselves by reprogramming the gene expression through activating a series of hypoxia-inducible factors (HIFs). Among these HIFs, HIF-1α, and HIF-2α are the most important transcript factors responsive to hypoxia, leading to the adaption to the stress (198, 199). Hypoxia signaling represents an important pathway in immune evasion (200–202). Hypoxia markedly induces the expression of PD-L1 on the surface of myeloid-derived suppressor cells (MDSCs), macrophages, DCs, monocytes, and tumor cells (201, 203, 204). Exposure of human or murine cancer cells to hypoxia leads to the upregulation of PD-L1, which induces T cell apoptosis in a HIF-1α-dependent manner. Furthermore, blocking the accumulation of HIF-1α in hypoxic cells by glyceryl trinitrate prevents hypoxia-induced PD-L1 expression (201). In another study, inhibiting HIF-1α through gene knockdown or PX-478 treatment also strikingly attenuates the elevation of PD-L1 induced by $CoCl_2$ (a hypoxia-mimic treatment) (205). Likewise, PD-L1 overexpression on monocytes is induced both *in vitro* and *in vivo* models of intermittent hypoxia, and by *HIF-1α* gene transfection (204). Moreover, HIF-1α was demonstrated to translocate into the nucleus and drive PD-L1 expression in human monocytes during endotoxin tolerance (206). Direct binding of HIF-1α to the promoter of *PD-L1* via hypoxia response element (HRE) has been unveiled in MDSCs by ChIP and luciferase reporter assay (203). Collectively, PD-L1 expression is regulated by HIF-1α in monocytes and tumor cells, including melanoma cells, breast cancer, prostate cancer, and lung cancer cells (201, 203, 204, 207). However, in clear cell renal cell carcinoma (ccRCC), cells with VHL (a component of oxygen and iron sensing pathway that regulates the HIF) mutation, HIF-2α, rather than HIF-1α, is specifically able to induce PD-L1 expression (208). The association between HIF-2α and PD-L1 was further verified in ccRCC by Messai et al. (209), where a direct binding of HIF-2α to a transcriptionally active HRE in human PD-L1 proximal promoter was revealed.

Angiogenesis in solid tumors is a multiple biological process that is induced by the overexpression of pro-angiogenic factors in the environment to support the tumor cell growth. However, in contrast to the vasculature of normal tissues, tumor vessels are usually twisted and disorganized accompanied with a reduced blood perfusion and oxygenation. Normalization of tumor vasculature with an appropriate dose of anti-angiogenic treatment, primarily through disruption of the VEGF/VEGFR axis, is able to reduce tissue hypoxia and reprogram the tumor microenvironment from immunosuppressive to immunoactive (210, 211). Remarkably, PD-L1 expression is positively correlated with VEGF and microvessel density in patients with uniformly treated cHL (212). Considering that hypoxia is capable of inducing PD-L1 expression, addition of anti-angiogenic reagent to PD-1/PD-L1 antibodies is likely to sensitize immune checkpoint therapy. This conjecture has been verified in both animals and human beings. For example, a preclinical study showed that combined anti-VEGF/anti-PD-L1 targeted therapy synergistically improves the treatment outcome, compared to both anti-PD-L1 or anti-VEGF monotherapy in an autochthonous mouse model of small cell lung cancer (SCLC) (213). Similarly, preliminary results from a phase III study (NCT02366143), which evaluated the efficacy of bevacizumab (the first anti-angiogenic drug) plus atezolizumab plus chemotherapy, bevacizumab plus chemotherapy, and atezolizumab plus chemotherapy in non-squamous NSCLC, has also revealed superior outcomes in patients receiving the first treatment (214). Choueiri et al. (215) recently reported a phase Ib trial based on avelumab plus axitinib, a VEGF receptor inhibitor as first-line therapy in patients with advanced ccRCC (NCT02493751). McDermott et al. (216) performed a phase II study of atezolizumab alone or combined with bevacizumab vs. sunitinib in treatment-naive metastatic RCC, and the preliminary data on antitumor activity are encouraging. A phase III trial assessing avelumab and axitinib compared with sunitinib monotherapy for first-line treatment of advanced RCC is ongoing (NCT02684006).

Previous Treatments

Radiation and conventional antineoplastics that are currently used for cancer therapy, such as chemotherapeutic drugs and epigenetic modifiers, may promote immunogenic cell death via introducing DNA damage. Importantly, it is increasingly evident that conventional radiotherapies and chemotherapies, as well as novel epigenetic modifiers and targeted anticancer agents cannot only induce tumor regression by triggering immunogenic death of tumor cells, but also result in tumor progression by dysregulating the immune system, including changes within inhibitory molecules across a wide range of malignancies. Radiation and a number of chemotherapy drugs induce PD-L1 expression through different mechanisms, which are likely responsible for the loss of antitumor immunity and acquired resistance (217, 218). Remarkably, the PD-1/PD-L1 pathway blockade reverses adaptive immune resistance and maintains the antitumor immunity (219–221). Of note, although radiation and most chemotherapies enhance PD-L1 expression upon most occasions, inconsistent results were also obtained. The detailed

information and involved signal pathways are listed in **Table 3** (67, 78, 113, 122, 127, 193, 217, 220–255).

