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REVIEW

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Programmed death receptor (PD-)1/PD-ligand (L)1 in urological cancers : the "all-around warrior" in immunotherapy

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Abstract

Programmed death receptor-1 (PD-1) and its ligand, programmed death ligand-1 (PD-L1) are essential molecules that are key in modulating immune responses. PD-L1 is constitutively expressed on various immune cells, epithelial cells, and cancer cells, where it functions as a co-stimulatory molecule capable of impairing T-cell mediated immune responses. Upon binding to PD-1 on activated T-cells, the PD-1/PD-L1 interaction triggers signaling pathways that can induce T-cell apoptosis or anergy, thereby facilitating the immune escape of tumors. In urological cancers, including bladder cancer (BCa), renal cell carcinoma (RCC), and prostate cancer (PCa), the upregulation of PD-L1 has been demonstrated. It is linked to poor prognosis and enhanced tumor immune evasion. Recent studies have highlighted the significant role of the PD-1/PD-L1 axis in the immune escape mechanisms of urological cancers. The interaction between PD-L1 and PD-1 on T-cells further contributes to immunosuppression by inhibiting T-cell activation and proliferation. Clinical applications of PD-1/PD-L1 checkpoint inhibitors have shown promising efficacy in treating advanced urological cancers, significantly improving patient outcomes. However, resistance to these therapies, either intrinsic or acquired, remains a significant challenge. This review aims to provide a comprehensive overview of the role of the PD-1/PD-L1 signaling pathway in urological cancers. We summarize the regulatory mechanism underlying PD-1 and PD-L1 expression and activity, including genetic, epigenetic, post-transcriptional, and post-translational modifications. Additionally, we discuss current clinical research on PD-1/PD-L1 inhibitors, their therapeutic potential, and the challenges associated with resistance. Understanding these mechanisms is crucial for developing new strategies to overcome therapeutic limitations and enhance the efficacy of cancer immunotherapy.

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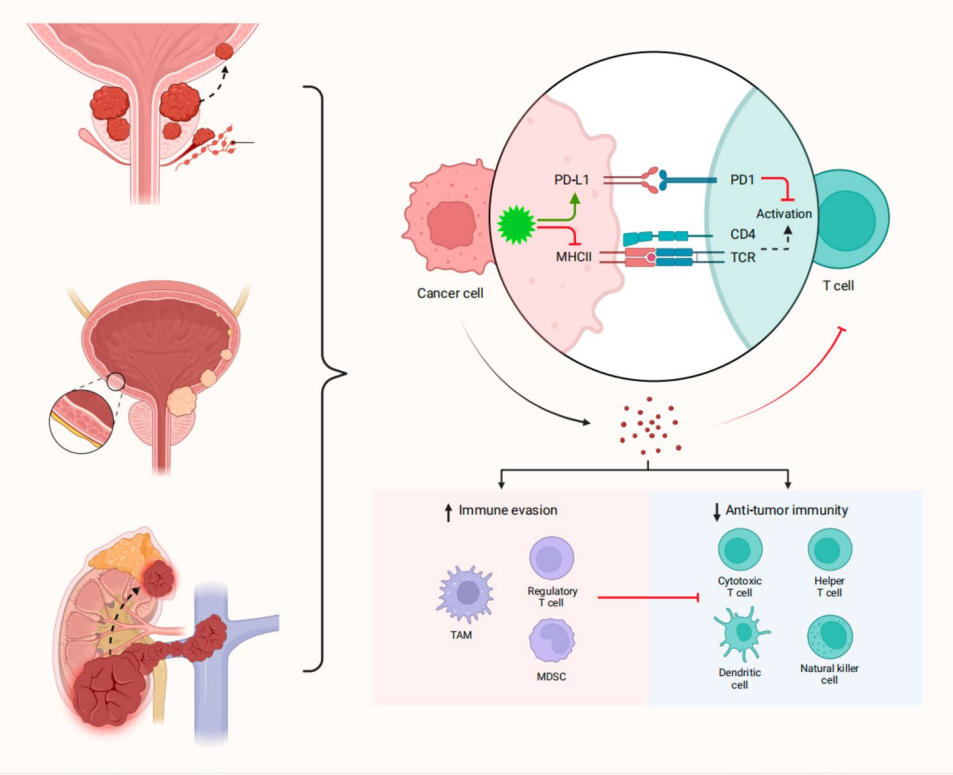
Graphic abstract



Keywords Tumor immunity, PD-1, PD-L1, Regulatory mechanism, Combination therapy

Introduction

Cancers of the urinary system, such as bladder cancer (BCa), renal cell carcinoma (RCC), and prostate cancer (PCa), pose substantial challenges in the field of oncology. BCa, which is mainly transitional cell carcinoma, occurs more frequently in men and can be classified by the degree of invasion into non-muscle invasive bladder cancer (NMIBC) and muscle-invasive bladder cancer (MIBC) [1–3]. The standard treatment for NMIBC usually includes transurethral resection of the bladder tumor (TURBT) along with localized therapies to reduce the risk of recurrence [4, 5]. However, NMIBC recurs locally in 60–70% of cases, with 15–40% progressing to MIBC or distant metastasis [6, 7]. Epidemiological data indicate that the incidence of BCa varies globally, with higher rates typically observed in developed countries. The primary risk factors include smoking, occupational exposure, and chronic inflammation [8]. Smoking is considered the most significant modifiable risk factor, with studies showing that smokers are more than three times as likely to develop BCa compared to non-smokers [9]. Additionally, occupational exposure to certain chemicals, such as aniline dyes, chlorides, and chemicals related to aluminum production, significantly increases the risk of developing BCa [2]. Long-term chronic bladder inflammation, urinary tract infections, and certain parasitic infections, such as schistosomiasis, are also closely associated with the development of BCa. In terms of diagnosis, cystoscopy is regarded as the gold standard for BCa diagnosis. Cystoscopy allows for direct visualization of the bladder mucosa, enabling early detection of tumor lesions and the possibility of performing biopsies to obtain pathological evidence. However, the sensitivity and specificity of cystoscopy may be limited by the size and location of the tumor. Therefore, imaging techniques play a crucial role in the diagnosis and staging of BCa. Computed tomography (CT) and magnetic resonance imaging (MRI) are particularly essential in assessing tumor invasion depth, lymph node involvement, and distant metastasis. In recent years, molecular testing techniques have increasingly been applied to the diagnosis and characterization of BCa. Ki-67, TP53, and CK20 are key biomarkers for diagnosing and predicting BCa outcomes [10]. Ki-67 indicates tumor cell growth, with higher levels suggesting more aggressive tumors and poorer prognosis. TP53 often mutates in BCa, contributing to tumor progression

and therapy resistance. CK20 can identify BCa subtypes, confirming urothelial origin and providing insights into tumor differentiation and invasiveness. Besides, FGFR3 and TERT promoter mutations have been identified as key molecular markers associated with BCa [11, 12]. These markers not only aid in the early diagnosis of tumors but also provide a basis for personalized treatment strategies. Surgery, chemotherapy, immunotherapy, and targeted therapies are essential for BCa treatment. For localized BCa, transurethral resection of bladder tumors (TURBT) and radical cystectomy are primary surgical treatments that effectively control the disease [13]. However, for advanced or metastatic cases, surgery alone is insufficient, making chemotherapy the preferred supplement. Cisplatin-based regimens like MVAC and GC are commonly used and effective. Recently, PD-1/PD-L1 immune checkpoint inhibitors have shown significant success in advanced BCa, providing an alternative for patients who cannot undergo chemotherapy [14]. Additionally, targeted therapies, such as those addressing FGFR3 mutations, offer personalized options for certain bladder cancer subtypes. Combining these treatments can improve survival rates and quality of life for bladder cancer patients. However, the 5-year survival rate remains relatively low at 20–40%, with around 50% of patients developing distant metastases within 3 years and a mere 10% surviving up to 5 years [7, 15]. RCC, which accounts for 2–3% of all cancers, originates from the renal tubular epithelium. The most common subtype is clear cell renal cell carcinoma (ccRCC) [16]. RCC is frequently asymptomatic in its early stages and is often diagnosed incidentally. At the time of diagnosis, up to 30% of cases have already metastasized [17, 18]. Despite surgical resection, about 30% of organ-confined cases experience metastasis during follow-up [19, 20]. The prognosis for advanced or metastatic RCC remains bleak, with a less than 10% survival rate at 5 years post-diagnosis, compounded by resistance to conventional therapies like chemotherapy and radiotherapy [18, 21]. PCa, prevalent in the male genitourinary system, demonstrates a promising 10-year overall survival rate of 99% for early-stage localized cases due to enhanced detection and treatment strategies [22, 23]. However, up to 25% of patients experience biochemical recurrence after initial treatment, progressing to metastatic castration-resistant prostate cancer (mCRPC) [24–26]. Once advanced, the median survival period drops to 13–32 months, with a 5-year survival rate of only 15% [27, 28]. Effective management strategies for urinary system tumors remain crucial given their profound impact on patient outcomes and societal health.

Programmed death receptor-1 (PD-1) and its ligand, programmed death ligand-1 (PD-L1), are essential immune checkpoint molecules that play a pivotal role in the evasion of tumor immune responses [29]. PD-1 is a transmembrane receptor predominantly located on activated T cells, B cells, NK cells, and monocytes [30], The ligand PD-L1, primarily found on the surfaces of tumor cells, interacts with its receptor PD-1 [31]. This interaction results in the suppression of T cells, hindering their ability to detect and destroy tumor cells, thus aiding immune evasion. Inhibitors that target the PD-1/PD-L1 pathway disrupt this interaction, thereby restoring the cytotoxic functions of T cells to efficiently attack and eliminate tumors, countering immune evasion [32]. Additionally, PD-L1 can be expressed by various cells within the tumor microenvironment (TME) [33, 34], creating an immunosuppressive milieu that further supports tumor progression [35, 36]. These cells not only suppress T cell activity via the PD-1/PD-L1 pathway but also secrete immunosuppressive cytokines, exacerbating immune evasion [37]. Additionally, conditions like hypoxia, elevated lactate levels, and nutrient deficiencies in the tumor microenvironment can lead to PD-L1 expression, thereby increasing the tumor's ability to avoid immune detection [38]. In recent years, immunotherapies targeting the PD-1/PD-L1 axis have made substantial progress [39–41]. Inhibitors such as Nivolumab and Pembrolizumab for PD-1, as well as Atezolizumab and Durvalumab for PD-L1, have shown notable advancements, and have demonstrated notable efficacy across diverse cancer types. These drugs function by disrupting PD-1/PD-L1 interactions, releasing T cells from suppression, restoring their anti-tumor activity, and thereby achieving therapeutic efficacy.

Anti-PD-L1 and PD-1 therapies, widely used and recommended by European Society for Medical Oncology (ESMO) and the National Comprehensive Cancer Network (NCCN), are effective for urological cancers [42–47]. Atezolizumab and pembrolizumab, in particular, show significant results in advanced or metastatic bladder cancer, renal cell carcinoma, and prostate cancer. These therapies are suggested as first or second-line treatments, especially for patients who have failed chemotherapy or are ineligible for it, and have become essential in standard treatment regimens, greatly improving patient outcomes. This review seeks to establish a foundational understanding of the immune system's structure and function, with a particular focus on the PD-1/PD-L1 axis. It summarizes key clinical trials that have resulted in the approval of the five PD-1/PD-L1 inhibitors currently used to treat urological cancers. Finally, the review addresses current and future challenges in the application of PD-1 and PD-L1 inhibitors, highlighting the essential role of predictive biomarkers.

PD-1/PD-L1 pathway: molecular and cellular mechanisms

Structure and function of PD-1 and PD-L1

PD-1 is a suppressive receptor found on the surface of immune cells such as T cells, B cells, and NK cells [48]. As a member of the immunoglobulin superfamily, PD-1 features an IgV-like extracellular domain, a transmembrane segment, and an intracellular region. The intracellular part includes an immunoreceptor tyrosine-based inhibitory motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM), both essential for PD-1 signaling [49]. Likewise, PD-L1, also part of the immunoglobulin superfamily, possesses an extracellular domain with IgV-like and IgC-like structures, a transmembrane component, and a cytoplasmic tail [50]. PD-L1 is broadly expressed in various cell types, including antigen-presenting cells (APCs), tumor cells, and certain non-immune cells [51]. The PD-1/PD-L1 pathway mainly dampens T cell activation and effector functions, ensuring immune system equilibrium [52]. The interaction between PD-1 and PD-L1 triggers downstream signaling pathways, particularly via the phosphatase SHP-2 containing Src homology 2 domain, which inhibits T cell receptor (TCR) and CD28 co-stimulatory signals [39, 53]. This results in suppressed T cell proliferation, cytokine production, and cytotoxic activity, potentially leading to T cell apoptosis or anergy [54, 55]. While this mechanism typically prevents autoimmune responses, tumor cells exploit it within the tumor microenvironment (TME) to escape immune detection.

