Molecular mechanisms and potential targeting strategies of ubiquitin-proteasome system-mediated PD-1/PD-L1 ubiquitination in tumor immune suppression (Review)

LI-HUI GU[1*], AI GUO[1*], YI-YUE DING[1*], XUE-JIE WANG[2], HONG-XING ZHANG[1], WAN-LI DUAN[3] and BAO-GANG ZHANG[1,2]

[1]Department of Diagnostic Pathology, School of Basic Medical Sciences, Shandong Second Medical University, Weifang, Shandong 261053, P.R. China; [2]Department of Diagnostic Pathology, Shaoxing People's Hospital, Shaoxing, Zhejiang 312000, P.R. China; [3]Medical Research Center, Shaoxing People's Hospital, Shaoxing, Zhejiang 312000, P.R. China

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Abstract. Cancer cells play a pivotal role in immune evasion by activating the programmed cell death protein 1 (PD-1)/PD-ligand (L)1 signaling pathway or immune cells within the tumor microenvironment. The ubiquitin-proteasome system (UPS), the primary pathway for intracellular protein degradation, has been increasingly implicated in mediating tumor immune escape and resistance to anti-PD-1/PD-L1 therapy. Targeting the UPS has demonstrated significant potential in improving the efficacy of tumor immunotherapy. Therefore, a deeper understanding of the molecular mechanisms by which UPS contributes to tumor resistance against PD-1/PD-L1 blockade, along with the optimization of UPS-targeted small-molecule drug design, holds scientific and clinical significance. In the present review, the role of UPS in tumor immune evasion through the regulation of PD-1/PD-L1 ubiquitination was discussed and potential therapeutic agents that may enhance the effectiveness of anti-PD-1/PD-L1 treatment are summarized. These insights provide a theoretical foundation for advancing cancer immunotherapy and developing novel combination strategies.

Contents

Correspondence to: Dr Bao-Gang Zhang, Department of Diagnostic Pathology, School of Basic Medical Sciences, Shandong Second Medical University, 4948 Shengli East Street, Kuiwen, Weifang, Shandong 261053, P.R. China
E-mail: zbg0903@hotmail.com

Mr. Wan-Li Duan, Medical Research Center, Shaoxing People's Hospital, 568 Zhongxing North Road, Shaoxing, Zhejiang 312000, P.R. China
E-mail: 1433985403@qq.com

*Contributed equally

Abbreviations: 19S RP, 19S regulatory particle; 20S CP, 20S core particle; ALDH2, aldehyde dehydrogenase 2; ARIH1, ariadne RBR E3 ubiquitin protein ligase 1; BCLAF1, BCL2-associated transcription factor 1; β-Trcp, beta-transducin repeat-containing protein; CAR-T, chimeric antigen receptor T; c-Cbl, Casitas B lymphoma; CDK4, cyclin-dependent kinase 4; CDK5, cyclin-dependent kinase 5; DUBs, deubiquitinating enzymes; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; ERK, extracellular signal-regulated kinase; FBXO38, F-box protein 38; FGFR3, fibroblast growth factor receptor 3; GSK3α, glycogen synthase kinase 3 alpha; GSK3β, glycogen synthase kinase 3 beta; ITCH, itchy E3 ubiquitin protein ligase; ITIM, immunoreceptor tyrosine-based inhibitory motif; ITSM, immunoreceptor tyrosine-based activation motif; KLHL22, kelch-like protein 22; LKB1, liver kinase B1; mAb, monoclonal antibodies; METTL3, methyltransferase-like 3; MIB2, mind bomb E3 ubiquitin protein ligase 2; NEDD4, neural precursor cell expressed developmentally downregulated 4; NK cell, natural killer cell; OTUB1, OTU deubiquitinase, ubiquitin aldehyde binding 1; OTUB2, OTU deubiquitinase, ubiquitin aldehyde binding 2; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PKP3, plakophilin-3; PROTAC, proteolysis-targeting chimera; RAB8, RAS-related protein Rab-8; RNF125, ring finger protein 125; SGLT2, sodium-glucose cotransporter 2; SHP-1, Src homology 2 domain-containing protein tyrosine phosphatase-1; SHP-2, Src homology 2 domain-containing protein tyrosine phosphatase-2; SPOP, speckle-type POZ protein; TNBC, triple-negative breast cancer; TNF-α, tumor necrosis factor-alpha; TRAF6, TNF receptor-associated factor 6; Trim21, tripartite motif-containing protein 21; USP2, ubiquitin-specific peptidase 2; USP7, ubiquitin-specific peptidase 7; USP8, ubiquitin-specific peptidase 8; USP22, ubiquitin-specific peptidase 22; YTHDC1, YTH domain-containing protein 1

Key words: ubiquitin-proteasome system, programmed cell death protein 1/programmed death-ligand 1, molecular mechanisms, cancer immunotherapy

1. Introduction

The biological hallmarks of cancer include uncontrolled cell proliferation and differentiation, dysregulated signaling pathways, genomic instability and metabolic reprogramming (1). These characteristics make the development of more effective cancer therapies a critical research priority. In recent years, the emergence of immunotherapy represents a major breakthrough in cancer treatment. As the fifth treatment modality following surgery, radiotherapy, chemotherapy and targeted therapy, immunotherapy works by re-establishing the tumor-immune cycle and restoring the body's normal anti-tumor immune response, thereby achieving tumor control and eradication (2,3). Immune checkpoint blockade therapy has been widely proven to be effective against various human tumors, while cell therapy has shown notable efficacy in hematological malignancies and remains in the clinical research stage for solid tumors. In the field of immune checkpoint inhibitors, the main approaches include: i) Monoclonal antibody therapy targeting programmed cell death protein 1 (PD-1) and its ligand PD-L1; ii) monoclonal antibody therapy targeting cytotoxic T-lymphocyte-associated protein 4 (CTLA-4); and iii) monoclonal antibody therapy targeting lymphocyte-activation gene 3. As for adoptive cell therapy, it primarily encompasses: i) Tumor-infiltrating lymphocyte therapy; ii) T cell receptor-engineered T cell therapy; iii) chimeric antigen receptor T cell (CAR-T) therapy; and iv) natural killer (NK) cell therapy (4).

PD-1/PD-L1 monoclonal antibody therapy has emerged as the most widely used immune checkpoint inhibitor in clinical practice, demonstrating notable efficacy across various malignancies (5). PD-1, also known as CD279, is a pivotal immune checkpoint molecule that plays a central role in maintaining immune homeostasis and regulating tumor immune evasion. PD-1 is predominantly expressed on the surface of B cells, T cells and NK cells, where it can specifically recognize and bind to two ligands expressed on tumor cells: i) PD-L1 (CD274); and ii) PD-L2 (CD273) (6). Unlike CTLA-4 which primarily regulates immune responses during the early stage of T cell activation, PD-1 predominantly suppresses effector T cell function in peripheral tissues and the tumor microenvironment during the effector phase (7). In the tumor microenvironment, the binding of PD-L1 expressed at high level on tumor cells to PD-1 on T cell surfaces induces conformational changes in PD-1. This leads to the exposure and phosphorylation of the immunoreceptor tyrosine-based inhibitory motif (ITIM) at Y223 and the immunoreceptor tyrosine-based switch motif (ITSM) at Y248. The phosphorylated ITSM preferentially recruits the SHP-2 protein tyrosine phosphatase, while the phosphorylated ITIM forms dimers with the SHP-1 protein tyrosine phosphatase. These molecular events collectively attenuate T cell activation signals, suppress T cell cytotoxic function and consequently mediate negative regulation of immune responses to maintain immune homeostasis (8-11). PD-L1 can also interact with the costimulatory molecule CD80, transmitting inhibitory signals to activated T cells (12). Currently, several PD-1/PD-L1 monoclonal antibodies such as nivolumab (13), pembrolizumab (14) and avelumab (15) have been widely used in clinical cancer treatment. Although these immune checkpoint inhibitors demonstrate notable efficacy against various solid tumors and hematological malignancies, acquired resistance remains a major clinical challenge (16).

