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Research Progress of Immune Checkpoint Inhibitors in the Treatment of Hepatocellular Carcinoma

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Abstract

Hepatocellular carcinoma cells are relatively prone to metastasis and have a high degree of heterogeneity, making a successful cure rather difficult. In recent years, an increasing number of immune checkpoint inhibitors have been approved for listing. Due to their strong targeting and relatively low toxic and side effects, the application of immune checkpoint inhibitors in the treatment of hepatocellular carcinoma has become more widespread. Currently, the research on immune checkpoint inhibitors mainly concentrates on PD-1/PDL1, CTLA-4, TIM-3, LAG-3, and TIGIT. Although they have certain advantages, the occurrence of drug resistance has also been frequently observed in clinical practice, presenting certain limitations. This study examined the structural features of key immune checkpoints, and explored the clinical implementation of their inhibitors and drug resistance mechanisms, aiming to offer insights for improved use of immune checkpoint inhibitors in clinical settings.

Keywords

Hepatocellular Carcinoma, Immune Checkpoint Inhibitor, Drug Resistance

1. Introduction

According to the data from the joint calculation results of the National Cancer Center and the International Agency for Research on Cancer, in 2022, the number of new cases of primary liver cancer in China was 367,700, ranking the fourth among all types of new cancer cases, and the incidence rate ranked the fifth. Since most patients present with advanced diseases, only 15% of the patients are eligible for potentially curative treatment methods such as surgical resection and liver transplantation [1]. In the treatment of liver cancer, immune checkpoint inhibitors

have gained significant importance in recent years. Since pembrolizumab and nivolumab were approved for the treatment of hepatocellular carcinoma in 2017, more types of immune checkpoint inhibitors have been used in the clinical treatment of liver cancer. Immune checkpoint inhibitors have made significant advancements in primary liver cancer by transitioning from single-drug therapy to the utilization of multiple drug combinations, thereby introducing innovative medication strategies and treatment approaches for the management of liver cancer through drug therapy.

2. Advancements in Immune Checkpoint Inhibitors for the Treatment of Hepatocellular Carcinoma

2.1. The Structures and Biological Functions of Immune Checkpoints Associated with Liver Cancer

Immune checkpoints include stimulatory and inhibitory checkpoint molecules. Recently, there has been increasing attention on immune inhibitory checkpoints like CTLA-4, PD-1, and PD-L1, which have been shown to effectively suppress the anti-tumor immune response in hepatocellular tumors. Moreover, numerous studies have demonstrated that apart from PD-1/PD-L1 and CTLA-4, TIGIT, LAG-3 and TIM-3 are also major inhibitory immune checkpoint receptors, which can either synergistically or independently suppress T cell activity and play a crucial role in maintaining self-tolerance; while CD28, GITR and OX40 are co-stimulatory immune checkpoint proteins that can enhance the proliferation of T cells.

2.1.1. The Organization and Biological Roles of PD-1/PD-L1

PD-1, a type 1 transmembrane protein affiliated with the CD28 superfamily, comprises 268 amino acids. PD-1 can be found on the surface of various immune cells, such as activated T cells, B cells, and myeloid cells. The PD-1 receptor is a T cell receptor that inhibits immune response and mainly interacts with two ligands known as PD-L1 (or B7-H1 or CD274) and PD-L2 (or B7-DC or CD273). These ligands are commonly found in the tumor microenvironment [2].

Numerous factors influence the transcriptional regulation of the PD-1 gene. Including but not limited to estrogen, PTEN, Lkb1, nuclear factor of activated T cells (NFAT), NOTCH, forkhead box protein (FOX) O1, and interferon (IFN) regulatory factor 9 (IRF9), among others. [3] [4].

PD-L1 is a transmembrane glycoprotein consisting of 290 amino acids and is classified as an immunomodulatory ligand within the B7 family. It is also the predominant ligand of PD-1. PD-L1 is extensively expressed in multiple cell types, such as T cells, B cells, dendritic cells, and macrophages, among others [5].