Regulation of PD-1/PD-L1 expression

The expression of PD-1 and PD-L1 is influenced by a range of genetic and epigenetic elements. The promoter region of PD-1 has numerous sites for transcription factor binding, including nuclear factor kappa B (NF-κB), activator protein 1 (AP-1), and interferon regulatory factors (IRF), among others [56, 57]. These transcription factors can enhance PD-1 gene transcription under different stimulatory conditions. DNA methylation and histone modifications also critically influence PD-1/PD-L1 expression [58, 59]. High methylation of the PD-1 promoter is associated with low expression, whereas demethylation promotes its expression. Additionally, inhibition of histone deacetylases (HDACs) can increase PD-1 expression [60, 61]. The expression of PD-L1 is controlled by various signaling pathways, including those involving interferon-gamma (IFN-γ) and transforming growth factor-beta (TGF-β) [62, 63]. IFN-γ directly enhances PD-L1 transcription by activating IRF-1 [64]. Additionally, certain microRNAs (miRNAs) play a role in modulating PD-L1 levels [65]. Elements within the tumor microenvironment (TME) also trigger PD-L1 expression, aiding tumor cells in evading the immune response [66, 67]. Hypoxia significantly influences PD-L1 regulation through hypoxia-inducible factor 1-alpha (HIF-1α), which stabilizes and increases PD-L1 gene expression under low oxygen conditions [68]. Lactic acid, another key component of the TME, upregulates PD-L1 via the STAT3 signaling pathway [69]. Furthermore, cytokines such as IFN-γ, tumor necrosis factor-alpha (TNF-α), and interleukin-10 (IL-10) markedly boost PD-L1 expression levels [70, 71], typically secreted by immune cells infiltrating the tumor, such as T cells, macrophages, and dendritic cells (DCs) [72]. The model of PD-L1 and PD-1 interaction is displayed in Fig. 1.

PD-1/PD-L1 signaling in cancer and immune cells

PD-L1 is prominently upregulated in various cancer types, including urogenital cancers, where its high expression on tumor cells binds to PD-1 on T cells, effectively inhibiting T cell anti-tumor activity and promoting tumor growth and progression [73]. Furthermore, PD-L1 can be released via exosomes, further enhancing its inhibitory effects by engaging PD-1 [74]. This mechanism of immune evasion allows tumors to evade host immune surveillance and expand. PD-L1 is not confined to tumor cells but can also be expressed in stromal cells surrounding the tumor, which induce PD-L1 expression through the secretion of cytokines and growth factors [75]. Additionally, hypoxic conditions in the TME regulate PD-L1 expression through upregulation of HIF-1α, adding complexity to treatment strategies [76]. Beyond its role in tumor cells, the PD-1/PD-L1 signaling pathway plays a pivotal role in immune cell interactions [77]. In APCs like DCs and macrophages, PD-L1 expression regulates their functions, influencing antigen presentation and cytokine secretion [78]. PD-L1 inhibits DC maturation and function, thereby reducing their capacity to activate T cells and suppressing anti-tumor immune responses [79]. Additionally, the PD-1/PD-L1 pathway is critical in regulatory T cells (Tregs), enhancing their suppressive functions. PD-1 expression in Tregs helps maintain immune tolerance by secreting inhibitory cytokines and directly suppressing effector T cells (Teffs), thereby preventing excessive immune responses and autoimmune diseases [80]. In the TME, Tregs' functions are exploited to support tumor immune evasion and growth. By augmenting Tregs' activities, the PD-1/PD-L1 pathway further suppresses Teffs' anti-tumor activity, fostering an immunosuppressive milieu that facilitates tumor survival and progression [81]. The potential mechanism of action of PD-1/PD-L1 in cells is shown in Fig. 2.

PD-1/PD-L1 in combination with other immune checkpoint inhibitors

The PD-1/PD-L1 pathway is one of several key immune checkpoints, along with molecules like cytotoxic

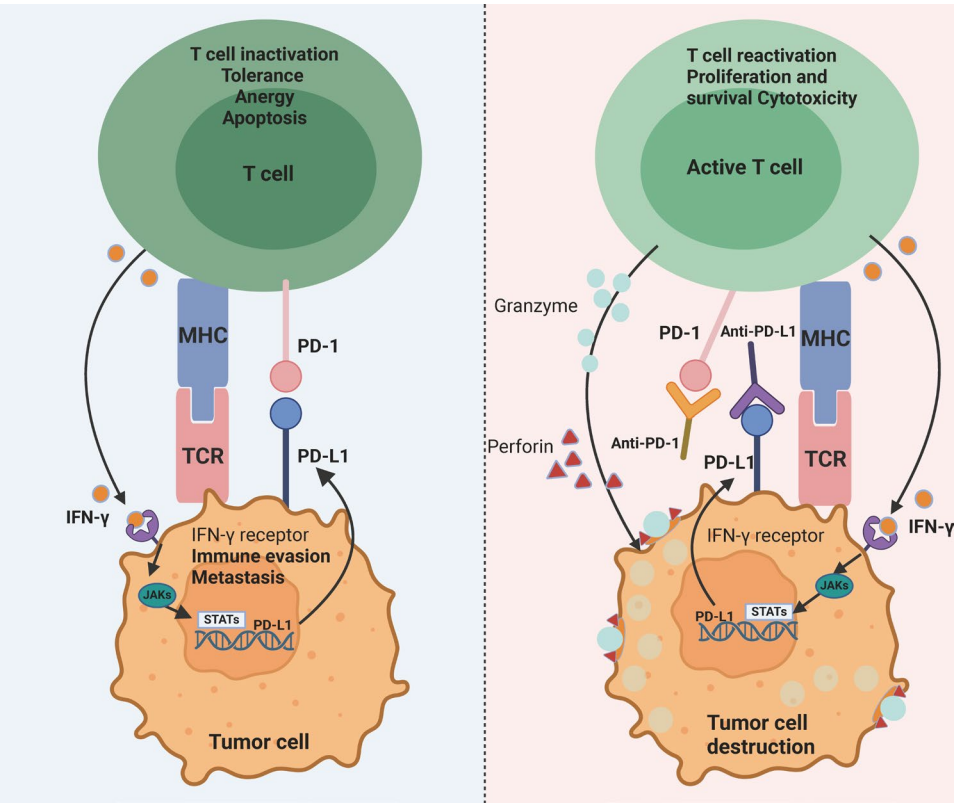


Fig. 1 The model of PD-L1 and PD-1 interaction. T cell apoptosis is initiated when PD-L1 binds to its receptor PD-1, leading to T cell exhaustion and immune evasion. PD-1/PD-L1 antibodies disrupt the interaction between PD-1 and PD-L1, enabling T lymphocytes to reactivate, proliferate, and target tumor cells for destruction. PD-L1 expression is upregulated in response to inflammatory signals such as IFN-γ produced by activated T cells

T-lymphocyte-associated protein 4 (CTLA-4) and T-cell immunoglobulin and mucin domain-containing protein 3 (TIM-3), all essential in managing immune responses [82]. CTLA-4 functions by competitively binding to B7 molecules (CD80/CD86) during the initial T cell activation phase, thereby inhibiting CD28-mediated co-stimulatory signals and suppressing T cell activation [83]. Although the CTLA-4 and PD-1 pathways exhibit unique temporal and spatial characteristics, they can work together under certain conditions to amplify immune suppression. TIM-3, mainly found on exhausted T cells, inhibits T cell function by interacting with its ligand galectin-9 [54]. TIM-3 and PD-1 are commonly co-expressed in chronic infections and tumors, collectively dampening antigen-specific T-cell responses [84]. Lymphocyte activation gene-3 (LAG-3) is another crucial immune checkpoint molecule frequently co-expressed with PD-1 on exhausted T cells [85]. By binding to major histocompatibility complex (MHC) class II molecules, LAG-3 inhibits T-cell activation [53, 86]. The interactions of PD-1 with these immune checkpoints provide a rationale for combined immune therapies. For instance, combining PD-1 inhibitors with CTLA-4 inhibitors has demonstrated enhanced anti-tumor effects in certain cancers [87, 88]. This strategy works by simultaneously releasing constraints imposed by multiple inhibitory pathways, thereby bolstering T-cell responses against tumors.

The mechanisms of PD-1/PD-L1regulation in urological tumors

Regulation of PD-1/PD-L1 transcript levels in urologic malignancies

Transcription factors are essential protein molecules that bind specifically to upstream sequences at the 5' end of genes, thereby regulating the expression of target genes with precise intensity at specific times and in particular spatial locations. Regulation at the transcriptional level plays a pivotal role in determining the level of gene expression. In models pertinent to urogenital tumors, numerous studies have elucidated mechanisms governing mRNA transcription, particularly focusing on PD-1/PD-L1 (especially PD-L1). These findings hold significant value for advancing our understanding of the role and underlying mechanisms of the PD-1/PD-L1 axis in the onset and progression of urogenital malignancies (Fig. 3; Table 1).

Several studies have examined the regulatory mechanisms influencing PD-L1 transcriptional levels in prostate cancer (PCa) models. For instance, Yin Yang 1 (YY1),

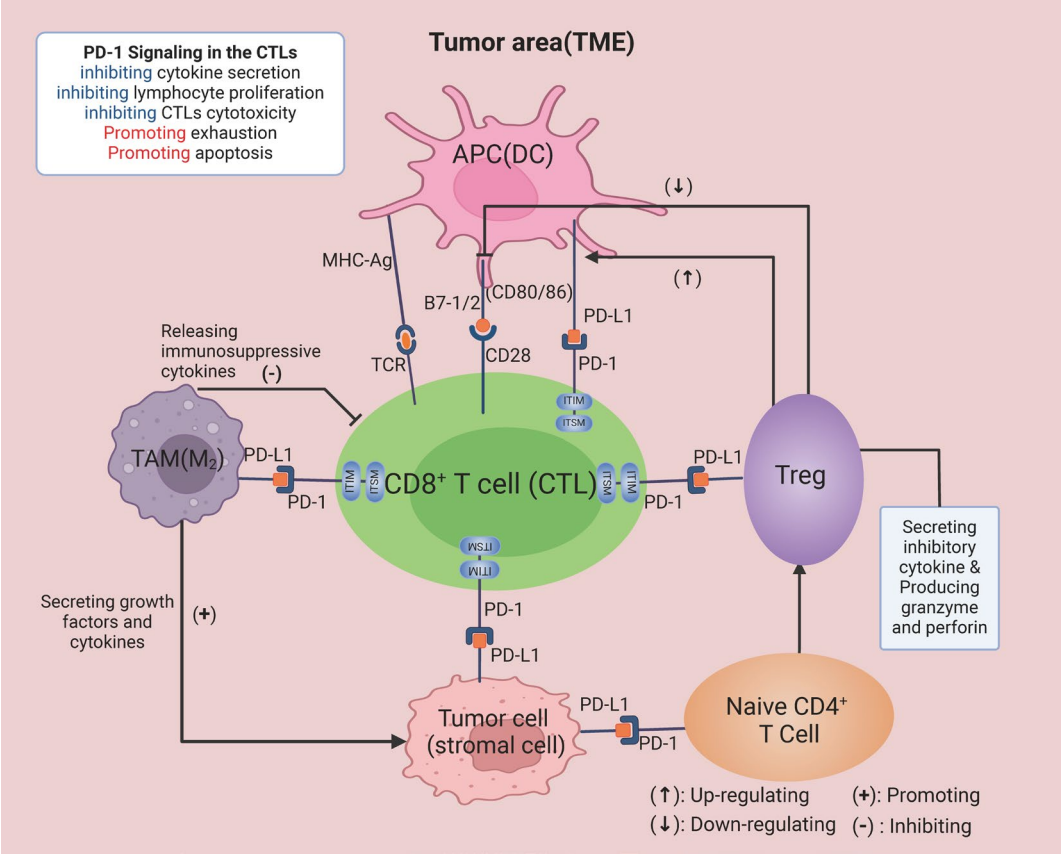


Fig. 2 The potential mechanism of action of PD-1/PD-L1 in cells. In the tumor immune microenvironment (TIME), various cells such as tumor (stromal) cells, certain antigen-presenting cells (APCs), regulatory T cells (Tregs), and M2 macrophages suppress the biological function of cytotoxic T lymphocytes (CTLs) through PD-1 signaling, leading to their exhaustion and apoptosis. Additionally, Tregs can downregulate the expression of CD80/CD86 costimulatory molecules on APCs and upregulate the expression of free PD-L1, exerting a dual inhibitory effect on CTLs. Furthermore, Tregs can secrete inhibitory cytokines and produce granzyme and perforin, causing damage to CTLs or APCs, thereby promoting tumor development. M2 macrophages also secrete growth factors and cytokines that contribute to tumor development and progression. Moreover, immunosuppressive cytokines are released to inhibit CTL metabolism and function