In addition to the genotoxicity therapy aforementioned, the correlations between PD-L1 expression and target therapy, as well as immunotherapy, were also documented. For example, epidermal growth factor receptor (EGFR), a commonly mutated oncogene in NSCLC, was reported to be associated with PD-L1 upregulation (256). Treatment with EGFR tyrosine kinase inhibitors (EGFR-TKIs) results in the downregulation of PD-L1 (240, 256, 257). In parallel, application of BRAF and MEK inhibitors is also associated with decreased PD-L1 expression (258). Interestingly, PD-L1 expression is upregulated through both JUN and STAT3 after acquiring resistance to BRAF inhibition in the cells (258, 259), and hence, the expression level of PD-L1 may serve as a biomarker for predicting the probability of response to the inhibitors (260). Different from EGFR and BRAF inhibitors, sorafenib, a multi-target antitumor drug, increases PD-L1 expression through inducing tumor hypoxia (261). Furthermore, several immunotherapies were found to upregulate PD-L1 expression (262, 263). Rice et al. (262) revealed an increase in PD-L1 expression on tumor cells during an HPV-E6/E7 immunotherapy. While the increased expression of PD-L1 is blunted and even reversed when combined with anti-PD-1 antibody, as a reduction in tumor PD-L1 expression was observed. These observations imply a role of anti-PD-1 therapy for regulating PD-L1. What's more, the dynamic change of PD-L1 expression on circulating tumor cells in advanced solid tumor patients undergoing PD-1 blockade therapy might serve as a predictor to indicate the therapeutic response at an early time (264). Collectively, these studies may open up new avenues for developing rational combination of cancer therapeutics in various solid tumors.

Intrinsic Control of PD-L1 Expression

Abnormal signal transductions induced by intrinsic oncogenic activation or loss of tumor suppressor can both regulate PD-L1 expression at various levels.

Oncogenic Signaling

Apart from the reports described above, the intrinsic cellular changes associated with PD-L1 expression have attracted much attention because such explorations can not only expand the investigation in regulatory mechanism of PD-L1, but also direct the concomitant use of immune checkpoint therapies and target therapies for optimizing clinical outcomes. Oncogenic signaling stemming from aberrant transcription factors, effectors and upstream receptors can regulate the expression of PD-L1.

A number of oncogenic transcription factors, such as MYC, AP-1, STAT, IRF1, HIF, and NF-κB, were reported to individually or cooperatively promote PD-L1 expression at the transcriptional level. MYC, a transcription factor governing a large number of gene expressions, plays a vital role in tumorigenesis through its multiple effects on tumor cells, typically by controlling cell proliferation and survival, and elevated expression of MYC was found in approximately 70% of human cancers (265). A recent study by Casey et al. (266) revealed a novel role of

MYC in cancer immunosurveillance. MYC binds to the *PD-L1* promoter transcriptionally regulating PD-L1 expression. Similarly, transient transfection with MYC plasmids upregulates PD-L1 in anaplastic large-cell lymphoma (ALCL) cells with low endogenous PD-L1 (267). In line with these observations, both pharmacological inhibition and geneticsilencing of MYC reduce PD-L1 expression in tumor cells (266–268). Moreover, a very recent study revealed a translational mechanism of MYC-mediated PD-L1 upregulation by bypassing the repressive effect of non-canonical upstream open reading frames in the 5′ untranslated region of PD-L1 on its translation (269). Of note, the translational inhibitor, eFT508, possesses a potent inhibitive effect on the cancer progression and metastasis by targeting PD-L1 mRNA translation, disclosing a new strategy for immunotherapy in PD-1/PD-L1 axis blocking.

AP-1 is a dimeric transcription factor comprised of Jun, Fos, and ATF protein families (270). As the best-known member of the AP-1 family, c-Jun is implicated in PD-L1 expression. An increased expression of PD-L1 was found in BRAF inhibitor-resistant melanoma cells. Knockdown of c-Jun results in a reduction of PD-L1 expression (259). AP-1 binding sites were identified in the first intron of *PD-L1*, and c-Jun and JUNB have been shown to be recruited to the *PD-L1* promoter (138, 271). Co-activation of STAT3 with c-Jun further enhances the transcriptional activity of PD-L1 (272, 273). Accordingly, concurrent knockdown of STAT3 and c-Jun contributes to a synergistic downregulation of PD-L1 (259). Not surprisingly, activated STAT3 alone can also increase PD-L1 expression by directly acting on the promoter of *PD-L1* in HNSCC and lymphoma cells (267, 274, 275), and STAT3 silencing leads to the downregulation of PD-L1 in ALK-negative ALCL cells and KRAS-mutant NSCLC cells (267, 271). As previously described, STAT1 and IRF1/7, downstream effectors of STAT1, can also induce PD-L1 expression (79, 169, 276). Similarly, HIF-1α and HIF-2α transcriptionally facilitate PD-L1 expression by binding to the HRE of its promoter (203, 209). Moreover, the interaction between STAT3 and HIF-1 involves in the regulation of HIF target genes. Inhibition of STAT3 decreases the expression of HIF-1 target genes in MDA-MB-231 and RCC4 cells (277), indicating a potentially cooperative effect for STAT3 and HIF-1 in regulating PD-L1. Binding of the RELA/p65-MUC1-C complex on the promoter of *PD-L1* was observed in NSCLC (278), suggesting that NF-κB may directly regulate PD-L1 transcription. Besides the above transcription factors, recent work have verified nuclear factor E2-related transcription factor 2 (NRF2) as an upstream transcriptional activator of PD-L1 in human primary keratinocytes and melanocytes after ultraviolet-B irradiation, and depletion of NRF2 significantly increases T cells infiltration in the tumors and suppresses melanoma progression (234).

Oncogenic signaling initiated by activating mutations or amplification in receptor tyrosine kinases plays an important role in regulating PD-L1. The MEK-ERK pathway is commonly activated by mutations in RAS GTPase, BRAF, and EGFR (279), and there are now abundant data suggesting that MEK-ERK signaling upregulates PD-L1 expression. Coelho et al. (280) revealed that RAS stabilizes *PD-L1* mRNA and upregulates cell-intrinsic PD-L1 expression via phosphorylation

TABLE 3 | Alteration of PD-L1 expression by previous treatments.