Research has demonstrated that dysregulation of the ubiquitin-dependent protein degradation pathway represents a crucial molecular mechanism in cancer pathogenesis (17,18). The UPS is an essential protein degradation mechanism in cells. This system primarily works by ubiquitinating damaged, abnormal, or functionally completed regulatory proteins and directing their degradation by the proteasome. (19). The UPS consists of a series of enzymes: i) Ubiquitin-activating enzyme E1 activates ubiquitin molecules; ii) ubiquitin-conjugating enzyme E2 mediates ubiquitin transfer; and iii) ubiquitin ligase E3 specifically recognizes substrate proteins and completes ubiquitin tagging (Fig. 1). These enzymes work cooperatively to ultimately achieve targeted protein degradation via the proteasome pathway (20,21). Ubiquitinated substrates are classified into different ubiquitination pathways based on the types of polyubiquitin chains, with K48 and K63 being the two most widely studied ubiquitination forms (22). Among these, K48-linked ubiquitination is recognized to direct target proteins for degradation via the proteasome pathway (23,24). K63-linked ubiquitination is primarily involved in proteasome-independent signaling pathways, typically associated with positive regulatory processes such as protein stabilization, subcellular localization and functional activation, including critical biological processes such as endocytic trafficking, DNA replication and signal transduction (25). Moreover, this modification can also facilitate substrate protein degradation through the autophagy-lysosome pathway (26).

The 26S proteasome is a multi-subunit proteolytic complex composed of a 20S core particle (CP) and a 19S regulatory particle (RP), which specifically recognizes polyubiquitin-tagged proteins and degrades them into short peptides (27). The 19S RP performs three key functions: i) Recognizing ubiquitinated substrate proteins; ii) regulating the deubiquitination process; and iii) delivering ubiquitinated proteins to the 20S CP. The 20S CP is a barrel-shaped proteolytic core containing active catalytic sites, where the final protein degradation occurs (28,29). Deubiquitinating enzymes (DUBs) can reverse protein ubiquitination, with their primary functions including: i) Maintaining cellular free ubiquitin levels; ii) releasing substrate proteins from the ubiquitin-proteasome degradation pathway; and iii) protecting target proteins from degradation (22). Research has revealed an increasingly clear connection between ubiquitination and cancer immunotherapy. Tumor cells can modulate the UPS to stabilize immune checkpoint protein expression and suppress immune-related protein function, thereby evading immune surveillance and promoting tumor progression.

In recent years, the regulatory role of the UPS in cancer immunotherapy has received growing attention. The present review summarized the key molecular mechanisms of UPS involvement in tumor immune regulation and discusses potential therapeutic strategies to enhance immunotherapeutic efficacy.

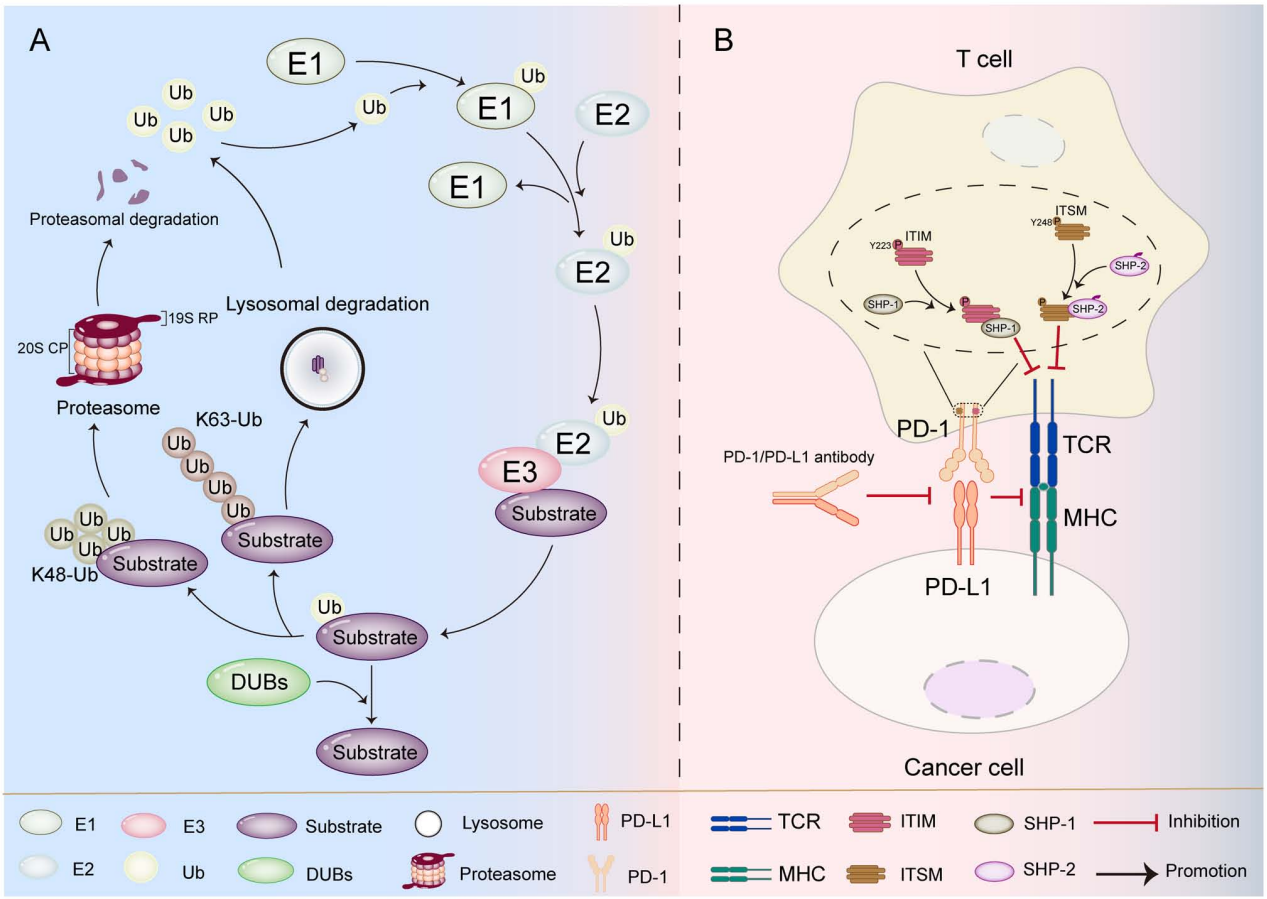


Figure 1. Protein degradation mediated by the UPS and tumor immune evasion mediated by PD-1/PD-L1. (A) The UPS consists of three components: a ubiquitination modification system mediated by a three-step enzymatic cascade, the proteasome; and the deubiquitination process. (B) In the tumor microenvironment, the heterodimer formed between the ITSM of PD-1 and SHP-2 inhibits TCR signal activation, while the dimer formed by ITIM and SHP-1 further enhances TCR suppression, thereby promoting tumor immune evasion. UPS, ubiquitin-proteasome system; PD-1, programmed death receptor 1; PD-L1, programmed cell death ligand 1; ITSM, immunoreceptor tyrosine-based activation motif; ITIM, immunoreceptor tyrosine-based inhibitory motif; SHP-2,Src Homology 2 domain-containing Protein Tyrosine Phosphatase-2; TCR, receptor-engineered; DUBs, deubiquitinating enzymes; SHP-1, Src Homology 2 domain-containing Protein Tyrosine Phosphatase-1; 19S RP, 19S regulatory particle; 20S CP, 20S core particle; MHC, major histocompatibility complex.

2. Mechanistic role of PD-1/PD-L1 ubiquitination in tumor immune evasion and immunotherapy

Regulatory role of the UPS in tumor immune escape. Ubiquitination is a series of biochemical reactions mediated by ubiquitin-activating enzyme (E1), ubiquitin-conjugating enzyme (E2) and ubiquitin ligase (E3) (20,21). E3 ubiquitin ligase is a key component of this system, which can recognize and target specific ubiquitinated substrate proteins (25). The UPS, through dynamically regulating the surface expression of PD-1/PD-L1, has become a crucial link in tumor immune evasion (Fig. 2) (30,31).