a critical transcriptional regulatory factor, is crucial for tumor cell survival, proliferation, metabolism, epithelial-mesenchymal transition (EMT), and resistance to chemotherapy. YY1 directly interacts with the promoter region of the PD-L1 gene, boosting its transcription. Furthermore, YY1 indirectly influences PD-L1 expression through mechanisms involving p53, cytokines, growth factors, and the PTEN/PI3K/mTOR/AKT pathway. The upregulation of PD-L1 by YY1 significantly decreases the proportion of tumor-infiltrating CD4+and CD8+T cells [89]. Another key transcription factor in cancer is NF-κB, which is activated by pro-inflammatory cytokines like TNF-α through the MAP3K7-IKK signaling axis, regulating PD-L1 mRNA expression across various cancers. Huang et al.'s CHIP-qPCR analysis discovered that the RelA/p65 protein within the NF-κB complex binds to the genomic sites of NF-κB target genes, including PD-L1. Furthermore, electrophoretic mobility shift assay (EMSA) confirmed the presence of a functional NF-κB binding site within the PD-L1 promoter. These findings indicate that NF-κB promotes PD-L1 transcription by directly binding to its promoter, thus facilitating immune evasion in tumors [90].

In BCa models, the transcriptional regulation of PD-L1 has also been extensively studied. c-Jun, part of the AP-1 transcription factor family, can be activated via the classic EGFR/MEK/ERK signaling pathway and binds to the enhancer region of the PD-L1 gene. This activation leads to increased PD-L1 expression and inhibits T-cell functions, identifying c-Jun as a key transcriptional regulator of PD-L1 expression [91]. Additionally, STAT3, a signal transducer and transcription activator, has been associated with the regulation of PD-L1 expression in BCa cells. Lu et al. investigated the interaction between SETD7 and STAT3, finding that STAT3 enhances immune evasion in BCa cells by increasing PD-L1 levels and facilitating tumor immune evasion. These insights suggest that STAT3 directly influences PD-L1 transcription by attaching to its promoter region. Nevertheless, further

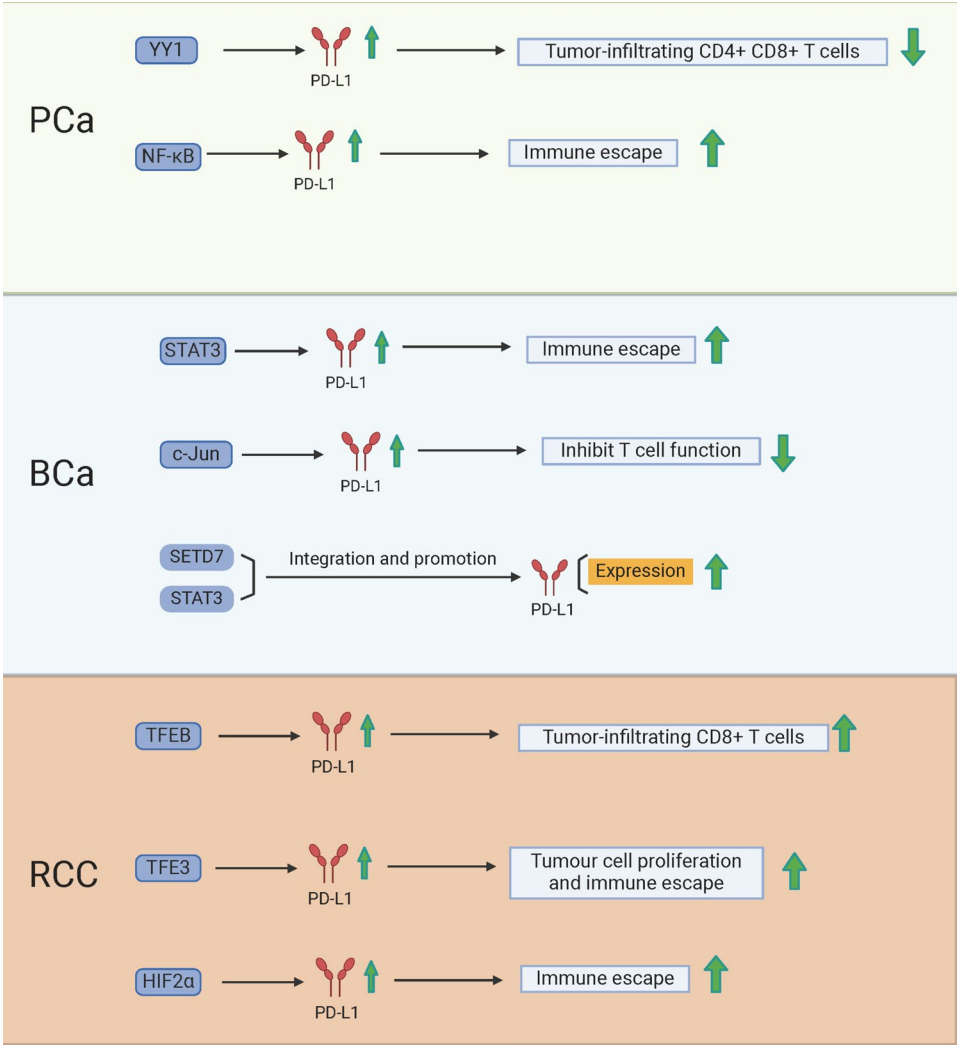


Fig. 3 Transcriptional regulation of PD-1/PD-L1 in urological malignancies. The key transcriptional mechanisms regulating the PD-1/PD-L1 axis in urological malignancies, including bladder, kidney, and prostate cancers. Highlighted are critical transcription factors (e.g., YY1, HIF-2α, STAT3, NF-κB) and their binding sites on the PD-L1 promoter, which enhance or suppress PD-L1 expression

Table 1 Transcriptional regulation of PD-1/PD-L1 in urological malignancies

Cancer	Target	Expression	Regulator	Bind site	Biological function	Reference
PCa	PD-L1	Upregulation	YY1	Promoter	Reduce tumor-infiltrating CD4 + CD8 + T cells	[89]
	PD-L1	Upregulation	NF-κB	Promoter	Promote immune escape	[90]
BCa	PD-L1	Upregulation	STAT3	Promoter	Promote immune escape	[92]
	PD-L1	Upregulation	c-Jun	Enhancer	Inhibit T cell function	[91]
RCC	PD-L1	Upregulation	TFEB	Promoter	Reduce tumor-infiltrating CD8 + T cells	[93]
	PD-L1	Upregulation	TFE3	Promoter	Promote tumour cell proliferation and immune escape	[94]
	PD-L1	Upregulation	HIF2α	Promoter	Promote immune escape	[95]

extensive research is required to confirm these hypotheses [92].

In RCC models, the transcriptional regulation of PD-L1 has been investigated as well. The transcription factor EB (TFEB), known for its role in lysosome biogenesis, autophagy, and metabolism regulation, has been linked to various human tumors. High expression of TFEB is associated with increased tumor cell proliferation and motility. Yang et al. discovered that TFEB directly attaches to the PD-L1 promoter region in RCC, thereby promoting PD-L1 transcription. This process inhibits the cytotoxic activity of tumor-infiltrating CD8 + T cells and enables immune evasion in RCC [93]. Similarly, the transcription factor E3 (TFE3), an essential oncogene in

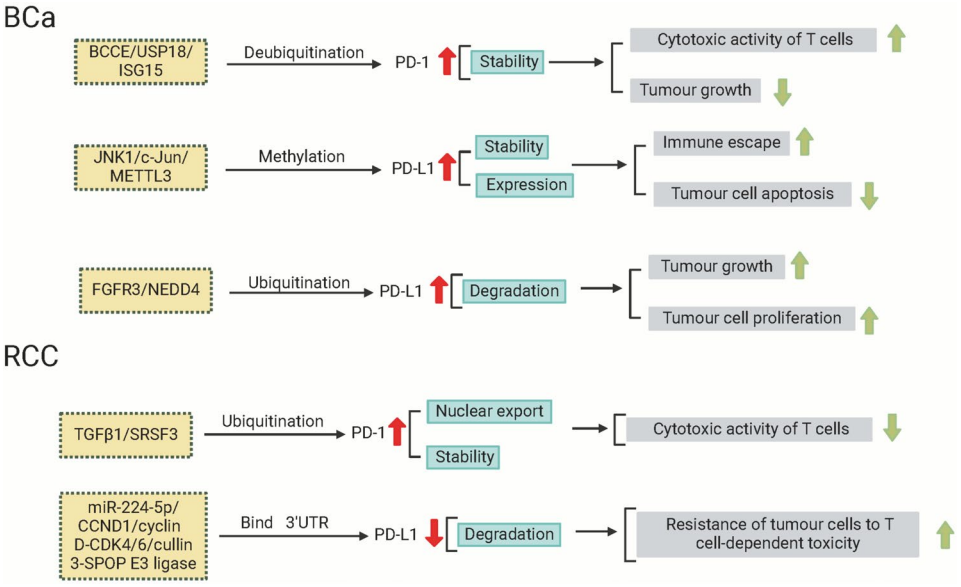


Fig. 4 Posttranslational modifications of PD-1/PD-L1 in urological malignancies. The various posttranslational modifications (PTMs) of PD-1 and PD-L1 proteins in urological malignancies, including bladder, kidney, and prostate cancers. It highlights modifications such as deubiquitination, methylation, poly-ubiquitination and their specific sites on PD-1/PD-L1 molecules. The figure illustrates how these PTMs affect protein stability, localization, and interaction with other cellular components, ultimately influencing immune checkpoint function

Table 2 Posttranslational modifications of PD-1/PD-L1 in urological malignancies

Cancer	Target	Epigenetics modifications	Regulatory mechanism	Effects on PD-1/PD-L1	Biological function	Reference
BCa	PD-L1	Deubiquitination	BCCE/USP18/ISG15	Enhance PD-L1 stability	Promote immune escape	[97]
	PD-L1	Methylation	JNK1/c-Jun/METTL3	Enhance PD-L1 stability and expression	Inhibit tumour cell apoptosis, promote immune escape	[98]
	PD-L1	Ubiquitination	FGFR3/NEDD4	Promote PD-L1 degradation	Promote cytotoxic activity of T cells	[99]
	PD-L1	Poly-ubiquitination	RNF144A	Promote PD-L1 degradation	Promote cytotoxic activity of T cells	[100]
RCC	PD-1	Bind 3'UTR	TGFβ1/SRSF3	Enhance PD-1 stability and nuclear export	Suppress cytotoxic activity of T cells	[101]
	PD-L1	Deubiquitination	miR-224-5p/CCND1/cyclin D-CDK4/6/cullin 3-SPOP E3 ligase	Suppress PD-L1 degradation	Promote the resistance of tumour cells to T cell-dependent toxicity	[102]

the proliferation of RCC cells, has been demonstrated to enhance PD-L1 expression by binding to its promoter. This regulatory pathway facilitates immune evasion and contributes to sunitinib resistance in RCC [94]. Moreover, hypoxia-inducible factor 2-alpha (HIF2-α), predominantly expressed in RCC cells, plays a significant role in promoting RCC progression. Kim et al. found that HIF2α attaches to hypoxia-response elements on the PD-L1 promoter, resulting in increased PD-L1 transcription. This mechanism also facilitates immune evasion in RCC [95].

Post-transcriptional modification of PD-1/PD-L1 in urologic malignancies

In the context of PD-1/PD-L1, negative regulation occurs through processes like ubiquitination, ubiquitin-like modifications, and methylation (Fig. 4; Table 2). Conversely, positive regulation involves deubiquitination, glycosylation, palmitoylation, ADP-ribosylation, and deacetylation [96]. Understanding these regulatory mechanisms and identifying new targets for modifying PD-1/PD-L1 are crucial for advancing precise immunotherapies for genitourinary malignancies.