The upregulation of PD-L1 is primarily associated with genomic rearrangement of the CD274 fragment on chromosome 9p24.1 [6]. Additionally, events such as amplification and mutation of the JAK family, enhanced activity of JAK2 signal transduction and STAT signaling pathways, can significantly elevate the protein expression level of PD-L1 by increasing the expression of PD-L1 RNA [7].

Concurrently, the expression of PD-L1 is also modulated by mitogen-activated protein kinase, PTEN/PI3K-AKT pathway, NF-κB pathway, JAK-STAT pathway [8].

2.1.2. The Structure and Biological Functions of CTLA-4

CTLA-4 is a suppressive receptor belonging to the CD28 immunoglobulin subfamily and is predominantly found on T lymphocytes [9]. Its cardinal functions are to curb the proliferation of T cells and the secretion of interleukin-2. CTLA-4 predominantly operates at the level of T cell activation in lymph nodes and contends with CD28 for binding to its ligands. The CTLA-4 protein consists of an extracellular V domain, a transmembrane domain, and a cytoplasmic tail. The membrane-bound isoforms function as homodimers connected by disulfide bonds, whereas the soluble isoforms act as monomers. The intracellular domain shows a likeness to the structure of CD28.

It has been demonstrated by studies that a vast array of factors can engender abnormal expression of CTLA-4, such as the expression levels of miRNAs, genetic polymorphisms within the promoter region, the existence of exons in alleles, et cetera [10]. The downregulation of miR-15a and miR-16 can potentiate the expression of CTLA-4 by enhancing the expression of FOXP3 [11]. Moreover, it has been recently discovered and attested in undifferentiated PBMCs, undifferentiated CD3+ cells, and CD4+ T cell subtypes that the cell surface expression of the CTLA-4 protein is impacted by the combined polymorphisms of the promoter and the first exon sequence [12]. The presence of specific alleles in the promoter region of CTLA-4, particularly at SNP sites-318 and -1772, can influence the modulation of CTLA-4 expression, potentially increasing its expression levels [13]. The deficiency of exon 2 and exon 3 can bring about overexpression of the CTLA-4 subtype, thereby eliciting T cell-mediated autoimmune diseases [14].

2.1.3. The Structure and Biological Functions of TIGIT

TIGIT is a receptor belonging to the extracellular immunoglobulin (Ig) superfamily and plays a vital role in restricting adaptive immunity and innate immunity. TIGIT is made up of an Ig variable domain, a type 1 transmembrane domain, and an intracellular domain [15]. TIGIT is present in both NK cells and T cells, contributing to the activation and maturation of both cell types. Additionally, the function of TIGIT in monitoring tumor immunity resembles that of the PD-1/PD-L1 pathway in tumor immunosuppression [16].

Research has shown that TIGIT expression is usually associated with IL-10, miRNAs such as miR-206, and transcription factors including BLIMP1, Bach2, Eomes, PRDM1, c-MAF. Within this group, the expression level of miR-206 shows a negative correlation with the translation level of the TIGIT protein. Eomes positively regulates the expression of TIGIT [17]. The transcription factors PRDM1 and c-MAF collaboratively regulate the co-inhibitory module and influence the activity of multiple inhibitory receptors. The specific regulatory pathways remain ambiguous and require further exploration in the future [18].

2.1.4. The Structure and Biological Functions of LAG-3

LAG-3 is a type-I transmembrane protein that shares a structural resemblance with CD4, consisting of four IgG-like domains known as domain 1 (D1) through domain 4 (D4). The extracellular region of LAG-3 exhibits an amino acid homology of approximately 20% with CD4 and is also constituted by four IgG-like domains. LAG-3 is an inhibitory co-receptor that exerts a crucial role in autoimmunity, tumor immunity and anti-infective immunity [19]. LAG-3 is typically expressed on mature T cells upon stimulation by CD4+ and CD8+, blocking exhausted T cells and augmenting anti-infective immunity.

