Epigenetic modifications: Critical participants of the PD-L1 regulatory mechanism in solid tumors (Review)

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Abstract. Immune checkpoint inhibitors targeting the programmed cell death protein 1 (PD-1)/programmed death ligand 1 (PD-L1) axis have achieved marked and durable efficacy in patients with different solid tumors and have improved their survival. However, the presence of primary or acquired resistance to immune checkpoint blockades results in only a small fraction of patients benefiting from the treatment. An increasing number of preclinical studies have reported that PD-L1 expression in tumor cells is involved in a number of epigenetic changes, including histone modifications, non-coding RNA regulation and DNA methylation. In addition, multiple epigenetic targeting drugs have been demonstrated to directly or indirectly interfere with PD-L1 expression in various cancer models. This provides opportunities to better characterize the regulatory mechanisms of PD-L1 expression and explore novel therapeutic strategies to improve immunosuppressant response rates and overcome drug resistance. The present review focuses on the latest findings and evidence on the epigenetic mechanism regulating PD-L1 expression and discusses the biological and clinical implications of this regulatory mechanism in solid tumors. A rational combination of epigenetic regulation and PD-1/PD-L1 axis blockade may improve the prognosis of patients with solid tumors.

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1. Introduction

Programmed death ligand 1 (PD-L1) is a type I transmembrane protein encoded by the CD274 gene (1,2). Immunohistochemical detection has revealed that PD-L1 mRNA and protein expression is upregulated in various cancer types (3). However, since PD-L1 mRNA is strictly post-transcriptionally regulated under normal physiological conditions, PD-L1 protein is scarcely expressed in normal cells (4). As a key member of the immune checkpoints, PD-L1, together with its receptor programmed cell death protein 1 (PD-1), serves an important role in tumor cell clearance and immune surveillance by mediating signaling processes that limit autoimmunity and prevent excessive immune responses (5). In addition, quantification of PD-L1 expression by immunohistochemistry on different detection platforms has been used in various clinical trials as a key determinant of the efficacy of checkpoint immunotherapy (6).

As one of the most promising approaches to activate the immune system, immune checkpoint blockade has achieved remarkable efficacy in antitumor therapy in the last decade (7). In addition, the exploration of drugs targeting the PD-1/PD-L1 axis has led to the development of a number of immune...
checkpoint inhibitors (ICIs), such as anti-PD-L1 monoclonal antibodies (atezolizumab, durvalumab and avelumab) and anti-PD-1 monoclonal antibodies (nivolumab, pembrolizumab and tislelizumab), which have become first-line therapy for various solid tumors (3,8,9). These ICIs enhance the immune system surveillance capacity and generate antitumor immune responses by manipulating the interaction between PD-L1 and PD-1, leading to improved overall survival (OS) and progression-free survival (PFS) of patients with cancer (3,10).

However, due to the diversity and complexity of the tumor immune microenvironment and the continuous genetic changes in tumor cells, immunotherapy is ineffective in most patients with advanced tumors (11,12). In addition, the complex drug resistance mechanism of cancer cells to immunotherapy influences the clinical outcomes of patients with cancer (13). Therefore, a combination therapy to improve the response rate to PD-1/PD-L1 blockade and overcome resistance to anti-PD-1/PD-L1 therapy is urgently required. Epigenetic modifications that serve an important role in interactions between the tumor microenvironment and tumor cells and in the development of cancer cells represent such opportunities (14).

Epigenetic modifications are heritable changes in gene expression caused by environmental, dietary, age and disease factors that do not include changes in the DNA sequence itself (15). Epigenetic modifications can reshape the tumor microenvironment and alter cellular phenotypes through aberrant histone patterns, non-coding RNAs levels and DNA methylation at specific promoters, enabling cells to grow and evade immune surveillance (16). Since epigenetic modifications are susceptible to external factors and are often reversible, they are considered to be potential therapeutic targets for various cancer types (17). Azacitidine, the first epigenetic drug approved by the Food and Drug Administration (FDA), marks a breakthrough in epigenetic medicine from theory to application (18). Tazemetostat, a small-molecule inhibitor of the histone methyltransferase enhancer of zeste homolog 2 (EZH2), has recently been approved by the FDA to treat solid tumors, including relapsed or refractory follicular lymphoma and locally advanced or metastatic epitheloid sarcoma (19). In addition, multiple DNA methyltransferase (DNMT) inhibitors and histone-modifying enzyme inhibitors have shown promising therapeutic effects in solid tumors highlighting the potential of epigenetic therapy in the treatment of solid tumors (20,21).

Detailed descriptions of the resistance mechanisms of ICIs targeting the PD-1/PD-L1 axis have been provided in several studies (22,23); therefore, these are only briefly summarized in the present review. In addition, the latest research progress and related mechanisms of epigenetic factors interfering with PD-L1 expression, including histone modifications such as acetylation and methylation, non-coding RNA regulation and DNA methylation, in solid tumors are summarized and discussed (Fig. 1). Among them (Table 1), a variety of chromatin-modifying enzymes can regulate PD-L1 expression by affecting the modifications that occur on lysine and arginine residues (24-26). Noncoding RNAs can inhibit PD-L1 expression by binding to the 3' UTR or act as upstream regulators of the PD-1/PD-L1 axis (27-29). The research on DNA methylation mainly focuses on its effect on the PD-L1 promoter (30). The present review aims to provide novel insights for further development of potential combination therapy strategies to improve the response rate and tolerability of immunotherapy in solid tumors.

2. Resistance mechanisms of ICIs targeting the PD-1/PD-L1 axis

ICIs that target the PD-1/PD-L1 axis have been extensively studied (31-33). Their mechanisms of action are mainly based on the following phenomena: i) Antigen-specific T cells are activated upon recognition of tumor antigens presented by major histocompatibility complex (MHC) on antigen-presenting cells, and subsequently, activated T cells release IFN-γ to upregulate PD-L1 expression on tumor cells (34); and ii) PD-L1 binds to PD-1 on the surface of T cells, triggering the negative regulation of the PD-1/PD-L1 axis, which will inhibit the antitumor effect of T cells (35,36). ICIs targeting the PD-1/PD-L1 axis reinvigorate T cells that were inactive because of the PD-1/PD-L1 signaling inhibition, and thereby, exert antitumor effects (36).