Wang et al. discovered a genetic variant (rs62483508) within the miRNA-responsive element of the long non-coding RNA BCCE4, which is significantly linked to a reduced risk of BCa in the Chinese population. Their research emphasized BCCE4's role in upregulating USP18 expression by competitively inhibiting miR-328-3p. USP18, a member of the USP subfamily of deubiquitinases, increases PD-L1 protein stability by removing interferon-induced protein 15 (ISG15), which aids in immune escape in BCa cells [97]. Elevated METTL3 expression

was also observed in BCa tissues. Further studies indicated that METTL3 expression is regulated through the JNK signaling pathway and the downstream transcription factor c-Jun. METTL3 enhances PD-L1 expression by affecting its methylation status, stabilizing PD-L1 mRNA, and reducing CD8+T cell cytotoxicity against BCa cells, thereby promoting immune evasion [98]. Additionally, Fibroblast Growth Factor Receptor 3 (FGFR3) has been shown to influence PD-L1 ubiquitination, impacting the tumor microenvironment in BCa. FGFR3 phosphorylates the NEDD4 E3 ubiquitin ligase, facilitating K48-linked polyubiquitination of PD-L1, which leads to its degradation and enhances CD8+T cell-mediated tumor cell death [99]. Lin et al. investigated the ubiquitination regulatory mechanisms of PD-L1 in BCa, focusing on the E3 ubiquitin ligase RNF144A, which is frequently mutated or epigenetically silenced in cancer and exerts tumor-suppressive effects. Their findings demonstrated that RNF144A interacts with PD-L1 on cell membranes and intracellular vesicles via its C-terminal region, promoting PD-L1 polyubiquitination and degradation. This mechanism enhances CD8+T cell cytotoxic function and inhibits BCa progression [100].

Li et al. studied the mechanisms behind elevated PD-1 expression in T cells within RCC. They found that transforming growth factor beta 1 (TGFβ1) activates p38, leading to Ser10 phosphorylation of histone H3. This modification recruits RelA/p65, which increases the expression of SRSF3 and SRSF5 in T cells. SRSF3 directly binds to the 3'UTR of PD-1 mRNA through its RNA recognition motifs, enhancing PD-1 mRNA stability and nuclear export, thus increasing PD-1 expression on T cell surfaces. This process inhibits T cell cytotoxicity against RCC cells [101]. Another study by Li et al. highlighted the significant upregulation of miR-224-5p in extracellular vesicles (EVs) derived from RCC patient urine. They found that miR-224-5p suppresses cyclin D1 expression, leading to decreased activity of the cyclin D-CDK4/6 complex. This reduction inhibits the cullin 3-SPOP E3 ubiquitin ligase-mediated pathway responsible for PD-L1 ubiquitination and degradation, resulting in elevated PD-L1 expression levels in RCC cells. RCC cells can transfer these regulatory mechanisms of PD-L1 expression through EVs, enhancing resistance to T cell-mediated cytotoxicity [102].

Molecular mechanisms regulating the expression of PD-1/PD-L1 in urologic cancers

PD-1 and its ligand PD-L1 play a critical role in tumor therapy by effectively regulating anti-tumor immune responses [103]. PD-L1 is found in various tumors, while PD-1 is predominantly located on T cells within tumor tissues [104]. The interaction between PD-L1 and PD-1 forms a molecular barrier that suppresses immune cell cytotoxicity. By modulating the expression of PD-1/PD-L1, it is possible to reactivate immune responses and overcome this immune suppression [105]. Numerous studies have shown the therapeutic benefits of monoclonal antibodies that target PD-1 and PD-L1 in the treatment of urological cancers [106]. Therefore, understanding the regulatory mechanisms of PD-1/PD-L1 expression is essential for optimizing cancer immunotherapy in these malignancies (Fig. 5; Table 3).

Suppressing the epigenetic regulator EZH2 activates the double-stranded RNA-STING-interferon signaling pathway, resulting in the upregulation of genes related to antigen presentation, Th1 chemokine signals, and interferon responses, including PD-L1. Studies have shown that inhibiting EZH2 directly increases PD-L1 mRNA levels in PCa cell lines and human PCa tissues, thereby enhancing PD-L1 expression and improving the responsiveness of PCa to PD-1 checkpoint inhibitors [107]. In metastatic castration-resistant PCa, researchers found that phosphorylated retinoblastoma protein (pRB) suppresses NF-κB activity by interacting with its RelA/p65 subunit, reducing PD-L1 expression and promoting anti-tumor immune responses. Traditional Chinese medicine CFF-1 has also been reported to inhibit PD-L1 expression in PCa by suppressing the EGFR/JAK1/STAT3 axis, thus impeding cancer progression [108]. Additionally, Mao et al. demonstrated that heterogeneous nuclear ribonucleoprotein L (HnRNP L) enhances YY1 stability by binding to YY1 mRNA, leading to increased YY1 expression. YY1, a transcriptional regulator, binds to the PD-L1 gene promoter, promoting PD-L1 transcription and inhibiting T-cell cytotoxicity [89]. Another study indicated that Neuropeptide-2 activates Rac1, promoting YAP/TAZ nuclear translocation and transcriptional activity, consequently upregulating PD-L1 expression and suppressing anti-tumor immune responses [109].

The JAK (Janus kinase) signaling pathway is essential for various physiological processes and disease development. This pathway includes JAK1, JAK2, JAK3, and TYK2 kinases, which relay external signals from cell membrane receptors like cytokine and immunoglobulin receptors. When these receptors are activated, JAK proteins get phosphorylated and activated, initiating downstream signaling. Activated JAK proteins then phosphorylate and activate STAT proteins, which move to the nucleus to regulate gene transcription, affecting cell proliferation, differentiation, and apoptosis. Thus, the JAK pathway is crucial for immune regulation, cell growth, and cancer development. Abnormal activation of this pathway is linked to inflammatory diseases, autoimmune disorders, and various cancers. Therefore, understanding and controlling the JAK pathway is vital for treating and preventing these conditions. In BCa, tumor-associated macrophages (TAMs), especially

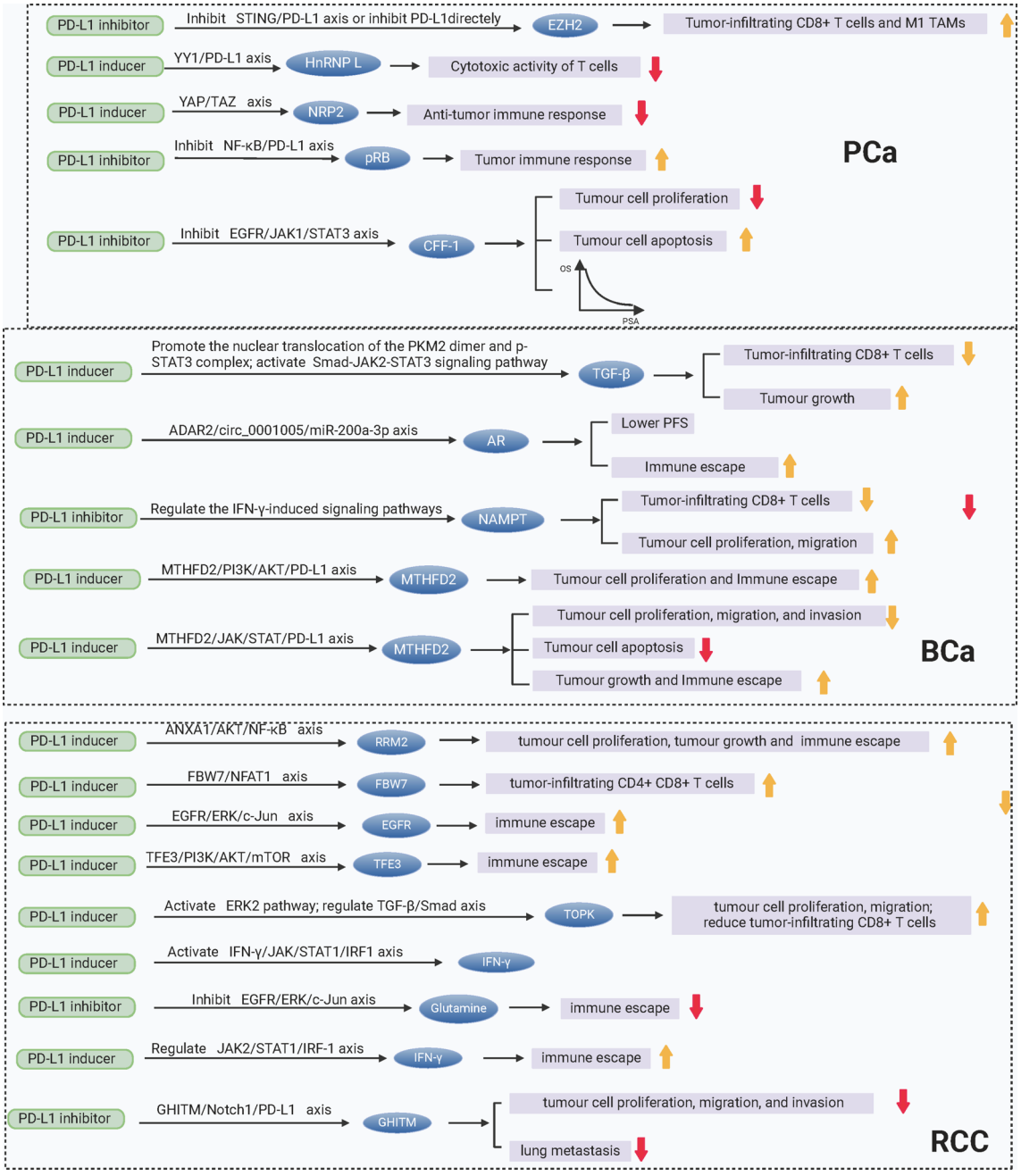


Fig. 5 The molecular mechanism of regulating PD-1/PD-L1 in urological malignancies. The molecular pathways and mechanisms involved in the regulation of PD-1/PD-L1 expression in urological cancers, including signaling cascades, transcription factors, and posttranslational modifications that contribute to immune evasion and tumor progression

M2-type TAMs, are crucial in promoting immune evasion and tumor progression. M2-type TAMs secrete TGF-β, which induces STAT3 phosphorylation and nuclear translocation, and promotes pyruvate kinase M2 (PKM2) dimerization, collectively enhancing PD-L1 expression. TGF-β also triggers the canonical Smad signaling pathway, which activates the JAK2/STAT3 signaling cascade, directly regulating PD-L1 expression and driving BCa progression [110]. Expression of FBW7, an F-box protein within the Skp1-Cul1-F-box protein ubiquitin ligase complex, is reduced in drug-resistant RCC models and patient samples, and its protein levels inversely associated with nuclear factor of activated T cells 1 (NFAT1) in RCC patients. FBW7 directly interacts with NFAT1 and regulates PD-L1 expression by modulating the JAK-STAT, TNF, and HIF pathways [111]. PD-L1 expression is differentially regulated in clear cell RCC and papillary RCC, with PD-L1 expression in clear cell

Table 3 The molecular mechanism of regulating PD-1/PD-L1 in urological malignancies

