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Exploration of the Mechanism of Action of Immune Checkpoint Inhibitors and Their Advancements in Cancer Immunotherapy

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Abstract. Immune checkpoint inhibitors (ICIs), which target novel immune receptors including programmed cell death protein-1 (PD-1), cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4), lymphocyte activation gene-3 (LAG-3), T-cell immunoglobulin and ITIM domain (TIGIT), and T-cell immunoglobulin and mucin domain 3 (TIM-3), have profoundly reshaped cancer treatment paradigms. Tumors exploit these signaling pathways to suppress T-cell activation and impair immune surveillance. By interrupting inhibitory signaling, ICIs mechanistically restore antitumor immune responses. In clinical practice, ICIs have demonstrated durable efficacy and wide-ranging applicability across multiple solid tumors, markedly increasing overall survival (OS) when utilized as monotherapy or in combination with chemotherapy or anti-angiogenic therapies. Nonetheless, significant clinical challenges persist, including heterogeneous patient responses, only approximately 20–40% achieve sustained remission, and immune-related adverse events (irAEs) affecting around 50–70% of recipients. Additionally, existing biomarkers, such as programmed cell death-ligand 1 (PD-L1) expression levels and tumor mutation burden, exhibit limited predictive accuracy across different cancer types. Moreover, irAEs, including severe pneumonitis and endocrine toxicities, require specialized clinical management. Moving forward, research should emphasize developing multi-omics-based biomarkers, refining combination treatment regimens, and unraveling resistance mechanisms to improve the precision and effectiveness of immunotherapy.

Keywords: immune checkpoint inhibitors, cancer immunotherapy, combination therapy, biomarkers, immune-related adverse events

1. Introduction

While traditional tumor treatments like have shown some success in clinical use, their limitations have become apparent. Chemotherapeutic drugs and ionizing radiation can trigger severe systemic toxic reactions while eliminating tumor cells. Tumor heterogeneity and genomic instability may result in drug resistance. More critically, tumor cells can circumvent immune system surveillance via immune escape mechanisms, progressively establishing an immune-suppressive microenvironment [1]. Recent research indicates that tumor cells overexpress immune checkpoint

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molecules, such as PD-L1, and specifically bind to PD-1 receptors on T cell surfaces. This binding induces T-cell exhaustion and disrupts immune synapse formation, establishing an immune-privileged microenvironment that facilitates tumor growth [2]. This biological trait not only clarifies the primary cause behind the failure of traditional therapies to achieve lasting remission but also lays the theoretical groundwork for the development of ICIs.

ICIs have nearly transformed the landscape of cancer therapy. Compared to traditional treatments, ICIs offer two key advantages: first, their effects are durable and involve immunological memory, with some patients achieving long-term remission [3]; second, these inhibitors have a broad spectrum of action, showing significant efficacy against various solid tumors [4, 5]. Moreover, the advancement of inhibitors aimed at emerging targets has broadened the scope of immunotherapy.

ICIs not only overturn the conventional cancer treatment paradigm but also progressively advance the evolution of precision medicine. First, their efficacy is closely linked to specific biomarkers, such as tumor mutation load, and viral infection status, which aids in the advancement of personalized therapy [6].For instance, patients with high PD-L1 levels benefit from monotherapy, whereas those with low PD-L1 levels might need combination therapy with chemotherapy [7]. Secondly, combining ICIs with other treatment methods has become a central focus of research.

2. Principles of action of immune checkpoints and inhibitors

2.1. PD-1 and PD-L1

The interaction between PD-1 and its ligand PD-L1 constitutes a critical mechanism by which cancer cells escape immune detection. PD-1, known as an essential immune checkpoint, is predominantly upregulated in activated T lymphocytes, B cells, and natural killer (NK) cells. In contrast, PD-L1 is frequently overexpressed in both tumor cells and immune cells infiltrating the tumor microenvironment (TME). When PD-L1 engages with PD-1 on the surface of T cells, it leads to suppression of T-cell function, marked by diminished cytokine secretion, limited cell proliferation, and ultimately T-cell exhaustion, thereby facilitating immune evasion by tumors [8]. The expression of PD-L1 is regulated by a range of intrinsic factors, including oncogenic signaling pathways, as well as extrinsic cues such as hypoxic conditions within the TME. For example, the transcription factor c-Myc, expressed by the oncogene MYC, has the ability to directly bind to the promoter region of PD-L1, driving its transcription. Similarly, insufficient supply of oxygen within tumors activates hypoxia-inducible factor 1-alpha (HIF-1α), thereby elevating the expression of PD-L1, reinforcing the immunoresistance of the tumors [9].