However, clinical data have indicated limited ICI efficacy in a large group of patients with primary resistance unresponsive to PD-1/PD-L1 blockade or acquired resistance after initial response (13). To the best of our knowledge, due to the complexity of antitumor immunity, the exact mechanism of resistance to ICIs targeting the PD-1/PD-L1 axis has not been fully elucidated or extensively reviewed. Resistance is triggered by various complex mechanisms (Fig. 2). Mechanisms leading to primary resistance include insufficient immunogenicity of tumor antigens formed by non-mutated proteins or mutant proteins that are not fully tolerated by T cells, irreversible exhaustion of T cells because of multiple inhibitory axes in the tumor microenvironment, which prevent tumor-specific T cells from becoming memory T cells, dysfunction of MHC class I complexes caused by β-2-microglobulin mutations, resistance to IFN-γ signaling caused by Janus kinase (JAK)1/2 mutations, and immunosuppression because of immunosuppressive cells, cytokines and tumor metabolites in the tumor microenvironment (37-43). The mechanisms of acquired resistance are primarily associated with tumor subclones, leading to increased numbers of tumor cells that can escape antitumor immunity, re-exhaustion of T cells because of persistently high antigen levels and activation of compensatory inhibitory signals (44-46). As previously mentioned, the mechanism of resistance to ICIs targeting the PD-1/PD-L1 axis is a complex intervention system that is constantly being updated with the increasing understanding of immunotherapy.

3. Regulation of PD-L1 expression in solid tumors by histone modifications

As one of the components of eukaryotic nucleosomes, histones can acquire a diverse set of post-translational modifications (47), of which acetylation and methylation are the most studied ones. In cancer cells, these modifications can alter the structural attributes of chromatin, regulate the function of nucleosomes, and affect the expression of specific genes, such as PD-L1 (48,49). Furthermore, histone modification, a dynamic and reversible process, is influenced by a number of
chromatin-modifying enzymes that exist as multicomponent protein complexes (50). These enzymes are divided into writers, erasers and readers, according to their different functions (51). In multiple cancer types, including colon cancer and lung cancer, PD-L1 expression is affected by different chromatin-modifying enzymes, particularly histone deacetylases (HDAC) and histone methyltransferases (52,53).

**Regulation of PD-L1 expression in solid tumors by histone acetylation.** The acetylation of histones at their tail lysine residue can reduce the affinity of histones for DNA by neutralizing positive charges, which will facilitate chromatin opening and transcription (51). Enhancement of histone H3 acetylation in the PD-L1 promoter is involved in PD-L1 expression in various drug-resistant cancer cells, including those of breast cancer, lung cancer and hepatocellular carcinoma (12). Histone acetylation serves as a key mediator in the regulation of gene expression, the levels and states of which are influenced by the balance of factors opposing HDACs and histone acetyltransferases (HATs) (54). HDACs are involved in regulating the transcription of PD-L1 by removing acetyl groups of lysine residues from histone substrates (12).

HDAC3 is the key HDAC isoform responsible for regulating PD-L1 transcription in tumors (55). Inhibition of HDAC3 expression can increase IFN-γ production and PD-L1 promoter region histone acetylation, thereby activating PD-L1 transcription in tumor cells and increasing the levels of PD-L1 in dendritic cells in the tumor microenvironment (55,56). Furthermore, HDAC3 maintains PD-L1 expression by inhibiting histone H3 acetylation at the PD-L1 promoter in drug-resistant cells of lung cancer, breast cancer and hepatocellular carcinoma (12). As an oncogenic transcription factor, STAT3 is activated in various cancer types, such as pancreatic cancer, breast cancer and osteosarcoma, and thus, affects the expression and transcription of genes involved in cellular immune responses, proliferation and chemoresistance (57). HDAC3 upregulates PD-L1 expression in pancreatic cancer by intervening in the STAT3 signaling pathway (58). In primary melanoma, HDAC8 can inhibit PD-L1 expression by controlling the transcriptional activation of PD-L1 by acting on STAT3-containing transcriptional complexes (59). HDAC6 upregulates PD-L1 expression in melanoma and osteosarcoma by recruiting and activating the transcription factor STAT3 (60,61). In addition, HDAC6 expression is positively associated with PD-L1 expression in ovarian cancer (62). HDAC10, another member of the class IIB HDAC family, has been reported to be positively associated with PD-L1 expression in patients with lung cancer (63).
### Table I. Epigenetic modifications of PD-L1 in solid tumors.