Therapeutic	Category/dose	Tumor type	PD-L1 expression	Targets	References
IR	10 Gy	Breast cancer	+	−	(222)
IR	10 Gy	Breast cancer	+	IFN-γ	(223)
IR	12 Gy	Breast cancer	+	−	(224)
IR	10 Gy	CRC	+	IFN-γ	(223)
IR	4 Gy/8G y	Glioma	+	−	(225)
IR	5 Gy/10 Gy	Glioma	+	EGFR/JAK2	(226)
IR	45 Gy/60 Gy	HCC	+ (sPD-L1)	−	(227)
IR	2 Gy	HNSCC	+	AXL-PI3K	(217)
IR	10 Gy	HNSCC	+	−	(228)
IR + chemotherapy	−	HNSCC	+	IL-6/STAT3	(229)
IR	10 Gy	Lung cancer	+	ATM/ATR/Chk1 STAT1/STAT3-IRF-1	(230)
IR	6 Gy × 1 − 6 Gy × 4	NSCLC	+	IL-6-MEK/ERK	(231)
IR	10 Gy	Melanoma	+	IFN-γ	(223)
IR	10 Gy	Osteosarcoma	+	ATM/ATR/Chk1 STAT1/STAT3-IRF-1	(230)
IR	−	PDAC	+	JAK/STAT1	(232)
IR	10 Gy	Prostate cancer	+	ATM/ATR/Chk1 STAT1/STAT3-IRF-1	(230)
IR	50 - 50.4 Gy	Sarcoma	+	−	(233)
UVR	100 J/m^2	HPKs/HPMs	+	NRF2	(234)
Arsenic trioxide	Undefined cytoxin	AML	+	MiR-34a	(122)
Azacytidine	DNMTi	NSCLC	+	−	(78)
Carboplatin	Alkylating agent	Ovarian cancer	+	JAK/STAT, antiviral defense	(235)
Carboplatin + paclitaxel	Alkylating agent + Antimicrotubule	Lung cancer	NC	−	(236)
Cisplatin	Alkylating agent	Hepatoma	+	MAPK/ERK	(237)
Cisplatin	Alkylating agent	HNSCC	+	IL-6/STAT3	(220)
Cisplatin	Alkylating agent	HNSCC	+	−	(238)
Cisplatin	Alkylating agent	HNSCC	+	MAPK/ERK	(239)
Cisplatin	Alkylating agent	Lung cancer	NC	−	(240)
Cisplatin	Alkylating agent	NSCLC	+	FASN/TGF-β1	(241)
Cisplatin	Alkylating agent	NSCLC	+	Akt, NF-κB p65	(221)
Cisplatin	Alkylating agent	NSCLC	+	PI3K/Akt	(242)
Cisplatin	Alkylating agent	SCLC	+	DNMT1,KIT	(243)
Cisplatin	Alkylating agent	NHL	+	ERK,GM-CSF	(244)
Cisplatin	Alkylating agent	Ovarian cancer	+	−	(245)
Cisplatin + gemcitabine	Alkylatingagent + Antimetabolite	Lung cancer	−	−	(236)
Decitabine	DNMTi	Myelodysplastic syndromes	+	−	(67)
Doxorubicin	Topoisomerase inhibitor	Breast cancer	− (surface) + (nuclear)	PI3K/Akt	(246)
Doxorubicin	Topoisomerase inhibitor	NHL	+	ERK,GM-CSF	(244)
Epirubicin	Topoisomerase inhibitor	Breast cancer	−	−	(247)
Etoposide	Topoisomerase inhibitor	Breast cancer	+	−	(248)
Etoposide	Topoisomerase inhibitor	Breast cancer	−	EMT/β-catenin/STT3	(193)
Etoposide	Topoisomerase inhibitor	CSCs	−	EMT/β-catenin/STT3	(193)
Etopside	Topoisomerase inhibitor	NHL	+	ERK,GM-CSF	(244)
Etoposide	Topoisomerase inhibitor	Retinoblastoma	+	MiR-513a-5p	(127)

(Continued)

TABLE 3 | Continued

Therapeutic	Category/dose	Tumor type	PD-L1 expression	Targets	References
Gemcitabine	Antimetabolite	Pancreatic cancer	+	JAK/STAT1	(232, 249)
Oxaliplatin	Alkylating agent	CRC	+	IFN-γ	(250)
Oxaliplatin	Alkylating agent	NHL	+	ERK,GM-CSF	(244)
Oxaliplatin	Alkylating agent	Prostate cancer	+	TGF-β	(251)
Paclitaxel	Antimicrotubule	Breast cancer	+	–	(247, 248)
Paclitaxel	Antimicrotubule	CRC	+	ERK1/2	(251)
Paclitaxel	Antimicrotubule	HCC	+	ERK1/2	(251)
Paclitaxel	Antimicrotubule	Ovarian cancer	+	NF-κB	(252)
Paclitaxel	Antimicrotubule	Pancreatic cancer	+	JAK2/STAT1	(249)
Platinum	Alkylating agent	NSCLC	+	MiR-197/CKSIB/STAT3	(113)
Trabectedin	Undefined cytoxin	Ovarian cancer	+	IFN-γ	(253)
Vincristine	Alkaloid	NHL	+	ERK,GM-CSF	(244)
Vinorelbine tubulin inhibitor	Antimicrotubule	Lung cancer	–	EMT	(240)
5-Fluorouracil	Antimetabolite	Breast cancer	+	–	(248)
5-Fluorouracil	Antimetabolite	CRC	+	–	(254)
5-Fluorouracil	Antimetabolite	Esophageal adenocarcinoma	+	–	(254)
5-fluorouracil	Antimetabolite	Pancreatic cancer	+	JAK2/STAT1	(249)