Inhibiting the PD-1/PD-L1 axis has emerged as an integral part of immunotherapeutic modalities in several cancers. An example agent, pembrolizumab, has been found to provide considerable survival advantage in melanoma patients as well as patients with non-small cell lung cancer (NSCLC [4, 10]. Nevertheless, numerous patients remain minimally responsive, highlighting the need for better therapeutic modalities. Combination of PD-1/PD-L1 inhibitors with other therapeutic modalities has the promise of substantially increasing their therapeutic efficacy. For example, ketogenic dietary therapies or pharmacological activation of AMP-activated protein kinase (AMPK) has the ability to increase anti-tumor immunity by redistribution of cellular metabolic pathways, thereby making therapies with PD-L1 blockade more effective [11]. Moreover, inhibition of cyclin-dependent kinase (CDK) 4/6 has been shown to improve responsiveness to PD-L1-targeted therapies by activation of endogenous retroviral sequences in tumor cells, with increased double-stranded RNA generation by them, subsequently leading to enhanced expression of PD-L1 [12].

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Emerging evidence also highlights the critical involvement of B cells and plasma cells in the response to PD-L1 inhibition. Elevated infiltration of B cells correlates with prolonged OS following PD-L1 blockade, independent of $CD8^+$ T-cell-driven mechanisms [13]. Additionally, heightened plasma cell signatures may serve as predictive markers for improved survival outcomes in patients undergoing PD-L1-targeted therapy. Collectively, these findings imply that B and plasma cells potentially bolster therapeutic efficacy by modulating the immune milieu within the TME.

2.2. CTLA-4

Another vital immune checkpoint, CTLA-4, functions in a way that complements but differs mechanistically from PD-1. CTLA-4 primarily acts during the initial stage of T-cell activation, where it controls immune responses by limiting T-cell expansion and preventing hyperactivation. On the other hand, PD-1 predominantly regulates T-cell activity at later phases, ensuring immune homeostasis during ongoing immune responses. Structurally, CTLA-4 is a member of the immunoglobulin superfamily (IgSF) and shares approximately 30% amino acid sequence identity with CD28, which delivers co-stimulatory signals to T cells [14]. Localized mainly on the surface and inside activated T cells, CTLA-4 inhibits immune activation by outcompeting CD28 for binding to the co-stimulatory molecules CD80 (B7-1) and CD86 (B7-2), thereby dampening T-cell responses.

CTLA-4-targeted therapies have demonstrated robust clinical effectiveness, particularly in treating metastatic malignant melanoma. Ipilimumab, a monoclonal antibody directed against CTLA-4, has consistently produced significant enhancements in objective tumor responses and durable clinical benefits for patients across multiple clinical trials involving advanced melanoma [15, 16]. Nonetheless, substantial evidence has also established a clear link between CTLA-4 blockade therapy and the occurrence of clinically significant irAEs [17].

Beyond its role as a therapeutic target, CTLA-4 and its related molecules (such as CTLA-4 promoter methylation) have also been explored as biomarkers for predicting treatment response. Studies have shown that the level of CTLA-4 promoter methylation is negatively correlated with CTLA-4 mRNA expression. In immune checkpoint blockade therapy, low methylation levels are largely associated with better treatment response and OS. This implies that CTLA-4 promoter methylation might act as a potential biomarker for identifying patients who gain from immune checkpoint blockade therapy, thus aiding in enhancing the precision and effectiveness of treatment [15].

