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Review Article

Unveiling the nexus of p53 and PD-L1: insights into immunotherapy resistance mechanisms in hepatocellular carcinoma

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Abstract: Hepatocellular carcinoma (HCC), the predominant form of primary liver cancer worldwide, continues to pose a substantial health challenge with limited treatment options for advanced stages. Despite progress in therapies such as surgery, transplantation, and targeted treatments, prognosis remains bleak for many patients. The advent of immunotherapy has revolutionized the landscape of advanced HCC treatment, offering hope for improved outcomes. However, its efficacy is limited, with a modest response rate of approximately 20% as a single-agent therapy, underscoring the urgent need to decipher mechanisms of immunotherapy resistance. Tumor protein 53 gene (*TP53*), a pivotal tumor suppressor gene, and Programmed death ligand 1 (PD-L1), a crucial immune checkpoint ligand, play central roles in HCC's evasion of immune responses. Understanding how tumor protein 53 (p53) influences PD-L1 expression and immune system interactions is essential for unraveling the complexities of immunotherapy resistance mechanisms. Elucidating these molecular interactions not only enhances our understanding of HCC's underlying mechanisms but also lays the foundation for developing targeted treatments that may improve outcomes for patients with advanced-stage liver cancer. Ultimately, deciphering the nexus of p53 and PD-L1 in immunotherapy resistance promises to advance treatment strategies and outcomes in the challenging landscape of HCC. This review delves into the intricate relationship between p53 and PD-L1 concerning immunotherapy resistance in HCC, offering insights that could pave the way for novel therapeutic strategies aimed at enhancing treatment efficacy and overcoming resistance in advanced stages of the disease.

Keywords: HCC, PD-L1, p53, immune resistance

Introduction

Hepatocellular carcinoma (HCC), the predominant form of primary liver cancer, remains a significant global health challenge and ranks as the second leading cause of cancer-related deaths worldwide [1]. Often diagnosed at advanced stages, HCC carries a particularly poor prognosis despite advancements in therapies such as chemotherapy, radiotherapy, and targeted treatments [2]. Immunotherapy, particularly immune checkpoint inhibitors (ICIs) targeting programmed cell death 1 (PD-1) and Programmed death ligand 1 (PD-L1), has revolutionized cancer treatment by showing remarkable efficacy in HCC [3]. However, a significant subset of HCC patients exhibits intrinsic or acquired resistance to PD-1/PD-L1 blockade and the mechanisms underlying immune evasion and resistance to therapy in HCC remain poorly understood [4]. In recent years, one notable point worth highlighting is the classic tumor protein 53 gene (*TP53*), encoding the tumor protein 53 (p53), which plays a pivotal role in maintaining genomic stability, regulating cellular responses to stress, and is critical for cancer development [5]. Dysregulation of p53 signaling is a hallmark across various cancers, including HCC, influencing tumor initiation, progression, and resistance to therapy [6]. Another significant area of focus is immune check point PD-L1. Concurrently, PD-L1 expression on

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tumor cells is implicated in immune evasion and resistance to immunotherapy across different cancers, including HCC [7]. Its interaction with PD-1 on immune cells suppresses antitumor immune responses within the tumor microenvironment (TME), contributing to therapeutic resistance, which underscores the complexity of immune evasion mechanisms within the TME.

Recent studies have shed light on the intricate interplay between p53 and PD-L1 in HCC. Mutations in *TP53* or alterations in p53 activity can directly impact PD-L1 expression levels, influencing immune evasion strategies employed by HCC cells [8-10]. Moreover, reciprocal feedback mechanisms between p53 and PD-L1 pathways further complicate their roles in HCC progression and therapeutic resistance [8, 11]. Consequently, understanding these molecular interactions is crucial for developing novel therapeutic strategies that can overcome immune evasion mechanisms and improve treatment outcomes in HCC. This review focuses on the aberrant regulation of PD-L1 in HCC and its correlation with immune resistance. We also summarize the role of p53 in immune resistance mechanisms and the mutual regulation between p53 and PD-L1. Finally, we propose a novel combined strategy targeting p53 and PD-L1 for treating HCC.

Abnormal PD-L1 regulation and immune resistance in HCC

The liver, as an immune-privileged organ, possesses unique immune tolerance, which plays a crucial role in maintaining normal liver function and preventing autoimmune diseases. This distinctive immune microenvironment is closely associated with the occurrence and progression of HCC and is one of the key reasons for its high heterogeneity [12]. This immunosuppressive microenvironment leads to the abnormal expression of immune checkpoint molecules in HCC, which in turn exacerbates the immunosuppressive environment, ultimately promoting immune evasion in HCC. Although various ICIs, such as PD-1, PD-L1, and cytotoxic T lymphocyte associate protein-4 (CTLA-4) inhibitors, have been applied in HCC patients in recent years, the overall response rate to monotherapy remains low. Additionally, a significant portion of patients develops immune resistance either at the beginning of treatment or after a period of treatment, indicating immune evasion by the tumor. However, the mechanisms of immune resistance in HCC are regulated by a complex and finely tuned interplay of both intra-tumoral and extra-tumoral factors. PD-L1 is often abnormally highly expressed in tumors, where it suppresses T lymphocyte (T cell) function by binding to the PD-1 receptor on activated T cells. Since PD-1 is only expressed on activated T cells, PD-L1 primarily escapes immune surveillance by depleting pre-existing activated T cells and does not affect T cells that have not yet been activated [13]. Furthermore, PD-L1 can also be secreted extracellularly in soluble or exosomal forms, promoting tumor metastasis and hindering immune responses [14]. Therefore, PD-L1 plays a critical role in regulating intra-tumoral signaling pathways and the TME.

PD-L1 and PD-1 are both type I transmembrane proteins belonging to the immunoglobulin superfamily. However, they differ in their intracellular domains. PD-L1 lacks the intracellular signaling-related domains found in PD-1, which determines that PD-L1 primarily functions as a ligand rather than a receptor in signal transduction. The PD-1/PD-L1 signaling pathway generally transmits signals from PD-L1 to PD-1, which is related to the cytoplasmic domain of PD-1 containing tyrosine-based signaling motifs. PD-1 expression can be observed on activated T cells, and PD-L1 can bind to PD-1, phosphorylating the intracellular immunoreceptor tyrosine-based inhibition motif/switch motif (ITIM/ITSM) of PD-1, which then recruits SH2 domain-containing phosphatases 1 and 2 (SHP-1 and SHP-2, respectively) to attenuate T cell activation signals [14]. This signal transmission typically does not occur in reverse, as PD-L1's intracellular domain does not contain the classical signaling motifs. However, some researchers suggest that PD-1/PD-L1 signaling can be bidirectional. This reverse signaling plays an important role in maintaining tumor cell viability and metabolism and does not rely on T cell activity [15]. Additionally, since PD-1 is also expressed on tumor cells to some extent, tumor cells may promote PD-L1 signaling through autocrine or paracrine interactions between

tumor cells. However, the exact mechanism of this process remains unclear.

Aberrant PD-L1 expression in HCC

The roles of targeting PD-L1 and PD-1 in the treatment of liver cancer are similar. Both mechanisms block the PD-1/PD-L1 signaling pathway, thereby reversing cytotoxic T lymphocytes (CTLs or Cluster of Differentiation (CD)8+ T cells) with an exhausted phenotype into an activated phenotype. This leads to the reprogramming of the immune microenvironment, converting a clinical "cold" tumor into a "hot" tumor. The primary difference between the two lies in the type of cells inhibited. PD-1 and PD-L1 expression exhibit relative cell specificity. PD-1 inhibitors competitively bind to PD-L1, directly promoting the activation of exhausted $CD8^+$ T cells, thereby enhancing their tumor-killing function. Since PD-1 is primarily expressed by activated T cells, other immune cells are relatively unaffected. In contrast, PD-L1 inhibitors primarily function by inhibiting PD-L1 expression on tumor cells, reducing its interaction with PD-1 on the surface of $CD8^+$ T cells, thereby indirectly activating $CD8^+$ T cells.

In the metabolic dysfunction-associated steatohepatitis (MASH) HCC mouse model, the distribution of PD-L1 shows significant spatial specificity, with its expression decreasing from the tumor center to the tumor periphery and adjacent non-tumor tissues [16]. This suggests that PD-L1 may exert its effects through interactions with other immune cells. Compared to PD-1 inhibitors, PD-L1 inhibitors may play a more complex role in reprogramming the immune microenvironment due to their direct inhibition of PD-L1 expression on tumor cells rather than the activation of a single immune cell type. Studies have confirmed that a "nano-epidrug" named MFMP, composed of hollow mesoporous manganese dioxide (MnO_2) nanoparticles, FIDAS-5 as a methionine adenosyltransferase 2A (MAT2A) inhibitor, macrophage membrane, and anti-PD-L1 therapy (anti-PD-L1 or aPD-L1), can target tumor cells via their internal anti-PD-L1 drugs, reversing the immune-suppressive microenvironment, promoting MFMP breakdown in the TME, activating the downstream the cyclic GMP-AMP synthase-stimulator of interferon genes (cGAS-STING) pathway, and inhibiting the epidermal growth factor receptor (EGFR) pathway to suppress HCC recurrence and metastasis [17].