−, negative; +, positive; NC, not change; IR, irradiation; UVR, ultraviolet radiation; CRC, colorectal cancer; HCC, hepatocellular carcinoma; HNSCC, head and neck squamous cell carcinomas; NSCLC, non-small cell lung cancer; PDAC, pancreatic ductal adenocarcinoma; HPKs, human primary keratinocytes; HPMs, human primary melanocytes; AML, acute myeloid leukemia; SCLC, small cell lung cancer; NHL, non-Hodgkin's lymphoma; CSCs, cancer stem-like cells; sPD-L1, soluable programmed death ligand-1; IFN-γ, interferon-γ; EGFR, epidermal growth factor receptor; JAK2, Janus kinase 2; AXL, tyrosine-protein kinase receptor UFO;IL-6, interleukin-6; STAT3, signal transducer and activator of transcription 3; ATM, ataxia telangiectasia mutated; ATR, ataxia telangiectasia and Rad3-related protein; IRF-1, interferon-responsive factor 1; NRF2, nuclear factor E2-related transcription factor 2;MAPK, mitogen-activated protein kinase; ERK, extracellular signal-regulated kinase; EMT, epithelial-mesenchymal transition; FASN, fatty acid synthase; TGFβ1, transforming growth factor β1; Akt, protein kinase B; NF-κB, nuclear factor kappa B; PI3K, phosphatidylinositol 3 kinase; DNMT1, DNA methyltransferase 1; KIT, receptor tyrosine kinase; GM-CSF, granulocyte macrophage colony-stimulating factor; CKS1B, CDC28 protein kinase regulatory subunit 1B.

and inhibition of the adenylate-uridylate-rich element-binding protein, tristetraprolin, in a p38 MAPK-dependent manner. Furthermore, MAPK signaling is responsible for the increased expression of PD-L1, since inhibition of MEK or ERK partially offset the ectopic expression of PD-L1 in both mouse and human KRAS-mutant lung cancer cells (271, 280, 281). However, in contrast to the positive relationship between MEK-ERK signaling and PD-L1 expression observed in most studies, MEK inhibitors are unable to change the PD-L1 expression in melanoma (282), and even increase the levels of PD-L1 in breast cancer and NSCLC cells (283, 284). Similarly, in BRAF mutation melanoma cells, which acquire resistance to BRAF inhibition, constitutive PD-L1 is elevated through cooperative activation of Jun (a primary target of MAPK signaling) and STAT3 (259). Induction of PD-L1 is dependent on MAPK activation in EGFR mutant NSCLC. Suppression of ERK1/2/c-Jun results in reduced PD-L1 expression (285). Evidences also imply the role of p65, AKT/STAT3, and JAK2/STAT1 as mediators in the regulation PD-L1 expression by EGFR signaling (168, 286, 287). Moreover, the increased PD-L1 expression upon EGFR activation is also mediated by the AKT-mTOR pathway, inhibition of which (with rapamycin) abolishes the increased expression of PD-L1 upon EGFR activation through increasing lysosomal protein degradation (174). Remarkably, although EGFR activation was shown to increase PD-L1 expression

through multiple signal pathways, a controversial correlation between EGFR activation mutations and PD-L1 expression was observed in NSCLC patients (256, 288–290), which may be attributed to the complicated regulation of PD-L1 expression (inducible and constitutive) *in vivo*. Therefore, despite how EGFR mutations upregulate the constitutive expression of PD-L1 in tumor cells, the concomitant shortage of activated tumor infiltrating lymphocytes in EGFR-mutated NSCLC (291, 292) may weaken the inducible PD-L1 expression. Recent studies have shielded light on the divergent effect of various subtypes of EGFR mutations on PD-L1 expression and the response to immune checkpoint therapy (293, 294). Thus, the discrepancies in PD-L1 expression caused by EGFR mutations may also result from the undistinguished subtypes of EGFR mutations.

The PI3K-AKT-mTOR signaling is another oncogenic pathway involved in constitutive regulation of PD-L1, which can both be activated by *PIK3CA* mutation and functional loss of PTEN (a negative regulatory of PI3K-AKT signaling) (295). In human glioma and CRC cells, loss of PTEN activates PI3K signaling, which leads to an elevation of PD-L1 expression (296, 297). A positive correlation between *PIK3CA* mutation and PD-L1 expression in squamous cell lung carcinoma was also revealed (298). Nevertheless, similar to the MEK inhibition, the influence of PI3K/AKT inhibition on PD-L1 expression varies in tumor cells and the mechanism is largely unknown

(299). Phosphorylation activation of S6K1 or inhibition of eIF4E-binding proteins (4E-BP, a negative regulator for eIF4E), which serve as the downstream effect for the activation of PI3K-AKT-mTOR pathway, are involved in the promotion of protein synthesis. Overexpression of S6K1, but not eIF4E, restores the translational efficiency of PD-L1, which is inhibited by ectopic expression of PTEN in U87 cells (a glioma cell lines with no PTEN expressed) through increased recruitment of PD-L1 transcript to the polysome. In line with this finding, rapamycin, an mTOR inhibitor, was shown to pose as an obstacle for polysomal component recruitment in PD-L1 transcripts (296). Interestingly, in a recent study carried out by Cerezo et al. (299), inhibition of eIF4F complex (consisting eIF4A, eIF4E, and eIF4G subunits) was shown to upregulate IFN-γ-induced PD-L1 expression by thwarting the translation of *STAT1* mRNA in melanoma, and the upstream regulator for the signaling remains to be identified. Additionally, NPM-ALK or EML4-ALK fusion protein constitutively activates ALK kinase and promotes PD-L1 expression via MEK-ERK and PI3K-AKT signaling pathways (300, 301).

Yes-associated protein/WW domain-containing transcription regulator 1 (YAP/TAZ), the well-known effectors in the Hippo pathway, are commonly dysregulated in cancers (302). Overexpression of YAP/TAZ has been found in many cancers due to abnormal amplification, loss of Hippo signaling by mutation, and/or downregulation of the core Hippo component (303). Recent publications supported the notion that YAP/TAZ emerges as a pivotal player in tumor immunity by regulating PD-L1 expression. YAP/TAZ interacting with the *PD-L1* promoter through the TEA domain transcription factor (TEAD) family of transcription factors enhances PD-L1 at the transcriptional level in human malignant pleural mesothelioma, melanoma, breast and lung cancer cells (304–309). Furthermore, in tumor tissues of NSCLC and melanoma, immunohistochemistry showed significantly positive staining for YAP and PD-L1 (305, 307). The role of the Hippo pathway in upregulating PD-L1 was further confirmed in breast and lung cancer cells as mammalian STE20-like kinase 1 and 2 (MST1/2) and large tumor suppressor 1 and 2 (LATS1/2), upstream kinases and inhibitors of canonical Hippo pathway are shown to suppress PD-L1 expression (306).