Multiple transcription factors, such as TOX, NFAT, NR4A, IRF4, and BIM, regulate the expression of LAG-3. Additionally, early growth response gene 2 (EGR2). It plays a role in the production of tired T cells, leading to the activation of LAG-3 expression. Among them, it has been verified that NFAT, NR4A, and TOX can enhance the expression level of LAG-3 when overexpressed in T cells. EGR2 is also a key transcription factor that induces the expression of LAG-3 in CD4+CD25-Foxp3 regulatory T cells [20] [21].

2.1.5. The Structure and Biological Functions of TIM-3

TIM-3, a type I transmembrane protein, is situated on human chromosome 5q33.2 and consists of 302 amino acids [22]. The main structure of TIM-3 is divided into four components, including the variable immunoglobulin domain (IgV), the mucin domain, the transmembrane region, and the intracellular stalk. The IgV domain consists of two antiparallel chains and four cysteines, forming two disulfide bridges [23]. The TIM-3 protein as a whole presents a pocket structure and can act as a ligand-binding site [24].

Studies have shown that the expression of TIM-3 is not regulated by the CpG of its promoter but is governed by AP-1 factors and NFAT. Additionally, its expression is also controlled by phosphatidylserine. Among them, c-Jun regulates TIM-3 transcription by interacting with the proximal promoter of TIM-3[25]. Hence, the reduction of IL-2 production by TIM-3-expressing CD4+ T cells can be achieved by blocking NFAT dephosphorylation and AP-1 transcription [26]. The binding of phosphatidylserine can also directly modulate the function of TIM-3 [27].

2.2. Overview of the Immune Regulatory Mechanism Involving Immune Checkpoints

2.2.1. The Immune Regulatory Mechanisms Associated with PD-1/PD-L1

PD-L1 is expressed in tumor cells as an" adaptive immune mechanism" for evading anti-tumor responses [28]. When activated T cells' receptors identify cancer antigens displayed by MHC molecules on cancer cells, the T cells release perforin and granzymes to trigger the apoptosis of cancer cells. They also release interferon-γ and other cytokines. At the same time, cancer cells increase the amount of PD-L1 expression, enabling PD-L1 to attach to PD-1 on T cells and transmit

inhibitory signals that decrease cytokine production and hinder T cell multiplication. This weakens the aggressiveness of T cells (i.e., leading to immune evasion or immune tolerance) [29] [30], thereby inducing the further occurrence and expansion of cancer. In this way, PD-L1 of the cells mediates the protection of cancer cells against CTL killing and maintains the degree of peripheral self-tolerance [31].

PD-L1 mediates another potential regulatory mechanism to suppress the chronic immune response during concurrent viral infection [32]. Cancer, being a chronic and frequently inflammatory disease, cancer cells may further utilize this immune protection pathway during the disease progression as a means to evade the host's autoimmune responses [33].

During the formation of cancer, PD-L1 can stimulate the growth and development of cancer cells and their high-level expression by activating key oncogenic pathways in the tumor. For instance, it upregulates the production of enzymes such as phosphatidylinositol 3-kinase (PI3K) and mitogen-activated protein kinase (MAPK), thereby activating cancer cell expression [34] [35].

2.2.2. The Immune Regulatory Mechanisms Associated with CTLA-4

The CTLA-4 molecule is usually found in high levels on regulatory T lymphocytes (Treg) and activated T lymphocytes. T lymphocyte activation necessitates the dual stimulation of two signaling pathways the interaction between the T cell receptor (TCR) and MHC-antigen peptide complexes displayed by antigen-presenting cells (APC), and the attachment of B7 molecules (B7-1 or B7-2) to the co-stimulatory molecule CD28 on T cell surfaces. After T cell activation, the highly expressed CTLA-4 molecule binds to B7 molecules and inhibits T cell activation, forming an immune negative feedback mechanism [36].