Although both PD-1 and PD-L1 inhibitors primarily function by blocking the PD-1/PD-L1 signaling pathway, their resistance mechanisms may differ. In addition to being mainly expressed on tumor cells, PD-L1 expression on other immune cells may also contribute to immune evasion in HCC. Spatial transcriptomics analysis of minimal residual disease (MRD) after chemotherapy embolization reveals that M2-like macrophages expressing PD-L1 can activate the transforming growth factor-β (TGF-β) pathway in stem cell-like cancer cells to maintain MRD [18]. It is important to note that tumor-initiating cells (TICs), which inherently possess resistance to immunotherapy, can recruit neutrophils via the C-X-C motif chemokine ligand 2 (CXCL2)/C-X-C motif chemokine receptor 2 (CXCR2) axis (CXCL2-CXCR2 axis), while the infiltrating neutrophils reprogram tumor cells into TICs by secreting C-C motif chemokine ligand 4 (CCL4) to evade immune surveillance [19]. This indicates that tumor cells maintain an immune-suppressive microenvironment through their "stemness" characteristics. However, whether these "stem-like" tumor cells are pre-existing during tumor initiation or induced later remains unclear. Furthermore, in HCC patients following transarterial chemoembolization (TACE) treatment, macrophages expressing triggering receptor expressed on myeloid cells 2 (TREM2) have been found to induce endothelial cells to express PD-L1, thereby inhibiting $CD8^+$ T cell migration and infiltration, as well as anti-tumor activity [20]. The levels of soluble PD-L1 (sPD-L1) in serum on the 3rd and 7th day post-TACE treatment correlate significantly with tumor vascular invasion and prognosis in HCC patients [21]. Spatial immunophenotyping of residual tumor cells after TACE treatment further reveals that stem-like tumor cells in residual HCC interact more frequently with M2 PD-L1+ macrophages, and PD-L1+ macrophages interact with $CD8^+$ T cells in the fibrous vascular bundle. However, M2-like macrophages seem to promote tumor cell stemness and $CD8^+$ T cell exhaustion only in specific spatial cellular neighborhoods (CN), not throughout the entire tumor [18]. This suggests that PD-L1 expression in various cells exhibits consistent pro-tumor synergy and can serve as an important biomarker to predict TME charac-

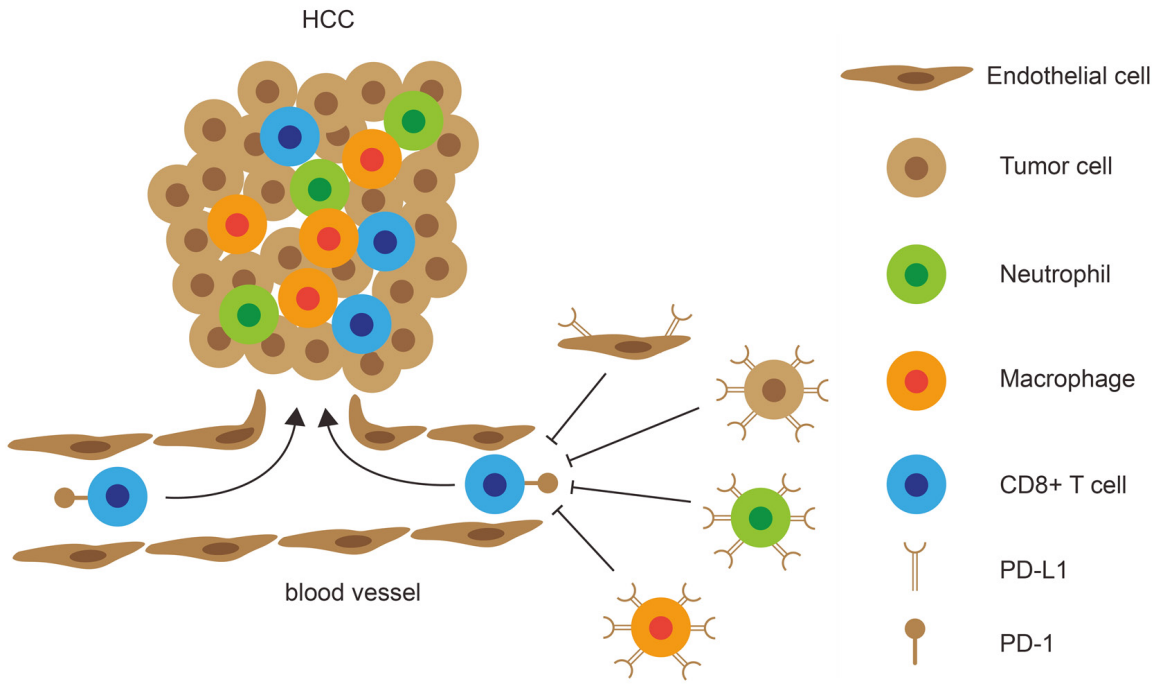

Figure 1. Expression of programmed death-ligand 1 (PD-L1) in the immune microenvironment of hepatocellular carcinoma (HCC) and its role in immune evasion. The figure illustrates the infiltration process of cytotoxic T lymphocytes ($CD8^+$ T cells) in HCC and the inhibitory effect of multiple cellular components within the immune microenvironment on $CD8^+$ T cells. In the tumor microenvironment (TME), epithelial cells, neutrophils, macrophages, and tumor cells exhibit high expression of PD-L1, which binds to programmed cell death 1 (PD-1) molecules on the surface of $CD8^+$ T cells, thereby activating the PD-1/PD-L1 signaling pathway. This activation subsequently results in diminished infiltration of $CD8^+$ T cells into the tumor and attenuated tumor-killing function.

teristics and responses to immunotherapy. However, it is crucial to note that any treatment may remodel the tumor immune microenvironment and influence the tumor's immune response, ultimately making the tumor either more sensitive or more resistant to immunotherapy, which shows in **Figure 1**.

The oxaliplatin/cyclophosphamide (Ox/Cy) treatment regimen can recruit various T cell chemokines (such as C-X-C motif chemokine receptor 6 (CXCR6), C-C chemokine receptor type 5 (CCR5), C-X-C motif chemokine ligand 9 (Cxcl9), and C-X-C motif chemokine ligand 10 (Cxcl10)) to promote C-X-C motif chemokine receptor 3 (CXCR3)-dependent recruitment of chimeric antigen receptor T-cell (CAR-T) cells. However, it also induces the enhancement of the PD-1/PD-L1 signaling pathway in the immune microenvironment, thus suppressing CAR-T cell activity [22]. Interestingly, activation of the PD-1/PD-L1 signaling pathway promotes liver cancer progression, while inhibiting non-small cell lung cancer (NSCLC) and colorectal cancer (CRC) development [14]. This bidirectional effect may arise from the differing downstream regulation of the PD-1/PD-L1 signaling pathway in different cancers. Overall, immune therapy targeting PD-L1 may not only exert immune modulation by targeting tumor PD-L1 but also requires consideration of the interactions between immune cells.

The role of PD-L1 in primary and secondary immune evasion

The dysregulated mechanism of PD-L1 in tumor cells is complex, involving multiple levels of regulation, including genomic mutations, epigenetic modifications, transcriptional regulation, post-transcriptional modifications, and post-translational modifications [23]. However, it remains unclear whether the abnormal expression of PD-L1 is the cause or result of tumor immune evasion, and whether it is more related to primary resistance or secondary resistance. Immune evasion in cancer usually occurs due to abnormalities in certain stages

of the cancer immune cycle, and the abnormal expression of PD-L1 (including various forms of PD-L1 expression and abnormal expression in different cells of the TME) primarily affects certain stages of the immune cycle, such as T cell transport, migration, and the process by which T cells recognize and kill cancer cells [24]. In vitro experiments show that sPD-L1 can inhibit T lymphocyte proliferation and promote apoptosis, and this inhibitory effect can be reversed by adding PD-L1 [25]. This indicates that sPD-L1 can suppress T cell function in vitro. Further studies have found that in lung cancer patients with resistance to anti-PD-L1 therapy, two splice variants of sPD-L1, c-terminal - deficient splicing variant of PD-L1 with truncated from g724 in exon 5 (PD-L1v242) and lacking exon 7 (PD-L1v229), can be stably secreted in the tumor tissue, capturing anti-PD-L1 antibodies competitively, thus inducing resistance to anti-PD-L1 therapy [26]. Therefore, sPD-L1 primarily plays a pro-tumor role locally in tumors. Exosomal PD-L1, as another important form of PD-L1 expression, primarily affects tumor invasion and metastasis. In patients with metastatic melanoma, tumor cells predominantly express PD-L1 in the form of exosomes. The level of circulating exosomal PD-L1 correlates positively with the level of interferon-gamma (IFN-γ). IFN-γ stimulation increases the number of PD-L1 molecules on these vesicles, inhibiting the function of $CD8^+$ T cells and promoting tumor growth [27]. This suggests that exosomal PD-L1 plays a crucial role in promoting tumor metastasis, and because IFN-γ regulates exosomal PD-L1, the abnormal expression of PD-L1 in metastatic melanoma may be related to post-transcriptional or post-translational modifications. Additionally, circulating exosomal PD-L1 may obstruct the migration and infiltration of T lymphocytes into secondary tumors. In patients with endometrial cancer, when PD-L1 is positive solely in tumor cells, they are more likely to benefit from anti-PD-L1 therapy, whereas PD-L1 positivity in immune cells is associated with lymphovascular invasion, non-endometrioid histology, and deep myometrial invasion [28]. This suggests that abnormal high expression of PD-L1 in immune cells may be associated with poor prognosis in patients using ICIs. Therefore, when evaluating a tumor's response to anti-PD-L1 therapy, the expression levels of PD-L1 in tumor cells and immune cells should be considered separately.