2.3. TIM-3

TIM-3, an important immunomodulatory receptor, was initially discovered due to its role in modulating interferon-γ secretion from $CD4^+$ and $CD8^+$ T cells [18, 19]. , an important immunomodulatory receptor, was initially discovered due to its role in modulating interferon-γ secretion from [20].

Recently developed, TSR-022 is a monoclonal antibody targeting human TIM-3, designed to counteract TIM-3-mediated immunosuppressive effects, thereby promoting T-cell proliferation and cytokine secretion. In preclinical studies, TSR-022 demonstrated notable antitumor activity, both as a single agent and in combination with anti-PD-1 therapeutics [21].

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2.4. LAG-3

LAG-3, another ICR belonging to the IgSF, is structurally similar to CD4 and has recently drawn increasing attention within immunological research. The human LAG-3 gene comprises eight exons, which encode a transmembrane protein of 498 amino acids featuring four extracellular IgSF domains. The first extracellular domain (V-SET) contains a distinctive intrachain disulfide linkage and an additional loop structure, whereas the subsequent three domains are classified as C2-SET domains. Structurally and genetically, LAG-3 shares significant homology with CD4, including comparable exon-intron organization and peptide sequences. Additionally, both genes reside closely at the distal segment of chromosome 12's short arm, supporting the hypothesis that LAG-3 may have arisen from gene duplication events [22]. The immune receptor LAG-3 is expressed on a variety of immune subsets, including NK cells and, most notably, plasmacytoid dendritic cells (pDCs) [23, 24]. In activated T lymphocytes, LAG-3 acts as an inhibitory modulator by curbing their proliferation, maintaining immune equilibrium, and supporting the suppressive function of regulatory T cells (Tregs) [25]. Interestingly, LAG-3 expression in pDCs is nearly ten times higher than in either activated effector Tregs or conventional Tregs [26].

Given its inhibitory role in immune regulation, LAG-3 is increasingly viewed as a promising target in cancer immunotherapy. Persistent LAG-3 expression, akin to PD-1 and CTLA-4, is associated with immune exhaustion in chronic diseases, leading to functional impairment of effector T cells. Antibodies targeting LAG-3 have shown the capability to suppress the immunosuppressive functions of Tregs, thereby enhancing antitumor immune responses. Furthermore, the expression of LAG-3 in pDC and its role in pDC homeostasis make it a key functional marker for pDC research, providing new targets for tumor immunotherapy. Future studies are required to elucidate LAG-3's specific roles within different immune cell contexts and assess its potential in clinical applications. Notably, activated T cells, NK cells, and pDCs prominently express LAG-3.

2.5. TIGIT

TIGIT, identified initially on T lymphocytes and NK cells, represents another co-inhibitory receptor characterized structurally by its immunoglobulin domain [27]. Within its cytoplasmic tail, TIGIT contains inhibitory signaling motifs, including the immunoreceptor tyrosine-based inhibitory motif (ITIM) and immunoglobulin tail tyrosine-like (ITT-like) motifs, both pivotal for its suppressive activities. Upon engagement with its ligands, TIGIT negatively modulates immune responses by indirectly influencing dendritic cell (DC) functions in T cells and directly suppressing NK cell cytotoxic activities by interrupting intracellular signaling, particularly via the PI3K and MAPK pathways [28]. Moreover, increased TIGIT expression is closely associated with tumor immune evasion. It boosts the production of immunosuppressive cytokines, like interleukin-10, which suppresses anti-tumor immune responses [27].

2.6. BTLA

Another inhibitory receptor belonging to the immunoglobulin superfamily, BTLA, is prominently found on NK cells, B lymphocytes, and T cells. BTLA's intracellular region features two ITIM domains. Upon activation, BTLA becomes upregulated on T lymphocytes, showing notably higher expression on Th1 cells relative to Th2 cells [29]. By interacting with specific ligands, including herpesvirus entry mediator (HVEM) and B7x [30, 31], BTLA dampens immune responses, specifically by inhibiting T-cell proliferation and reducing cytokine secretion, notably IL-2 [30].

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Studies in BTLA-deficient mice reveal significantly augmented T-cell immunity, highlighting BTLA's importance in immune regulation and homeostasis.