Effect of PD-L1 ubiquitination on tumor immune evasion and immunotherapy. Multiple studies have shown that speckle-type POZ protein (SPOP) plays a crucial role in mediating the ubiquitination process of PD-L1 and the mechanism of tumor immune evasion (31-33). Zhang *et al* (31) found that in colorectal cancer cells, the E3 ubiquitin ligase SPOP can promote the ubiquitination and degradation of PD-L1. Meanwhile, the ALDH2 expressed at high levels in cancer cells can competitively bind to PD-L1 with SPOP, thereby inhibiting the ubiquitination process of PD-L1 mediated by SPOP and ultimately weakening the antitumor effect of T cells. In addition, in hepatocellular carcinoma, the transcription factor BCLAF1 can inhibit the ubiquitination of PD-L1 by SPOP by targeting and binding to SPOP. This mechanism enhances the stability of PD-L1 and promotes tumor immune evasion (32). Ding *et al* (34) found that SGLT2 can competitively bind to PD-L1 with the E3 ubiquitin ligase SPOP, thereby preventing PD-L1 from being degraded through the proteasome pathway. The small-molecule SGLT2 inhibitor canagliflozin can disrupt the interaction between SGLT2 and PD-L1, prompting SPOP to recognize PD-L1 and promote its ubiquitination, followed by degradation via the proteasome pathway, thereby enhancing the antitumor activity of T cells. Zhang *et al* (33) found that in various types of cancer, CDK4 can directly promote the phosphorylation of SPOP at Ser6. The phosphorylated SPOP can bind to the scaffold protein 14-3-3γ, thereby blocking the binding of SPOP to the complex activator FZR1, stabilizing the expression level of SPOP, enabling it to recognize and promote the K48 ubiquitination of PD-L1 and eventually leading to its degradation via the proteasome pathway.

While SPOP serves as a well-characterized E3 ligase regulating PD-L1 stability, other ubiquitin ligases also contribute markedly to this regulatory network. In non-small cell lung

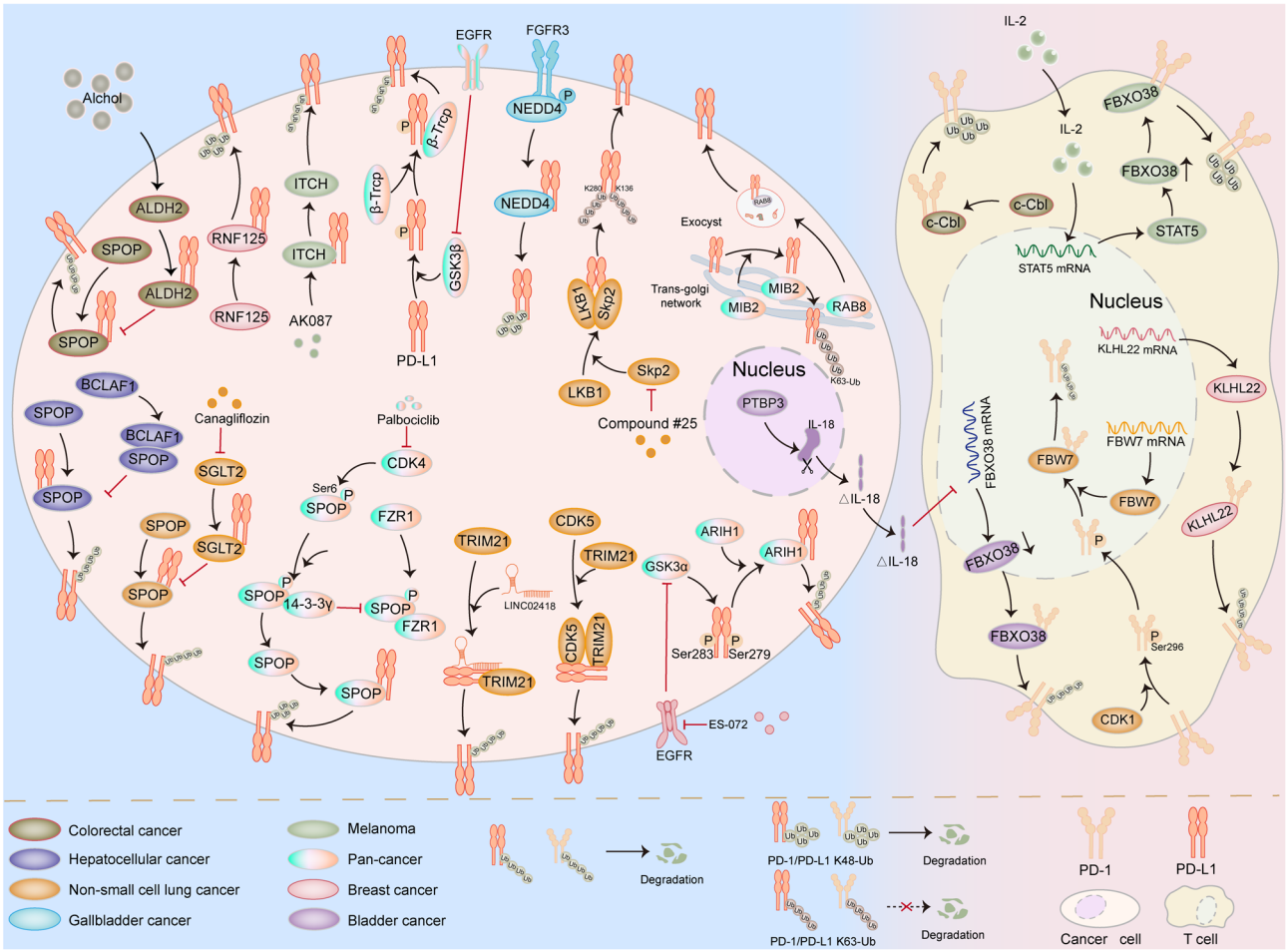


Figure 2. The role of ubiquitination in the treatment with anti-PD-1/PD-L1 mAb. The ubiquitination functions of E3 ubiquitin ligases SPOP, TRIM21, ARIH1, MIB2, Skp2, NEDD4, β-TrCP, ITCH and RNF125 can affect the immune capacity of tumors by regulating the expression level of PD-L1. The ubiquitination functions of E3 ubiquitin ligases FBXO38, KLHL22, FBW7 and c-Cbl can influence the immune function of T cells by regulating the expression level of PD-1. PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; mAb, monoclonal antibodies; SPOP, speckle-type POZ protein; TRIM21, tripartite motif-containing protein 21; ARIH1, ariadne RBR E3 ubiquitin protein ligase 1; MIB2, mind bomb E3 ubiquitin protein ligase 2; Skp2, S-phase kinase-associated protein 2; NEDD4, neural precursor cell expressed developmentally downregulated 4; β-Trcp, beta-transducin repeat-containing protein; ITCH, itchy E3 ubiquitin protein ligase; ITIM, immunoreceptor tyrosine-based inhibitory motif; RNF125, ring finger protein 125; FBXO38, F-Box protein 38; KLHL22, kelch-like protein 22; FBW7 F-Box and WD repeat domain-containing 7; c-Cbl, Casitas b lymphoma; ALDH2, aldehyde dehydrogenase 2; BCLAF1 BCL2-associated transcription factor 1; β-Trcp beta-transducin repeat-containing protein; CDH1 cadherin 1; CDK1 cyclin-dependent kinase 1; CDK4 cyclin-dependent kinase 4; CDK5 cyclin-dependent kinase 5; EGFR, epidermal growth factor receptor; FGFR3, fibroblast growth factor receptor 3; GSK3α, glycogen synthase kinase 3 alpha; GSK3β glycogen synthase kinase 3 beta; IL-2, interleukin-2; IL-18, interleukin-18; LKB1, liver kinase B1; RAB8, RAS-related protein Rab-8; SGLT2, sodium-glucose cotransporter 2; STAT5, signal transducer and activator of transcription 5.