The Role of Tumor Suppressors

In addition to the involvement of oncogenes in the regulation of PD-L1, tumor suppressors also play a role in controlling PD-L1 expression. *Tp53*, also known as p53, is a well-known tumor suppressor and commonly mutated in cancer (310). As a transcription factor, p53 regulates the expression of numerous downstream target genes involved in cell cycle progression, cell death, and metabolism (311, 312). Increasing evidence for p53 in regulating immune responses made it intriguing for researchers (313, 314). P53 regulates immune responses by targeting immune checkpoints, including PD-L1. The effect of p53 on PD-L1 expression is likely to be mediated by several p53-regulated miRNAs. Cortez et al. (120) revealed that p53 decreases PD-L1 expression via upregulating miR-34 in NSCLC. A recent study showed that the miR-200 family, another miRNA cluster regulated by p53 (315), downregulates

PD-L1 by directly targeting 3′-UTR in HCC, AML and NSCLC cells (114–116). In addition, p53 and PD-L1 expression are inversely correlated in hepatocellular carcinoma and NSCLC patients (120, 316). Coincidently, inactive mutation of p53 is associated with elevated PD-L1 level in lung adenocarcinoma and ovarian cancer (317–319). However, paradoxical results were also found by researchers, indicating an ambivalent role of p53 in PD-L1 regulation. MiR-18a increases PD-L1 levels by targeting SOX6 (p53 pathway activator) to inhibit p53 signaling in cervical cancer (104), and nutlin-3a, a small molecule activator of wild-type p53, enhances the expression of PD-L1 in breast cancer (320). Moreover, a high rate of PD-L1 expression was observed in p53-positive primary pulmonary lymphoepithelioma-like carcinoma patients, compared to the p53-negative group (321).

Tumor suppressor gene *PTEN* is one of the most frequently mutated genes in human cancers (322). PTEN acts as a tumor suppressor through the action of its phosphatase protein product, which catalytically dephosphorylates phosphatidylinositol(3,4,5)-trisphosphate (PIP3) converted to phosphatidylinositol(4,5)bisphosphate (PIP2) (323). The enzymatic activity of PTEN further modulates PD-L1 expression through the PI3K/AKT pathway (174, 296, 297, 324). In these studies, loss or knockdown of PTEN leads to the activation of the PI3K/AKT pathway, and hence, upregulation of PD-L1. In glioma, loss of PTEN function upregulates PD-L1 expression at the translational level through AKT-mTOR-S6K1 signal axis (296). In CRC, miR-20b, miR-21, and miR-130b inhibit PTEN, resulting in PD-L1 overexpression (99). A similar effect of miR-18a was revealed in cervical cancer (104). In contrast to the findings in CRC and cervical cancer, miR-142-5p was reported to promote antitumor immunity in NSCLC by suppressing PD-L1 protein expression via the PTEN pathway (100). Loss of PTEN cytoplasmic expression is related to lower PD-L1 expression in DLBCL with AKT hyperactivation (325), suggesting that mechanisms unrelated to AKT may also be involved in PD-L1 expression in cells with different PTEN status.

Strikingly, concurrent *TP53* and *PTEN* deletion facilitates the formation of undifferentiated pleomorphic sarcomas, with elevated PD-L1 expression, that induced immune tolerance in C57BL/6J mice (326). Simultaneous loss of *PTEN* and *LKB1* (a tumor suppressor, also known as serine-threonine kinase 11) contributes to the development of murine lung squamous cell carcinoma with higher PD-L1 expression, while PD-L1 in the tumor is not induced by individual deficiency of either *PTEN* or *LKB1* (327). Likewise, concomitant knockout of Kelch-like ECH-associated protein 1 (*KEAP1*) and *PTEN* in the mouse lung promotes the occurrence of adenocarcinoma with altered immune microenvironment exhibiting increased expression of PD-L1 (328). Tumor suppressor candidate 2 (TUSC2, also known as FUS1) represents another suppressor in controlling PD-L1 by recent work. TUSC2 overexpression was observed to decrease PD-L1 expression and associate with an immunologic response (329, 330). TUSC2 was shown to negate the kinase activity of EGFR, AKT, and mTOR according to previous studies (331, 332). Indeed, the reduction of PD-L1 expression

in NSCLC cell lines by TUSC2 is likely due to reduced mTOR activity (330).

The retinoblastoma protein (RB), a well-acknowledged tumor suppressor, acts as a multifunctional protein to regulate various aspects of cellular activities and tumor development (333, 334). Transcription factor E2F1 is a major target for RB to exhibit its tumor suppression efficacy, un- or hypo-phosphorylated RB binds to E2F1, leading to the inhibited expression of E2F1 target genes and arrested G1/S cell cycle transition. However, during a normal cell cycle, RB transforms into hyperphosphorylated status, mediated by cyclin/CDK complexes such as CYCLIN D/CDK4/6 in the late G1 phase, which contributes to the release of E2F1 and advance of the cell cycle (335). Interestingly, an E2F1-independent tumor suppression effect of phosphorylated RB has been unveiled by Jin et al. (336), and it is said that CDK4/6 mediated phosphorylation of RB at S249/T252 enhances its interaction with NF-κB p65 within nucleus and reduces the expression of NF-κB target genes, including PD-L1. RL-S249/T252D, a small phospho-mimetic peptide of RB, is able to inhibit tumor growth in immune-proficient mice, and the regression of tumor may be partly attributed to the blocked expression of PD-L1 by RL-S249/T252D. Finally, mutations of the breast cancer type 1 and 2 susceptibility (*BRCA1/2*) genes, that are associated with familial breast cancer and ovarian cancer, were documented to be involved in immune dysfunction (337, 338).The observation of increased expression of PD-L1 in *BRCA1/2*-mutated ovarian cancer implies a possible role of BRCA1/2 for PD-L1 regulation, although the underlying mechanism remains to be explored (319, 338, 339).