CTLA-4 promotes T cell movement and disrupts the communication between T cells and APCs mediated by TCR signals, thereby limiting the clustering of TCR molecules at the immune synapse [37]. These mechanisms collectively increase the threshold of signals required by TCR. The binding of CTLA-4 to TCR also blocks the formation of kinases containing zap-70, resulting in the ineffective transmission of downstream signals for T cell proliferation. CTLA-4 also enhances its own tolerance through mechanisms such as participating in intracellular phosphatases SRC homology 2 (SH2)-domain phosphatases (SHP2) and protein phosphatase 2A (PP2A) [38] [39].

2.2.3. The Immune Regulatory Mechanisms Associated with TIGIT

TIGIT is associated with NK cell depletion in the body and various cancer individuals. It not only regulates the survival of NK cells [40], but also mediates T cell depletion. Animal experiments show that TIGIT indirectly suppresses the function of T cells by binding to CD155 on DCs. The binding of TIGIT to DCs induces phosphorylation of the CD155 protein and triggers a signal cascade that promotes the formation of immune tolerance DCs, downregulating the production of IL-12

and mediating the increase of IL-10.

In clinical studies, TIGIT inhibits the degranulation, cytokine generation, and CD155+ tumor cell-mediated cytotoxicity of NK cells. This further diminishes the capability of NK cells to trigger apoptosis and autophagy. Additionally, TIGIT impedes CD155-mediated CD226 activation. TIGIT binds to CD155 with a higher affinity than CD226, thus limiting CD226-mediated activation. Furthermore, TIGIT directly cis-binds to CD226 on cells, destroying its ability to bind to CD155 homodimers [41] [42].

2.2.4. The Immune Regulatory Mechanisms Associated with LAG-3

LAG-3 is mainly involved in regulating the activities of B cells, T cells, NK cells, and antigen-presenting cells. Afterward, it suppresses the immune system's activity and keeps the organism's immune balance in check. The membrane-bound LAG-3 expressed on Treg cells can combine with MHC-II class molecules on dendritic cells, thereby suppressing the maturation of DCs and inducing the formation of tolerogenic DCs, and thus inhibiting the activation and proliferation of T cells [43].

In the absence of MHC-II class molecules, LAG-3 can interact with the TCR-CD3 complex, migrate to the immune synapse. As LAG-3 accumulates, the repetitive acidic glutamic acid-proline sequence at the tail of LAG-3 leads to a decrease in the local pH value of the IS, thereby causing Zn^{2+} to dissociate from the lymphocyte-specific protein tyrosine kinase of the co-receptor, further influencing the downstream signal transduction of the TCR and thereby affecting the activity of T cells [44] [45].

When NK cells are stimulated and activated, LAG-3 is induced to be expressed and migrates to the cell surface. Subsequently, LAG-3 signal transduction can arrest the cell cycle of CD1d-restricted NK cells at the S phase, thereby inhibiting the function of NKT cells [46].

2.2.5. The Immune Regulatory Mechanisms Associated with TIM-3

Tim-3, as a negative regulatory factor, causes cell death by binding to its ligand Galectin-9, thereby regulating the immune function of Th1 cells. PtdSer is a molecular entity that is displayed on the exterior of apoptotic cells. It not only binds to TIM-3 but also interacts with TIM-1 and TIM-4, which is associated with the uptake of apoptotic cells and antigen cross-presentation mediated by macrophages and dendritic cells [47]. 19HMGB1, a damage-associated molecule, has also been demonstrated to bind and interact with the TIM-3 protein. The TIM-3 protein also interacts with CEACAM-1. The cis interaction between these two proteins is crucial for the glycosylation, stability of TIM-3, and its ability to inhibit T cell function. CEACAM-1 and the TIM-3 protein can also have a trans interaction, thereby negatively regulating the T cell immune response [48]. At the same time, TIM-3 is also implicated in both promoting and inhibiting the activities of monocytes and macrophages [49].