#### A. Histone acetylation

| First author/s, year | Tumor types | Key findings | (Refs.) |
|----------------------|-------------|--------------|---------|
| Wang et al, 2020     | Breast cancer | HDAC3 could maintain PD-L1 expression by inhibiting histone H3 acetylation at the PD-L1 promoter | (12) |
| Shen et al, 2021     | Breast cancer | HDAC1/2 could be recruited by TET2 proteins to the PD-L1 promoter to deacetylate H3K27ac and thereby inhibit the transcription of PD-L1 | (24) |
| Xu et al, 2021       | HDAC2 could affect IFN-γ-induced PD-L1 expression by activating the JAK-STAT1 pathway | (64) |
| Darvin et al, 2019   | HDAC1 and HAT affected EMT-induced upregulation of PD-L1 expression | (65) |
| Wang et al, 2020     | Lung cancer | HDAC3 could maintain PD-L1 expression by inhibiting histone H3 acetylation at the PD-L1 promoter | (12) |
| Liu et al, 2020      | HDAC10 was positively associated with PD-L1 expression | (63) |
| Shin et al, 2022     | PD-L1 protein expression levels were dose-dependently decreased by Nexturastat A | (79) |
| Briere et al, 2018   | Mocetinostat upregulated PD-L1 | (71) |
| Wang et al, 2020     | Hepatocellular carcinoma | HDAC3 could maintain PD-L1 expression by inhibiting histone H3 acetylation at the PD-L1 promoter | (12) |
| Mondello et al, 2020 | Lymphomas | HDAC3 inhibition led to the upregulation of PD-L1 expression | (56) |
| Huang et al, 2018    | Lymphomas | Class I-selective HDACis upregulated PD-L1 expression | (74) |
| Deng et al, 2019     | HDAC3 inhibitors could rapidly increase recruitment of bromodomain protein BRD4 at the promoter region of the PD-L1 gene, leading to activation of its transcription | (55) |
| Wang et al, 2018     | Pancreatic cancer | HDAC3 regulated PD-L1 expression by intervening in the STAT3 signaling pathway | (59) |
| Fan et al, 2019      | Pancreatic cancer | Upregulation of HAT1 expression is not only associated with poor prognosis but can also enhance PD-L1 transcription by promoting the binding of BRD4-containing complex to acetylated histone H4 | (25) |
| Hu et al, 2019       | Melanomas | HDAC8 participated in the transcriptional activation of PD-L1 by acting on STAT3 containing transcriptional complexes | (58) |
| M et al, 2016        | Osteosarcoma | HDAC6 controlled PD-L1 expression by affecting the recruitment and activation of STAT3 | (60) |
| Woods et al, 2015    | Osteosarcoma | Class I HDACis upregulated PD-L1 expression | (75) |
| Keremu et al, 2019   | Osteosarcoma | Transcription factor STAT3 mediated the regulation of PD-L1 expression by HDAC6 | (61) |
| Que et al, 2021      | Chondrosarcoma | Chidamide upregulated PD-L1 expression by activating the transcription factor STAT1 | (72) |
| Sheikh et al, 2021   | Chondrosarcoma | Class I HDACis elevated PD-L1 expression | (73) |
| Liu et al, 2020      | Prostate cancer | SAHA increased the histone H3 acetylation of the CD274 promoter to induce CD274 transcription, which led to the upregulation of PD-L1 expression | (76) |
| Shi et al, 2021      | Colorectal cancer | Romidepsin increased PD-L1 expression through regulation of histone acetylation | (52) |
| Chen et al, 2019     | Colorectal cancer | MPT0G612 downregulated PD-L1 expression induced by IFN-γ | (78) |
| Kuroki H, 2021       | Urothelial cancer | Inhibition of HDAC6 resulted in decreased expression levels of PD-L1 | (80) |

#### B. Histone methylation

| First author/s, year | Tumor types | Key findings | (Refs.) |
|----------------------|-------------|--------------|---------|
| Sasidharan, 2020     | Colorectal cancer | Transcriptional upregulation of PD-L1 was positively associated with H3K4me3 and negatively associated with H3K9me3 | (84) |
| Nair et al, 2020     | Colorectal cancer | | |
## Table I. Continued.

### B. Histone methylation

| First author/s, year | Tumor types          | Key findings                                                                 | (Refs.) |
|----------------------|----------------------|------------------------------------------------------------------------------|---------|
| Liu et al., 2021     | Silencing of KDM4B reduced PD-L1 expression by promoting H3K27me3 expression and decreasing HOXC4 expression | (90)    |
| Liu et al., 2021     | IOX1 downregulated PD-L1 expression in a concentration-dependent manner | (93)    |
| Darvin et al., 2019  | Breast cancer        | Inhibitory histones H3K9me3 and H3K27me3 regulated PD-L1 expression           | (65)    |
| Qin et al., 2019     | HCI-2509 upregulated PD-L1 expression in a dose-dependent manner            | (92)    |
| Liu et al., 2021     | IOX1 downregulated PD-L1 expression in a concentration-dependent manner   | (93)    |
| Jiang et al., 2021   | Cervical cancer       | PRMT5 promoted the transcription of STAT1, and thus, PD-L1 expression via symmetric dimethylation of histone H3R2 | (86)    |
| Lu et al., 2017      | Pancreatic cancer     | MLL1 catalyzed H3K4me3 to activate the transcription of PD-L1 by directly binding to the CD274 promoter | (26)    |
| Zingg et al., 2017   | Melanoma              | Knockdown of WDR5 reduced IFN-γ-induced PD-L1 mRNA and protein levels         | (87)    |
| Zhao et al., 2019    | Lung cancer           | EZH2 was positively associated with PD-L1 levels and regulated PD-L1 expression through HIF-1α | (89)    |
| Soldi et al., 2020   | Ovarian cancer        | SP-2577 promoted PD-L1 expression by inhibiting LSD1                           | (91)    |

### C. Histone phosphorylation

| First author/s, year | Tumor types          | Key findings                                                                 | (Refs.) |
|----------------------|----------------------|------------------------------------------------------------------------------|---------|
| Wang et al., 2021    | Hepatocellular carcinoma | EGF phosphorylated histone H3 at thr11, which induced PD-L1 expression | (30)    |