PD-L1 in primary resistance mechanisms: Most cancer patients develop resistance to PD-L1 blockade therapy either at the onset (primary immune evasion) or after some time of treatment (secondary immune evasion) [24]. Both types of resistance are typically associated with abnormally low expression of PD-L1, as tumors with high PD-L1 expression are considered more suitable for PD-L1 inhibitor therapy [29, 30]. However, tumors with low PD-L1 expression not only exhibit less sensitivity to PD-L1-targeted therapy but also reduce the signaling of PD-1/PD-L1, promoting the reactivation of exhausted $CD8^+$ T cells. The most likely reason for this reverse effect is that the $CD8^+$ T cells pre-existing in the TME during tumor formation are already in a high activation threshold state [29]. Even with low PD-1/PD-L1 signaling, their exhausted state cannot be reversed. Another possibility is that tumor cells overexpress other immune checkpoint molecules (such as CTLA-4, T cell immunoglobulin domain and mucin domain-3 (TIM3), lymphocyte activation gene-3 (LAG3), etc.), thus reducing their dependence on PD-1/PD-L1 signaling. For example, although B7 homologue 3 (B7-H3), also called CD276, inhibitor treatment in a prostate cancer mouse model increases the infiltration of regulatory cells (Tregs) in the tumor and enhances the expression of PD-L1 in tumor cells and immune cells (tumor associated macrophages (TAMs) and dendritic cells (DCs)), combining B7-H3 inhibitors with CTLA-4 inhibitors shows much better results than combining PD-L1 inhibitors. Interestingly, the upregulated PD-L1 level in tumor cells is much lower than in immune cells (TAMs and DCs) [31]. This suggests that in the case of B7-H3 inhibition, CTLA-4 signaling, rather than PD-1/PD-L1 signaling, plays a dominant role in maintaining the immunosuppressive TME. Meanwhile, in mice treated with Ox/Cy, CAR-T cells infiltrating tumor cells can induce TAMs to express PD-L1, thereby inhibiting the function of PD-1+ CAR-T cells. Ox/Cy and anti-PD-L1 treatment significantly improved the survival rate of kirsten rat sarcoma viral oncogene homolog ($Kras)^{LSL\text{-}G12D/+}$; $p53^{f/f}$ (KP) mice model by introducing a receptor tyrosine kinase-like orphan receptor 1 (ROR1) transgene into the Cre lentivirus used to induce tumors

(KP^{ROR1} mice) mediated by CAR-T cells, and after ex vivo re-stimulation of CAR-T cells from Ox/Cy-treated mice, LAG-3 and TIM-3 expression decreased, while IFN-γ and tumor necrosis factor-alpha (TNF-alpha or TNF-α) production increased, indicating that the functional suppression of CAR-T cells in the immunosuppressive microenvironment of Ox/Cytreated mice is mainly mediated by PD-1/PD-L1 signaling [22]. Therefore, different tumors or treatment methods lead to distinct dominant signaling pathways for immune resistance. Tumors with low PD-L1 expression seem to be more closely related to primary resistance, but the mechanism remains unclear, possibly related to constitutive changes in PD-L1 expression in tumors. However, a recent study in CRC patients indicates that pathway-induced constitutive upregulation of PD-L1 is a cause of primary immune resistance [32]. Thus, PD-L1 alone cannot predict whether a patient will have primary resistance to PD-L1 inhibitors. In lung cancer, the different combinations of *TP53*, *EGFR*, and serine/threonine kinase 11 (*STK11*) mutations, along with PD-L1 expression in tumor cells, are closely associated with the response to immunotherapy [33]. Although *KRAS/TP53* co-mutation is a predictive biomarker for high PD-L1 expression (≥50%) and prognosis of lung adenocarcinoma patients receiving pembrolizumab monotherapy, and the high expression of PD-L1 mRNA in *TP53*-mutated tumors is independent of *KRAS* mutation [34], lung adenocarcinoma patients with *STK11/TP53/KRAS* mutations, even with high PD-L1 expression, still exhibit primary resistance to pembrolizumab [35]. However, regardless of whether p53 is wild-type or mutated, NSCLC patients treated with atezolizumab show significantly improved overall survival (OS) compared to docetaxel therapy [36]. A phase III clinical trial also confirmed that atezolizumab combined with bevacizumab and chemotherapy is an effective first-line treatment for metastatic NSCLC subgroups with mutant KRAS (mKRAS) and simultaneous *STK11* and/or kelch-like ECH-associated protein 1 (*KEAP1)* or *TP53* mutations and/or high PD-L1 expression [37]. This suggests significant differences in the therapeutic effects of PD-1 and PD-L1 inhibitors. Additionally, mouse cell lines with genetic and phenotypic characteristics of intrahepatic cholangiocarcinoma (iCCA), such as the hydrodynamic injection of a dominant-negative form of WD repeat domain containing protein 7 (Fbxw7ΔF) coupled with protein kinase B (AKT) activation inducing iCCA mouse model (FAC model), show distinct mutational features compared to yes-associated protein $(YAP)^{S127A}$/Akt and $Kras^{G12D}p53^{L/L}$ (KPPC) models, and their responses to nivolumab or durvalumab differ [38]. This indicates that tumors with different mutational features have completely different immune microenvironments and exhibit varying responses to immunotherapy. In conclusion, due to the widespread expression of PD-L1 in the immune microenvironment and its highly complex regulatory mechanisms, its role as a marker of primary resistance is limited, and its resistance mechanism needs to be elucidated in combination with the tumor's mutational background.

PD-L1 in secondary resistance mechanisms: The mechanisms of secondary resistance are commonly believed to be related to the loss of immunogenic antigens and the selection of cancer cell clones that lack T cell recognition of antigens [24]. Since PD-L1 primarily functions as a signaling molecule in tumors to activate downstream signaling pathways, it remains unclear whether abnormal changes in PD-L1 itself (including alterations in protein expression levels and structural modifications) can induce anti-tumor responses as an antigen. Furthermore, PD-L1's positive signaling through PD-1 can be mediated by various cells within the immune microenvironment, not just between tumor cells and $CD8^+$ T cells. Therefore, whether PD-L1 can serve as an antigen to induce or suppress anti-tumor responses remains uncertain, as its effects may be overshadowed by the PD-1/PD-L1 signaling pathway. When considering the mechanisms of secondary resistance, it is important to take into account not only the role of the PD-1/PD-L1 signaling pathway but also the involvement of other immune checkpoint molecules [24].

For patients with secondary resistance to anti-PD-L1 treatment, tumor PD-L1 expression may either be high or low due to factors induced by PD-L1 inhibitors. Tumors may upregulate PD-L1 to counteract the effects of PD-L1 inhibitors and thus increase their dependency on the PD-1/PD-L1 pathway, or they may downregulate PD-L1 expression to reduce reliance on the PD-1/PD-L1 signaling pathway, thereby increasing dependency on other immune-sup-

pressive signals (such as CTLA-4). Even when using anti-PD-1 therapy instead of anti-PD-L1 therapy, it has been observed that both tumor cell PD-L1 expression and T cell PD-1 expression levels decrease [39]. This not only explains the coexistence of high and low PD-L1 expression in secondary resistant HCC patients but also suggests that treatment strategies for secondary resistant patients can be adjusted based on their PD-L1 expression. For example, patients with high PD-L1 expression who are more dependent on the PD-1/PD-L1 signaling pathway can be switched to PD-1 inhibitors, while patients with low PD-L1 expression, having lower dependency on the PD-1/PD-L1 signaling pathway, may benefit from CTLA-4 inhibitors. Additionally, a combination therapy targeting both PD-1 and CTLA-4 may provide significant efficacy for PD-L1-resistant patients.

A retrospective study indicated that the combination of cadonilimab (targeting both PD-1 and CTLA-4) with lenvatinib showed an overall response rate (ORR) of 37.9%, disease control rate (DCR) of 82.8%, median progression-free survival (mPFS) of 8.1 months, and median time to progression (mTTP) of 8.2 months in advanced HCC patients. Furthermore, 93.1% of patients experienced at least one treatment-related adverse event (TRAE) [40]. In another single-arm clinical trial, different doses of cadonilimab (6 mg/kg in group A and 15 mg/kg in group B) combined with lenvatinib for advanced HCC patients yielded similar results (ORR of 35.5% and 35.7%, median duration of response (DoR) of 13.6 months and 13.67 months, mPFS of 8.6 months and 9.8 months, and overall survival [OS] of 27.1 months for group A, with group B not yet reached). Additionally, 66.1% of patients reported ≥3 grade TRAEs [41]. Even with cadonilimab monotherapy, significant efficacy and safety were observed in advanced HCC patients (ORR of 16.7% with no significant TRAEs) [42]. However, these clinical trials lacked control groups, so it is difficult to assess whether cadonilimab offers advantages over traditional ICIs. Moreover, while cadonilimab has shown good efficacy and safety in previously untreated HCC patients, its effectiveness in patients who developed resistance after prior anti-PD-L1 treatment is still unknown. Further clinical trials are needed to determine whether HCC patients resistant to anti-PD-L1 therapy can benefit from cadonilimab.

The mechanism of p53 in immune resistance in HCC

TP53 is one of the most important tumor suppressor genes in the human body, involved in regulating various biological processes such as the cell cycle, apoptosis, senescence, and DNA damage repair. However, its role in tumor immunity is largely unknown. Due to the relatively high mutation frequency of *TP53* in various cancers and the growing body of research confirming its critical role in regulating tumor immune responses [43-47], p53 not only reverses the immunosuppressive microenvironment but also further enhances anti-tumor immune responses by inducing immunogenic cell death (ICD) [48]. However, how p53 regulates the anti-tumor immune response in HCC remains unclear.

p53 frequently undergoes functional mutations (mutant p53, also named mt-p53 or mut-p53) in various cancers, but a considerable portion of tumors exhibit p53 that does not undergo functional mutations or is only suppressed at the expression level, including nonsense mutations of p53 and wild-type p53 (wt-p53). These different p53 mutation states may coexist within the same tumor type, which is highly heterogeneous, reflecting the inter-tumor and intra-tumor heterogeneity of p53 mutations. Whole-exome sequencing of 363 HCC cases from The Cancer Genome Atlas (TCGA) revealed that 31% of HCC patients have mutations in p53. However, by evaluating p53 function through p53 target gene expression, it was found that both mutant *TP53 (mt-TP53)* and wild-type *TP53 (wt-TP53)* were present in HCC patients [49]. Generally, *mt-TP53* is considered a carcinogenic factor, whereas *wt-TP53* is considered the opposite. However, whether mt-p53 or wt-p53, in addition to being related to the dysregulation of biological processes such as cell cycle, DNA damage repair, and apoptosis, p53 abnormalities also promote carcinogenesis by influencing tumor immune responses. This is mainly achieved by affecting the immune microenvironment (including immune cell recruitment, cytokine secretion regulation, and inflammatory signaling pathways) to modulate tumor cell responses to the immune system. However, mt-p53 can also act as an antigen to induce immune responses [43]. Recent studies have confirmed that different p53 states in HCC can

affect the mammalian target of rapamycin (mTOR) target through completely opposite pathways, thus regulating the expression of PD-L1 in tumor cells, and have verified the potential role of wt-p53 in immune therapy [8]. Furthermore, in the context of wt-p53, senescent liver cancer cells can recruit natural killer cells (NK cells) infiltration by secreting the chemokine ligand 2 (CCL2), thereby improving the immunosuppressive microenvironment [50]. In the context of p53 haploinsufficiency, HCC can promote transketolase (TKT) ubiquitination and activation through the abnormally high expression of F-box and leucine-rich repeat 6 (FBXL6), and further increase the expression of PD-L1 and vaccinia-related kinase 2 (VRK2) by regulating the downstream reactive oxygen species (ROS)-mTOR axis, leading to immune evasion and HCC metastasis [51]. In summary, under the context of *TP53* mutations, HCC can regulate tumor immune responses through various pathways, but whether p53 directly regulates tumor immune responses by modulating its downstream targets is still unclear. Based on the detailed information of pathway alterations in the TCGA liver hepatocellular carcinoma (LIHC) cohort, three key pathways (p53, phosphatidylinositol 3-kinase (PI3K), and wingless (WNT)) were selected, and patients were divided into three dominant phenotypes with altered pathways (adenosine diphosphate (ADP)). The p53|PI3K ADP phenotype exhibited high immune infiltration, homologous recombination deficiency (HRD), and immune checkpoint molecules such as HERV-H LTR-associating 2 (HHLA2), CD40 and CD276, indicating a strong correlation between alterations in the p53 pathway and the immune microenvironment in HCC [52]. A recent study showed that serine and arginine rich splicing factor 10 (SRSF10) can downregulate p53 protein by directly inhibiting the murine double minute 4 (MDM4)-p53 axis, thereby suppressing $CD8^+$ T cell infiltration, suggesting that p53 may directly participate in the regulation of the HCC TME [53]. Although the importance of wt-p53 and mt-p53 in regulating the HCC tumor immune microenvironment is recognized, the specific mechanisms by which different p53 states remodel the HCC TME still require further exploration.