cancer, the E3 ubiquitin ligase TRIM21 can ubiquitinate PD-L1 and promote its degradation. LINC02418, acting as a molecular sponge, can form a ternary complex with TRIM21 and PD-L1. This complex enhances the ubiquitination of PD-L1 by TRIM21, ultimately leading to resistance to anti-PD-L1-based immunotherapy in non-small cell lung cancer (35). Gao *et al* (36) found that CDK5 can promote the ubiquitination process of PD-L1 by TRIM21 by interacting with TRIM21 and PD-L1. This mechanism notably exacerbates the resistance of patients with non-small cell lung cancer to anti-PD-L1-based immunotherapy. Wu *et al* (37) showed that in lymphosarcoma and non-small cell lung cancer cells, glycogen synthase kinase 3 alpha (GSK3α) can enhance the recognition and ubiquitination of PD-L1 by the E3 ubiquitin ligase ARIH1 by promoting the phosphorylation of PD-L1 at Ser279 and Ser283. However, the inhibitory effect of epidermal growth factor (EGF) receptor (EGFR) on GSK3α in cancer cells mediates tumor immune treatment resistance. The combined application of the EGFR inhibitor ES-072 and immunotherapy can effectively enhance the efficacy of immunotherapy (37). Wei *et al* (38) found that RNF125 can directly interact with PD-L1, promote the K48 ubiquitination of PD-L1, thereby accelerating its degradation and ultimately inhibiting the immune evasion of tumor cells. Yang *et al* (39) found that in melanoma cells, ITCH can promote the ubiquitination and degradation process of PD-L1. The small-molecule ITCH agonist AK087 can effectively reduce the accumulation of PD-L1 induced by MAPK inhibitors, thereby weakening the tumor immune evasion and acquired resistance to anti-PD-L1 treatment induced by MAPK inhibitors. Glycogen synthase kinase 3β (GSK3β), a serine/threonine kinase, has the function of catalyzing the phosphorylation of substrates. Moreover, the phosphorylation mediated by GSK3β usually promotes the recognition of substrates by E3 ubiquitin ligases (40).

Li *et al* (41) showed that GSK3β can interact with the E3 ligase β-TrCP and PD-L1, prompting β-TrCP to ubiquitinate PD-L1 in a phosphorylation-dependent manner, thereby accelerating the degradation of PD-L1. In basal-like breast cancer, the EGF/EGFR signaling can stabilize PD-L1 by inhibiting the activity of GSK3β, thereby mediating tumor immune treatment resistance. The combination of the EGFR-targeted inhibitor gefitinib and anti-PD-L1 treatment markedly enhances the efficacy of tumor immunotherapy. In bladder cancer, the E3 ubiquitin ligase NEDD4 can target PD-L1 and promote its K48 ubiquitination. Fibroblast growth factor receptor 3 (FGFR3) can activate the enzymatic activity of NEDD4 by phosphorylating it, thereby promoting the degradation of PD-L1. Therefore, the use of FGFR3 inhibitors to treat bladder cancer may lead to the occurrence of immune evasion in bladder cancer (42).

K63 ubiquitination is a type of non-proteolytic ubiquitination, which is usually closely associated with positive regulatory processes such as the maintenance of protein stability, subcellular localization and functional activation (25). It has been shown that MIB2 can promote the K63 ubiquitination of PD-L1 and stabilize the expression of PD-L1. This mechanism drives the RAB8-mediated exocytosis, facilitating the transportation of PD-L1 from the trans-Golgi network to the plasma membrane and ultimately mediating tumor immune evasion (43). In non-small cell lung cancer, S-phase kinase-associated protein 2 (Skp2), as a key linker molecule between LKB1 and PD-L1, has been shown to be able to stabilize the expression level of PD-L1 by promoting the K63 ubiquitination of K136 and K280 residues on PD-L1. In addition, LKB1 can promote the expression of Skp2 and PD-L1. This series of actions ultimately mediates the phenomenon of immune evasion in non-small cell lung cancer (44).

Effect of PD-1 ubiquitination on tumor immune evasion and immunotherapy. Studies have shown that FBXO38 can promote the K48 ubiquitination of PD-1 and accelerate its degradation process. Exogenous interleukin (IL)-2 can enhance the transcriptional activity of signal transducer and activator of transcription 5, upregulate the expression level of FBXO38 and thereby enhance the anti-tumor ability of T cells (30). In gallbladder cancer (GBC), PTBP3 which is expressed at high levels can promote the production of the IL-18 splice variant ΔIL-18. ΔIL-18 can downregulate the transcriptional level of FBXO38. This mechanism inhibits the ubiquitination process of PD-1 mediated by FBXO38, ultimately promoting the immune treatment evasion phenomenon in GBC (45). Zhou *et al* (46) demonstrated that the E3 ubiquitin ligase KLHL22 can recognize PD-1 and promote its ubiquitination. This process reduces the expression level of PD-1 on the surface of breast cancer cells and ultimately enhances the immune function of T cells. Liu *et al* (47) demonstrated that CDK1 can promote the nuclear translocation of PD-1 by enhancing the phosphorylation of PD-1 at Ser296. This mechanism facilitates the interaction between the E3 ubiquitin ligase F-box and WD repeat domain-containing 7 in the nucleus and PD-1, thereby mediating the ubiquitination and degradation process of PD-1 in non-small cell lung cancer and ultimately enhancing the anti-tumor ability of T cells. In colorectal cancer, c-Cbl binds to and interacts with PD-1, leading to its degradation via the ubiquitin-proteasome pathway. This reduces PD-1 expression levels, enhances the anti-tumor activity of T cells and promotes immunotherapy efficacy (48).

3. Mechanistic role of PD-1/PD-L1 deubiquitination in tumor immune evasion and immunotherapy

Regulation of cellular functions by DUBs through modulation of protein metabolism. DUBs can regulate the metabolic level of substrate proteins by cleaving monoubiquitin or polyubiquitin molecules, thereby modulating a variety of cellular activities, such as gene transcription, tumorigenesis and inflammatory immune responses (Fig. 3) (49).

Effect of PD-L1 deubiquitination on tumor immune evasion and immunotherapy. The ubiquitin-specific proteases (USP) family is a group of enzymes that specifically participate in protein deubiquitination modification and belongs to the DUB family. Studies have shown that the USP family plays a crucial role in regulating the deubiquitination of PD-L1 to mediate tumor immune evasion (50-52). Wang *et al* (51) found that that USP7 can directly target PD-L1 and deubiquitinate it, thereby stabilizing the expression level of the PD-L1 protein and ultimately promoting the process of immune evasion in gastric cancer. Another study showed that USP8 can directly bind to PD-L1 and remove its ubiquitination modification, thereby stabilizing the protein expression level of PD-L1 and ultimately promoting the process of immune evasion in pancreatic cancer (52). USP8 can not only directly mediate the deubiquitination of PD-L1, but has also been proved to stabilize the expression of TRAF6 by deubiquitinating TRAF6 in various types of cancer. Once TRAF6 is stably expressed, it will further promote the K63 ubiquitination of PD-L1 mediated by itself, ultimately stabilizing PD-L1 and promoting tumor immune evasion. The inhibition of USP8 by DUBs-IN-2 can effectively enhance the antitumor activity of T cells (53). In colorectal cancer and prostate cancer cells, USP2 can directly interact with PD-L1 and promote the K48 deubiquitination of PD-L1. This process stabilizes the expression of PD-L1 and then mediates tumor immune evasion (54). In liver cancer, USP22 can deubiquitinate PD-L1 and thereby mediate the antitumor immune resistance in liver cancer (55). In colorectal cancer, the inhibition of enhancer of zeste homolog 2 upregulates the expression of USP22 at the transcriptional level. The upregulated USP22 further deubiquitinates and stabilizes PD-L1, ultimately promoting the process of tumor immune evasion (56). In breast cancer, lung cancer and melanoma, the derivative peptide A11 of annexin A1 can competitively bind to PD-L1 with USP7, which is a deubiquitinase of PD-L1. This process inhibits the deubiquitination process of PD-L1 mediated by USP7, thereby promoting the degradation of PD-L1 and ultimately leading to the phenomenon of immune treatment resistance in tumors (57).