### D. miRNA

| First author/s, year | Tumor types          | Key findings                                                                 | (Refs.) |
|----------------------|----------------------|------------------------------------------------------------------------------|---------|
| Tang et al., 2018    | Lung cancer          | miR-3127-5p induced PD-L1 expression by promoting p-STAT3                    | (107)   |
| Xia et al., 2021     | Lung cancer          | Inhibition of miR-377-3p and miR-155-5p expression directly led to upregulated PD-L1 levels | (27)    |
| Hong et al., 2020;   | Ovarian cancer       | Overexpressed let-7 miRNA inhibited the mRNA levels of PD-L1                 | (109, 110) |
| Zhang et al., 2021   |                      | Overexpression of miR-140 suppressed PD-L1 expression by directly binding to its 3’ UTR | (111)   |
| Xie et al., 2018     |                      | miR-200b regulated PD-L1 expression and was negatively associated with PD-L1 expression | (113)   |
| Katakura et al., 2020| Ovarian cancer       | miR-200c decreased PD-L1 expression                                          | (114)   |
| Anastasiadou et al., 2021 | Ovarian cancer | miR-200c inhibited PD-L1 upregulation                                       | (115)   |
| Rogers et al., 2019  | Breast cancer        | miR-92 could upregulate PD-L1 expression by promoting YAP1 phosphorylation   | (118)   |
| Dou et al., 2020     |                      | miR-5119 improved antitumor immunotherapy efficacy possibly by downregulating PD-L1 expression | (119)   |
| Zhang et al., 2020   |                      | miR-570-3p inhibited proliferation, invasion and migration, and induced apoptosis by targeting CD274 | (120)   |
| First author/s, year        | Tumor types    | Key findings                                                                 | (Refs.) |
|-----------------------------|----------------|-------------------------------------------------------------------------------|---------|
| **D, miRNA**                |                |                                                                               |         |
| Yang et al, 2018            | miR-195 and miR-497 modulated CD274 expression by binding to the 3' UTR | (121)   |
| Li et al, 2019              | miR-3609 bound to the 3' UTR of PD-L1 to regulate PD-L1 expression          | (122)   |
| Yao et al, 2020             | Oral cancer    | miR-27a-3p could upregulate PD-L1 by activating the PTEN-AKT/PI3K pathway      | (125)   |
| Li et al, 2019              | Gastric cancer | miR-21 downregulated PTEN and thereby increased PD-L1 expression              | (126)   |
| Li et al, 2020              | Exosomal miR-16-5p specifically targeted and downregulated PD-L1           | (127)   |
| Miliotis et al, 2021        | miR-105-5p suppressed PD-L1 expression by directly targeting important cis-acting regulatory regions in the PD-L1 3' UTR | (128)   |
| Wang et al, 2012            | miR-148a-3p bound to the 3' UTR region of PD-L1 to reduce the levels of PD-L1 | (130)   |
| Liu et al, 2021             | miR-124 directly targeted a specific region in the PD-L1 3' UTR to downregulate its expression | (131)   |
| Bian et al, 2021            | HCG18 upregulated PD-L1 by sponging miR-20b-5p                             | (132)   |
| Javadashid et al, 2021      | miR-493 downregulated PD-L1 expression                                     | (136)   |
| Wang and Cao, 2021          | miR-612 reduced PD-L1 expression                                           | (137)   |
| Cioffi et al, 2017          | miR-93 and miR-106b can inhibit the expression of PD-L1 at the mRNA and protein levels | (138)   |
| Fan et al, 2022             | IncRNA KRT19P3 reduced PD-L1 expression                                    | (148)   |
| Zhang et al, 2020           | IncRNA GATA3-AS1 could regulate CSN5-mediated PD-L1 deubiquitination      | (149)   |
| Shang et al, 2019           | IncRNA OIP5-AS1 could trigger CD8+ T cell apoptosis by regulating PD-1/PD-L1 | (150)   |
| Chen et al, 2021            | IncRNA HOTTIP upregulated PD-L1 expression in neutrophils by promoting the secretion of IL-6 | (151)   |
| Huang et al, 2022           | SNHG12 increased the expression stability of PD-L1 through binding of the HuR gene | (152)   |
| Shi et al, 2022             | IncRNA IFITM4P upregulated PD-L1 expression                                | (153)   |
| Wang et al, 2021            | IncRNA HOTAIR activated the NF-kB pathway to abnormally express PD-L1     | (154)   |
| Mineo et al, 2020           | Primary transcript of IncRNA INCR blocks inhibition of the neighboring gene PD-L1 by binding to HNRNPH1 | (156)   |
| Xu et al, 2019              | IncRNA MIR17HG could increase PD-L1 expression by directly binding PD-L1  | (157)   |

| **E, lncRNA**               |                |                                                                               |         |
| Fan et al, 2022             | Breast cancer  | IncRNA KRT19P3 reduced PD-L1 expression                                    | (148)   |
| Zhang et al, 2020           | Esophageal cancer | IncRNA GATA3-AS1 could regulate CSN5-mediated PD-L1 deubiquitination      | (149)   |
| Shang et al, 2019           | Esophageal cancer | IncRNA OIP5-AS1 could trigger CD8+ T cell apoptosis by regulating PD-1/PD-L1 | (150)   |
| Chen et al, 2021            | Ovarian cancer  | IncRNA HOTTIP upregulated PD-L1 expression in neutrophils by promoting the secretion of IL-6 | (151)   |
| Huang et al, 2022           | Lung cancer     | SNHG12 increased the expression stability of PD-L1 through binding of the HuR gene | (152)   |
| Shi et al, 2022             | Oral cancer     | IncRNA IFITM4P upregulated PD-L1 expression                                | (153)   |
| Wang et al, 2021            | Glioma          | IncRNA HOTAIR activated the NF-kB pathway to abnormally express PD-L1     | (154)   |
| Mineo et al, 2020           | Renal cancer    | IncRNA MIR17HG could increase PD-L1 expression by directly binding PD-L1  | (157)   |
### Table I. Continued.

| E, lncRNA | First author/s, year | Tumor types | Key findings | (Refs.) |
|-----------|----------------------|-------------|--------------|--------|
| Ni et al, 2021 | | | When the expression of lncRNA SNHG29 was inhibited, PD-L1 expression was downregulated | (147) |

| F, circRNA | First author/s, year | Tumor types | Key findings | (Refs.) |
|------------|----------------------|-------------|--------------|--------|
| Li et al, 2021 | Lung cancer | hsa_circ_0003222 inhibition reduced anti-PD-L1 resistance in vivo | | (163) |