The complexity of p53 in the regulation of PD-L1

p53 plays a crucial role in regulating the immune response in HCC, but the relationship between immune checkpoint molecules, particularly PD-L1, and p53 is not fully understood. Although abnormal p53 expression is associated with PD-L1 levels in various cancers [34, 54-63], and has potential for predicting the response to ICIs and prognosis [59, 64-70], some studies have shown no significant correlation between p53 and treatment response or patient prognosis [71, 72]. This suggests that there is a complex and fine-tuned regulatory mechanism between p53 and PD-L1. However, there are no reports to date indicating that p53 can directly regulate the expression of PD-L1. Therefore, the abnormal regulation of PD-L1 expression by p53 in tumors appears to be a result of different p53 states, meaning that p53 indirectly influences PD-L1 expression in tumor cells by directly regulating various target genes/signaling pathways. Moreover, the impact of different signaling pathways on PD-L1 expression is not the same, and the different roles of *TP53*/p53 at different levels in regulating PD-L1 need to be considered, which are showed in **Figure 2**.

Regulation of PD-L1 at the transcriptional level

p53 typically acts as a transcription factor to directly regulate downstream target genes, but whether it can directly regulate the expression of PD-L1 remains unclear. Different states and expression levels of p53 have been confirmed to be significantly correlated with PD-L1 in various cancers [55, 57, 58, 64, 73]. Generally, in wt-p53 and nonsense mutation-type tumors, p53 expression is negatively correlated with PD-L1 levels, while in functional mt-p53 tumors, the expression levels of both are positively correlated [30, 64, 74]. Moreover, different states of p53 primarily affect the inducible expression of PD-L1, with little significant impact on its baseline expression [74]. In melanoma cells, inactivating the *TP53* gene or using the mouse double minute 2 homolog (MDM2) ligand Nutlin-3 alters the expression of the immune checkpoint receptor PD-L1, indicating that the *TP53* gene status can affect the level of PD-L1 on the cell surface [75]. PD-L1 expression is primarily regulated by the IFN-γ/janus kinase (JAK)/signal transducer and activator of transcription (STAT)/IFN-regulatory factor 1 (IRF1) axis, and IRF1 can directly bind to the PD-L1 promoter to promote its transcription [76]. Therefore, p53 may regulate PD-L1 expression by influencing IRF1 expression. In fact,

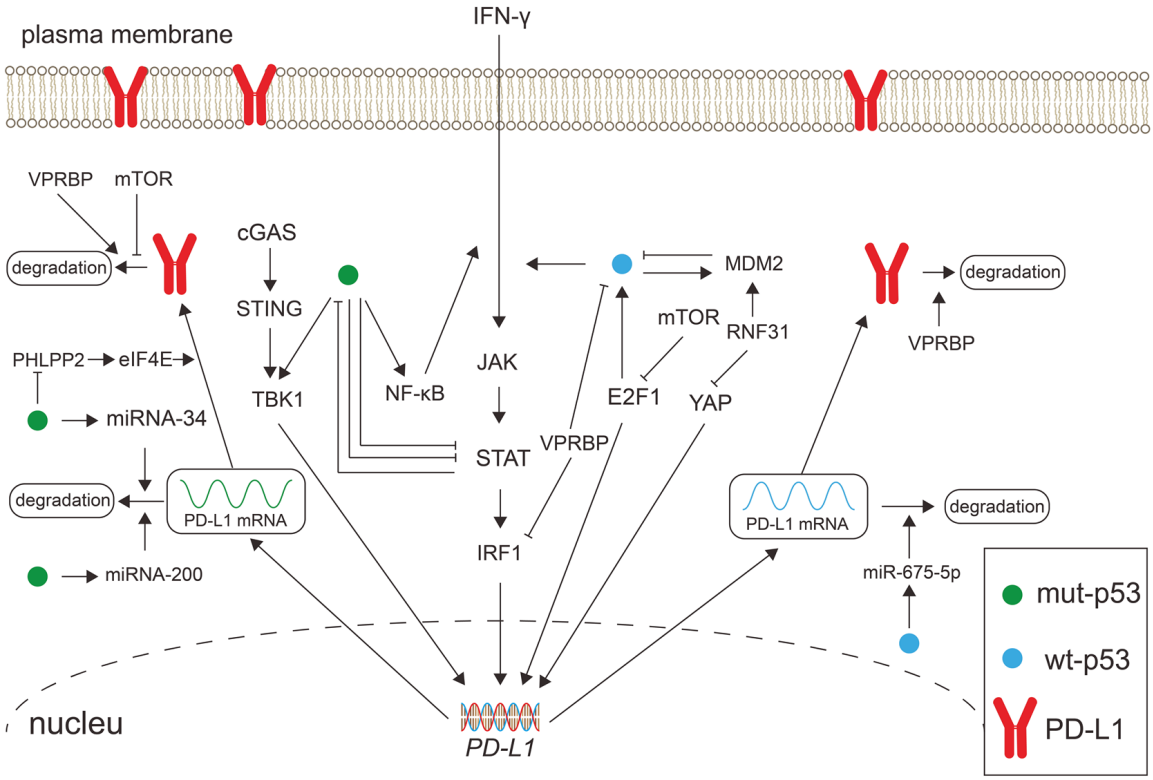

Figure 2. Involvement of tumor protein 53 (p53) in the regulation of programmed death-ligand 1 (PD-L1). This schematic diagram illustrates the molecular mechanisms by which wild-type p53 (wt-p53, right) and mutant p53 (mut-p53, left) regulate the expression of PD-L1 through multiple interconnected pathways with Interferon-gamma (IFN-γ)/Janus kinase (JAK)/signal transducer and activator of transcription (STAT)/IFN-regulatory factor 1 (IRF1) as the core regulatory axis of PD-L1. (1) Wt-p53: At the transcriptional level, wt-p53 predominantly activates the IFN-γ/JAK/STAT/IRF1 axis, whereas its activity is negatively regulated by virus protein R binding protein (VPRBP) and Mouse Double Minute 2 homolog (MDM2) and positively regulated by E2F transcription factor 1 (E2F1). Through these interactions, wt-p53 indirectly forms a complex regulatory network with the mammalian target of rapamycin (mTOR) pathway, yes-associated protein (YAP), and ring finger protein 31 (RNF31), thereby influencing PD-L1 expression. At the post-transcriptional level, wt-p53 facilitates PD-L1 messenger RNA (mRNA) degradation via the microRNA 675-5p (miR-675-5p) pathway. At the translational level, wt-p53 promotes PD-L1 degradation by regulating VPRBP. (2) Mut-p53: At the transcriptional level, mut-p53 exerts dual regulatory effects. It directly suppresses STAT molecules and JAK/STAT signaling while also activating the IFN-γ/JAK/STAT/IRF1 axis via nuclear factor kappa-B (NF-κB). Additionally, mut-p53 enhances the cyclic GMP-AMP synthase-stimulator of interferon genes (cGAS/STING)/TANK-binding kinase 1 (TBK1) pathway, further promoting PD-L1 transcription. A negative feedback loop between p53 and STAT contributes to the intricate regulation of PD-L1 expression. At the post-transcriptional level, mut-p53 enhances PD-L1 mRNA degradation via microRNA 34 (miR-34) and microRNA 200 (miR-200). At the translational level, mut-p53 suppresses PD-L1 mRNA translation by inhibiting the PH domain leucine-rich repeat protein phosphatase 2 (PHLPP2)/eukaryotic initiation factor 4E (eIF4E) axis. Furthermore, the figure highlights the critical roles of the mTOR pathway and VPRBP in regulating PD-L1 protein degradation.

it has been confirmed that the presence of wt-p53 protein, rather than its transcriptional activity, determines the level of IFN-γ-induced PD-L1 expression in melanoma. Knockout of p53 protein results in a reduction of IFN-γ-induced PD-L1 expression. However, overexpression of janus kinase 2 (JAK2) can partially restore IFN-γ-induced PD-L1 expression in p53-knockdown cells [74]. Additionally, in breast cancer cells treated with doxorubicin (which activates p53 expression and induces a senescence-like state), an increase in tumor cell chromatin accessibility to IRF1 was observed, enhancing the IFN-γ-induced PD-L1 expression [39]. This suggests the importance of the JAK2-STAT-IRF1 pathway in regulating PD-L1 and the potential regulatory role of p53 in this pathway. Another study also found that inhibiting the mTOR pathway can suppress the binding of E2F transcription factor 1 (E2F1) to

wt-p53, thereby promoting the nuclear translocation of E2F1, which binds to the PD-L1 promoter and ultimately promotes PD-L1 expression [8]. Although mt-p53 proteins can also interact with E2F1 and form complexes to regulate downstream gene expression [77], it is still unclear whether the effect of mt-p53 on PD-L1 depends on E2F1. Activation of the nuclear factor kappa-B (NF-κB) pathway can directly induce PD-L1 upregulation at the transcriptional level [78], and mt-p53 regulates IFN-γ-induced PD-L1 levels through direct interaction with NF-κB [79], but has no effect on constitutive PD-L1 expression [80]. Additionally, mt-p53 can inhibit the cGAS-STING pathway by interacting with TANK-binding kinase 1 (TBK1) [43], while the cGAS-STING-TBK1 axis activates IFN signaling to upregulate PD-L1 expression [81]. PD-L1 is usually abnormally overexpressed in *KRAS/TP53* gene-mutated lung cancer cell lines, and when the tumors receive either mitogen-activated extracellular signal-regulated kinase (MEK) inhibitor or PD-L1 blockade therapy, PD-L1 and mitogen-activated protein kinase (MAPK) signaling are mutually activated [30]. Activation of the MAPK signaling pathway can downregulate nuclear factor-kappa B p65 (NF-κBp65), reducing its binding to the proximal PD-L1 promoter and thereby inhibiting PD-L1 expression [82]. Therefore, both wt-p53 and mt-p53 can regulate PD-L1 expression at the transcriptional level, and different mutant states of p53 can modulate PD-L1 expression through various pathways.