Cancer	Drug/Target	PD-1/PD-L1 expression (inducer/inhibitor)	Mechanism	Biological function	Reference
PCa	EZH2	PD-L1 inhibitor	Inhibit STING/PD-L1 axis or directely inhibit PD-L1	Increase tumor-infiltrating CD8 + T cells and M1 TAMs	[107]
	HnRNP L	PD-L1 inducer	YY1/PD-L1 axis	Inhibit cytotoxic activity of T cells	[89]
	NRP2	PD-L1 inducer	YAP/TAZ axis	Inhibit anti-tumor immune response	[109]
	pRB	PD-L1 inhibitor	Inhibit NF-κB/PD-L1 axis	Enhance tumor immune response	[90]
	CFF-1	PD-L1 inhibitor	Inhibit EGFR/JAK1/STAT3 axis	Inhibit tumour cell proliferation, promote tumour cell apoptosis; lower PSA, better OS	[108]
BCa	TGF-β	PD-L1 inducer	Promote the nuclear translocation of the PKM2 dimer and p-STAT3 complex; activate Smad-JAK2-STAT3 signaling pathway	Reduce tumor-infiltrating CD8 + T cells; promote tumour growth	[110]
	AR	PD-L1 inducer	ADAR2/circ_0001005/miR-200a-3p axis	Promote immune escape; lower PFS	[122]
	NAMPT	PD-L1 inhibitor	Regulate the IFN-γ-induced signaling pathways	Promote tumour cell proliferation, migration; reduce tumor-infiltrating CD8 + T cells	[123]
	MTHFD2	PD-L1 inducer	MTHFD2/PI3K/AKT/PD-L1 axis	Promote tumour cell proliferation and immune escape	[120]
	MTHFD2	PD-L1 inducer	MTHFD2/JAK/STAT/PD-L1 axis	Promote tumour cell proliferation, migration, and invasion, inhibit tumour cell apoptosis; promote tumour growth and immune escape	[113]
RCC	RRM2	PD-L1 inducer	ANXA1/AKT/NF-κB axis	Promote tumour cell proliferation, tumour growth and immune escape	[124]
	FBW7	PD-L1 inducer	FBW7/NFAT1 axis	Increase tumor-infiltrating CD4 + CD8 + T cells	[111]
	EGFR	PD-L1 inducer	EGFR/ERK/c-Jun axis	Promote immune escape	[116]
	TFE3	PD-L1 inducer	TFE3/PI3K/AKT/mTOR axis	Promote immune escape	[121]
	TOPK	PD-L1 inducer	Activate ERK2 pathway; regulate TGF-β/Smad axis	Promote tumour cell proliferation, migration; reduce tumor-infiltrating CD8 + T cells	[22]
	IFN-γ	PD-L1 inducer	Activate IFN-γ/JAK/STAT1/IRF1 axis	/	[122]
	Glutamine	PD-L1 inhibitor	Inhibit EGFR/ERK/c-Jun axis	Inhibit immune escape	[119]
	IFN-γ	PD-L1 inducer	Regulate JAK2/STAT1/IRF-1 axis	Promote immune escape	[95]
	GHITM	PD-L1 inhibitor	GHITM/Notch1/PD-L1 axis	Inhibit tumour cell proliferation, migration, and invasion; inhibit lung metastasis	[125]

RCC being dependent on intact IFN-γ signaling, activating JAK2/STAT1/IRF1 to promote PD-L1 transcription. Conversely, PD-L1 expression in papillary RCC is independent of IFN-γ signaling, highlighting distinct mechanisms in different RCC subtypes [95, 112]. Heng et al. also linked elevated MTHFD2 expression in BCa cells and tissues with adverse clinical outcomes, showing that MTHFD2 promotes PD-L1 expression by activating the JAK/STAT signaling pathway, highlighting its role in immune regulation within the BCa microenvironment [113].

The ERK (extracellular signal-regulated kinase) signaling pathway is a vital intracellular mechanism essential for cell proliferation, differentiation, survival, and migration. It is part of the RAS-RAF-MEK-ERK cascade, also known as the MAPK (mitogen-activated protein kinase) pathway. This pathway detects external signals via cell surface receptors, such as growth factor and cytokine receptors. Signal transduction starts with receptor activation, leading to RAS protein activation, which then activates RAF kinase. RAF kinase phosphorylates and activates MEK, which subsequently activates ERK. Activated ERK moves into the nucleus to phosphorylate target proteins, including transcription factors, thus regulating gene expression and cell functions. Dysregulation of the ERK pathway is linked to various diseases, particularly cancer, where it promotes uncontrolled cell proliferation and resistance to apoptosis. The ERK pathway also plays roles in cardiovascular, neurological, and immune diseases. Understanding its regulatory mechanisms is crucial for uncovering the molecular basis of these diseases and developing new treatments. The TME is marked by hypoxia and acidity from glycolysis-induced lactate buildup, facilitating tumor cell migration

and invasion [114, 115]. Niu et al. found that glucose metabolism influences PD-L1 expression in RCC via the EGFR/ERK/c-Jun pathway. Elevated PD-L1 expression also upregulates PFKFB3 to regulate glycolysis, suggesting potential combined therapeutic targets in RCC [116]. T-LAK cell-originated Protein Kinase (TOPK) regulates PD-L1 expression to promote immune evasion in RCC through two mechanisms. TOPK forms a positive feedback loop with ERK2 and enhances the TGF-β/Smad pathway by directly binding to Smad4, thereby promoting PD-L1 expression [117]. Glutamine is a versatile nutrient crucial for various metabolic pathways within tumor cells. In the TME, glutamine levels are notably low, often reaching undetectable levels compared to normal tissues [118]. Studies highlight that reduced glutamine metabolism in RCC cells correlates with high PD-L1 expression levels. Mechanistically, glutamine deprivation activates the Epidermal Growth Factor Receptor (EGFR), ERK1/2, and c-Jun, resulting in high PD-L1 expression. In turn, high PD-L1 levels contribute to T-cell suppression and facilitate immune evasion of RCC [119].

The PI3K/AKT pathway is an essential intracellular signaling route that regulates cell growth, proliferation, metabolism, and survival. This pathway involves PI3K and AKT, which respond to signals from various receptors like growth factor, insulin, and cytokine receptors. Activation of these receptors leads to PI3K activation at the cell membrane, converting PIP2 to PIP3. PIP3 then activates AKT, which phosphorylates targets like mTOR, GSK-3β, and BAD, controlling cell functions. Abnormal PI3K/AKT activation is linked to diseases such as cancer, where it promotes rapid growth, apoptosis resistance, increased metabolism, and invasiveness. It also plays roles in diabetes, cardiovascular, and neurodegenerative diseases. Understanding this pathway is essential for disease research and developing new treatments. Methylenetetrahydrofolate dehydrogenase 2 (MTHFD2) has been implicated in various malignancies, including BCa. Higher MTHFD2 expression in BCa tissues is associated with poor prognosis, increased tumor immune cell infiltration, and elevated PD-L1 levels. Transcriptome analysis reveals that MTHFD2 expression correlates positively with the activation of the PI3K/AKT signaling pathway, which enhances PD-L1 expression [120]. TFE3, involved in autophagy and lysosome biogenesis, shows elevated expression and activity in various human cancers, including RCC. TFE3 upregulates PD-L1 expression by activating the PI3K/AKT/mTOR pathway, and mTOR inhibitors may further enhance PD-L1 expression by increasing TFE3 activity [121].

In addition, other pathways also play important roles in regulating PD1/PD-L1. The androgen receptor (AR) positively influences PD-L1 expression; miR-200a-3p targets the 3'UTR region of PD-L1 mRNA to suppress its expression. AR upregulates circ_0001005 by modulating the ADAR2 enzyme, and circ_0001005 acts as a competitive inhibitor of miR-200a-3p, thereby reducing miR-200a-3p levels and increasing PD-L1 expression, diminishing NK cell cytotoxicity and promoting immune evasion in BCa [122]. Finally, Nicotinamide phosphoribosyltransferase (NAMPT) has been identified as a negative regulator of PD-L1 expression in BCa. Upregulated NAMPT levels in BCa patients inversely correlate with immune cell infiltration, and it has been shown that NAMPT downregulates PD-L1 expression via an IFN-γ-dependent mechanism, suggesting NAMPT as a potential target for immune checkpoint regulation [123]. Ribonucleotide Reductase Regulatory Subunit M2 (RRM2) is crucial for deoxyribonucleotide synthesis following ribonucleotide reduction and is considered a proto-oncogene due to elevated expression in various cancers. Jin et al. demonstrated that RRM2 upregulates ANXA1 levels, activation, and subsequent PD-L1 expression enhancement, which augments the antitumor efficacy of PD-1 blockade therapy [124]. Growth hormone-inducible transmembrane protein (GHITM), a member of the the Bax inhibitor-1 family, is downregulated in RCC and correlates with adverse patient prognosis. Furthermore, Wang et al. demonstrated that GHITM indirectly inhibits PD-L1 expression by suppressing the oncogene Notch1 thereby reducing RCC tumor progression and lung metastasis, suggesting its potential as a therapeutic target [125].

Anti-PD-1 /PD-L1 combination therapy in urinary malignancies

Because of the inherent variability of cancer and the genetic diversity among individuals, single-agent therapies that target the PD-1/PD-L1 pathway have failed to yield satisfactory results [126]. As a result, there is a pressing need for personalized combination therapies designed for individual patients to enhance response rates to PD-1/PD-L1 inhibitors and to overcome resistance to anti-PD-1/PD-L1 treatments. Recent research highlights that integrating anti-PD-1/PD-L1 therapy with other immune checkpoint inhibitors (ICIs) targeted therapies against VEGF/VEGFR, tumor vaccines, oncolytic viruses (OVs), and approaches that can increase the efficacy of PD-1/PD-L1 blockade [127, 128]. Significantly, these strategies have demonstrated initial success in the treatment of genitourinary malignancies (Fig. 6; Table 4).

LAG-3 is an immune checkpoint inhibitor primarily found on activated T-cells, which curtails T-cell function and proliferation, thereby reducing anti-tumor immune responses. In mouse models of prostate cancer, simultaneous blocking of PD-1 and LAG-3 results in increased infiltration of CD4+and CD8+T cells into tumors. Specifically, CD8+T cells predominantly exhibit effector

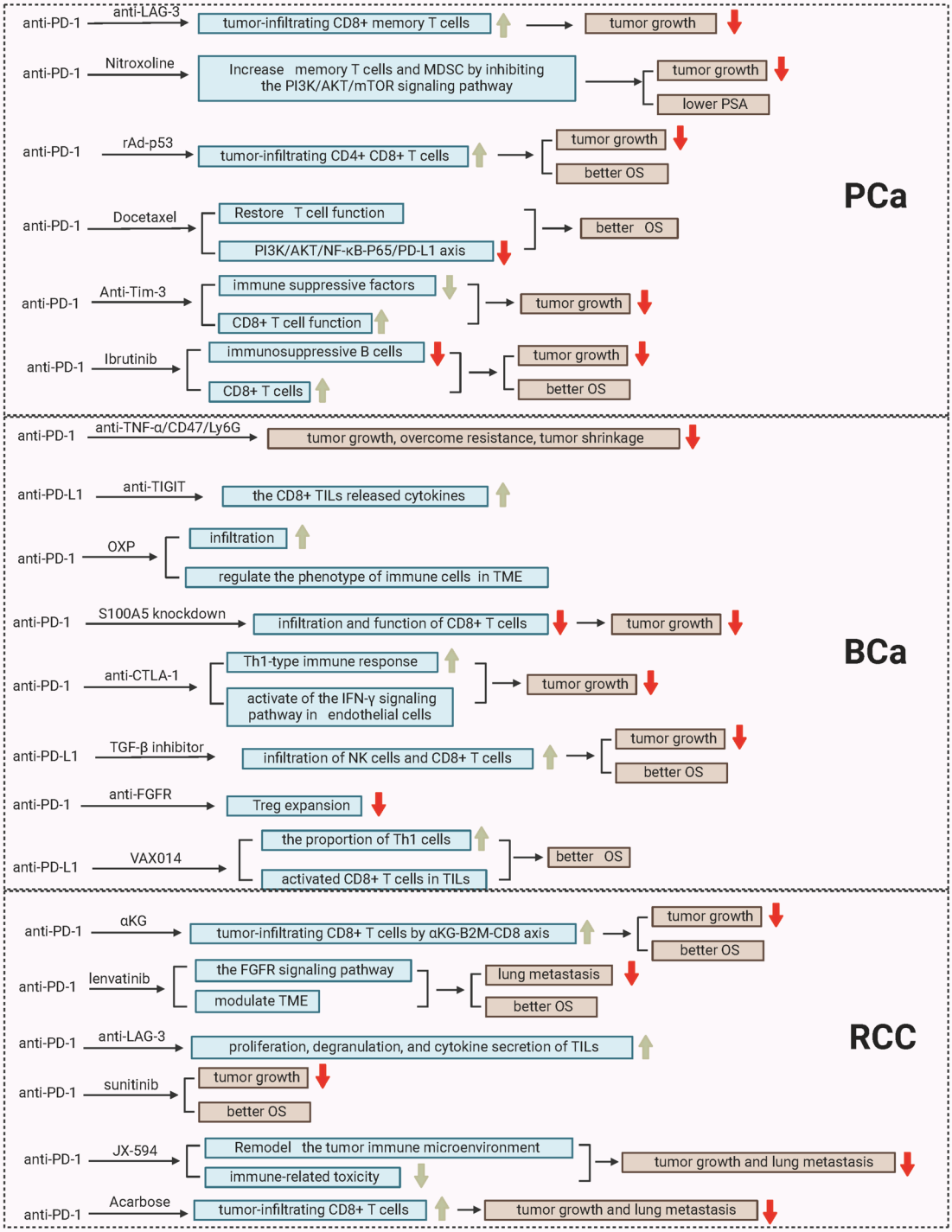


Fig. 6 Combined therapy with anti-PD-1/PD-L1 in the treatment of urological malignancies. Co-administration of anti-PD-1/PD-L1 therapies in urological malignancies demonstrates enhanced antitumor efficacy

memory and tissue-resident memory traits. This combination therapy markedly suppresses tumor growth compared to the use of PD-1 or LAG-3 inhibitors alone [129]. Tim-3, co-expressed with PD-1 in TME, represents a marker of T-cell exhaustion and research shows that blocking PD-1 increases Tim-3 levels. Using inhibitors targeting both PD-1 and Tim-3 enhances anti-tumor immunity by improving CD8 + T cell activity, diminishing tumor-supportive factors, and further reducing tumor growth [130]. Nitroxoline, commonly utilized for urinary tract infection treatment, has shown promise as an anti-cancer agent effective against multiple cancer forms [131,