Currently, BTLA-related studies are increasingly relevant in tumor immunology research. Aberrant expression of BTLA on both immune and tumor cells has been linked to tumor progression and worse clinical outcomes. For example, dysregulated interactions of BTLA with HVEM in chronic lymphocytic leukemia (CLL) are associated with immune suppression and poor prognostic implications [30]. Blockade of BTLA has demonstrated partial restoration of NK cell-mediated cytotoxicity, subsequently inhibiting tumor progression. Furthermore, studies on ovarian cancer suggest that microRNA-32, which targets BTLA, substantially reduces tumor cell proliferation, migration, and invasion. These findings highlight BTLA's potential as a therapeutic target in cancer immunotherapy [32].

BTLA's cell subset-specific mechanisms remain poorly defined. Interactions with other checkpoints and synergistic effects in cancer immunotherapy require further exploration. Future research may focus on developing BTLA-targeted antibodies or small-molecule inhibitors to unlock its clinical potential in tumor immunotherapy.

2.7. B7 family

Members of the B7 molecular family can function either as co-stimulatory or co-inhibitory regulators, influencing T-cell activation, proliferation, and overall immune functionality through receptor-ligand interactions. Recent studies exploring the B7 family members and their ligands have underscored B7-H3, B7-H4, and VISTA as critical therapeutic targets in oncology immunotherapy, primarily due to their essential contributions to tumor-mediated immune escape and their involvement in autoimmune pathology.

2.7.1. B7-H3

Members of the B7 family are defined by bifunctionality—the ability to act as either co-stimulatory or co-inhibitory receptors—that regulate T-cell proliferation, activation, and effector activities via interaction with their specific ligands. More current studies investigating their roles in mechanisms of autoimmune diseases as well as immune evasion induced by tumors has highlighted B7-H3, B7-H4, as well as VISTA, as notably promising cancer immunotherapy targets [33, 34]. Owing to their restricted expression in normal tissues, these proteins are particularly desirable targets for therapeutic interference. Expressed primarily upon antigen-presenting cells (APCs), B7-H3 primarily acts as an inhibitory regulator upon T-cell proliferation and activation, thereby having considerable control over immune regulation. In the TME, B7-H3 not only supports immune evasion through suppression of antigen-specific immune reactivity toward cancer cells but also supports enhanced tumor growth with immune-independent mechanisms. These involve supporting epithelial-mesenchymal transition (EMT), generation of chemotherapeutic resistances, activation of angiogenic processes, as well as supportive increased invasiveness as well as migratory abilities of cancer cells [35].

Recent preclinical studies involving B7-H3 antibodies have exhibited strong antitumor activities with encouraging safety profiles. In particular, preliminary Phase I clinical trial data evaluating a monoclonal antibody against B7-H3 with ADCC functionality has revealed encouraging preliminary efficacy [34]. Additionally, multiple therapeutic modalities targeting B7-H3, such as bispecific antibodies, monoclonal antibody blockage, CAR-T cell therapies, small molecule inhibition, as well as combinational treatment regimens, continuously exhibit encouraging performance in preclinical

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studies [34]. Moreover, another Phase I clinical trial evaluating intraperitoneal radioimmunotherapy (RIT) directed against B7-H3 in cancer patients with DSRCT and other cancers demonstrated minimal irradiation exposure of normal tissues, acceptable safety, and lack of dose-limiting toxicities. Ongoing clinical studies continue to evaluate the therapeutic efficacy and safety profiles of several other new B7-H3-targeted antibodies.

2.7.2. B7-H4

The B7-H4 (VTCN1, B7x, or B7S1) belongs to the B7 family, which is notable for its role in immune regulation and tumor immune evasion. It primarily engages with inhibitory co-receptors on T cells to foster antigen tolerance [36, 37].