3. Studies Investigating the Clinical Applications of Immune Checkpoint Inhibitors in Relation to Liver Cancer

3.1. The Current Situation of PD-1/PD-L1 Immune Checkpoint Inhibitors Therapy

3.1.1. Status of Immune Checkpoint Inhibitors for Hepatocellular Carcinoma

In a clinical environment, drugs that target PD-1/PD-L1 primarily fall into two categories antibody-based drugs and small molecule drugs. Among them, both anti-PD-1 and anti-PD-L1 types are antibody drugs.

3.1.2. Anti-PD-1-Type Immunosuppressant

Over the past decade, the utilization of monoclonal antibodies in targeted cancer therapy has witnessed a remarkable escalation, yielding substantial clinical outcomes in the treatment of multiple cancer types [50]. Currently, the anti-PD-1 immunosuppressants employed in clinical practice mainly encompass nivolumab, pembrolizumab, and cemiplimab, among others. Pembrolizumab and nivolumab are distinguished as humanized (-zumab) and human (-umab) monoclonal antibodies, respectively. Both monoclonal antibodies are generated by initiating an immune response through the initial immunization of mice with human target proteins (PD-1) [51]. A considerable volume of clinical data has attested that PD-1 immunosuppressants possess certain broad-spectrum properties, persistence, and low toxicity. PD-1 blockade immunotherapy has demonstrated a longer duration of drug action in the clinical setting and exhibits superior tolerability compared to traditional therapeutic approaches [52].

3.1.3. Anti-PD-L1-Type Immunosuppressant

At present, the FDA has approved three anti-PD-L1 immunosuppressants for clinical application, namely atezolizumab, durvalumab, and avelumab [53].

Atezolizumab is a human IgG1 antibody that specifically targets PD-L1. According to protein structure analysis, both the variable domain (VH) and the light chain variable domain (VL) in the heavy chain of atezolizumab can interact with PD-L1. Atezolizumab blocks the PD-1/PD-L1 interaction by competing with PD-1 for the same epitope on PD-L1, thereby exerting immunosuppressive effects. Durvalumab has a pharmacological effect similar to that of atezolizumab, while compared to durvalumab and atezolizumab, avelumab has a stronger affinity for PD-L1 [54]. The clinical efficacy in patients with multiple tumor types has indicated that atezolizumab, durvalumab, and avelumab have good tolerance and strong safety [55].

3.1.4. Small-Molecule Inhibitors

When considering the advantages of small molecule inhibitors over monoclonal antibodies, factors like tumor tissue permeability and immunogenicity stand out. Therefore, small molecule compounds demonstrate superior capabilities in clinically inhibiting tumor growth and migration, and exhibit good biosafety [56].

Small molecule inhibitors are mainly categorized into three types: blocking the

combination of PD-1 and PD-L1, reducing the expression level of PD-L1, and facilitating the degradation of PD-1. Within this group, inhibition of the interaction between PD-1 and PD-L1 can be primarily classified into two categories peptide inhibitors and non-peptide inhibitors.

Peptide inhibitors are mainly AUNP-12 and DPPA-1. CA-170 is the only small molecule modulator targeting PD-L1 and VISTA proteins in current clinical trials, and it uses AUNP-12 as the precursor substance. Based on the findings of experiments and computer modeling, there is no direct binding observed between CA-170, its peptide precursor AUNP-12, and PD-L1 [57]. Therefore, when using peptide-based small molecule inhibitors, changing the mechanism that directly blocks the interaction between hPD-1/hPD-L1 and CA-170-type drugs may bring new opportunities for improving drug efficacy and other aspects.