Table 4 Combined therapy with anti-PD-1/PD-L1 in the treatment of urological malignancies

Cancers	anti-PD-1/PD-L1	Combined drug	Biological function	Outcome	Reference
PCa	anti-PD-1	anti-LAG-3	Increase tumor-infiltrating CD8 + memory T cells	Suppress tumor growth	[129]
	anti-PD-1	Nitroxoline	Increase memory T cells and MDSC by inhibiting the PI3K/AKT/mTOR signaling pathway	Suppress tumor growth, lower PSA	[133]
	anti-PD-1	rAd-p53	Increase tumor-infiltrating CD4 + CD8 + T cells	Suppress tumor growth, better OS	[134]
	anti-PD-1	Docetaxel	Restore T cell function; inhibit PI3K/AKT/NF-κB-P65/PD-L1 axis	better OS	[135]
	anti-PD-1	Anti-Tim-3	Reduce immune suppressive factors and enhance CD8 + T cell function	Suppress tumor growth	[130]
	anti-PD-1	Ibrutinib	Inhibit immunosuppressive B cells and increase CD8 + T cells	Suppress tumor growth, better OS	[136]
BCa	anti-PD-1	anti-TNF-α/CD47/Ly6G	/	Suppress tumor growth, overcome resistance, tumor shrinkage	[139]
	anti-PD-L1	anti-TIGIT	Increase the CD8 + TILs released cytokines	/	[137]
	anti-PD-1	OXP	Increase infiltration and regulate the phenotype of immune cells in TME	/	[140]
	anti-PD-1	S100A5 knockdown	Suppress the infiltration and function of CD8 + T cells	Suppress tumor growth	[141]
	anti-PD-1	anti-CTLA-1	Promote Th1-type immune response and activate of the IFN-γ signaling pathway in endothelial cells	Suppress tumor growth	[138]
	anti-PD-1	anti-FGFR	Inhibit Treg expansion	/	[142]
	anti-PD-L1	VAX014	Increase the proportion of Th1 cells and activated CD8 + T cells in TILs	better OS	[143]
RCC	anti-PD-1	αKG	Increase tumor-infiltrating CD8 + T cells by αKG-B2M-CD8 axis	Suppress tumor growth, better OS	[144]
	anti-PD-1	lenvatinib	Inhibit the FGFR signaling pathway; modulate TME	Suppress tumor growth, better OS	[145]
	anti-PD-1	anti-LAG-3	Promote proliferation, degranulation, and cytokine secretion of TILs	/	[147]
	anti-PD-1	sunitinib	/	Suppress lung metastasis, better OS	[146]
	anti-PD-1	JX-594	Remodel the tumor immune microenvironment; reduce immune-related toxicity	Suppress tumor growth and lung metastasis	[3]
	anti-PD-1	Acarbose	Increase tumor-infiltrating CD8 + T cells	Suppress tumor growth and lung metastasis	[148]

132]. Huang et al.'s research demonstrate that Nitroxoline, when combined with PD-1 blockade, shows significant potential in treating PCa. Nitroxoline inhibits the PI3K/AKT/mTOR pathway to reduce PD-L1 expression, thereby boosting the immune response of PD-1 blockade. This therapeutic approach increases memory T cells and decreases myeloid-derived suppressor cells, presenting a promising treatment option [133]. Gene therapy can be used to stimulate immune responses within the TME by directly injecting virus vectors carrying specific genes into tumor sites. For example, the replication-deficient recombinant adenovirus vector rAd-p53, which carries the human p53 gene, boosts the infiltration of CD4+and CD8+T cells into tumors and increases PD-L1 expression on tumor cells, thus improving the effectiveness of anti-PD-1 antibody therapy [134]. Docetaxel, an FDA-approved taxane used for prostate cancer (PCa) chemotherapy, has been studied in conjunction with PD-1 inhibitors in PCa mouse models. This combined therapy mitigates the docetaxel-induced increase in PD-L1 expression, reversing tumor immune evasion. Furthermore, it enhances the infiltration of CD4+and CD8+T cells into tumors, restores immune functionality, and inhibits the PI3K/AKT/NF-κB-P65/PD-L1 signaling pathway. Consequently, it overcomes chemotherapy resistance induced by docetaxel and promotes apoptosis in tumor cells [135]. Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF) anchored vaccine represents a novel immunotherapy method. By fixing GM-CSF protein on tumor cell surfaces using a biotin-avidin system, this approach stimulates bone marrow cell proliferation and enhances anti-tumor immune responses.

Infiltrating B lymphocytes within the PCa TME exhibit immunosuppressive properties that promote tumor growth. Bruton's tyrosine kinase (BTK), a critical regulator of B cell function, is targeted by the inhibitor ibrutinib, which demonstrates anti-tumor effects in PCa. While monotherapy with ibrutinib reduces B cell infiltration and activation in the TME without shrinking tumors, combined therapy of ibrutinib and anti-PD-1 ICIs significantly enhances anti-tumor immune responses and reduces tumor volume in preclinical models [136].

T-cell immunoglobulin and ITIM domain (TIGIT) is a negative immune checkpoint receptor found on activated T cells. Its interaction with the ligand CD155 leads to diminished anti-tumor activity of CD8+T cells by inducing exhaustion. Studies show that blocking TIGIT boosts cytokine production by CD8+tumor-infiltrating lymphocytes (TILs) and works in tandem with PD-1 blockade in breast cancer (BCa) patients. This indicates that TIGIT and PD-1 jointly inhibit CD8+T cell effector function, supporting the combined blockade to revive anti-tumor responses [137]. CTLA-4, another inhibitory immune checkpoint receptor present on activated T cells, suppresses their activation and proliferation. Within the BCa TME, CTLA-4 aids in immune evasion. Simultaneously blocking PD-1 and CTLA-4 in mouse BCa models significantly curtails tumor growth by enhancing Th1-type immune responses and triggering IFN-γ signaling pathways in endothelial cells [138]. To combat resistance to PD-1/PD-L1 therapy in bladder cancer, Dumontet and colleagues created a resistant mouse model and investigated combination therapy targets. They found that targeting TNF-α, CD47, and Ly6G in conjunction with anti-PD-1 treatment significantly inhibited tumor growth and overcame resistance more effectively than anti-PD-1 monotherapy [139]. Oxaliplatin (OXP), a second-line chemotherapy for bladder cancer (BCa), when paired with anti-PD-1 inhibitors, demonstrates superior efficacy in reducing tumor growth compared to either treatment used individually. This therapy combination improves immune cell infiltration into the tumor microenvironment (TME) and adjusts immune cell phenotypes to strengthen anti-tumor immune responses [140]. S100A5, a tumor-specific protein, inhibits CD8+T cell proliferation and cytotoxicity, thereby promoting tumor survival. Indeed, knocking down S100A5 or using anti-PD-1 monotherapy boosts CD8+T cell infiltration and cytotoxicity, significantly hindering tumor growth and a combination of S100A5 knockdown along with anti-PD-1 therapy demonstrates superior anti-tumor efficacy [141]. Fibroblast Growth Factor Receptor (FGFR) mutations activate Tregs in the TME, impeding anti-PD-1 therapy efficacy. Erdafitinib, an FGFR inhibitor, reverses this immunosuppressive effect. Combining Erdafitinib with PD-1 inhibitors enhances CD8+T cell infiltration, augments anti-tumor immune response, and therapeutic outcomes [142]. VAX014, an engineered bacterial minicell-based oncolytic agent, selectively targets and kills α3β1 and α5β1 integrin-expressing tumor cells, inducing anti-tumor immune responses. Intravesical VAX014 combined with systemic PD-L1 blockade enhances systemic anti-tumor immunity, prolonging survival by increasing Th1 cells and activating CD8+T cells among TILs [143].

αKG (alpha-ketoglutarate) serves as a critical intermediate in the tricarboxylic acid (TCA) cycle. In RCC tissues, αKG levels are markedly reduced compared to normal tissues and inversely correlate with tumor malignancy. This suggests a protective role for αKG in inhibiting tumor initiation and progression. Research by Wang et al. further demonstrated that αKG alone or in combination with anti-PD-1 antibodies can inhibit tumor growth, as expected combination therapy was shown to be more effective than monotherapy. By modulating the αKG-B2M-CD8 axis, combination therapy enhances the infiltration of CD8+T cells into the TME and extends overall survival in murine models [144]. Renetinib, a multi-target tyrosine kinase inhibitor that inhibits VEGFR1-3, FGFR1-4, PDGFR-α, RET, and KIT, has been approved for advanced RCC treatment. Studies show that Renetinib enhances tumor cell sensitivity to IFN-γ signaling by inhibiting the FGFR pathway. Preclinical models demonstrate that using a combination of Renetinib and anti-PD-1 antibodies significantly decreases tumor size and extends survival more effectively than anti-PD-1 monotherapy [145]. Sunitinib, a small molecule inhibitor targeting VEGFRs, demonstrates efficacy in RCC by prolonging survival and inhibiting metastasis. However, its efficacy alone may be limited. Research indicates that combining Sunitinib with anti-PD-L1 therapy is more effective than either treatment alone, significantly extending survival and suppressing lung metastasis [146]. PD-1 blockade leads to increased LAG-3 expression on CD4+and CD8+T cells. Combined PD-1 and LAG-3 blockade enhances IFN-γ secretion by CD8+T cells and improves the overall functionality of TILs compared to PD-1 blockade alone [147]. JX-594, a genetically modified oncolytic virus expressing GM-CSF, activates dendritic cells and induces anti-tumor effects through oncolysis and immune stimulation. Combination therapy with JX-594 and PD-1 inhibitors in metastatic RCC reshapes the tumor immune microenvironment, enhances anti-tumor immune responses, and reduces immune-related toxicity, demonstrating efficacy and safety in preclinical models. Acarbose, an inhibitor of oligosaccharide hydrolysis, modulates glucose metabolism in the TME, enhancing CD8+T cell anti-tumor immune function. Combination therapy with acarbose and anti-PD-1 significantly enhances the cytotoxic function of CD8+T

cells infiltrating tumors, inhibits RCC tumor growth, and reduces lung metastases compared to anti-PD-1 monotherapy [148].

The clinical trial of PD-1/PD-L1 inhibitors in urological tumors

In the domain of urological cancers such as BCa, RCC, and PCa, PD-1/PD-L1 inhibitors have become essential treatment options. BCa, in particular, has gained significant attention, as illustrated by the IMvigor210 trial, which assessed the efficacy of the PD-L1 inhibitor Atezolizumab in patients with advanced urothelial carcinoma after chemotherapy. The trial revealed notable antitumor effects, achieving an objective response rate (ORR) of 15% [149, 150]. Similarly, KEYNOTE-045 investigated Pembrolizumab, a PD-1 inhibitor, showing improved overall survival compared to chemotherapy in advanced BCa [151, 152]. Promising results have been observed with PD-1/PD-L1 inhibitors in advanced RCC treatment. The CheckMate 025 trial assessed Nivolumab in patients with advanced RCC, revealing better overall survival and higher ORRs compared to Everolimus [153, 154]. Moreover, the CheckMate 214 study investigated the combination of Nivolumab and the CTLA-4 inhibitor Ipilimumab, yielding notable outcomes in patients with intermediate and poor risk [155]. PCa exhibits limited response to PD-1/PD-L1 inhibitors overall, though promising efficacy has been observed in specific subgroups. The KEYNOTE-199 trial in metastatic castration-resistant PCa revealed modest overall ORRs in patients treated with Pembrolizumab but efficacy in subgroups carrying DNA repair gene mutations [156]. Future research directions include optimizing PD-1/PD-L1 inhibitor applications through combination therapies, identifying patient subgroups most likely to benefit, and expanding exploration into their potential across urological cancers. While significant strides have been made, further investigations are crucial to fully harnessing their therapeutic potential in clinical practice. The ongoing clinical trials exploring the efficacy of anti-PD-1 and anti-PD-L1 in urological malignancies are shown in Tables 5 and 6.