However, in pan-cancer studies, the ubiquitin-specific protease 2 (USP2) - virus protein R binding protein (VPRBP) axis has been found to be involved in the regulation of p53 and PD-L1. On the one hand, VPRBP can inhibit IRF1-mediated transactivation of the PD-L1 gene by directly interacting with IRF1. On the other hand, VPRBP is an effective inhibitor of p53. Inhibition of VPRBP can activate both p53 and PD-L1, but knockout of p53 does not affect the activation of PD-L1 by suppressing VPRBP, indicating that the activation of PD-L1 by inhibiting VPRBP is independent of the p53 status [11]. Additionally, ring finger protein 31 (RNF31) stabilizes the MDM2 protein, which increases the polyubiquitination of p53, leading to reduced p53 protein stability [83]. Depletion of RNF31 not only increases p53 levels but also inhibits the ubiquitination of YAP at 48 lysine (K48) and K76 sites, thereby upregulating YAP levels. YAP promotes PD-L1 transcription by binding to an enhancer region 13 kb upstream of the PD-L1 transcription start site. Depletion of RNF31 upregulates YAP levels and subsequently increases PD-L1 expression, but infiltration of CD45-positive immune cells and $CD8^+$ T cells increases [84]. This increase in immune cell infiltration may be a result of p53's regulation of other pathways rather than PD-L1 upregulation. These studies did not identify a linear regulatory model between p53 and PD-L1 in tumor immune responses. Instead, p53 and PD-L1 work together in a synergistic mode to suppress tumor progression. Moreover, signal transducer and activator of transcription 3 (STAT3) can bind to the mt-p53 promoter to suppress p53 expression [85], and simultaneously, STAT3 can bind to the PD-L1 promoter to promote PD-L1 expression [86]. Although this contradicts the consistency observed in most tumors between mt-p53 and PD-L1 expression levels, it may be related to the heterogeneity between different tumors, leading to differences in gene expression profiles. It has been confirmed that different point mutations in p53 are associated with significant differences in prognosis for CRC patients [87]. Furthermore, it was discovered that the mt-p53 protein with the arginine 248 to glutamine mutation (R248Q mutation) can bind to STAT3 and enhance STAT3 phosphorylation activation by replacing the phosphatase SHP-2 [88], while in pancreatic cancer cells, the mt-p53 protein with arginine 248 to tryptophan mutation (R248W mutation) can lead to the dephosphorylation of STAT3 [89]. This suggests that different p53 mutation states may play different regulatory roles in different tumors, which partly explains the heterogeneity of PD-L1 expression even in tumors with the same mt-p53. However, it remains unclear whether and how the p53-STAT3 feedback loop functions in HCC. In conclusion, p53 plays a very important role in regulating PD-L1 transcription, and when considering the impact of mt-p53 on PD-L1, the influence of different mutation sites of p53 should be specifically considered.

Regulation of PD-L1 post-translational modifications

PD-L1 is also regulated by post-translational modifications. Studies have found that in the

context of p53 mutations, the 3' untranslated region (UTR) of PD-L1 messenger RNA (mRNA) contains a predicted microRNA 34 (miR-34) binding site at positions 932-938 [73]. This suggests that PD-L1 may be influenced by p53 at the post-transcriptional level. Furthermore, increasing the levels of miR-34 in tumors not only helps inhibit tumor growth and downregulate PD-L1 expression [90, 91], but also increases the number of tumor-infiltrating $CD8^+$ T cells, while reducing the number of exhausted $CD8^+$ PD1+ T cells, macrophages, and Treg cells [73]. Additionally, cytotoxin-associated gene A (CagA) enhances the PD-L1 levels in exosomes derived from gastric cancer cells by inhibiting p53 and microRNA 34a (miRNA-34a), thereby suppressing $CD8^+$ T cell proliferation and anticancer activity [92]. Moreover, mt-p53 can also suppress PD-L1 expression through microRNA 200 (miR-200), although the exact binding site on the 3' UTR is unclear [93]. However, in tumors with wt-p53, EGFR activation significantly enhances p38 mitogen-activated protein kinase (p38-MAPK) signaling by increasing p38-MAPK phosphorylation, which inhibits microRNA 675-5p (miR-675-5p) levels, reducing its binding to the 3' UTR of PD-L1 mRNA, thus inducing PD-L1 upregulation [94]. Therefore, p53 is able to regulate the expression of PD-L1 at the post-transcriptional level and reshape the TME.

Regulation of PD-L1 at the translational level

Another important aspect of p53's regulation of PD-L1 expression is through its impact on PD-L1 protein levels, primarily involving two pathways: translation and post-translational modifications. At the translational level, mt-p53 directly binds to the promoter of PH domain leucine-rich repeat protein phosphatase 2 (PHLPP2) to suppress its transcription and activates the downstream AKT/4E-binding protein 1 (4EBP1)/eukaryotic initiation factor 4E (eIF4E) axis to enhance PD-L1 translation without affecting PD-L1 mRNA levels [95]. Post-translational regulation of PD-L1 mainly occurs through ubiquitination in the ubiquitin-proteasome pathway. In melanoma cells expressing wt-p53, the protein level of IRF1 is low, whereas in p53-null cells, IRF1 levels are elevated, with no impact on IRF1 mRNA levels. Further inhibition of the proteasomal pathway showed a significant increase in PD-L1 levels, suggesting that p53 activation, in addition to being a transcriptional activator of IRF1, may also involve mechanisms of protein synthesis or degradation [96]. Inhibition of the mTOR pathway can also promote the ubiquitin-mediated degradation of PD-L1 in HCC with mt-p53 [8]. Additionally, VPRBP can induce ubiquitin-mediated PD-L1 degradation by serving as a substrate recognition subunit of the cullin4 (CUL4)/Damage-specific DNA binding protein 1 (DDB1) ubiquitin E3 ligase complex ($CRL4^{VPRBP}$ E3 ligase complex) when p53 expression is suppressed [11]. Therefore, although p53 mainly regulates PD-L1 at the transcriptional level, different states of p53 also have a significant impact on the ubiquitin-proteasome pathway's degradation of PD-L1. p53 plays an important role in regulating autophagy, but it has not yet been confirmed whether p53 regulates PD-L1 protein levels through the autophagy-lysosome pathway. More researches are needed in the future to confirm whether p53's regulation of PD-L1 involves multi-pathway degradation.

Prospects of combined targeting of p53 and PD-L1

Given the important role of p53 in tumor immune regulation, particularly its significant impact on the expression of immune checkpoint molecules (including PD-1, PD-L1, and CTLA-4) under different states, combining targeted p53 therapy with ICIs is likely to be more beneficial for treating HCC patients. It is important to note that due to the structural characteristics of the p53 protein, there are currently no direct p53-targeting drugs [6], and in most cases, p53 can only be indirectly affected by activating p53-related signaling pathways. Therefore, the combined therapeutic strategy targeting both p53 and PD-L1 focuses on altering the upstream and downstream effector molecules of p53 to reshape the immune microenvironment or simultaneously targeting both molecules, which shows in **Figure 3A**. various targeted drugs include nanoparticles, phytochemicals, cancer vaccines, small molecule inhibitors, platinum-based complexes, and oncolytic viruses, which are showed in **Figure 3B** and summarized in **Table 1**.

Nanoparticles

In recent years, the combined therapeutic strategy targeting both p53 and PD-L1 in