The OTUB family is a part of the DUB family. Studies have shown that the OTUB family also plays an important role in mediating the ubiquitination of PD-L1 (58-60). Zhu *et al* (59) found that in various types of cancer, OTUB1 can directly bind to PD-L1 and remove its K48 ubiquitination modification. This process inhibits the degradation of PD-L1 through

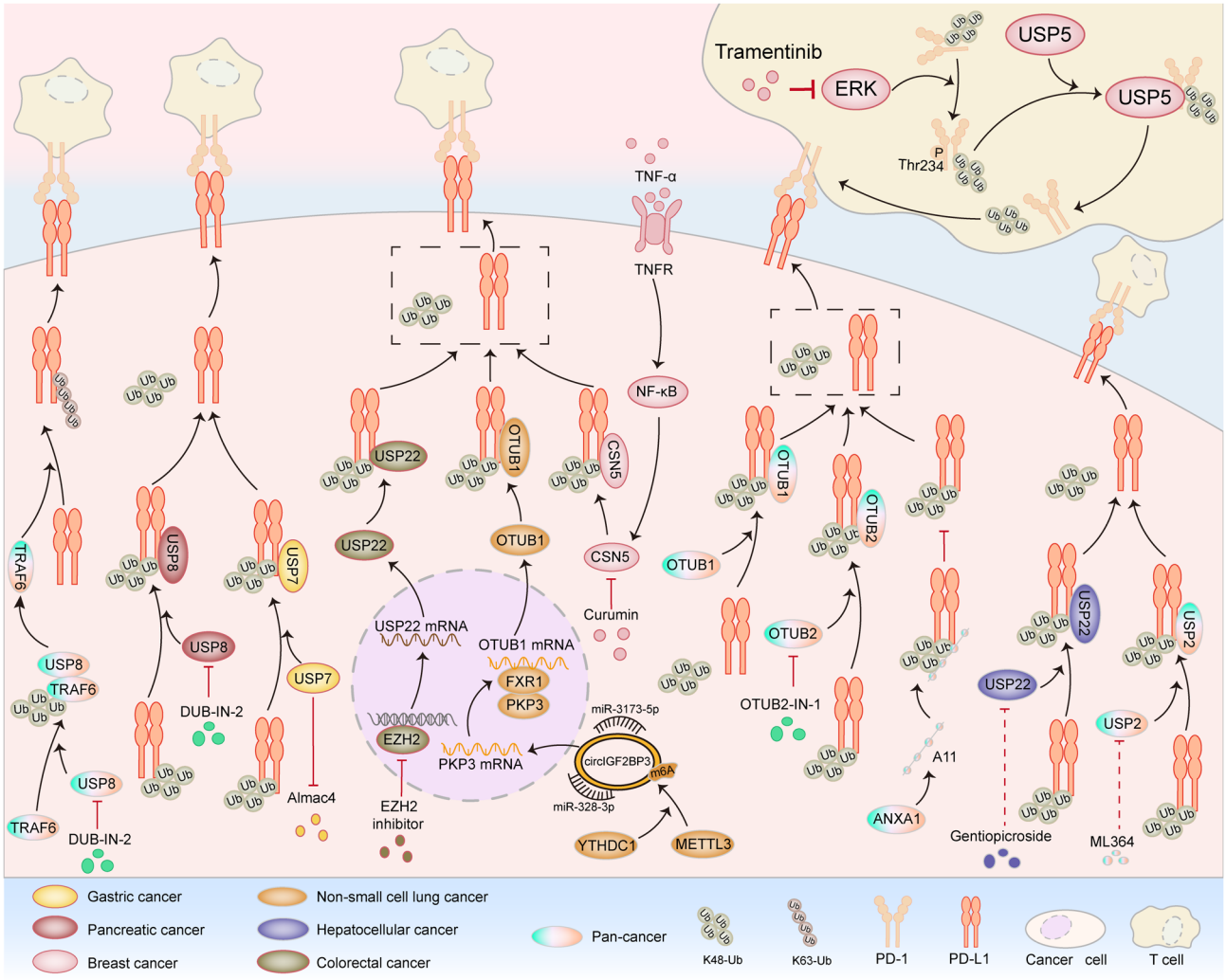


Figure 3. The role of deubiquitination in the treatment with anti-PD-1/PD-L1 mAb. In cancer cells, deubiquitinating enzymes such as CSN5, OTUB1, OTUB2, TRAF6, USP2, USP7, USP8 and USP22 exert their deubiquitination functions to regulate the expression level of PD-L1, thereby promoting tumor immune evasion. In immune cells, the deubiquitinating enzyme USP5 exerts its deubiquitination function to regulate the expression level of PD-1, thereby promoting tumor immune evasion. PD-1, programmed death receptor 1; PD-L1, programmed cell death ligand 1; mAb, monoclonal antibodies; CSN5, COP9 signalosome subunit 5; OTUB1, OTU deubiquitinase, ubiquitin aldehyde binding 1; OTUB2, OTU deubiquitinase, ubiquitin aldehyde binding 2; TRAF6, TNF receptor-associated factor 6; USP2, ubiquitin-specific peptidase 2; USP7, ubiquitin-specific peptidase 7; USP8, ubiquitin-specific peptidase 8; USP22, ubiquitin-specific peptidase 22; USP5, ubiquitin-specific peptidase 5; ANXA1, Annexin A1; ERK, extracellular signal-regulated kinase; EZH2, enhancer of zeste homolog 2; FXR1, fragile x mental retardation syndrome-related protein 1; METTL3, methyltransferase-like 3; PKP3, plakophilin-3; TNF-α, tumor necrosis factor-alpha; TNFR, TNF receptor; YTHDC1, YTH domain-containing protein 1; K48, ubiquitin lysine 48-linked;

the endoplasmic reticulum-associated degradation pathway, ultimately promoting tumor immune evasion. In addition, in non-small cell lung cancer, METTL3 mediates m6A modification in a YTHDC1-dependent manner, thereby promoting the circularization of circIGF2BP3. Acting as a molecular sponge for microRNA (miR)-328-3p and miR-3173-5p, circIGF2BP3 upregulates the expression of PKP3. Subsequently, PKP3 stabilizes OTUB1 mRNA through fragile x mental retardation syndrome-related protein 1 and ultimately, through the OTUB1-mediated deubiquitination of PD-L1, inhibits the function of $CD8^+$ T cells (61). OTUB2 has also been proven to be able to directly interact with PD-L1 and deubiquitinate it. This process inhibits the ubiquitination and degradation of PD-L1 in the endoplasmic reticulum. The OTUB2 inhibitor OTUB2-IN-1 can effectively interfere with the DUB activity of OTUB2, thereby markedly enhancing the antitumor immune effect (60). COP9 signalosome 5 (CSN5), as a subunit of the COP9 signalosome, possesses DUB activity and can remove ubiquitin chains from substrate proteins, thereby preventing substrate proteins from being degraded by the proteasome. In triple-negative breast cancer (TNBC), tumor necrosis factor-α upregulates the expression level and activity of CSN5 through the nuclear factor-κB signaling pathway, thereby promoting the deubiquitination process of PD-L1 mediated by CSN5 and ultimately enhancing the resistance of cancer cells to PD-1/PD-L1 immunotherapy. The CSN5-targeting inhibitor curcumin can promote the degradation of PD-L1 and thus enhance the efficacy of tumor immunotherapy (62).

Effect of PD-1 deubiquitination on tumor immune evasion and immunotherapy. Xiao *et al* (63) found that in T cells, USP5 can interact with PD-1, deubiquitinate it, thereby stabilizing the expression level of PD-1 and enhance the tumor's immune evasion ability. Meanwhile, the extracellular signal-regulated

kinase (ERK) can further promote the deubiquitination process of PD-1 mediated by USP5 by phosphorylating the Thr234 site of PD-1. The combination of the USP5 inhibitor and the ERK inhibitor trametinib can effectively enhance the antitumor immune effect.