| G, DNA methylation | First author/s, year | Tumor types | Key findings | (Refs.) |
|---------------------|----------------------|-------------|--------------|--------|
| Lv et al, 2020 | Gastric cancer | PD-L1 promoter methylation was associated with PD-L1 protein expression | | (167) |
| Lu et al, 2021 | Chondrosarcomas | 5-azacytidine increased PD-L1 expression, gemcitabine inhibited PD-L1 expression | | (169) |
| Sheikh et al, 2021 | Hepatocellular carcinoma | DNMT inhibitors induced PD-L1 protein expression | | (73) |
| Liu J, 2017 | | High DNMT1 expression was positively associated with overexpression of PD-L1 in sorafenib-resistant cells | | (170) |
| Wang et al, 2021 | Melanoma | MEF2D methylation elevated PD-L1 expression | | (139) |
| Chatterjee et al, 2018 | Ovarian cancer | DNMT3A was inversely associated with PD-L1 expression, and DNMT inhibitors increased PD-L1 levels | | (171) |
| Peng et al, 2015 | Prostate cancer | DNMT inhibitors augmented the efficacy of PD-L1 blockade therapy | | (172) |
| Li et al, 2019 | Recombinant plasmids containing the C-terminal domains of both DNMT1 and DNMT3A methyltransferase inhibited PD-L1 expression more potently than DNMT3A alone | | (173) |
| Asgarova et al, 2018 | Non-small cell lung cancer | TGFβ1 induced PD-L1 promoter demethylation by reducing the content of DNMT1, which led to PD-L1 expression | | (175) |
| Zhang et al, 2017 | | Methylation of the PD-L1 promoter downregulated PD-L1 expression | | (176) |
| Lai et al, 2018 | | IFN-γ-related genes IRF-1 and IRF-7 were negatively associated with CD274 expression encoding PD-L1, and decitibine could demethylate IRF-1 and IRF-7, thereby restoring PD-L1 levels | | (177) |
| Mu et al, 2018; Briand J, et al 2019 | Gliomas | Hypomethylation of the PD-L1 promoter mediated overexpression of PD-L1 | | (178) |
| Elashi et al, 2018 | Breast cancer | Hypomethylation of the PD-L1 promoter mediated overexpression of PD-L1 | | (179) |
| Jacot et al, 2020 | Colorectal cancer | BRCA1 promoter hypermethylation was associated with PD-L1 expression | | (180) |
| Elashi et al, 2018 | | Hypomethylation of the PD-L1 promoter mediated overexpression of PD-L1 | | (180) |
HDAC1/2, which belong to the class I HDAC family, can be recruited by tet methylcytosine dioxygenase 2 proteins to the PD-L1 promoter to deacetylate H3K27 acetylation, thereby inhibiting the transcription of PD-L1 in breast cancer (24). Additionally, HDAC2 promotes PD-L1 expression by upregulating the phosphorylation of JAK1, JAK2 and STAT1, as well as translocation of STAT1 to the nucleus and recruitment of STAT1 to the PD-L1 promoter (64). HDAC1 expression is consistently upregulated in tumor spheres derived from breast cancer and affects the epithelial-mesenchymal transition (EMT)-induced upregulation of PD-L1 expression (65). In addition, EMT-induced upregulation of PD-L1 expression in breast cancer is also affected by HATs (65). HATs are involved in histone acetylation by catalyzing the transfer of acetyl groups (54). HAT1 was the first HAT to be discovered, HAT1 expression is upregulated in various solid tumors and HAT1 acts as a transcription factor to regulate the expression of multiple genes (66,67). In pancreatic cancer, upregulation of HAT1 expression is not only associated with poor prognosis but can also enhance PD-L1 transcription by promoting the binding of bromodomain-containing 4 (BRD4)-containing complex to acetylated histone H4 (25).

HDAC inhibitors (HDACis) can inhibit HDAC-mediated deacetylation, leading to the hyperacetylation of histones and re-expression of epigenetically silenced genes (68). At present, only a few HDACis, such as vorinostat, romidepsin, belinostat and Panobinostat, have been approved by the FDA to treat malignancies, while other HDACis are undergoing various clinical trials as options for the treatment of malignancies (69). HDACis exert antitumor effects by inducing cell apoptosis, inhibiting angiogenesis, and regulating cell autophagy and immune responses; however, to the best of our knowledge, the mechanisms by which they regulate PD-L1 have not been well defined (70,71).

Class I HDACis can elevate PD-L1 expression in a variety of tumors, including chondrosarcoma, Hodgkin’s lymphoma, melanoma, lung cancer, prostate cancer and colorectal cancer (52,71‑77). Among them, chidamide can upregulate PD-L1 expression in chondrosarcoma by activating the transcription factor STAT1 (72). In addition, it could enhance the antigen presentation process in a chondrosarcoma mouse model to improve therapeutic efficacy (72). When suberoylanilide hydroxamic acid is used to treat prostate cancer cells, it can increase histone H3 acetylation of the CD274 promoter to induce CD274 transcription, leading to upregulation of PD-L1 expression (76). As a naturally occurring selective inhibitor of HDACs 1 and 2, romidepsin increases PD-L1 expression in colorectal cancer, mainly through the regulation of histone acetylation and the transcription factor BRD4 (52). Furthermore, HDAC6 inhibitors, as class II HDACis, can dose-dependently reduce PD-L1 expression in colorectal, lung and urothelial cancer (78‑80). A study suggests that HDACis can enhance the response to immunotherapy via increasing tumor antigen levels and reactivation of proapoptotic genes (81). However, HDACis have side effects, such as lymphopenia, that limit the efficacy of immunotherapy (82).

Regulation of PD-L1 expression in solid tumors by histone methylation. Histone methylation is a reversible process on arginine and lysine residues: Arginine is symmetrically or
asymmetrically methylated, while lysine can be monomethylated, dimethylated or trimethylated (83). Among these, H3K4, H3K36 and H3K79 are associated with transcriptional activation of genes, whereas H3K9, H3K27 and H4K20 are associated with the transcriptional repression of genes (83). For example, in colorectal cancer, the transcriptional upregulation of PD-L1 is positively associated with H3K4me3 and negatively associated with H3K9 tri-methylation (H3K9me3) (84). Inhibitory H3K9me3 and H3K27me3 also regulate PD-L1 expression in breast cancer tumor-forming cells (65).

Histone methylation is a complex modification process regulated by various methyltransferases and demethylases. Protein arginine methyltransferase 5 (PRMT5) catalyzes the symmetric dimethylarginine of histone and non-histone proteins and is closely associated with tumor cell proliferation, invasion and metastasis (85). In cervical cancer, PRMT5...
promotes the transcription of STAT1, and thus, PD-L1 expression through symmetric dimethylation of histone H3R2 (86). As one of the H3K4 methylation-specific histone methyltransferases, mixed lineage leukemia 1 catalyzes H3K4me3 to activate the transcription of PD-L1 in pancreatic cancer cells by directly binding to the CD274 promoter (26). Knockdown of WD repeat domain 5, a key component of the patient SE transcription locus 1/MLL histone methyltransferase complex, reduces IFN-γ-induced PD-L1 mRNA and protein levels in prostate cancer (87). EZH2 is a core component of the polycomb repressive complex 2 and possesses histone methyltransferase activity (88). In melanoma, EZH2 inactivation can lead to decreased PD-L1 mRNA levels (53). Similarly, EZH2 is also positively associated with PD-L1 levels in lung cancer tissues and regulates PD-L1 expression through hypoxia-inducible factor 1-α (89).