The Role of Post-translational Modifications in PD-L1 Expression

PD-L1 protein can be phosphorylated, ubiquitinated, and glycosylated after translation. These post-translational modifications (PTMs) collaboratively or competitively regulate the level of PD-L1 in cells.

The potential phosphorylation sites of PD-L1 have been predicted using the PhosphoSite database (PhosphoSite Plus Protein Page: Pd-L1 Human, 2018). However, in spite of this, the phosphorylation of PD-L1 has been sparsely reported. Horita et al. (340) identified atyrosine phosphorylation of PD-L1 induced by EGF, through a set of high-affinity and high-specificity post-translational modification enrichment tools, with no specific mechanism or mediator described. Only very recently, studies have started to shine light on the regulators for phosphorylation modification of PD-L1. Glycogen synthase kinase 3β (GSK3β) was shown to phosphorylate PD-L1 and an evolutionarily conserved GSK3β phosphorylation motif (S/TXXXS/T) at T180 and S184 was found in *PD-L1* (173). Another serine/threonine protein kinase AMP-activated protein kinase (AMPK), a sensor of cellular energy, was latterly revealed to directly phosphorylate PD-L1 at S195 (341). Both AMPK- and GSK3β-mediated phosphorylation of PD-L1 reduce the expression of PD-L1 via increasing its degradation, and disparate mechanisms were exploited to this end. Phosphorylation

of PD-L1 at S195 by AMPK activation induces abnormal endoplasmic reticulum (ER) mannose trimming and produces aberrant glycoprotein of PD-L1 with mannose-rich glycan structures, which triggers the ER-associated degradation of PD-L1 (341). In contrast, GSK3β-mediated phosphorylation often facilitates ubiquitin E3 ligase recognition, which targets proteins to proteasomal degradation (342, 343). Thus, GSK3β phosphorylates non-glycosylated PD-L1 and further initiates the interaction of PD-L1 with β-TrCP to form a complex, leading to the poly-ubiquitination of PD-L1. Furthermore, enhanced PD-L1 expression, induced by EGF stimulation, may be attributed to its effect on inhibiting GSK3β-mediated phosphorylation and poly-ubiquitination of non-glycosylated PD-L1 (173). EGF is also involved in upregulating the ubiquitination of glycosylated PD-L1, and the ubiquitination of glycosylated PD-L1 is identified to be mono- and multi-ubiquitnation, but not poly-ubiquination (340). In contrast to GSK3β induced poly-ubiquitination of non-glycosylated PD-L1, that promotes its degradation via the proteasome pathway, EGF-stimulated mono- and multi-ubiquitination of glycosylated PD-L1 has yielded PD-L1 overexpression, as blocking the enzyme activity of ubiquitin E1 decreases PD-L1 mono- and multi-ubiquitination coupled with reduced PD-L1 level (340). The cooperative regulation of non-glycosylated and glycosylated PD-L1 induced by EGF may collaboratively increase the level of PD-L1. In a recent study, ubiqutin E3 Cbl-b/c-Cbl was revealed to be negatively correlated with PD-L1 expression in EGFR wild-type NSCLC (344). Similarly, in cervical and breast cancer cells, cyclin D1-CDK4 kinase was reported to destabilize PD-L1 and increase TILs via phosphorylating cullin 3-speckle type POZ protein (CUL3^SPOP) E3 ligase, leading to the ubiquitination of PD-L1 (345, 346). DCUN1D1, a regulator of ubiquitin E3 activity, was significantly increased in NSCLC tumor tissues and positively associated with PD-L1 expression, which leads to enhanced tumor metastasis and poor prognosis of the patients (347). Moreover, a ubiquitously expressed type-3 transmembrane protein, CKLF-like MARVEL transmembrane domain containing protein 6 (CMTM6), was recently identified as a novel positive regulator of PD-L1 via increasing its half-life, which is presumably due to the reduction of ubiquitination and prevention of lysosome-mediated degradation during protein recycling (348–350). Notably, this function is shared by its closest family member, CMTM4 (349). In CRC, huntingtin-interacting protein 1-related protein (HIP1R), a newly discovered regulator of PD-L1, was found to promote lysosome-mediated degradation of PD-L1 by directly binding and transporting it to lysosome via the lysosomal sorting motif of HIP1R (351). Finally, in addition to the transcriptional regulation of PD-L1, TNF-α-mediated nuclear translocation and downstream transactivation of p65 increase PD-L1 expression by transcriptionally upregulating CSN5, which functionally hydrolyzes the ubiquitin chain from ubiquitin-PD-L1 and further enhances the PD-L1 stabilization in breast cancer cells (167, 186).

PD-L1 is a ∼33 kDa type-1 transmembrane protein. However, detection of PD-L1 by immunoblotting revealed heterogeneous expression patterns on SDS-PAGE, and the high molecular weight of PD-L1 displays ∼15-kDa molecular weight shift

down by glycosylation inhibitors, suggesting that PD-L1 is highly glycosylated in human tumor tissues and cancer cell lines. Further studies identified that the type of glycosylation is primarily N-glycosylation rather than O-glycosylation since glycosylation of PD-L1 was completely inhibited by N-linked glycosylation inhibitor tunicamycin (TM) but not O-glycosidase (173). N-glycosylation occurred on the asparagine residue of an Asn-X-Ser/Thr motif (X is any amino acid except proline) in protein and is catalyzed by oligosaccharyltransferase, acting as a biosynthetic secretory pathway in ER and Golgi apparatus (352, 353). Amino-acid sequence comparation across different species identifies four evolutionarily conserved NXT motifs (N refers to Asn) in PD-L1 extracelluar domain and exclusive N-glycosylation of PD-L1 at N35, N192, N200, and N219 is further demonstrated by mass spectrometry and mutagenesis assays. Furthermore, N-glycosylations on the N192, N200, and N219 of PD-L1 cause a spatial hindrance for its interplay