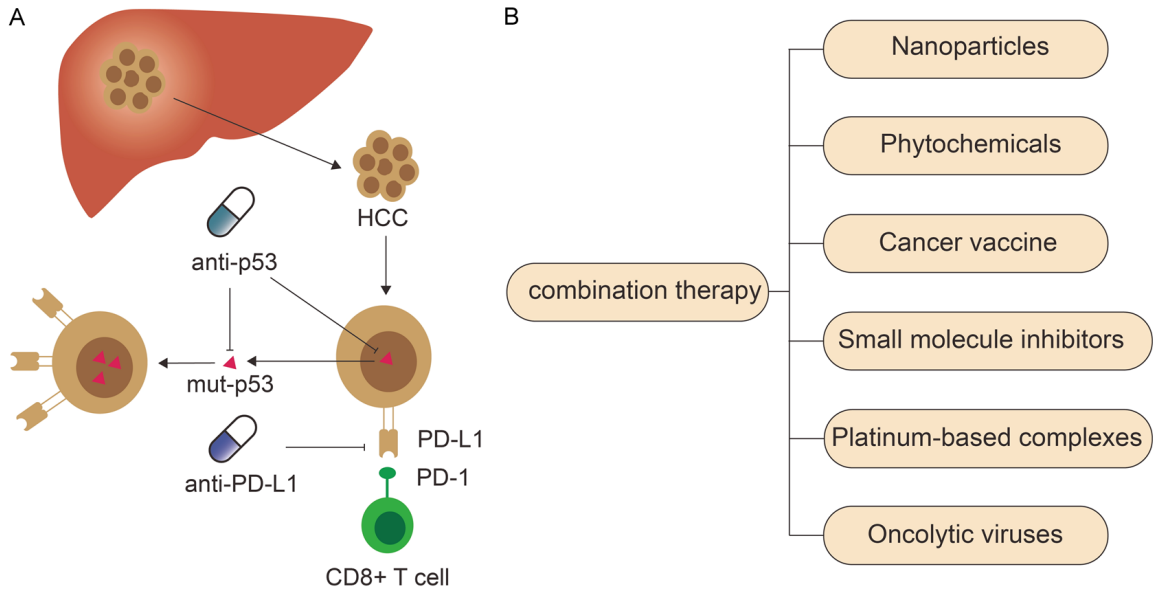

Figure 3. Mechanisms and strategies of combined therapy targeting tumor protein 53 (p53) and programmed cell death 1/programmed death-ligand 1 (PD-1/PD-L1) signaling. A. The figure elucidates two principal aspects of the combined therapeutic approach. First, targeting mutant p53 (mut-p53) through anti-p53 therapy substantially reduces PD-L1 expression in hepatocellular carcinoma (HCC), thereby attenuating the PD-1/PD-L1 signaling pathway. Second, anti-PD-L1 immunotherapy further mitigates the inhibitory effect of tumor cell-expressed PD-L1 on cytotoxic T lymphocytes ($CD8^+$ T cells), augmenting the PD-1/PD-L1 signaling suppression induced by anti-p53 therapy. The combination of p53 and PD-L1-targeted therapy maximally inhibits the PD-1/PD-L1 signaling pathway, consequently enhancing the tumor-killing activity of $CD8^+$ T-cells. B. The figure presents various therapeutic modalities employed for the dual targeting of p53 and PD-L1, including nanoparticles, phytochemicals, cancer vaccines, small-molecule inhibitors, platinum-based complexes, and oncolytic viruses.

tumors has shown significant anti-tumor effects in preclinical models. By optimizing nanoparticle delivery systems, drugs can be accurately targeted to tumor tissues and exert local anti-tumor effects, offering high efficacy and safety. MnO_2-modified zeolitic imidazolate framework-8 (ZIF-8@MnO_2), a recently developed nanoparticle containing inorganic metal ions, can precisely target tumor regions through changes in the environmental pH. In vitro experiments have shown that ZIF-8@MnO_2 specifically targets p53-mutant tumor cells, inhibiting their proliferation, invasion, and metastasis. Additionally, in vivo experiments demonstrated that ZIF-8@MnO_2 not only has good safety but also significantly increases $CD8^+$ T cell activity. By upregulating the PD-L1 level in the TME, ZIF-8@MnO_2 combined with anti-PD-L1 treatment shows significant tumor-suppressive effects [97]. The newly developed I-124 labeled cancer cell membrane-mimetic nanovesicles containing polyphenolic VI (PPVI) and cisplatin (CDDP) (also named 124I-P/C@CMLvs) can precisely target tumor cells and activate downstream signals by promoting p53 deubiquitination and stimulating reactive oxygen species (ROS) production, leading to ferroptosis and pyroptosis. The combination with anti-PD-L1 treatment further synergistically promotes the regression of NSCLC [98]. Additionally, transferrin-modified calofibin platinum(IV) nanoparticles (Tf-NPs@CPF2-Pt(IV)) not only mediate severe DNA damage responses by upregulating human phosphorylated histone (γ-H2AX) and p53 but also stimulate anti-tumor immunity by blocking the immune checkpoint PD-L1 and increasing $CD3^+$ and $CD8^+$ T lymphocytes in the tumor [99]. Besides combination with anti-PD-L1 treatment, targeting p53 in combination with PD-1 therapy also shows significant anti-tumor effects. In a mouse model of glioblastoma, anti-PD-1 therapy alone was unable to inhibit tumor progression, but combining tumor-targeting nanoparticle drug - scl immunoliposome nanocomplex encapsulating p53 plasmid DNA (SGT-53) with anti-PD-1 therapy inhibited tumor growth, induced tumor cell apoptosis, and increased T cell infiltration in the tumor. SGT-53 also upregulated PD-L1 expression both in vitro and in vivo [100]. In

Table 1. Summary of six drug types that simultaneously target tumor protein 53 (p53), including both mutant p53 (mut-p53) and wide type p53 (wt-p53), as well as programmed death-ligand 1 (PD-L1)

Drug types	Name	Cancer type(s)	Main effects on p53 and/or immune regulation	Reference
Nanoparticles	MnO_2-modified zeolitic imidazolate framework-8 (ZIF-8@MnO_2)	Breast cancer (BC)	Inducing the degradation of mut-p53 and upregulating PD-L1 level both in vitro (MCF7, MDA-MB231, BT549, SKBR3 cells) and in vivo (4T1 allografts)	[97]
	I-124 labeled cancer cell membrane-mimetic nanovesicles containing polyphenolic VI (PPVI) and Cisplatin (CDDP) (124I-P/C@CMLvs)	Non-small cell lung cancer (NSCLC)	Promoting p53 deubiquitination in vitro (A549 cell) and increasing the sensitivity of NSCLC to anti-PD-L1 in vivo (LLC allografts)	[98]
	Transferrin-modified calofibin platinum(IV) nanoparticles (Tf-NPs@CPF2-Pt(IV))	BC	Upregulating p53 level and blocking PD-L1 both in vitro (4T1 cell) and in vivo (4T1 allografts)	[99]
	ScL immunoliposome nanocomplex encapsulating p53 plasmid DNA (SGT-53)	Glioblastoma	Upregulating p53 and PD-L1 level in vitro (GL261 cell) and increasing the sensitivity of glioblastoma to anti-programmed cell death 1 (PD-1) in vivo (GL261 allografts)	[100]
Phytochemicals	Oridonin (Ori)	Melanoma and BC	Upregulating P53 and inhibiting PD-L1 expression in vitro (B16F10 and MCF-7 cells)	[101]
	Acacetin	NSCLC	Upregulating P53 and inhibiting PD-L1 expression in vitro (A549 cell) and in vivo (A549 allografts)	[102]
	Arsenic sulfide (As_4S_4)	NSCLC	Targeting p53/miR-34a-5p/PD-L1 axis in A549/cisplatin (DDP) cell (p53 wild-type, DDP-resistant cells) and in A549/DDP xenograft mouse models	[103]
	6-gingerol	NSCLC and embryonic cancer	Activating p53 and downregulating PD-L1 expression by inducing microRNA-34a/200c in vitro (A549, H460, CRL-2073, CRL-1973 cells)	[104, 105]
	Hesperidin extract	NSCLC	Targeting the p53/microRNA-34a/PD-L1 signalling pathway in vitro (A549 and H460 cells)	[106]
	Nobiletin	NSCLC	Inhibiting PD-L1 expression by targeting epidermal growth factor receptor (EGFR)/Janus kinase 2 (JAK2)/signal transducer and activator of transcription 3 (STAT3) and microRNA-197/STAT3/PD-L1 signaling in vitro (A549, H292, H460 cells)	[107]
Cancer vaccine	In situ vaccination (ISV) with dendritic cells engineered to secrete CCL21 (CCL21-DC) (CCL21-DC ISV)	NSCLC	Upregulation of PD-L1 in the tumor microenvironment (TME) and enhancing NSCLC Sensitivity to Anti-PD-1 Therapy in Murine models of NSCLC with distinct driver p53 mutations	[108]
Small molecule inhibitors	Siremadlin (HDM201)	Colorectal cancer (CRC), BC, melanoma	Enhancing the efficacy of anti-PD-1/PD-L1 in a wt-p53-dependent manner in vivo (Colon26, MC38, 4T1, Cloudman S91 allografts)	[109]
	AMG-232 (KRT-232)	Ovarian cancer	Enhancing the efficacy of anti-PD-1 by activating p53 signaling in vitro (OVTOKO and OVMANA cells)	[110]
	APG-115	Hepatocellular carcinoma (HCC)	Upregulating PD-L1 expression by activation of p53 and STAT3 signaling pathway in vitro (MH-22A cell) and enhancing the therapeutic response of tumors with different p53 backgrounds to anti-PD-1 treatment in vivo (MH-22A, MC38 allografts)	[111]