B7-H4 expression is markedly elevated in multiple cancer types, prominently on tumor-associated macrophages (TAMs) and tumor cells themselves, and is intimately connected to immune escape processes. Interestingly, although B7-H4 is commonly observed in fresh primary tumor specimens and tumor xenograft models, its expression diminishes rapidly under in vitro conditions, indicating a dependency on in vivo microenvironmental factors. Functionally, B7-H4 suppresses T-cell proliferation and activation, facilitates immune evasion, and possibly induces T-cell exhaustion through increased expression of the transcription factor Eomes, consequently impairing antitumor immune responses [38].

Clinically, high levels of B7-H4 expression strongly correlate with unfavorable prognostic indicators in various cancer types [37, 38]. Blocking B7-H4 interactions with its cognate receptors can significantly enhance T-cell-mediated antitumor immunity. Indeed, specific anti-B7-H4 antibodies isolated from single-chain variable fragment (scFv) libraries derived from ovarian cancer patients effectively reverse B7-H4-mediated suppression, restoring tumor-specific T-cell activation. Animal-based preclinical experiments further indicated that treatment with intraperitoneally administered anti-B7-H4 scFv effectively delayed tumor progression, highlighting significant therapeutic potential.

2.7.3. VISTA

V-domain immunoglobulin T-cell activation suppressor (VISTA), a recently identified immune-modulating molecule belonging to the IgSF, exhibits high expression primarily within hematopoietic-derived cells, particularly bone marrow APCs and T lymphocytes [39, 40]. VISTA primarily mediates its immunosuppressive functions through interactions involving its extracellular domain and PSGL-1 expressed on T-cell surfaces. This interaction suppresses T cell proliferation. These inhibitory effects are more evident in the acidic conditions typically present in the TME [41]. VISTA also induces Foxp3 expression, further suppressing immune responses [39]. Recently, VSIG-3 was identified as a VISTA ligand, with the VSIG-3/VISTA pathway inhibiting human T-cell function, providing new cancer treatment strategies [42].

VAntibodies that block VISTA, much like those targeting CTLA-4 and PD-1, selectively inhibit VISTA-PSGL-1 interactions in acidic conditions, reversing immune suppression and boosting T-cell-mediated antitumor responses.

3. Combination immunotherapy targeting immune checkpoints

Increasingly, combination therapy approaches have gained attention as essential methods for improving the effectiveness of ICIs in tumor treatment. For example, numerous studies have

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confirmed that simultaneous blockade of PD-1 and CTLA-4 pathways generates synergistic effects, significantly increasing therapeutic responses and patient survival. Furthermore, combining ICIs with chemotherapy, radiotherapy, targeted therapies, or anti-angiogenic drugs has produced promising clinical outcomes.

Notably, the CheckMate 067 clinical trial showed that previously untreated advanced melanoma patients treated concurrently with the anti-PD-1 antibody nivolumab and the anti-CTLA-4 antibody ipilimumab achieved marked improvements in OS and progression-free survival (PFS). Specifically, combination therapy produced a median OS of 72.1 months, compared to 36.9 months with nivolumab monotherapy and 19.9 months with ipilimumab monotherapy. Importantly, these clinical advantages remained evident after prolonged follow-up extending to nearly 6.5 years [4, 5].

Similarly, clinical studies in extensive-stage small cell lung cancer (ES-SCLC) showed that combination therapies with conventional chemotherapy plus either the anti-PD-1 antibody serplulimab or the anti-PD-L1 antibody adebrelimab resulted in better clinical effects compared with chemotherapy alone. These combinations effectively increased both OS and PFS [7]. In addition, combination with anti-angiogenic agents and ICIs has presented remarkable clinical effects, as indicated in the IMpower150 trial, where patients with advanced NSCLC exhibited significant increases in OS and PFS following administration with atezolizumab (anti-PD-L1 antibody) plus bevacizumab (anti-VEGF antibody) in combination [43, 44].