Discussion and prospects

The use of PD-1 and PD-L1 inhibitors in the treatment of malignant urinary system tumors presents significant challenges due to the development of resistance that needs to be overcome. Central to this issue is the TME, which includes diverse cell types such as TAMs, TILs, and fibroblasts [33, 157]. These components alter immune dynamics by secreting cytokines and growth factors, influencing the effectiveness of PD-1/PD-L1 inhibitors. Resistance also stems from specific genetic mutations and aberrant signaling pathways. For instance, mutations in JAK1/2 genes can disrupt IFN-γ signaling, enabling tumor cells to evade immune surveillance [158]. Furthermore, dysregulated activation of the PI3K/AKT/mTOR pathway is associated with resistance to PD-1/PD-L1 inhibitors. The regulation of PD-L1 expression plays a pivotal role in determining the efficacy of PD-1/PD-L1 inhibitors. Tumor cells can also modulate PD-L1 expression through genomic and epigenomic mechanisms [159]. Epigenetic modifications such as DNA methylation and histone alterations enable tumor cells to reduce PD-L1 gene expression, thereby enhancing resistance to inhibitor therapies. Additionally, tumors employ various strategies to evade immune detection, including elevated expression of immune checkpoint molecules, secretion of immunosuppressive factors, and stimulation of immune-suppressive cell proliferation [52, 160]. Collectively, these mechanisms contribute to resistance against PD-1/PD-L1 inhibitors. Combining PD-1/PD-L1 inhibitors with other ICIs represents a promising strategy to bolster anti-tumor immune responses and surmount resistance encountered with single-agent therapies. By targeting multiple immune regulatory pathways simultaneously, combination therapies hold the potential to enhance treatment outcomes in patients with urinary system malignancies.

Combining PD-1/PD-L1 inhibitors with various treatment modalities enhances anti-tumor effects in urinary system cancers by leveraging complementary mechanisms. Radiotherapy induces tumor cell apoptosis and releases antigens, priming the immune system to recognize tumors, synergizing with PD-1/PD-L1 inhibitors [52, 161]. Emerging therapies like cancer vaccines, OVs, and CAR-T cell therapy boost immune responses through distinct mechanisms, such as direct tumor cell lysis and antigen release [88, 162]. Targeted therapies specific to the TME, such as TAM inhibitors, anti-angiogenics, and TGF-β pathway inhibitors, reduce immunosuppression in the TME, enhancing PD-1/PD-L1 inhibitor efficacy [163]. Gene editing tools like CRISPR/Cas9 address resistance by manipulating genes responsible, restoring immune recognition of tumors [164]. Epigenetic regulators like DNA methyltransferase inhibitors (DNMTi) and histone deacetylase inhibitors (HDACi) alter gene expression, sensitizing tumors to immune attack and reversing immune suppression [50, 165]. These approaches collectively overcome resistance, offering avenues to improve clinical outcomes with PD-1/PD-L1 inhibitors in urinary system cancers.

Personalized medicine offers significant promise in treating urinary system tumors by enhancing treatment efficacy through tailored therapeutic approaches. Genomic sequencing identifies specific mutations, gene expression patterns, and genomic instability in tumors, crucial for predicting responses to PD-1 and PD-L1 ICI. Proteomic analysis examines protein expression and

Table 5 The ongoing clinical trials exploring the efcacy of anti-PD-1 in urological malignancies

Cancer type	Clinical trial	Anti-PD-1	Phase	Primary outcome measures
PCa	NCT03637543	Nivolumab	2	Disease Control
	NCT03093428	Pembrolizumab	2	Number of Participants With Increased Immune Cell Infiltration Across Arms
	NCT05733351	Vudalimab	1	Incidence of Adverse Events
				Radiographic Progression-Free Survival
	NCT05848011	Lorigerlimab	2	Median radiographic progression free survival (rPFS)
	NCT03506997	Pembrolizumab	2	To evaluate tumour response
	NCT03910660	Pembrolizumab	1 + 2	Phase 2a: Estimate the composite response rate of the combination of BXCL701 + PEMBRO
				Phase 2b: Evaluate response rates in patients treated with the combination of BXCL701 + PEMBRO and with BXCL701 monotherapy
BCa	NCT05564897	Camrelizumab	2	complete response (CR)
	NCT05975307	Toripalimab	2	Clinical complete response (cCR) rate
	NCT05401279	Tislelizumab	2	Two-year bladder-intact disease-free survival rate
	NCT05072600	Pembrolizumab	2	PFS
	NCT05241340	Sasanlimab	2	Composite outcome for Feasibility and Safety
				Clinical benefit rate defined as pathologic complete response (pT0)
	NCT04134000	Atezolizumab	1	Dose limiting toxicity (DLT)
				Recurrence free survival
	NCT03179943	Atezolizumab	2	Maximum tolerated dose of Guadecitabine in combination of Atezolizumab in safety run-in phase
				Objective Response Rate (RECIST v 1.1) in Phase II
RCC	NCT04006522	Atezolizumab	2	Correlation between 89Zr-DFO-Atezolizumab and PD-L1
				Correlation between 89Zr-DFO-Atezolizumab and anti-PD1/PD-L1 therapy
	NCT05148546	Nivolumab	2	Pathologic response rate
	NCT03172754	Nivolumab	1 + 2	Incidence of treatment-related adverse events
				Overall response rate (ORR)
	NCT05215470	Nivolumab	2	Overall Survival
				Progression-free survival
	NCT05935748	Sasanlimab	2	Number of Participants with Dose Limiting Toxicity (DLT) events during the DLT monitoring period (first 28 days of dosing) in the Lead-in Phase
				Objective Response Rate (ORR) determined by the Investigator
	NCT06364631	Nivolumab	3	Overall Survival (OS)
	NCT05877820	Tislelizumab	2	Objective Response Rate (ORR) Per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1)
	NCT03260894	Pembrolizumab	3	Objective Response Rate (ORR) of Pembrolizumab + Epacadostat Versus Standard of Care (SOC)
	NCT05969496	Pembrolizumab	2	Evaluate Change in IVC Tumor Thrombus Extent Based on the Mayo Classification
				Evaluate a change in IVC TT Size from Baseline
	NCT04370509	Pembrolizumab	2	Proportion of participants with > = 2-fold increase in the number of tumor-infiltrating immune cells (TIICs)

modifications in tumors and their microenvironment, providing insights into tumor biology and potential targets for therapy. Understanding PD-L1 expression and its regulation in the TME optimizes combination immunotherapy strategies. High-throughput screening technologies like single-cell sequencing and mass spectrometry provide detailed insights into tumor heterogeneity and the immune microenvironment, guiding precise treatment planning to improve patient outcomes. Integrating genomic and proteomic data enables personalized treatment regimens tailored to individual molecular profiles, prioritizing PD-1/PD-L1 inhibitors for patients with high PD-L1 expression and considering combined therapies for those with specific mutations or other molecular characteristics.

Liquid biopsy technology, a non-invasive method, analyzes circulating tumor cells (CTCs) and circulating tumor DNA (ctDNA) in blood to monitor real-time genomic changes and resistance mechanisms in tumors. This facilitates prompt adjustments to treatment plans, assessment of treatment efficacy, and early detection of recurrence. Personalized therapy requires consideration of the patient's immune microenvironment, including immune cell infiltration, cytokine expression

Table 6 The ongoing clinical trials exploring the efcacy of anti-PD-L1 in urological malignancies

Cancer type	Clinical trial	Anti-PD-L1	Phase	Primary outcome measures
PCa	NCT03795207	Durvalumab	2	Two-years Progression-free survival
	NCT04751929	Atezolizumab		6-month Progression free survival (PFS) rate
				Objective response rate (ORR)
				Rate of Dose Limiting Toxicity (DLT)
				Rate of Adverse Events
	NCT04009967	Pembrolizumab	2	The antitumor activity of pembrolizumab assessed as the tumor response rate based on the change in tumor volume as measured by 18FDG-PET
				Mean difference change in proliferative index in prostate cancer patients between patients treated with pembrolizumab and the control cohort
				Immune cell infiltration and immune checkpoint expression
	NCT02998567	Pembrolizumab	1	Establish maximum tolerated dose (MTD)
				Measure Adverse Events according to CTCAE v4.0
	NCT02312557	Pembrolizumab	2	PSA response, defined by a PSA decrease of at least 50% confirmed by a second measurement at least 3 weeks later
	NCT04191096	Pembrolizumab	3	Radiographic Progression-free Survival (rPFS) Per Prostate Cancer Working Group (PCWG)-Modified Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) as Assessed by Blinded Independent Central Review (BICR)
				Overall Survival (OS)
	NCT02861573	Pembrolizumab	1 + 2	Percentage of Participants With a Decrease of ≥ 50% in Prostatic Specific Antigen (PSA)
				Number of Participants with Adverse Events (AEs)
				Number of Participants Discontinuing Study Drug Due to AEs
				Objective Response Rate (ORR) Based on Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) Assessed by Blinded Independent Central Review (BICR)
	NCT05568550	Pembrolizumab	2	Clinical Response Rate
	NCT03506997	Pembrolizumab	2	To evaluate tumour response
BCa	NCT05843448	Pembrolizumab	1	Incidence of adverse events
	NCT03697850	Atezolizumab	2	Disease Free Survival
	NCT04106115	DURvalumab	1 + 2	Occurrence of Dose Limiting Toxicity (Phase 1b)
				Pathological Disease Free Survival Rate (DFSR) (Phase 2)
	NCT03732677	Durvalumab	3	Pathologic complete response (pCR) rates at time of cystectomy
				Event-free survival (EFS) per central review defined as time from randomization to event
	NCT03601455	Durvalumab	2	Incidence of adverse events assessed by Common Terminology Criteria for Adverse Events (CTCAE) version (v.) 4.03 criteria (Safety lead-in cohort)
				Progression- free survival (PFS) assessed by Response Evaluation Criteria in Solid Tumors (RECIST) v 1.1 (Expansion cohort)
	NCT04138628	Atezolizumab	2	Complete response (CR) after treatment with investigational agent initiated by ctDNA positive status after radical cystectomy (with or without concomitant visible metastases on CT).
	NCT04134000	Atezolizumab	1	Dose limiting toxicity (DLT)
				Recurrence free survival
	NCT06305767	Pembrolizumab	2	Disease Free Survival (DFS)
	NCT03924895	Pembrolizumab	3	Event-Free Survival (EFS) between Arm C and Arm B
	NCT02625961	Pembrolizumab	2	Cohort A: Complete Response (CR) Rate of High-Risk Non-Muscle Invasive Bladder Cancer (NMIBC)
				Cohort B: 12-month Disease-Free Survival (DFS) Rate of High-Risk NMIBC
				Cohort C: 12-month CR Rate of High-Risk NMIBC
				All Cohorts: Number of Participants Who Experience an Adverse Event (AE)
				All Cohorts: Number of Participants Who Discontinue Study Treatment Due to an AE
	NCT05406713	Pembrolizumab	2	Clinical Complete Response Rate (CRR)
				Benefit from Treatment
	NCT03924856	Pembrolizumab	3	Event-Free Survival (EFS)
	NCT03711032	Pembrolizumab	3	Complete Response Rate (CRR) by Blinded Independent Central Review (BICR) (Cohort A)
				Event-Free Survival (EFS) (Cohort B)
	NCT03513952	Atezolizumab	2	Objective response rate (ORR)

Table 6 (continued)