Lysine demethylase 4B (KDM4B) is a demethylase that acts on lysine, and its silencing can reduce PD-L1 expression by promoting H3K27me3 expression and reducing homeobox C4 (HOXC4) expression in colorectal cancer cells (90). In addition, lysine-specific histone demethylase 1 (LSD1) regulates the chromatin landscape and gene expression by demethylating proteins, such as histone H3 (91). H3C-2509, a noncompetitive highly potent reversible LSD1 inhibitor, upregulates PD-L1 expression in breast cancer cells in a dose-dependent manner (92). SP-2577, which is currently undergoing a phase I clinical trial, is also a potent and reversible LSD1 inhibitor that can promote PD-L1 expression in small cell carcinoma of the ovarian hypercalcemic type cells by inhibiting LSD1 (91). Based on these developments, LSD1 inhibition may be a promising epigenetic adjunctive therapy to ICIs. In addition, 5-carboxy-8-hydroxyquinoline (IOX1), a histone demethylase inhibitor that inhibits Jumonji domain 1A of histone demethylases, can downregulate PD-L1 expression in a concentration-dependent manner in various cancer cells, including CT26, HCT116 and MCF-7 cells (93). IOX1 could also reverse doxorubicin-induced upregulation of PD-L1 expression (93).

4. Regulation of PD-L1 expression in solid tumors by non-coding RNAs

Non-coding RNAs are an abundant component of the human transcriptome. Since ncRNAs have the ability to regulate gene expression, protein translation and growth pathways, they can regulate a variety of cellular processes, such as growth, differentiation and drug resistance, which are highly related to the occurrence and development of cancer (99). Furthermore, non-coding RNAs, particularly microRNAs (miRNAs/miRs), long non-coding RNAs (lncRNAs) and circular RNAs (circRNAs), can regulate the expression of immune genes, such as PD-L1, in a variety of tumors, thereby serving an important role in immunotherapy (100).

Regulation of PD-L1 expression in solid tumors by miRNAs. miRNAs are highly conserved small non-coding RNAs comprising 19-22 nucleotides that inhibit gene expression by binding to complementary nucleotides in the 3’ untranslated region (3’ UTR) of mRNA targets (101,102). The mechanism of this interaction occurs under both physiological and pathological conditions, and thus, serves an important role in a number of biological processes, including cell proliferation, metastasis, apoptosis and metabolism (103,104). Aberrant miRNA expression during tumorigenesis can affect several cancer-related signaling pathways and transcripts, thereby aberrantly expressed miRNAs are becoming important diagnostic markers and attractive therapeutic candidates for multiple cancer types (105). In addition, a study has indicated that miRNAs can exert profound regulatory effects on the expression levels of PD-L1 through complex regulatory mechanisms (106).

In lung cancer, elevated levels of PD-L1 promote cell proliferation, invasion, migration and immune escape, and contribute to chemoresistance (107). miR-3127-5p induces PD-L1 expression in lung cancer cells by promoting phosphorylation of STAT3 (107). PD-L1 serves as a common downstream target of miR-377-3p and miR-155-5p, and inhibiting their expression can directly lead to upregulated PD-L1 levels (27). Let-7 miRNA serves a tumor-suppressive role in multiple cancer types by participating in the post-transcriptional expression of PD-L1 and has been implicated in the regulation of tumor immunotherapy (28,108). Hong et al (109) reported that Let-7 miRNA could be enriched by probes in the 3’ UTR region of PD-L1 mRNA in lung cancer cells, and overexpression of Let-7 miRNA could inhibit PD-L1 mRNA expression in lung cancer cells (110). Similarly, overexpression of miR-140 can also suppress PD-L1 expression by directly binding to its 3’ UTR and participating in the miR-140/PD-L1/cyclin E pathway in lung cancer to regulate the cell cycle and proliferation (111).

The miR-200 family, consisting of five members, miR-200a, miR-200b, miR-200c, miR-429 and miR-141, has also been implicated in the regulation of PD-L1 and inhibition of tumor cell proliferation and migration (112). Among them, miR-200b may regulate PD-L1 expression in lung cancer cells and is negatively associated with PD-L1 expression in patients with lung cancer (113). miR-200c, which is located on chromosome 12p13, can inhibit PD-L1 upregulation in ovarian and breast cancer cells to slow cell proliferation (114,115). In breast cancer, high PD-L1 expression is associated with poor
prognosis (116,117), and miR-92 can upregulate PD-L1 expression by promoting YAP1 phosphorylation (118). miR-5119 improved antitumor immunotherapy efficacy in a mouse breast cancer model, possibly by downregulating PD-L1 expression (119). Furthermore, miR-570-3p, miR-195 and miR-497 induce apoptosis in breast cancer cells by binding to the 3' UTR to regulate CD274 expression (120,121). miR-3609 can also bind to the 3' UTR of PD-L1 to regulate its expression and reverse the chemoresistance of breast cancer cells by blocking the PD-L1 immune checkpoint (122).

Exosomes, subcellular vesicles with a diameter of 30-150 nm, contain numerous miRNAs, mRNAs and functional proteins, which are released after fusion of multivesicular bodies with the cell surface (123). Therefore, the identification of exosome contents may provide more information about specific tumor biomarkers. As an important part of the tumor microenvironment, exosomes are one of the most important factors in promoting tumor metastasis and progression by regulating immune responses, promoting angiogenesis and blocking EMT (124). As one of the highly enriched miRNAs found in exosomes of breast cancer cells, miR-27a-3p can upregulate PD-L1 in macrophages and promote immune evasion of breast cancer cells by activating the PTEN-AKT/P3K pathway (125). PTEN expression is also inhibited by miR-21 mediated by oral cancer exosomes, which upregulate PD-L1 expression (126). Exosomal miR-16-5p can specifically target and downregulate PD-L1 in gastric cancer cells and block the PD-1/PD-L1 checkpoint to inhibit gastric cancer cell proliferation, leading to T-cell activation (127). Furthermore, aberrant expression of PD-L1 in gastric cancer is associated with miR-105-5p and miR-570 (128,129). In addition, miR-105-5p suppresses PD-L1 expression by directly targeting important cis-acting regulatory regions in the PD-L1 3' UTR to combat immune escape (128). Furthermore, guanine to cytosine mutations in the 3' UTR region can disrupt miR-570 binding, leading to upregulation of PD-L1 expression (129).