Apart from well-established immune checkpoints, new immune-regulatory molecules have raised considerable interest recently. For example, LAG-3, an inhibitory T-cell receptor playing a role in the negative regulation of T-cell function, has exhibited significant safety and antitumor efficacy in phase I evaluation of the anti-LAG-3 antibody LAG525 alone with the anti-PD-1 antibody PDR001 [45]. In an equally encouraging manner, TIGIT, an immunoreceptor with known binding capabilities with its ligand, CD155 (poliovirus receptor, PVR), demonstrated encouraging therapeutic effects with manageable safety profiles. Clinical assessment of TIGIT-targeted agent vibostolimab with pembrolizumumab (anti-PD-1) exhibited encouraging efficacy in advanced-stage solid malignancies [46]. TIM-3, another T-cell immunosuppressive receptor with galectin-9 interaction, hence inhibiting T-cell activation, has been therapeutically investigated. Combination evaluation in phase I between the TIM-3 antagonist LY3321367 with an anti-PD-L1 antibody, LY3300054, resulted in favorable clinical responses with acceptable safety, thus exploring newer combinations of immunotherapy [47-49].

4. Limitations of immune checkpoint blockade technology in clinical applications

The advent of ICIs has signaled the start of the cancer immunotherapy era. However, their clinical application still faces many challenges. These challenges are mainly observed in the diverse treatment responses among patients, the complexity of managing irAEs, and the lack of accurate predictive biomarkers.

Clinical responses to ICIs vary substantially among different patient populations. Studies have revealed that while certain patients achieve durable clinical benefits, the majority experience minimal, temporary, or no significant responses to ICIs. Factors potentially underlying such variable therapeutic outcomes include inherent tumor-specific characteristics, individual patient immune conditions, and unique features of the TME. Therefore, the mutation burden of tumor cells, their antigen-presenting capacity, and the presence of an immunosuppressive microenvironment may all influence the efficacy of ICIs. Additionally, the host's genome, epigenome, and immune cell composition also play important roles [50, 51]. Nevertheless, the current understanding of these

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complex molecular interactions remains insufficiently comprehensive, and reliable methods to accurately identify potential responders prior to initiating ICI treatment are still lacking.

Adverse effects associated with ICI therapy differ significantly from those induced by traditional chemotherapy. irAEs can involve diverse organ systems, including the hepatic, pulmonary, gastrointestinal, endocrine, and integumentary systems [52]. Although the incidence and severity of irAEs depend heavily upon the specific type and regimen of ICIs employed, their potential seriousness and irreversibility necessitate careful clinical management. For instance, immune-related endocrine disorders (like hypophysitis, thyroid dysfunction, and adrenal insufficiency) might necessitate long-term hormone replacement therapy, while immune-related pneumonitis and colitis can lead to serious complications or even death [52, 53].The clinical manifestations of irAEs are diverse and nonspecific, increasing the difficulty of diagnosis and management.

Another key challenge confronting the clinical application of ICIs is the current lack of reliable and precise biomarkers for predicting therapeutic responsiveness. Although several potential biomarkers, such as tumor mutational burden (TMB), PD-L1 protein expression, and the composition of gut microbiota, are being actively investigated, their accuracy and consistency remain inadequate [54]. PD-L1 levels are often considered critical predictive indicators of ICI effectiveness, yet their predictive capability varies significantly depending on cancer type, and clinical benefits can still be observed in certain patients exhibiting low PD-L1 expression [50]. Biomarkers such as tumor mutation burden and gut microbiota composition have shown some potential, but their clinical application still needs further validation [54]. Hence, developing biomarkers that can more accurately predict the effectiveness of ICIs is a key research focus at present. It is essential for optimizing patient selection, enhancing treatment outcomes, and minimizing unnecessary toxicity.

5. Conclusion

ICIs have revolutionized oncology by reinvigorating antitumor T-cell responses through blockade of PD-1/PD-L1, CTLA-4, LAG-3, TIM-3, TIGIT and other key pathways, yielding durable survival benefits across multiple solid tumors. Nevertheless, clinical utility remains constrained by modest response rates (20–40%), immune-related adverse events affecting 50–70 % of patients, and limited predictive power of current biomarkers. Future efforts should leverage multi-omics approaches to elucidate resistance mechanisms, refine combination regimens (e.g., ICIs plus chemotherapy, anti-angiogenic agents or metabolic modulators), and develop more precise predictive models, thereby advancing truly personalized, effective and safer cancer immunotherapy.

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