4. Potential strategies to improve the efficacy of tumor immune checkpoint inhibitors by targeting the UPS

The UPS is the core mechanism for maintaining protein homeostasis within cells. During tumor immune evasion, UPS mainly regulates the dynamic balance of immune checkpoint molecules, antigen presentation processes and immunosuppressive cells through ubiquitination tagging and proteasomal degradation (64). Studies have confirmed that small-molecule drugs targeting the UPS play an important role in improving the therapeutic effects of tumor immune checkpoint inhibitors (Table I) (51,52,60). In pancreatic cancer, DUB-IN-2 inhibits the deubiquitination function of USP8, reduces the expression level of PD-L1 and thereby reverses the immunosuppressive state in the tumor microenvironment (52). In gastric cancer, the use of the small-molecule inhibitors Almac4 and P5091 targeting USP7 can inhibit the deubiquitination activity of USP7, thereby suppressing the proliferation of cancer cells. In addition, these two inhibitors can also downregulate the expression level of PD-L1 and enhance the anti-tumor immune response (51). In melanoma and colorectal cancer, the small-molecule inhibitor OTUB2-IN-1 can notably inhibit the DUB activity of OTUB2 and reduce the expression level of PD-L1 in tumor cells in a dose-dependent manner, thereby promoting antitumor immune function (60).

Recent studies have further revealed that specific small-molecule compounds can modulate the stability of PD-L1 through ubiquitination pathways. In non-small cell lung cancer, compound #25 can enhance the anti-tumor immune response by inhibiting the Skp2-mediated K63 ubiquitination process of PD-L1 (44). The small-molecule agonist AK087 of ITCH can effectively promote the ubiquitination and degradation process of PD-L1 mediated by ITCH and notably inhibit the resistance of tumors to PD-1/PD-L1 treatment (39).

In addition, some small-molecule drugs have shown great potential in the field of tumor immunotherapy. OTUB1/USP8-IN-1 is a dual inhibitor targeting OTUB1 and USP8, which can effectively inhibit the functions of these two DUBs and is a potential small-molecule drug for tumor immunotherapy (65). Natural compounds also play a marked role in the field of tumor immunotherapy. Lu *et al* (66) found that the natural compound gentiopicroside can inhibit the DUB activity of USP22, thereby reducing the expression level of PD-L1 in lung adenocarcinoma and enhancing the body's anti-tumor immune ability. Curcumin, as a natural dietary supplement, has been proven to have the potential for anti-tumor immunity. In TNBC, curcumin can inhibit the DUB activity of CSN5, reduce the stability of PD-L1, induce the ubiquitination and degradation of PD-L1 and thereby enhance the immune system's ability to attack tumor cells (62). In lung cancer, CSN5 can promote the deubiquitination process of PD-L1, thereby inducing tumor immune evasion. The natural compound berberine can inhibit the DUB activity of CSN5, reduce the expression level of PD-L1 and thus enhance the body's anti-tumor immune ability (67). In colorectal and lung cancers, demethylzeylasteral specifically binds to USP22 and induces its degradation, thereby promoting ubiquitin-dependent proteasomal degradation of PD-L1 and ultimately enhancing T cell-mediated antitumor immune responses (68).

Small-molecule inhibitors targeting the UPS have shown great potential in the field of tumor immunotherapy and are very likely to be one of the important strategies for cancer treatment in the future.

5. Discussion

During the occurrence and development of tumors, tumor cells can evade the strict surveillance of the immune system through a variety of complex mechanisms. Among these mechanisms, the activation of immune checkpoint pathways is one of the core mechanisms by which tumors achieve immune evasion. At present, anti-PD-1/PD-L1 therapy, as a representative of immune checkpoint inhibitor therapy, is one of the most widely used tumor immunotherapy strategies in clinical practice (5). Although anti-PD-1/PD-L1 therapy has shown good efficacy in some patients, a considerable number of patients still do not respond to the treatment after receiving it and even develop acquired resistance due to anti-PD-1/PD-L1 therapy (69). Therefore, elucidating further the potential molecular mechanisms underlying tumor resistance to anti-PD-1/PD-L1 and exploring effective combination therapy strategies are of great significance for improving the therapeutic efficacy of anti-PD-1/PD-L1 and prolonging the survival of patients (Table II).

The UPS, as a crucial molecular mechanism responsible for protein degradation and stabilization within cells, plays a pivotal role in regulating various biological processes such as cell cycle progression, signal transduction networks and immune response reactions. It is one of the main pathways mediating protein degradation or stabilization inside cells (70,71). The UPS has the ability to precisely recognize and selectively tag damaged, abnormal, or function-completed proteins with ubiquitin 'tags'. Subsequently, the proteasome recognizes these tagged proteins and precisely regulates the degradation process of the proteins (19). In recent years, with the continuous deepening of research, an increasing number of studies have shown that the UPS plays a crucial role in the pathological and physiological processes of tumor proliferation, invasion, metastasis, immune regulation and drug resistance (72-74). It has been confirmed that the UPS can mediate tumor immune evasion and drug resistance induced by immune checkpoint inhibitor therapy by regulating the ubiquitination level of PD-1/PD-L1 (31,51,52). In-depth exploration of the potential molecular mechanisms by which the UPS regulates PD-1/PD-L1 will not only help improve the efficacy of tumor immunotherapy, but also provide a solid theoretical basis for the development of novel therapeutic strategies.

In recent years, targeting the UPS for disease treatment has become an important direction in drug development, showing great therapeutic potential in a number of fields such as autoimmune diseases and neurodegenerative diseases and cancer (75,76). Studies have shown that targeting the ubiquitination process of PD-1/PD-L1 mediated by the UPS has achieved notable effects in inhibiting tumor immune evasion and improving tumor resistance to anti-PD-1/PD-L1 therapy.

Table I. Potential drugs with the potential to target the UPS for enhancing the efficacy of tumor immune checkpoint inhibitors.

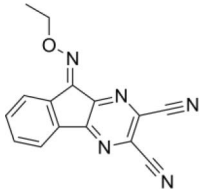
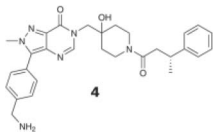
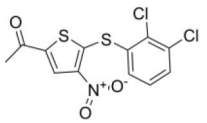
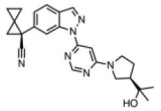
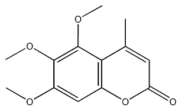
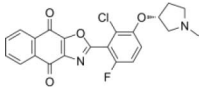
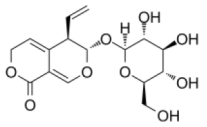
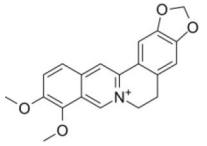
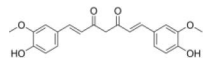
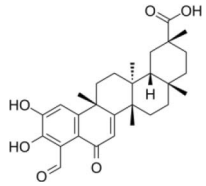
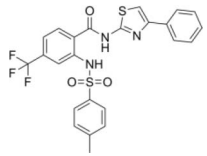
First author/s, year	Enhancing PD-1/ PD-L1 therapy	Name	Target	Function	Structure	Research progress	(Refs.)
Yang *et al*, 2023	Validated to exhibit anti-tumor effects in combination with anti-PD-1/PD-L1 therapy	DUB-IN-2	USP8	Inhibition of the deubiquitinating enzyme activity of USP8		Preclinical	(52)
Wang *et al*, 2021		Almac4	USP7	Inhibition of the deubiquitinating enzyme activity of USP7		Preclinical	(51)
Wang *et al*, 2021		P5091	USP7	Inhibition of the deubiquitinating enzyme activity of USP7		Preclinical	(51)
Lv *et al*, 2024		Compound#25	Skp2	Inhibition of the deubiquitinating enzyme activity of Skp2		Preclinical	(44)
Yang *et al*, 2022		AK087	ITCH	Activation of ITCH ubiquitin ligase activity		Preclinical	(39)
Tan *et al*, 2022	Potential small-molecule drugs that enhance the efficacy of anti-PD-1/ PD-L1	OTUB1/USP8-IN-1	OTUB1, USP8	Inhibition of the deubiquitinating enzyme activity of OTUB1		Preclinical	(65)
Lu *et al*, 2024	therapy.	Gentiopicroside	USP22	Inhibition of the deubiquitinating enzyme activity of USP22		Preclinical	(66)
Liu *et al*, 2020		Berberine	CSN5	Inhibition of the deubiquitinating enzyme activity of CNS5		Phase 4	NCT04697186 (67)

Table I. Continued.