Non-peptide-based small molecule inhibitors are currently mainly biphenyl compounds, such as BMS-202 and BMS-200. A majority of these compounds exhibit beneficial inhibitory effects on the PD-1/PD-L1 interaction [58].

Studies have demonstrated that this small molecule compound acts on the surface of the PD-L1 protein, resulting in the dimerization of PD-L1. After dimerization, the surface where PD-L1/PD-L1 interacts is highly similar to that where PD-1/PD-L1 interacts, which leads to the inability of PD-1 and PD-L1 to interact normally, ultimately blocking the conduction of the signal pathway and achieving the purpose of inhibiting tumor growth [59]. In recent years, researchers have synthesized a dibromine-based PD-1/PD-L1 immune checkpoint small molecule inhibitor. This compound disrupts the PD-1/PD-L1 complex by acting as a PD-L1 antagonist. Meanwhile, it has a low production cost and may be non-immunogenic [60]. This provides a new direction to produce small molecule inhibitors with better drug efficacy.

3.2. The Current Therapeutic Situation of CTLA-4 Immune Checkpoint Inhibitors

In clinical practice, the inhibitors that target CTLA-4 primarily consist of abatacept, belatacept, ipilimumab, tremelimumab, and cadonilimab. Among these, ipilimumab and tremelimumab are novel humanized monoclonal antibodies, with cadonilimab being the first bispecific antibody capable of simultaneously targeting PD-L1 and CTLA-4.

Furthermore, drugs like vemurafenib, dabrafenib, and trametinib are extensively utilized in clinical settings [61]. Dabrafenib competitively binds to the ATP-binding site of the BRAF protein, inhibiting its kinase activity, thereby blocking the MAPK signaling pathway and suppressing the growth of tumor cells. Vemurafenib is an orally available inhibitor of low molecular weight that targets mutant forms of the BRAF serine-threonine kinase, such as BRAF V600E [62]. Vemurafenib also blocks several other kinases including CRAF, ARAF, wild-type BRAF, SRMS, ACK1, MAP4K5, and FGR at comparable levels. Certain mutations in the BRAF gene, such as V600E, result in constantly activated BRAF proteins that can

drive cell proliferation even in the absence of the regular growth factors needed for cellular growth [63].

3.3. The Current Therapeutic Situation of Other Immune Checkpoint Inhibitors

At present, the monoclonal antibodies targeting TIGIT mainly include tiragolumab and ociperlimab (BCG-A1217). Tiragolumab is a fully humanized monoclonal antibody. Tiragolumab disrupts the activation of CD226 by competing with CD226 for binding to CD155 and other mechanisms [64]. Ociperlimab (BCG-A1217) possesses complete Fc function. Preclinical studies have revealed that ociperlimab has approximately four times stronger affinity for TIGIT than Roche's tiragolumab [65].

Sabatolimab (MBG453) is currently under research and development as a humanized IgG4 (anti-TIM-3 monoclonal antibody), which can bind to TIM-3, block its interaction with the ligand phosphatidylserine (PtdSer), and partially block the interaction between TIM-3 and galectin-9 [66] [67]. Another drug, M6903, is a fully humanized anti-TIM-3 monoclonal IgG2 antibody [68]. It can inhibit the binding of TIM-3 to its ligands and compete with TIM-3 ligands such as Gal-9 for binding to TIM-3. Meanwhile, studies have shown that Gal-9 has multiple binding sites on TIM-3, indicating that it may have stronger affinity than other monoclonal antibody drugs [69].

Relatlimab is a human immunoglobulin G4 monoclonal blocking antibody, and relatlimab can bind to LAG-3 and block its ability to bind to MHC-II ligands. This inhibition leads to the suppression of the inhibitory effect of LAG-3 on T cells, thereby restoring the immune activity of T cells and enhancing the killing ability of T cells against cancer cells [70] [71].