	DS-5272	Acute myeloid leukemia (AML)	Upregulating PD-L1 expression by activating hypoxia-inducible factor-1alpha (HIF-1α)-PD-L1 axis and enhancing AML sensitivity to anti-PD-L1 in vivo (AML model driven by Mixed-Lineage Leukemia-AF9 Fusion Protein (MLL-AF9) and patient-derived xenograft (PDX) models of human AML)	[112]
	Talazoparib	CRC	Upregulating PD-L1 by activating the cyclic GMP-AMP synthase-stimulator of interferon genes (cGAS/STING) pathway in vitro (HCT116, CT26-LUC, MC38, LoVo cells) and combining with anti-PD-L1 to enhance efficacy in vivo (CT26 allografts)	[81, 113]
	Targeting CKLF-like MARVEL transmembrane domain 6 (CMTM6) inhibitors	CRC, lung cancer, melanoma	Reducing PD-L1 ubiquitination and inhibit tumor cell proliferation in a p53-dependent manner in vitro (A375, DLD1, RKO, H2030, H2122, WM2664, COLO679 cells)	[114-116]
	Targeting eukaryotic translation initiation factor 4E family member 1B protein (EIF4E1B) inhibitors	Glioma	Inhibiting PD-L1 expression through the p53 signaling pathway and increaseing sensitivity to anti-PD-L1 in vitro (U251 and LN229 cells)	[117]
	ORY-1001	Cervical cancer	Targeting the p53/microRNA-34a/PD-L1 signalling pathway in vitro (SiHa and C33A cells) and increaseing sensitivity to anti-PD-L1 in vivo (TC-1 allografts)	[118]
	"All-in-one" peptide (TAP)	CRC	Blocking the PD-1/PD-L1 axis and activating p53 in vitro (MC38 cells) and in vivo (PDX model)	[119]
Platinum-based complexes	Ligustrazine (LSZ) platinum(IV) complex	NSCLC, BC	Increaseing the expression of p53 and reducing tumor PD-L1 expression in vitro (A549 cell) and in vivo (4T1 allografts)	[120]
	Chloroquine (CLQ) platinum(IV) complex	BC	Increaseing the expression of p53 and reducing tumor PD-L1 expression in vitro (4T1 cell) and in vivo (4T1 allografts)	[121]
	Hydroxychloroquine (HCQ) platinum(IV) complex	BC	Increaseing the expression of p53 and reducing tumor PD-L1 expression in vitro (4T1 cell) and in vivo (4T1 allografts)	[122]
	Flurbiprofen (FLP) and zaltoprofen (ZTP) platinum(IV) complexes	NSCLC, CRC	Increaseing the expression of p53 and reducing tumor PD-L1 expression in vitro (A549 cell) and in vivo (CT26 allografts)	[123]
	Ketoprofen (KP) and lofepramine (LP) platinum(IV) complexes	NSCLC, BC	Increaseing the expression of p53 and reducing tumor PD-L1 expression in vitro (A549 cell) and in vivo (4T1 allografts)	[124]
	Canadine platinum(IV) complex	BC	Increaseing the expression of p53 and reducing tumor PD-L1 expression in vitro (4T1 cell)	[125]
	Cyclopropylketone (CPX) platinum(IV) complex	BC	Reducing tumor PD-L1 expression in vitro (4T1 cell) and in vivo (4T1 allografts)	[126]
Oncolytic viruses	Oncolytic adenovirus (OBP-702)	Pancreatic ductal adenocarcinoma (PDAC)	Inducing p53 expression and blocking PD-L1 in vitro (PAN02 cell) and increaseing sensitivity to anti-PD-L1 in vivo (PAN02 allografts)	[127]
	OBP-702	Gastric cancer (GC)	Inducing p53-wild type and p53-null type cancer p53 expression in vitro (NUGC-4 and KATOIII cells), and downregulating p53-mutant type cancer p53 level in vitro (GCIY)	[129]
	OBP-702	GC	Inducing PD-L1 expression in vitro (T3-2D and MKN45 cells) and increaseing sensitivity to anti-PD-1 in vivo (T3-2D)	[130]
	Adenoviral-mediated TP53 (Ad/CMV-TP53) gene therapy	NSCLC	Inducing p53 expression in vitro (344SQ, CMT167, M109 cells) and reverse NSCLC resistance to anti-PD-1 therapy in vivo (M109 allografts)	[131]

summary, using nanoparticle delivery systems to induce upregulation of wt-p53 in tumor cells and combining it with ICIs offers promising anti-tumor efficacy.

Phytochemicals

Multiple studies have confirmed that natural compounds targeting p53 and improving the immune microenvironment exhibit significant anti-tumor effects, inhibiting tumor progression in both in vivo and in vitro experiments. For example, in a melanoma mouse model, oridonin (Ori) significantly increased the expression of *TP53*, thereby transcriptionally inhibiting hypoxia-inducible factor-1alpha (HIF-1α), which led to the downregulation of PD-L1 expression and enhanced T cell infiltration into cancer stem cells (CSCs), restoring their sensitivity to immune responses [101]. Both in vivo and in vitro studies show that acacetin reshapes the immune microenvironment by activating the p53/microRNA 34a (miR-34a)/PD-L1 axis. Knockdown of p53 expression reverses acacetin's induction of miR-34a expression [102], further indicating the important role of acacetin in targeting p53 and regulating the immune microenvironment. Similarly, arsenic sulfide ($As_4 S_4$) can sensitize NSCLC cells to cisplatin by targeting the p53/microRNA 34a-5p (miR-34a-5p)/PD-L1 axis [103]. As a phenolic compound with broad anti-cancer activity, 6-gingerol induces upregulation of p53 expression in NSCLC cells in vitro. It upregulates PD-L1 by inhibiting the EGFR/JAK2/signal transducer and activator of transcription 5b (STAT5b) pathway and increasing the expression of microRNA 200c (miR-200c) and miR-34a [104]. In embryonic CSCs, 6-gingerol also upregulates Phosphatase and tensin homolog (PTEN), thereby activating the PI3K/AKT/p53 signaling pathway to suppress PD-L1 expression. The upregulated PTEN further mediates the downregulation of microRNA 20b (miR-20b), microRNA 21 (miR-21), and microRNA 130b (miR-130b) to suppress PD-L1 levels [105]. This indicates that 6-gingerol exerts its anti-cancer effects in vitro through dual targeting of p53 and PD-L1. However, further in vivo experiments are needed to verify whether the combined anti-PD-L1 treatment can sustainably inhibit tumor progression. Hesperidin extract can promote the expression of P53 and miR-34a in lung cancer cells in vitro while simultaneously downregulating PD-L1 expression [106], suggesting its potential role in reversing the TME. However, some natural compounds can directly regulate PD-L1 without relying on p53. In NSCLC, nobiletin inhibit PD-L1 expression through EGFR/JAK2/STAT3 signaling, a mechanism that does not depend on p53 expression [107].

Cancer vaccine

In situ vaccination (ISV) with DCs engineered to secrete C-C motif chemokine ligand 21 (CCL21) (CCL21-DC ISV), which targets the secretion of CCL21 by DCs, can reverse the resistance of NSCLC mice to anti-PD-1 treatment. It primarily works by eliminating pro-cancer neutrophils and enhancing the infiltration of $CD8^+$ T cells into the tumor, thereby reversing the tumor's immunosuppressive microenvironment. The combination of CCL21-DC in situ vaccine and anti-PD-1 therapy results in sustained tumor regression in NSCLC immune-resistant mouse models [108].

Small molecule inhibitors

Some small molecule inhibitors can target p53 and the immune microenvironment to achieve significant anti-tumor effects. The classic p53-targeting inhibitor, MDM2 inhibitor (siremadlin, also named HDM201), combined with anti-PD-L1 therapy, can increase the number of tumor regressions and provide a novel treatment option for p53 wild-type tumors [109]. In ovarian cancer cells, knocking down MDM2 or using the MDM2 inhibitor (AMG-232(KRT-232)) can downregulate interleukin-6 (IL-6) and upregulate p53 levels. Additionally, in T cell and ovarian cancer cell co-culture systems, the combination of pembrolizumab and AMG-232 can significantly inhibit tumor cell growth [110]. Beyond targeting tumor cells, the MDM2 inhibitor APG-115 can also upregulate p53 in macrophages and downregulate cellular myelocytomatosis viral oncogene and musculoaponeurotic fibrosarcoma oncogenehomolog (c-Myc and c-Maf) to reduce M2 macrophage polarization, promote T cell activity, and increase tumor cell PD-L1 expression [111]. Another MDM2 inhibitor, DS-5272, significantly inhibits the progression of mixed-lineage leukemia-AF9 fusion protein (MLL-AF9) leukemia both in vitro and in vivo in a p53-dependent manner. It activates the Hif1α-PD-L1 axis in MLL-AF9 cells to upregulate

PD-L1 expression. Combining DS-5272 with anti-PD-L1 treatment improves the survival rate of leukemia mice [112]. These results show that different MDM2 inhibitors suppress tumor progression through multiple molecular mechanisms and demonstrate strong anti-cancer effects when combined with anti-PD-L1 therapy. Moreover, MDM2 inhibitors show significant anti-tumor effects when combined with PD-1 therapy.

The poly (adenosine diphosphate-ribose) polymerase (PARP) inhibitor (PARPi) talazoparib activates the p53/p21 senescence signaling pathway by inhibiting p53 ubiquitination, and when combined with palbociclib, it promotes cell senescence and activates the cGAS/STING pathway, further inducing anti-tumor immune responses mediated by senescence-associated secretory phenotype (SASP) [113]. Since cGAS/STING pathway activation directly upregulates PD-L1 [81], the combination of PARPi with PD-L1 therapy can simultaneously target both p53 and PD-L1, thereby reshaping the immunosuppressive microenvironment. Further in vivo studies confirm that the combination of talazoparib, palbociclib, and aPD-L1 significantly controls tumor progression in mice [113].

Additionally, molecules that co-regulate p53 and PD-L1 can significantly alter the immune-suppressive microenvironment. CKLF-like MARVEL transmembrane domain 6 (CMTM6) not only binds to PD-L1 protein, reducing its ubiquitination and increasing the half-life of PD-L1 protein [114], but also maintains its expression on the tumor cell membrane [115]. CMTM6 can inhibit tumor cell proliferation in a p53-dependent manner [116]. Therefore, the combination of CMTM6 activators and PD-L1 inhibitors can both reduce tumor cell proliferation and maximize the expression of PD-L1 on the tumor cell membrane, making it more sensitive to PD-L1 inhibitors. In glioma cells, knockdown of eukaryotic translation initiation factor 4E family member 1B protein (EIF4E1B) expression leads to increased PD-L1 and p53 expression, while overexpression of EIF4E1B decreases PD-L1 and p53 expression, suggesting that overexpression of EIF4E1B inhibits PD-L1 expression through the p53 signaling pathway [117]. This indicates that inhibitors targeting EIF4E1B may reverse the tumor's immunosuppressive microenvironment and increase tumor cell sensitivity to anti-PD-L1 therapy. Knockdown of lysine-specific histone demethylase 1 (LSD1) significantly activates the p53/miR-34a/PD-L1 axis to reduce PD-L1 levels. Furthermore, the LSD1 inhibitor (ORY-1001) combined with anti-PD-L1 monoclonal antibody can more effectively inhibit tumor growth in cervical cancer mouse models than using PD-L1 blockade alone [118].

A recent study developed a highly efficient and versatile "all-in-one" peptide (TAP), which has the ability to self-assemble, block the PD-1/PD-L1 axis, inhibit the formation of the RNA-binding motif protein 38 (Rbm38)-eIF4E complex, and activate p53. In vivo experiments showed that this peptide can block the PD-1/PD-L1 signaling pathway, increase NK cell and T cell activity, and reverse the immunosuppressive microenvironment in multiple tumor mouse models [119]. This small molecule peptide overcomes the lack of synergy seen with the use of multiple drugs and maximizes anti-tumor effects with a single drug. In summary, inhibitors (or activators) targeting molecular pathways of both p53 and PD-L1 need further validation in other tumors to improve the generalizability of these targets.