In colorectal cancer, PD-L1 expression has been demonstrated to be regulated by several miRNAs, such as miR-15a, miR-148a-3p, miR-124 and miR-20b-5p (90,130-132). miR-15a potently represses HOXC4 transcription by targeting KDM4B in colorectal cancer cells, thereby reducing PD-L1 expression and ultimately inhibiting immune evasion in colorectal cancer cells (90). miR-148a-3p may directly bind to the 3' UTR region of PD-L1 to reduce the level of PD-L1 on the surface of colorectal cancer cells to reduce T-cell apoptosis and restore its activity (130). It has been reported that the frequency and activity of regulatory T cells (Tregs) were increased in human cancer types and that PD-L1 may be involved in Treg development and enhance their immunosuppressive capacity (133,134). miR-124 can directly target a specific region in the PD-L1 3' UTR to downregulate its expression and inhibit Treg differentiation, thereby promoting T cell-mediated antitumor responses in colorectal cancer cells (131). HLA complex group 1B (HCG18) serves an oncogenic role as a competitive endogenous RNA for several miRNAs (135). In colorectal cancer, HCG18 promotes proliferation, inhibits apoptosis, upregulates PD-L1 by sponging miR-20b-5p, enhances resistance to cetuximab, and inhibits CD8α T-cell activation by targeting the miR-20b-5p/PD-L1 axis (132). In other cancer types of the digestive tract, several miRNAs exhibit inhibitory effects on the expression of PD-L1. Bian et al (136) found that miR-493 overexpression could downregulate PD-L1 expression in esophageal cancer. Transfection with miR-612 reduces PD-L1 expression in pancreatic cancer cells (137). In pancreatic cancer cells, miR-93 and miR-106b can inhibit the expression of PD-L1 at the mRNA and protein levels (138). A study has demonstrated that miR-329-3p inhibited PD-L1 expression by targeting and downregulating lysine demethylase 1A, and it enhanced the response of hepatocellular carcinoma cells to T cell-induced cytotoxic effects (139). Furthermore, miR-22 and miR-24 are negatively associated with plasma PD-L1 levels in renal cancer, suggesting that the miRNA network can suppress PD-L1 expression (140). Studies suggest that miRNA-based drugs (miRNA mimics or miRNA antagonists) are promising and may be a novel strategy for cancer treatment (141,142).

**Regulation of PD-L1 expression in solid tumors by IncRNAs.** IncRNAs, RNA transcripts of >200 nucleotides, do not have protein-coding potential, but appear to be less expressed than protein-coding genes and have more tissue-specific features (143,144). IncRNAs can target multiple mechanisms by affecting different genes, and their abnormal expression is associated with the occurrence of different diseases, particularly cancer (145). In particular, increasing evidence suggests that IncRNAs have significant potential in immunotherapy by regulating PD-L1 expression in the tumor microenvironment (146,147).

In breast cancer, IncRNA KRT19P3 may inhibit tumor progression by reducing PD-L1 expression in tumor cells and activating the tumor-killing potential of CD8α T cells (148). However, IncRNA GATA3-AS1 can promote immune evasion of breast cancer cells by regulating COP9 signalosome subunit 5-mediated PD-L1 deubiquitination (149). In esophageal cancer and ovarian cancer, IncRNAs can also mediate immune escape by affecting PD-L1 expression (29,150,151). After binding to glutathione peroxidase 4, IncRNA OIP5-AS1 can trigger CD8α T cell apoptosis by regulating PD-1/PD-L1, thus promoting immune escape of esophageal cancer cells (29). Furthermore, IncRNA HOTTIP upregulates PD-L1 expression in neutrophils by promoting the secretion of IL-6, thereby inhibiting T cell activity and antitumor immunity (150). Additionally, IncRNA PVT1 promotes PD-L1 expression in ovarian cancer by upregulating STAT3 phosphorylation levels (151). Furthermore, IncRNA small nuclear RNA host gene 12 promotes non-small cell lung cancer (NSCLC) cell proliferation and immune escape by increasing the expression stability of PD-L1 through binding of the human antigen R gene (152).

A study has demonstrated that IncRNA IFITM4P induced PD-L1 expression in oral cancer via two mechanisms (153). First, in the nucleus, IFITM4P decreases PTEN transcription by enhancing lysine demethylase 5A binding to the PTEN promoter, thereby upregulating PD-L1 expression (153). Second, in the cytoplasm, IFITM4P acts as a scaffold, promoting SAM and SH3 domain containing 1 binding and phosphorylating transforming growth factor β-activated kinase 1, which in turn increases the phosphorylation of NF-κB, while inducing PD-L1 expression (153). The IncRNA HOTAIR promotes the immune escape of glioma cells by activating...
the NF-κB pathway to abnormally express PD-L1 (154). It has been reported that IncRNAs could regulate different biological processes, including gene expression and RNA metabolism, after binding to protein partners (155). The primary transcript of IncRNA INCR blocks inhibition of the neighboring gene PD-L1 by binding to heterogeneous nuclear ribonucleoprotein H1 (156). Notably, in colorectal cancer, IncRNA MIR17HG can increase PD-L1 expression levels by directly binding PD-L1 (157). Furthermore, when IncRNA SNHG29 expression is inhibited, PD-L1 expression is downregulated in colorectal cancer cells to promote antitumor immunity (147).

**Regulation of PD-L1 expression in solid tumors by circRNAs.** circRNAs comprise a large class of endogenous non-coding RNAs with covalently closed loops that function independently of linear transcripts transcribed from the same gene (158). circRNAs are mostly generated through a process of ‘back splicing’, in which downstream splice donor sites are covalently linked to upstream splice acceptor sites, and are abundant in the cytoplasm (159). On the one hand, circRNAs can act as transcriptional regulators, miRNA sponges or protein decoys to serve an important role in tumor development and metastasis (160,161). On the other hand, circRNAs can alter drug concentrations in tumor cells by regulating the expression levels of related genes, such as multidrug resistance-associated protein-1 and multidrug resistance gene 1, which affects the drug resistance of tumor cells, such as glioma and liver cancer cells (162). In a mouse model of NSCLC, combined anti-PD-L1 and hsa_circ_0003222 inhibitory therapy not only reduced the tumor volume, but hsa_circ_0003222 inhibition also reduced the anti-PD-L1 resistance of NSCLC cells in vivo (163).

### 5. Regulation of PD-L1 expression in solid tumors by DNA methylation

As the most extensively studied type of epigenetic modification necessary for the regulation of gene transcription, DNA methylation is a covalent modification of the nucleotide cytosine at the 5-position (164). Although it does not alter the DNA sequence, it has an important effect on gene expression and is often associated with gene silencing (165). A study has demonstrated that DNA hypomethylation may lead to the expression of PD-L1 and inhibitory cytokines, which can be immunosuppressive (166). Therefore, the analysis of the specific mechanism of DNA methylation in regulating PD-L1 gene expression may have important clinical and biological implications.