with GSK3β and competitively antagonize the GSK3β-mediated phosphorylation of PD-L1, and thus contribute to PD-L1 protein stability. Additionally, glycosylation of PD-L1 appears to affect its interaction with PD-1 and T-cell-mediated cytolysis (173, 354). Increasing in the affinity for PD-1 to glycosylated PD-L1 was also corroborated in another study (355). FKBP51s, a spliced isoform of 51 KDa FK506-binding protein (FKBP51), which is a cochaperone and plays a role in immunoregulation and basic cellular processes involved in protein folding and trafficking, was shown to physically interact with the naïve PD-L1 in the ER and catalyze PD-L1 folding, thus contribute to the glycosylation of PD-L1 in glioma as proposed by D'Arrigo et al. (225). Consistently, silencing of FKBP51s significantly reduces the level of glycosylated PD-L1 (225). Latterly, an emerging report by Maher et al. (356) demonstrated a physical association between multifunctional chaperone/scaffolding protein sigma1 and early formed glycosylated PD-L1 in the ER in triple-negative
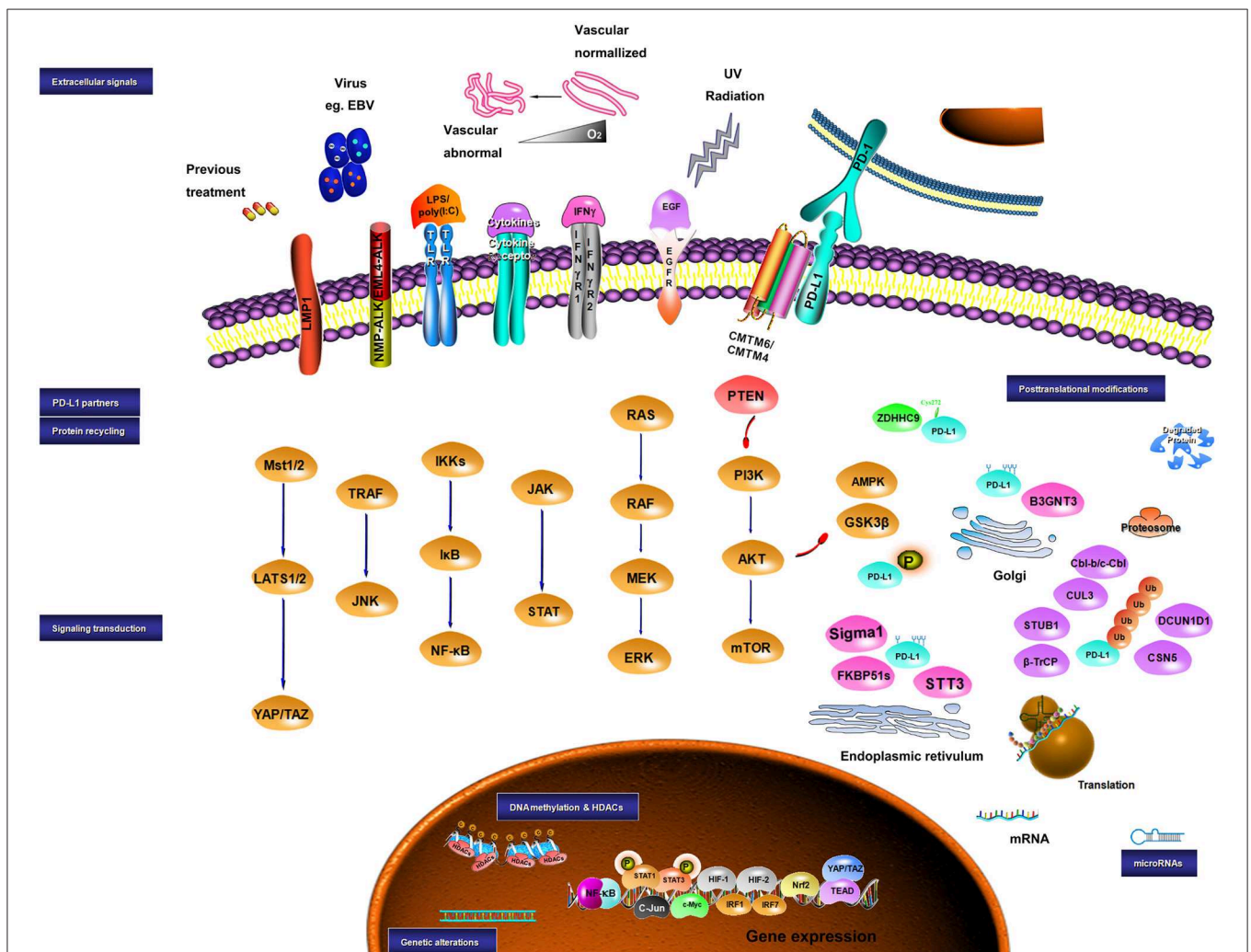
FIGURE 1 | Sketch diagram for regulatory mechanisms in PD-L1 expression. Multiple factors are involved in the regulation of PD-L1 at different levels. The intrinsic and extrinsic signals implicating the regulation of PD-L1 are presented.

breast cancer (TNBC) and prostate cancer cells. The co-occurrence of reduced PD-L1 expression in both the intracellular membrane and plasma membrane induced by sigma1 inhibition indicates that both protein stability and trafficking are involved in the regulation of PD-L1 by sigma1 (356). Collectively, stabilization of PD-L1 by FKBP51s and sigma1 are both related to the glycosylation process in the ER (225, 356). Besides, dysregulation of PD-L1 glycosylation in the ER induced by AMPK activation decreases the stability of PD-L1 and triggers its ER-associated degradation (341). Furthermore, evidence has also been obtained for a possible link of EMT to PD-L1 stabilization through glycosylation regulation. EMT transcriptionally upregulates the N-glycosyltransferase STT3 through β-catenin, and subsequently induces STT3-dependent PD-L1 N-glycosylation (193). Strikingly, the latest results have proven that glycosylated PD-L1 could serve as valuable therapeutic target for cancer (341, 354, 357). Eradication of triple-negative breast cancer cells can be achieved by treatment with STM108-MMAE, a drug-conjugated antibody specifically targeted to glycosylated PD-L1, via promoting PD-L1 internalization and lysosomal degradation (354, 357). Owing to the aberrant glycosylation of PD-L1 in the ER, mediated by metformin, the combination of anti-CTLA4 antibody and metformin successfully invigorates a potent anti-cancer effect and enhances tumor elimination compared to the monotherapy in a syngeneic mouse model of melanoma, breast, and colon cancer (341).