Cancer type	Clinical trial	Anti-PD-L1	Phase	Primary outcome measures
	NCT04660344	Atezolizumab	3	Investigator-assessed DFS
	NCT02812420	Durvalumab	1	Incidence of adverse events determined by extreme toxicity
	NCT03528694	Durvalumab	3	The efficacy of Durvalumab + BCG (induction plus maintenance) combination therapy compared to SoC in terms of Disease free survival (DFS) in patients with NMIBC
	NCT03244384	Tislelizumab	3	Overall survival
				Disease-free survival
	NCT03179943	Atezolizumab	2	Maximum tolerated dose of Guadecitabine in combination of Atezolizumab in safety run-in phase
				Objective Response Rate (RECIST v 1.1) in Phase II
RCC	NCT04006522	Atezolizumab	2	Correlation between 89Zr-DFO-Atezolizumab and PD-L1
				Correlation between 89Zr-DFO-Atezolizumab and anti-PD1/PD-L1 therapy
	NCT02853331	Pembrolizumab	3	Progression-Free Survival (PFS) Per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) as Assessed by Blinded Independent Central Imaging Review
				Overall Survival (OS)
	NCT04955743	Pembrolizumab	2	Best brain metastasis response rate (BMRR)
	NCT03142334	Pembrolizumab	3	Disease-free Survival (DFS) as Assessed by the Investigator
	NCT05899049	Pembrolizumab	3	Progression Free Survival (PFS) According to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) as Assessed by Blinded Independent Central Review (BICR)
				Overall Survival (OS)
	NCT04698213	Avelumab	2	Overall response rate (ORR)
	NCT05024318	Pembrolizumab	2	mPR post-SABR with or without pembrolizumab
				CD8 + TRM in baseline biopsy and post-nephrectomy specimen, all measured as a continuous variable.
				TCF-1 + tumour infiltrating lymphocytes (TILs) in baseline biopsy and post-nephrectomy specimen, measured as a continuous variable
	NCT04704219	Pembrolizumab	2	Objective Response Rate (ORR)
	NCT02684006	Avelumab	3	Progression Free Survival (PFS) in PD-L1 positive patients
				Overall Survival in PD-L1 positive patients
	NCT06307431	Pembrolizumab	2	Disease-Free Survival (DFS)
	NCT04736706	Pembrolizumab	3	Progression Free Survival (PFS) According to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) as Assessed by Blinded Independent Central Review (BICR)
				Overall Survival (OS)
	NCT05567588	Pembrolizumab	2	ORR
	NCT05239728	Pembrolizumab	3	Disease-Free Survival (DFS)
	NCT03308396	Durvalumab	1 + 2	Phase Ib: Dose limiting toxicities will be assessed to determine if the trial is stopped before the Phase II portion.
				Objective response rate

levels, and immune-suppressive conditions within the TME, all of which significantly impact the effectiveness of PD-1/PD-L1 inhibitors. By comprehensively analyzing these factors, treatment responses can be accurately predicted, optimizing therapeutic strategies. Despite substantial progress in PD-1/PD-L1 inhibitors for treating urinary system cancers, many patients remain unresponsive to current therapies. Hence, attention is increasingly focused on developing next-generation ICIs targeting novel checkpoints. Ongoing research explores new targets such as CTLA-4, TIM-3, LAG-3, and others. CTLA-4 inhibitors, like Ipilimumab, show synergistic effects when combined with PD-1/PD-L1 inhibitors, and was recently approved for advanced RCC treatment. Clinical trials are evaluating the safety and efficacy of inhibitors against other emerging targets such as TIM-3 and LAG-3. Additionally, novel immune therapies like bispecific antibodies and fusion proteins are emerging. These agents simultaneously target multiple immune checkpoints, effectively reversing tumor immune suppression and enhancing treatment outcomes. For example, bispecific antibodies can inhibit both PD-1 and LAG-3, thereby bolstering anti-tumor immune responses. Preclinical studies have demonstrated that LAG-3 inhibitors exhibit significant anti-tumor activity and synergistic effects in combination with PD-1 inhibitors [166–168]. Early clinical trials further validate the safety and efficacy of these drugs in patients, supporting their potential therapeutic role. Various combination therapies involving ICIs have also shown promising

prospects in early clinical trials. The future of treating urological cancers will likely embrace personalized medicine approaches integrating genomic and proteomic analyses, alongside tailored therapies aligned with individual patient profiles.

The heterogeneity of urological malignancies substantially impacts the effectiveness of PD-L1 and PD-1 blockade therapies [41, 169, 170]. Although these ICIs have demonstrated impressive efficacy in the treatment of BCa and RCC, their utilization in PCa has yet to achieve widespread endorsement. This discrepancy is primarily attributed to the lower immunogenicity of PCa, characterized by a paucity of neoantigens in the TME, thereby impeding the immune system's ability to identify and eliminate malignant cells (Fig. 7). Conversely, BCa and RCC typically exhibit a higher mutational burden and a more diverse antigenic repertoire, enhancing the responsiveness to ICIs. In BCa and RCC, anti-PD-L1 and PD-1 therapies function by inhibiting the PD-1/PD-L1 axis, thus relieving T cell suppression and augmenting the immune response against neoplasm. However, due to the low immunogenicity and intricate TME of PCa, the response to immunotherapy is often suboptimal. Research indicates that the TME in PCa is infiltrated by a significant number of immunosuppressive cells, such as regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs), which secrete inhibitory cytokines to diminish the anti-tumor immune response. Moreover, while certain immunotherapeutic agents have shown substantial efficacy in BCa and RCC, their effectiveness is not uniform across all urological cancers. Analyzing their mechanisms of action suggests that this variability may be linked to the distinct microenvironmental characteristics, mutational landscapes, and immune evasion strategies inherent to different tumor types. Therefore, when evaluating the application of immunotherapy in urological malignancies, it is crucial to consider the heterogeneity of these tumors and tailor therapeutic approaches accordingly. A comprehensive understanding of these differences can facilitate the optimization of treatment protocols, ultimately enhancing patient survival rates and quality of life.

Anti-PD-1 and anti-PD-L1 immunotherapies have demonstrated potential in managing urological malignancies, notably BCa and RCC. Nevertheless, their therapeutic efficacy in these cancers is comparatively modest, particularly when juxtaposed with malignancies such as melanoma. PCa exemplifies this disparity, exhibiting lower clinical response rates. The inherent heterogeneity of urological neoplasms and the intricate TME present significant obstacles that attenuate the effectiveness of these therapies. Specifically, the low immunogenicity and immunosuppressive milieu of PCa impede the therapeutic impact of anti-PD-1 and anti-PD-L1 agents, resulting in suboptimal clinical outcomes. To circumvent these challenges, researchers are intensively investigating the potential of combinatory therapeutic strategies. Integrating ICIs with other treatment modalities, including chemotherapy, radiotherapy, targeted therapies, and additional forms of immunotherapy, may potentiate immune responses and augment therapeutic efficacy. For instance, clinical studies have indicated that the concurrent administration of anti-PD-1/PD-L1 agents with platinum-based chemotherapy significantly enhances overall response rates and extends survival in patients with urothelial carcinoma. Moreover, emerging clinical trials are focusing on novel combinatorial approaches to bolster the effectiveness of these therapies. These strategies encompass the integration of immunotherapy with cancer vaccines, adoptive cellular therapies, or other immunomodulatory agents, aiming to robustly activate the patient's immune system for a more efficacious antitumor

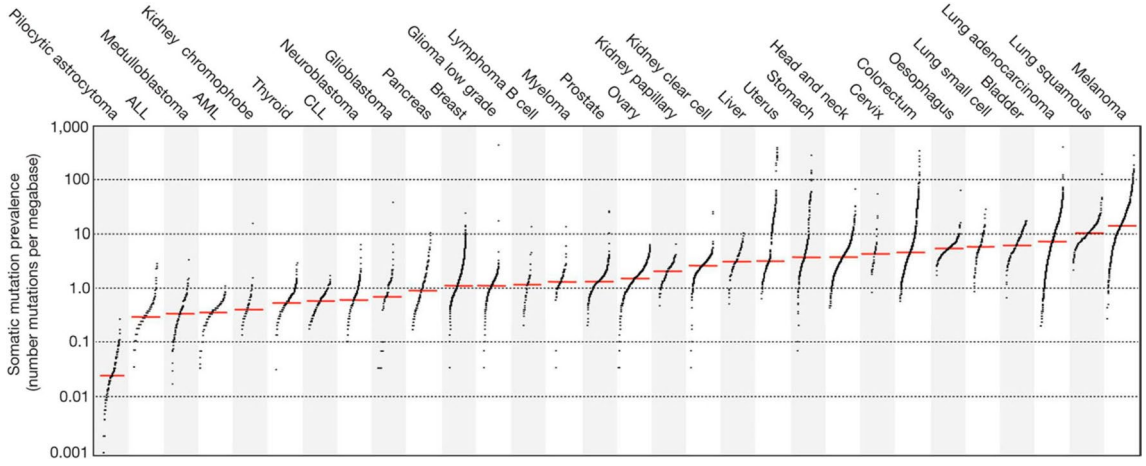


Fig. 7 Mutational loads across different tumor types correlate with tumor immunogenicity.Reproduced with permission [171]. Copyright 2018, Springer Nature

response. In summary, although anti-PD-1 and anti-PD-L1 therapies encounter limitations in the treatment of urological malignancies, their therapeutic potential can be further realized through rational combination strategies and innovative clinical trial designs, thereby providing more efficacious treatment avenues for patients.

Conclusion

In this detailed review, we describe the crucial function of the PD-1/PD-L1 pathway in urological malignancies, including BCa, RCC, and PCa. Aberrant PD-1/PD-L1 signaling has been recognized as a significant factor in these cancers, facilitating immune evasion, tumor progression, and metastasis. Both preclinical and clinical studies have repeatedly demonstrated that inhibiting PD-1/PD-L1 interactions boosts anti-tumor immune responses and effectively suppresses tumor growth. These results highlight the therapeutic promise of PD-1/PD-L1 inhibitors in urological cancers.

Abbreviations

PD-1	Programmed death receptor 1
PD-L1	Programmed death ligand-1
BCa	Bladder cancer
RCC	Renal cell carcinoma
PCa	Prostate cancer
NMIBC	Non-muscle invasive bladder cancer
MIBC	Muscle invasive bladder cancer
ccRCC	Clear cell renal cell carcinoma
mCRPC	Metastatic castration-resistant prostate cancer
NK	Natural killer
ITIM	Immunoreceptor tyrosine-based inhibitory motif
ITSM	immunoreceptor tyrosine-based switch motif
APCs	Antigen-presenting cells
TCR	T cell receptor
NF-κB	Nuclear factor kappa B
AP-1	Activator protein 1
IRF	Interferon regulatory factors
HDACs	Histone deacetylases
IFN-γ	Including interferon-gamma
TGF-β	Transforming growth factor-beta
miRNAs	MicroRNAs
TME	Tumor microenvironment
HIF-1α	Hypoxia-inducible factor 1-alpha
TNF-α	Tumor necrosis factor-alpha
DCs	Dendritic cells
DCs	Dendritic cells
Tregs	Regulatory T cells
Teffs	Effector T cells
CTLA-4	Cytotoxic T-lymphocyte-associated protein 4
TIM-3	T-cell immunoglobulin and mucin domain-containing protein 3
LAG-3	Lymphocyte activation gene-3
MHC	Major histocompatibility complex
YY1	Yin Yang 1
EMSA	Electrophoretic mobility shift assay
TFEB	Transcription factor EB
TFE3	Transcription factor E3
HIF2α	Hypoxia-inducible factor 2-alpha
PTMs	Post-transcriptional modifications
ISG15	Interferon-induced protein 15
FGFR3	Fibroblast Growth Factor Receptor 3
TGFβ1	Transforming growth factor beta 1
EVs	Extracellular vesicles
pRB	Phosphorylated retinoblastoma protein
HnRNP L	Heterogeneous nuclear ribonucleoprotein L
TAMs	Tumor-associated macrophages
PKM2	Pyruvate kinase M2
AR	Androgen receptor
MTHFD2	Methylenetetrahydrofolate dehydrogenase 2
RRM2	Ribonucleotide Reductase Regulatory Subunit M2
NFAT1	Nuclear factor of activated T cells 1
TOPK	T-LAK cell-originated Protein Kinase
EGFR	Epidermal Growth Factor Receptor
GHITM	Growth hormone-inducible transmembrane protein
GM-CSF	Granulocyte-Macrophage Colony-Stimulating Factor
BTK	Bruton's tyrosine kinase
TIGIT	T-cell immunoglobulin and ITIM domain
BCa	Breast cancer
OXP	Oxaliplatin
FGFR	Fibroblast Growth Factor Receptor
αKG	Alpha-ketoglutarate
TCA	Tricarboxylic acid
ORR	Objective response rate
TILs	Tumor-infiltrating lymphocytes
Ovs	Oncolytic viruses
DNMTi	DNA methyltransferase inhibitors
HDACi	Histone deacetylase inhibitors
ICI	Immune checkpoint inhibitors

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