First author/s, year	Enhancing PD-1/ PD-L1 therapy	Name	Target	Function	Structure	Research progress	(Refs.)
Lim *et al*, 2016		Curcumin	CSN5	Inhibition of the deubiquitinating enzyme activity of CSN5		Phase 2	NCT00094445 (62)
Zhang *et al*, 2024		Demethylzeylasteral	USP22	Inhibition of the deubiquitinating enzyme activity of USP22		Preclinical	(68)
Yi *et al*, 2023		ML364	USP2	Inhibition of the deubiquitinating enzyme activity of USP2		Preclinical	(77)

CSN5, COP9 signalosome 5; ITCH, itchy E3 ubiquitin protein ligaseitchy E3 ubiquitin protein ligase; OTUB1, OTU deubiquitinase, ubiquitin aldehyde binding 1; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; Skp2, S-phase kinase-associated protein 2; UPS, ubiquitin-proteasome system;USP2, ubiquitin-specific peptidase2; USP7, ubiquitin-specific peptidase 7; USP8, ubiquitin-specific peptidase 8; USP22, ubiquitin-specific peptidase22.

Table II. Effect of key UPS regulators on programmed PD-1/PD-L1 expression in cancer immunotherapeutic responses.

First author/s, year	Enzyme type		Cancer	Effect on immunotherapy	(Refs.)
Meng *et al*, 2018	E3 ubiquitin ligase	FBXO38	Melanoma	IL-2 activates STAT5 to transcribe FBXO38, ubiquitinates PD-L1 and inhibits immune evasion.	(30)
Zhou XA, 2020		KLHL22	Breast cancer	Promotes PD-1 ubiquitination and inhibits immune escape.	(46)
Liu *et al*, 2022		FBW7	Non-small cell lung cancer	CDK1 promotes PD-1 nuclear translocation and enhances FBW7-mediated PD-1 ubiquitination and inhibits immune escape.	(47)
Zhao *et al*, 2024		FBXO38	Gallbladder cancer	ΔIL-18 downregulates FBXO38, suppresses PD-1 ubiquitination and promotes immune escape.	(45)
Lyle *et al*, 2019		c-Cbl	Colorectal cancer	Promotes ubiquitination of PD-1 and inhibits immune escape.	(48)
Zhang *et al*, 2021		SPOP	Colorectal cancer	ALDH2 competitively binds with SPOP, inhibits PD-L1 ubiquitination and promotes immune escape.	(31)
Yu *et al*, 2024		SPOP	Hepatocellular cancer	BCLAF1 binds to SPOP, inhibits PD-L1 ubiquitination and promotes immune escape.	(32)
Ding *et al*, 2023		SPOP	Non-small cell lung cancer	SGLT2 competitively binds PD-L1 with SPOP, inhibits PD-L1 ubiquitination and promotes immune escape.	(34)
Zhang *et al*, 2018		SPOP	Pan-cancer	CDK4 promotes SPOP phosphorylation, stabilizes SPOP expression, enhances K48-linked ubiquitination of PD-L1 and suppresses immune escape.	(33)
Sun *et al*, 2023		TRIM21	Non-small cell lung cancer	LINC02418 functions as a molecular sponge to form a ternary complex with TRIM21 and PD-L1, promoting PD-L1 ubiquitination and suppressing immune escape.	(35)
Gao *et al*, 2021		TRIM21	Non-small cell lung cancer	Promotes PD-L1 ubiquitination and inhibits immune evasion	(36)
Wu *et al*, 2021		ARIH1	Pan-cancer	GSK3α phosphorylates PD-L1, promotes ARIH1-mediated ubiquitination of PD-L1 and inhibits immune evasion.	(37)
Yu *et al*, 2023		MIB2	Pan-cancer	Promotes K63-linked ubiquitination of PD-L1 to facilitate immune evasion.	(43)
Lv *et al*, 2024		Skp2	Non-small cell lung cancer	Promotes K63-linked ubiquitination of PD-L1 to facilitate immune evasion	(44)
Jing *et al*, 2022		NEDD4	Gallbladder cancer	Promotes K48-linked ubiquitination of PD-L1 to inhibit immune evasion.	(42)
Li *et al*, 2016		β-Trcp	Breast cancer	Promotes PD-L1 ubiquitination to inhibit immune evasion.	(41)
Yang *et al*, 2022		ITCH	Melanoma	Promotes PD-L1 ubiquitination to inhibit immune evasion.	(39)
Wei *et al*, 2022		RNF125	Breast cancer	Promotes K48-linked ubiquitination of PD-L1 to inhibit immune evasion.	(38)
Xiao *et al*, 2023	DUBs	USP5	Breast cancer	Promotes PD-1 deubiquitination to facilitate immune evasion.	(63)
Yang *et al*, 2023		USP8	Pancreatic cancer	Promotes PD-L1 deubiquitination by inhibiting USP8 with DUBs-IN-2, thereby suppressing immune evasion.	(52)
Wang *et al*, 2021		USP7	Gastric cancer	Promotes PD-L1 deubiquitination to facilitate immune evasion.	(51)
Yu *et al*, 2023		USP7	Pan-cancer	A11 competitively binds PD-L1 with USP7, inhibits PD-L1 deubiquitination and suppresses immune evasion.	(57)

Table II. Continued.

First author/s, year	Enzyme type	Cancer	Effect on immunotherapy	(Refs.)
Huang *et al*, 2024	USP22	Colorectal cancer	Promotes PD-L1 deubiquitination to facilitate immune evasion.	(56)
Liu *et al*, 2021	OTUB1	Non-small cell lung cancer	Promotes PD-L1 deubiquitination to facilitate immune evasion.	(61)
Lim *et al*, 2016	CSN5	Breast cancer	TNF-α upregulates CSN5 expression and activity via the NF-κB signaling pathway, promotes PD-L1 deubiquitination and facilitates immune evasion.	(62)
Zhu *et al*, 2021	OTUB1	Pan-cancer	Promotes PD-L1 deubiquitination to facilitate immune evasion.	(59)
Ren *et al*, 2024	OTUB2	Pan-cancer	Promotes PD-L1 deubiquitination and enhances anti-tumor efficacy using OTUB2-IN-1.	(60)
Huang *et al*, 2019	USP22	Hepatocellular cancer	Promotes PD-L1 deubiquitination to facilitate immune evasion.	(55)
Kuang *et al*, 2023	USP2	Pan-cancer	Promotes PD-L1 deubiquitination to facilitate immune evasion.	(54)
Xiong *et al*, 2022	TRAF6	Pan-cancer	Promotes K63-linked ubiquitination of PD-L1 to facilitate immune evasion.	(53)

ALDH2, aldehyde dehydrogenase 2; ARIH1, ariadne RBR E3 ubiquitin protein ligase 1; BBR, berberine; BCLAF1, BCL2-associated transcription factor 1; β-Trcp, beta-transducin repeat-containing protein; c-Cbl, Casitas B lymphoma; CDH1, cadherin 1; CDK1, cyclin-dependent kinase 1; CDK4, cyclin-dependent kinase 4; CSN5, COP9 signalosome subunit 5; DUBs, deubiquitinating enzymes; protein 4; FBW7, F-box and WD repeat domain-containing 7; FBXO38, F-box protein 38; GSK3α, glycogen synthase kinase 3 alpha; IL-2, interleukin-2; IL-18, interleukin-18; ITCH, itchy E3 ubiquitin protein ligase; K48, Ubiquitin Lysine 48-linked; K63, Ubiquitin Lysine 63-linked; KLHL22, kelch-like protein 22; MIB2, mind bomb E3 ubiquitin protein ligase 2; NEDD4, neural precursor cell expressed developmentally downregulated 4; OTUB1, OTU deubiquitinase, ubiquitin aldehyde binding 1; OTUB2, OTU deubiquitinase, ubiquitin aldehyde binding 2; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; RNF125, ring finger protein 125; SGLT2, sodium-glucose cotransporter 2; Skp2, S-phase kinase-associated protein 2; STAT5, signal transducer and activator of transcription 5; SPOP, speckle-type POZ protein; TNF-α, tumor necrosis factor-alpha; TRAF6, TNF receptor-associated factor 6; Trim21, tripartite motif-containing protein 21; USP2, ubiquitin-specific peptidase 2; USP5, ubiquitin-specific peptidase 5; USP7, ubiquitin-specific peptidase 7; USP8, ubiquitin-specific peptidase 8; USP22, ubiquitin-specific peptidase 22;