Besides the post-translational modifications mentioned above, protein lipidations, such as prenylation, myristylation, and palmitoylation, are another prevalent type of post-translational modification. Among them, palmitoylation (also known as S-acylation) is quite different due to its reversible feature and may serve as a therapeutic target for diseases, including tumor (358). Palmitoylation is proven to play a pivotal role in regulating protein traffic, membrane localization, and interaction (359). Palmitoylated proteins also display altered protein stability and signal transduction (358–360). Since the discovery of palmitoylation modification of proteins, it has been revealed that nearly 1,000 proteins can be palmitoylated in human beings (361). Intriguingly, a single palmitoylation site at Cys272 of PD-L1, which is located in cytosolic domain, has been unveiled based on online prediction (csspalm.biocuckoo.org) and further verified by acyl-biotin exchange assays combined with mutation (362). Palmitoylation of PD-L1 in tumor cells contributes to its increased stability and avoidance of immune surveillance. It is believed that palmitoylation can spontaneously occur *in vitro*, and *in vivo*, it is usually catalyzed by protein acyltransferases (PATs). Although palmitoylation has been discovered for a long time, related PATs were identified much later (363, 364). Most PATs that mediated protein palmitoylation belong to the zinc finger protein family and possess a conserved Asp-His-His-Cys (DHHC) domain (364). In the study by Yang et al. (362), palmitoyltransferase ZDHHC9 was demonstrated to be responsible for the palmitoylation of PD-L1. The interaction between ZDHHC9 and PD-L1 is affirmed, knockdown of ZDHHC9 in cancer cells induces a significant reduction of PD-L1 palmitoylation and sensitizes T-cell-mediated

killing, hence inhibiting tumor growth. This study raises a possible approach for targeting PD-L1 palmitoylation to restore the immune surveillance and cytolytic activity of T cells for cancer treatment. This was further demonstrated by Yao et al. recently (365). In contrast to the findings in breast cancer, Yao et al. have identified palmitoyltransferase ZDHHC3 (DHHC3) as the main acyltransferase required for the palmitoylation of PD-L1 in CRC cells, inhibition of which by 2-bromopalmitate and a synthetic peptide successfully decreases PD-L1 expression and enhances T-cell immunity against the tumors.

PTMs may affect the conformation, activity, and interactions of proteins. Although the PTMs, e.g., glycosylation, phosphorylation, ubiquitination, and palmitoylation of PD-L1, have been reported to influence its expression, the possible effects of these PTMs on the conformation and molecular interactions of PD-L1/PD-1 remain rather limited. PD-L1 can also be acetylated and SUMOylated in response to EGF (340). Thus, to fully understand the role of PTMs in PD-L1 regulation, more studies are needed to (1) characterize the types of PTMs of PD-L1, (2) decode the modification sites and the functional consequences of PTMs, (3) clarify the interactions among these PTMs, (4) evaluate the availability of PD-L1 PTMs as potential targets in PD-1/PD-L1 axis for cancer treatment.

Collectively, the expression of PD-L1 is controlled by both intrinsic and extrinsic signaling, which may share similar molecular mechanisms. Crosstalk among these signaling pathways also plays a role in PD-L1 expression (184, 366). In summary, the level of PD-L1 in a tumor can be modulated by the genomic aberrances, epigenetic alterations, and extracellular stimuli in a very complex way, which may mechanistically work through transcriptional control, mRNA stability, oncogenic signaling pathway, and protein stability (**Figure 1**).

SUMMARY

Despite considerable improvement of cancer therapy, which has been achieved through PD-1/PD-L1 blockade, the knowledge regarding the biology of these regulators in cancer immune surveillance is still relatively limited. Many mechanisms have been revealed to regulate the expression of PD-L1 including genetic alterations, epigenetic modifiers, extracellular stimulations, signaling pathways, transcriptional factors, and post-transcriptional modulators. Generally, PD-L1 on tumor cells is regulated with two patterns: inducible and constitutive expression. Inducible expression of PD-L1 by the inflamed microenvironment within a tumor or by previous treatments may portend a better response to anti-PD-1/PD-L1 therapies and provide an opportunity for overcoming acquired resistance to prior treatments. Uncovering the mechanisms of constitutive PD-L1 expression driven by oncogenic signaling is valuable for developing new strategies for cancer therapy through directly targeting PD-L1 (269, 299). Similarly, synthetic peptides that either target PD-L1 degradation or post-translational modifications have shown a strong efficiency in animal studies,

which may serve as a novel therapy for cancer treatment (351, 365). Notably, this kind of therapy that directly targets PD-L1 is of great significance and may be more effective as compared with blockade of PD-1/PD-L1 axis due to PD-1-independent functions of PD-L1 in the promotion of malignant phenotypes and drug resistance (367, 368). Altogether, an extensive understanding of the mechanisms by which PD-L1 is governed will help us to reach a comprehensive evaluation of PD-1/PD-L1 targeting therapy, and further potentiate the efficacy and expand the usage of this kind of cancer therapy via patient selection and rational combination with other antineoplastic agents, as well as develop new effective strategies for cancer immunotherapy.

AUTHOR CONTRIBUTIONS

XS wrote the manuscript. Z-XX contributed to the conception and writing. JL drew the tables and created the figure in the manuscript. LZ, YL, and YW revised the manuscript. All authors read and approved the final manuscript.

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