Platinum-based complexes

A series of platinum-based chemotherapy drug complexes have shown good anti-cancer effects, including the ligustrazine (LSZ) platinum(IV) complex [120], chloroquine (CLQ) platinum(IV) complex [121], hydroxychloroquine (HCQ) platinum(IV) complex [122], flurbiprofen (FLP) and zaltoprofen (ZTP) platinum(IV) complexes [123], ketoprofen (KP) and lofepramine (LP) platinum(IV) complexes [124], canadine platinum(IV) complex [125], and cyclopropylketone (CPX) platinum(IV) complex [126]. These complexes can cause severe DNA damage in anti-tumor responses and increase the expression of γ-H2AX and p53. They induce autophagy through activation of the mitochondrial apoptosis pathway (B-cell lymphoma-2 (Bcl-2)/Bcl-2 associated X protein (Bax)/caspase-3) and upregulation of L chain 3 (LC3) I/II and sequestosome 1 (SQSTM1 or p62) expression, thus promoting tumor cell apoptosis. Additionally, they can reduce tumor PD-L1 expression, promote $CD8^+$ T cell infiltration, and improve the immune microenvironment [120].

Although this effect may be attributed to the increase in tumor neoantigens and activation of different T lymphocyte subclones, the downregulation of PD-L1 can indeed lower the activation threshold of $CD8^+$ T cells pre-existing in the tumor [29]. While this change may lead to tumor insensitivity to anti-PD-L1 responses. these complexes, by inducing the p53 pathway and regulating autophagy, do exert immunoregulatory effects by downregulating the immune checkpoint PD-L1. However, further in vivo studies are needed to verify whether these complexes have an impact on prognosis.

Oncolytic viruses

Some oncolytic viruses can significantly modulate the TME, primarily by inducing overexpression of wt-p53 in tumor cells, which triggers ICD and promotes $CD8^+$ T cell infiltration while inhibiting other immunosuppressive cells, such as immunosuppressive myeloid cells (MDSCs) [127, 128]. For instance, the wt-p53-loaded telomerase-specific oncolytic adenovirus (OBP-702) induces p53-mediated apoptosis and autophagy while inhibiting receptor tyrosine kinases [129], thereby inducing ICD in gastric cancer cells and upregulating PD-L1 expression [130]. In vivo studies show that OBP-702 treatment promotes $CD8^+$ T cell infiltration in the peritoneum of gastric cancer mice model, while upregulating PD-1 expression on peritoneal CD4+ and $CD8^+$ T cells. The combination of OBP-702 and anti-PD-1 antibody (Ab) significantly extends the OS of mice with peritoneal metastasis (PM), suggesting that it can significantly reshape the immune microenvironment and suppress tumor progression [130]. Further studies also confirm that OBP-702 inhibits granulocyte-macrophage colony-stimulating factor (GM-CSF)-mediated MDSCs accumulation, significantly suppressing the growth of gemcitabine (GEM)-resistant PAN02 tumors. The combination of OBP-702 with PD-L1 inhibitors also significantly suppresses the tumor growth of gemcitabine-resistant pancreatic cancer in mice, demonstrating its ability to remodel the tumor-suppressive microenvironment [127]. Similarly, in a mouse model of lung cancer resistant to single-agent anti-PD-L1 therapy, adenovirus-mediated *TP53* (Ad/CMV-*TP53*) gene therapy can reverse tumor resistance to anti-PD-L1 therapy. When combined with anti-PD-L1 therapy, it demonstrates significant anti-tumor effects [131]. However, it is important to note that different p53 mutations (including wild-type) have different effects on the tumor immune microenvironment, so the p53 mutation background of the tumor should be considered when inducing wt-p53 overexpression in tumor cells.

Targeting both p53 and PD-L1 also requires attention to the occurrence of resistance in combination therapy. In lung cancer cells with a *KRAS/TP53* mutation background, combining a MEK inhibitor with anti-PD-L1 therapy can increase the number of tumor-infiltrating $CD8^+$ and $CD4^+$ T cells and enhance the anti-tumor response and survival outcomes in lung cancer mice [132]. However, this combination therapy is only effective during the initial treatment phase. After resistance develops, the tumor's resistant microenvironment is characterized by widespread infiltration of Th17 cells. The use of an IL-17A antibody can reverse this resistance microenvironment and enhance the effects of the combination therapy with PD-L1 and MEK inhibitors [30]. Therefore, identifying new resistance markers in the tumor immune-resistant microenvironment is one of the key areas for future research. In fact, even in the presence of p53 mutations, single-agent PD-1/PD-L1 targeted therapies have been shown to significantly prolong patient survival [133]. However, large-scale clinical trials are still required to validate their efficacy.

Conclusion

PD-L1, as a critical immune checkpoint molecule, plays a vital role in anti-tumor immunity. By targeting PD-L1, the PD-1/PD-L1 signaling pathway can be significantly inhibited, thereby remodeling the tumor immune-suppressive microenvironment. PD-L1 is widely distributed on both tumor and immune cells, indicating its significant role in regulating interactions between tumor cells and immune cells, as well as between immune cells themselves. While PD-L1 alone may not be a perfect biomarker for tumor immune-suppression resistance, its abnormal expression is indeed significantly correlated with resistance to ICIs. The abnormal regulatory mechanisms of PD-L1 in primary and secondary resistance may not be identical, possibly related to the altered expression of other immune checkpoint molecules. Given

that HCC is a highly heterogeneous tumor, more caution is needed when considering the use of PD-L1 as a biomarker for immune resistance.

In recent years, the role of the p53 molecule in immune regulation has gained increasing attention. However, it remains unclear whether and how p53 regulates the expression of various immune checkpoint molecules and their mechanisms of action. Among these, PD-L1, as one of the most important immune checkpoint molecules, is particularly noteworthy regarding its regulation by p53. Recent studies have shown that p53 can directly or indirectly regulate PD-L1 expression through multiple pathways, and combination therapies targeting both p53 and PD-L1 have demonstrated the ability to reverse tumor sensitivity to anti-PD-L1 treatments in both in vitro and in vivo experiments.

However, several points need to be considered: 1. Tumor Heterogeneity: Due to the high heterogeneity among tumors, the regulatory effect of p53 on PD-L1 may not be the same across different tumors and could even be opposite in some cases. 2. p53 Regulation in Immune Cells: The discussion has primarily focused on the regulation of PD-L1 by p53 in tumor cells. However, PD-L1 is also frequently aberrantly expressed in immune cells. Therefore, it is essential to consider how p53 mutations in immune cells within the TME may regulate PD-L1 expression, which may differ from the regulation observed in tumor cells. 3. Reverse Signaling of PD-L1: PD-L1 has some reverse signaling capabilities, but it is still unclear whether abnormal PD-L1 expression can, in turn, affect p53. This reciprocal interaction needs further investigation.

For tumor heterogeneity, the molecular regulation of PD-L1 is highly complex, and its expression varies across different tumors, such as HCC [8] and breast cancer [90]. PD-L1 is precisely and stringently regulated to ensure that tumor cells acquire the ability to evade the immune system. Owing to this complexity, it is challenging to inhibit tumor immune evasion solely by targeting PD-L1, which is also a consequence of tumor heterogeneity, particularly in HCC, leading to immune resistance. In contrast to PD-L1, which is subject to complex regulation due to tumor heterogeneity, we propose focusing on a molecule that is highly homogeneous across tumors and capable of regulating PD-L1: p53. p53 mutations are highly prevalent in most tumors, and it has been demonstrated that p53 can directly or indirectly regulate PD-L1 expression. Therefore, adopting a combination therapy strategy that leverages a constant target (p53) to address a variable target (PD-L1) can maximize the efficacy of immunotherapy across different tumor types. This approach also reduces the uncertainty associated with PD-L1 regulation, thereby enhancing the safety of clinical trials.

For p53 regulation in immune cells, the precise mechanism by which p53 regulates PD-L1 expression in immune cells within the TME remains to be elucidated. However, intraperitoneal administration of OBP-702 significantly increased PD-1 expression on intraperitoneal $CD8^+$ T cells and PD-L1 expression on TAMs and MDSCs [130]. These observations suggest that p53 plays a role in modulating immune checkpoint molecules (PD-1 and PD-L1) in the immune cells. Furthermore, the inhibition of $CD8^+$ T cells may be partially attributed to the upregulation of PD-L1 in TAMs and MDSCs, which promotes the PD-1/PD-L1 signaling pathway. This reveals a complex immune-suppressive regulatory network in which $CD8^+$ T cells are suppressed not only by tumor cells but also by other immune cells. Anti-PD-L1 therapy may attenuate these immunosuppressive interactions among immune cells, further supporting the rationale for combining anti-PD-L1 therapy with p53-targeted treatment.

For reverse signaling of PD-L1, in conventional anti-PD-L1 therapy, alterations in p53 expression in both tumor and immune cells are frequently disregarded, as p53 is traditionally considered to regulate PD-L1 in a unidirectional manner. However, it is essential to acknowledge that PD-L1 functions by binding to PD-1, thereby activating the PD-1/PD-L1 signaling pathway. Given that both PD-1 and PD-L1 are ubiquitously expressed in the TME, the PD-1/PD-L1 axis may, to some extent, influence p53 activity. For instance, the inhibitory effect of PD-L1 on $CD8^+$ T cell proliferation may not be solely attributable to insufficient tumor antigen activation but rather to the impact of PD-1/PD-L1 signaling on p53 within $CD8^+$ T cells. Such observations have been documented during OBP-702 treatment, wherein the functional-

ity of $CD8^+$ T cells is augmented; however, the majority of $CD8^+$ T cells continue to exhibit elevated PD-1 expression levels [130]. This underscores the necessity of reevaluating tumor immune suppression from the perspective of inhibitory mechanisms (such as immune checkpoint molecules like PD-L1), rather than exclusively focusing on stimulatory mechanisms (such as tumor antigens). Merely enhancing immune cell proliferation and activation addresses only superficial issues, whereas the underlying root cause of immune dysfunction resides in multiple layers of immune suppression rather than a lack of stimulation. To overcome tumor resistance and achieve a fundamental cure for cancer, it is imperative to reverse the immunosuppressive TME rather than merely enhancing immune cell function.

In conclusion, more basic researches are required to address these issues, and combination therapies targeting both p53 and PD-L1 should be further validated in HCC. Additionally, more clinical trials are needed to confirm their effectiveness and safety.

Disclosure of conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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