For example, the small-molecule agonist AK087 of ITCH can effectively promote the ubiquitination and degradation of PD-L1 mediated by ITCH and markedly inhibit the resistance of tumors to anti-PD-1/PD-L1 treatment (39). The USP8 inhibitor DUB-IN-2 can effectively inhibit the deubiquitination process of PD-L1 mediated by USP8. This action notably inhibits tumor immune evasion and can effectively improve the efficacy of tumor immunotherapy (53). The small-molecule compound ML364 directly binds to USP2 and inhibits its deubiquitinase activity (77). The UPS not only determines the protein stability of PD-L1, but also forms a 'positive-negative feedback' loop with the IFN-γ/JAK-STAT signaling pathway through key nodes including TRIM25/SOCS1/USP18. Targeting this regulatory loop can amplify or suppress IFN-γ signaling across different cancer types, thereby guiding combination strategies between UPS inhibitors and immune checkpoint inhibitors (78,79).

This therapeutic model targeting the UPS has a unique mechanism of action. Instead of directly blocking protein functions, it regulates the stability and degradation of proteins from the source, thereby affecting the levels of abnormal proteins. Meanwhile, this therapeutic model has precise targeting ability, which can reduce the biological toxicity caused by broad-spectrum inhibition. Due to tissue specificity, the functions of E3 ubiquitin ligases also vary. The 'functional switch' of the same E3 ubiquitin ligase in different cancers is collectively determined by protein expression in the tumor microenvironment, signaling pathways and post-translational modifications. For instance, the mutational inactivation and dysregulated expression of SPOP in various types of cancer can affect its E3 ubiquitin ligase activity. Notably, Skp2-mediated PD-L1 K63 ubiquitination in non-small cell lung cancer depends on LKB1 inactivation (Fig. 2), whereas BRAF inhibitors in melanoma suppress PD-L1 ubiquitination by inhibiting the ERK-GSK3β-β-TrCP axis (41,80). This explains the reason Skp2 inhibitors (compound #25) can enhance the efficacy of PD-1 antibodies in non-small cell lung cancer, while melanoma requires combined MAPK inhibition to relieve β-TrCP suppression. For example, preclinical data on the USP7 inhibitor P5091 in gastric cancer showed that *H. pylori*-positive patients (with concomitant USP7 overexpression) had a 3.2-fold higher response rate compared with negative patients ($P<0.01$), suggesting that future trials should stratify patients based on microbiome-UPS co-mutation status (51). By contrast, a phase II trial of the CSN5 inhibitor curcumin in TNBC (trial no. NCT00094445) demonstrated limited efficacy due to the lack of screening for CSN5-high populations, highlighting the necessity of biomarker-guided therapy. Although UPS-targeted drugs such as USP8 inhibitors may develop resistance due to mutations or compensatory pathways, current evidence suggests that such resistance mechanisms are independent of PD-1/PD-L1 ubiquitination regulation. Future studies should explore whether resistance to UPS-targeted drugs upregulates PD-L1 through non-UPS pathways such as through transcriptional reprogramming or exosome release, thereby indirectly leading to immunotherapy failure. It is recommend that future studies employ cancer-specific organoid models to validate UPS-targeting drugs, thereby mimicking the effect of stromal cells on ubiquitination regulation within the tumor microenvironment.

Although some molecular drugs targeting the UPS have achieved preliminary progress in improving tumor immunotherapy, the number of those in clinical verification stage is still limited. As of November 2024, <20 UPS-targeting agents have entered clinical stages globally, with most concentrated in the proteolysis-targeting chimera (PROTAC). Notably, UPS modulators specifically targeting PD-1/PD-L1 remain in Phase I or earlier development (81). High expression of E3 ubiquitin ligases such as CRBN and VHL in the liver and kidneys often leads to hematological and renal toxicity, Excessive PROTACs may form nonfunctional binary complexes, disrupting UPS activity and causing drug 'rebound effects' (82). Dong *et al* (83) encapsulated VPS18/11 inhibitors such as RD-N into lung-targeted nanoparticles, effectively reversing tumor resistance and suppressing metastasis. Similar strategies could enable tissue-specific delivery of deubiquitinase inhibitors, minimizing off-target effects and systemic toxicity. UPS gene mutations or compensatory pathway activation can result in adaptive resistance during long-term treatment (84). Real-time drug concentration tracking, combined with artificial intelligence and machine learning-based predictive models, may optimize pharmacokinetic profiles and address long-term adaptive resistance.

The PROTAC technology, as an emerging therapeutic strategy for targeted protein degradation in recent years, has gradually attracted widespread attention (85,86). The PROTAC consists of three parts: i) A target protein-binding ligand; ii) an E3 ligase ligand; and iii) a linker. Its main mechanism of action is to induce the binding of the E3 ligase to the target protein, mediate the ubiquitination of the target protein and subsequently promote the degradation of the target protein (87). This technology has overcome the limitation of the 'undruggable' status of certain proteins and can reversibly regulate the expression levels of proteins over time. However, PROTAC drugs usually have a relatively large molecular weight, which leads to limited bioavailability. Therefore, the drug design of PROTAC still needs further optimization.

Conventional PROTACs suffer from high molecular weight, poor membrane permeability and low oral bioavailability, leading to weak *in vitro-in vivo* association and limited clinical translation. To overcome these hurdles, Sun *et al* (88) developed tumor microenvironment (TME)-responsive enzyme-activated click-forming PROTACs (ENCTACs). By exploiting cathepsin B overexpressed in >90% of solid tumors as a biological trigger, an orthogonal cleavage-click reaction assembles the active degrader *in situ*, selectively eliminating the epigenetic regulator BRD4 and consequently downregulating PD-L1 to remodel the immune microenvironment. In the 4T1 TNBC mouse model, ENCTACs achieved a 65% tumor-growth inhibition, a three-fold deeper tissue penetration and negligible systemic toxicity compared with traditional PROTACs. In parallel, a recent study conjugated a CD47 antibody with a folate ligand to create a Folate Receptor Targeting Chimera (FRTAC). Leveraging the high folate-receptor expression on cancer cells, FRTAC drives CD47 into lysosomal degradation via receptor-mediated endocytosis, markedly potentiating macrophage-mediated phagocytosis while sparing normal tissues (89). At present, multiple PROTAC drugs for tumor treatment have entered the clinical stage, such as ARV-110 for

prostate cancer (90) and ARV-471 for ER^+ breast cancer (91). Looking ahead, next-generation PROTAC platforms that integrate TME-specific activation with nanoparticle-based delivery are poised to surmount the dual barriers of cellular permeability and off-target toxicity, offering unprecedented opportunities for cancer immunotherapy.

In conclusion, the present review discussed the potential molecular mechanisms by which the UPS plays a role in tumor immune evasion and resistance to anti-PD-1/PD-L1 therapy and has summarized the potential targeted drugs that can inhibit tumor immune evasion and overcome resistance to immune checkpoint therapy by targeting the UPS. Future research should focus on the following key aspects: i) Further in-depth exploration of the regulatory mechanisms of the UPS on various immune checkpoints in different tumor types and immune microenvironments; ii) optimization of the design of targeted UPS drugs to improve their targeting ability and bioavailability; and iii) development of combined treatment regimens of immune checkpoint inhibitors and targeted UPS drugs to enhance the synergistic therapeutic effect. These research directions will lay a solid theoretical foundation for the development of the next-generation precision immunotherapy strategies.

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Availability of data and materials

Not applicable.

Authors' contributions

LHG and WLD were involved in conceptualization. LHG, AG, YYD, XJW, HXZ and WLD performed the literature search, data collection and writing. WLD and BGZ reviewed and edited the manuscript. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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