In gastric cancer, PD-L1 promoter methylation is associated with PD-L1 protein expression, lymph node stage and the prognosis of advanced gastric cancer (167). A study has demonstrated that patients with gastric cancer with a methylated PD-L1 promoter exhibited shorter PFS and OS times than those without a methylated PD-L1 promoter (167). DNA methylation is mainly catalyzed by a family of DNMTs (168). In addition, 5-azacytidine, as a DNMT inhibitor, can increase PD-L1 expression in gastric cancer MKN-45 cells, whereas gemcitabine, a DNA demethylation inhibitor, can inhibit PD-L1 expression in these cells (169). Chondrosarcomas do not typically express PD-L1 to act as an immune-cold tumor; however, DNMT inhibitors can induce PD-L1 protein expression (73). In sorafenib-resistant hepatocellular carcinoma, high DNMT1 expression is positively associated with upregulation of PD-L1 expression (170). Myocyte enhancer factor 2D (MEF2D) is a transcription factor involved in a number of tumorigenic processes, and the reduction of MEF2D methylation increases its binding to the PD-L1 promoter and elevates PD-L1 expression in hepatocellular carcinoma (139). In melanoma, DNMT3A is inversely associated with PD-L1 expression at both the mRNA and protein levels, and treatment with DNMT inhibitors strongly increases PD-L1 levels on the surface of melanoma cells (171). DNMT inhibitors may also augment the efficacy of PD-L1 blockade therapy in ovarian cancer (172). Li et al (173) evaluated the synergistic effect of DNMT3A and DNMT1 on PD-L1 expression in DU145 prostate cancer cells. Recombinant plasmids containing the C-terminal domains of DNMT1 and DNMT3A methyltransferases inhibit PD-L1 expression more potently than those containing DNMT3A alone (173).

After EMT, tumor cells have increased capacities for proliferation and metastasis by evading the immune system (174). Asgarova et al (175) found that, during EMT signaling in NSCLC, TGFβ1 induced PD-L1 promoter demethylation by reducing the content of DNMT1, leading to the expression of PD-L1. In epidermal growth factor receptor tyrosine kinase inhibitor-resistant NSCLC, methylation of the PD-L1 promoter may contribute to the downregulation of PD-L1 expression (176). In anti-PD-1/PD-L1 therapy, IFN-γ-induced PD-L1 expression predicts a higher response rate (175). Lai et al (177) reported that the IFN-γ-related genes interferon regulatory factor (IRF)-1 and IRF-7, which are hypermethylated in lung cancer tissues, were negatively associated with CD274 expression. The methylation inhibitor decitabine can demethylate IRF-1 and IRF-7, thereby restoring PD-L1 levels (177). In gliomas, increased methylation of the PD-L1 promoter downregulates the mRNA and protein expression levels of PD-L1 (178). Therefore, hypomethylation of the PD-L1 promoter mediates upregulation of PD-L1 expression (179). A similar relationship has been demonstrated in patients with breast and colorectal cancer: The higher the hypomethylation levels were, the higher the PD-L1 expression levels were (180). In addition, PD-L1 expression in breast cancer cells is also associated with BRCA1 promoter hypermethylation (181). In patients with colorectal cancer, PD-L1 expression is more readily observed in microsatellite unstable cancers caused by mutL homolog 1 promoter methylation (182). The DNMT inhibitor 5-azacytidine also inhibits the downregulation of PD-L1 mRNA and protein levels in colorectal cancer cells (183).

### 6. Conclusions

This review summarizes the most comprehensive understanding of epigenetic factors affecting PD-L1 expression in solid tumors, including histone modifications, noncoding RNAs and DNA methylation (Table 1). In terms of their potential contribution to PD-L1 expression in solid tumors, studies of histone modifications have mostly focused on acetylation, methylation and phosphorylation (54,94). During this process, multiple chromatin-modifying enzymes, such as HDACs, HATs, histone methyltransferases and histone
demethylases, regulate PD-L1 expression by affecting modifications that occur on lysine and arginine residues. Most studies on miRNAs have focused on their binding to the 3′ UTR of PD-L1 (109-111). As one of the key factors affecting PD-L1 expression, various miRNAs can inhibit PD-L1 expression by binding to the 3′ UTR of miRNAs. IncRNAs mainly act as upstream regulators of the PD-1/PD-L1 axis to affect antitumor immunity. Finally, research on DNA methylation has exclusively focused on its effect on the PD-L1 promoter, and hypomethylation of the PD-L1 promoter often leads to upregulation of PD-L1 expression, thereby exerting immunosuppressive effects (30).

A large number of preclinical studies have revealed the critical role of epigenetic factors in antitumor immune responses and reversal of immunosuppression, particularly in PD-L1/PD-1 blockade (72,91,172,184). The rational application of a combination of multiple epigenetic targeted drugs, including DNMT inhibitors and histone-modifying enzyme inhibitors, with anti-PD-L1 immunotherapy, represents an opportunity to improve antitumor efficacy, enhance response rates to PD-1/PD-L1 blocking antibodies and reverse drug resistance. However, combinations are still in the early stages of development and there are still certain problems. First, the additional toxicity afforded by these epigenetic molecules cannot be underestimated. Some epigenetic drugs may develop more precise and effective drugs and treatments by identifying more potential therapeutic targets and mechanisms of action. Epigenetic combination therapies will be combined in an optimal manner to enhance the prognosis of patients.

In conclusion, at present, a large amount of work is still required to explore epigenetic changes in depth. Future studies may develop more precise and effective drugs and treatment regimens by identifying more potential therapeutic targets and mechanisms of action. Epigenetic combination therapies will ultimately be combined in an optimal manner to enhance the effectiveness of anti-PD-L1 immunotherapy in solid tumors, improving the prognosis of patients.

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Authors’ contributions

The research project was designed by XM and CS, organized by XM, JW and BW, and reviewed and critiqued by CS. The first draft of the manuscript was written by XM. The content and grammar of the manuscript was revised by JW, BW, CL, LL and CS. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript. Data authentication is not applicable.

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

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