3.4. Drug Resistance Caused by Immune Checkpoint Inhibitors Associated with Liver Cancer

Immune checkpoint blockade therapy has been authorized as the primary therapeutic choice for various cancer types. Nevertheless, issues of limited clinical efficacy keep emerging, among which drug resistance is one of the crucial causes. Currently, PD-1/PD-L1 immune inhibitors are the most widely used immune checkpoint blockade therapy in clinical settings, with drug resistance being a prominent focus in related reports.

The drug resistance of tumor cells mainly includes acquired resistance and intrinsic resistance, and both resistances involve PD-1/PD-L1. The drug resistance mediated by PD-1/PD-L1 may be associated with abnormal PD-L1 expression, abnormal neoantigen expression and presentation, and the suppression of the tumor microenvironment [72].

3.4.1. Abnormal PD-L1 Expression

After drug treatment, PD-L1 expression increases accordingly and in turn contributes to immune resistance. Current studies have indicated that the anti-tumor

immune response induced by dendritic cell (DC) vaccination in glioblastoma mediates immune resistance. Simultaneously, cancer cells with upregulated PD-L1 exhibit increased resistance to IFN-mediated apoptosis through reverse signaling within the cancer cells [73]. Additionally, abnormal mutations inactivating JAK1 protein/2, methylation of the PD-L1 promoter, and downregulation of PD-1 expression mediate abnormal PD-L1 expression, thereby inducing tumor resistance [74] [75].

3.4.2. Abnormal Expression of Neoantigens

Abnormal expression of neoantigens also mediates the development of drug resistance in tumor cells, which is mainly associated with low levels of tumor mutational burden, microsatellite deficiency, and DNA mismatch repair defects [76].

3.4.3. Abnormal Presentation of Neoantigens

The abnormal presentation of neoantigens is similar to the abnormal expression of neoantigens and mediates tumor cell resistance to a certain extent. It is primarily associated with the β2-microglobulin expression. The absence or reduction of functional β2-microglobulin leads to abnormal neoantigen presentation and subsequently induces drug resistance in tumor cells [77].

3.4.4. Suppression of the Tumor Microenvironment

The suppression of the tumor microenvironment is mainly related to immunosuppressive chemokines and cytokines, regulatory T cells, and the suppression of tumor-associated macrophages, as illustrated in the mechanism below.

Cancer cells possess numerous immune checkpoints. Besides PD-1/PD-L1, they also include TIM-3, CTLA-4, LAG-3. The upregulation of the expression levels of these immune checkpoints might also result in a certain degree of resistance of cancer cells to the blockade of PD-1 [78].

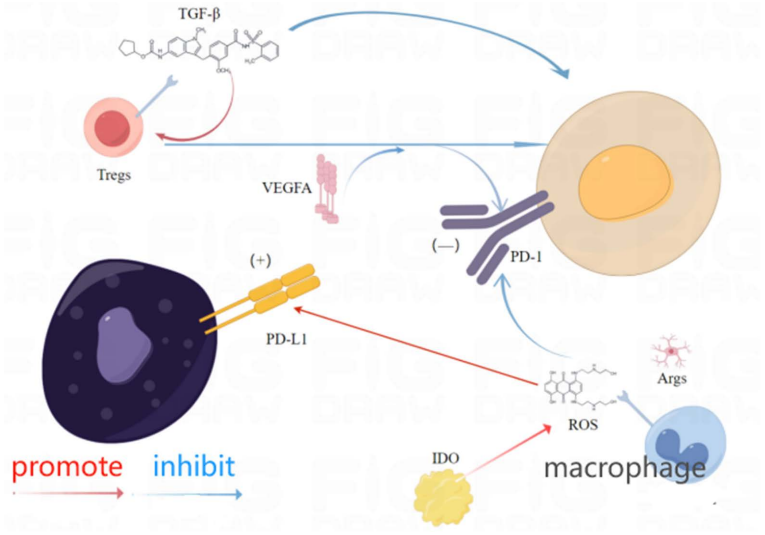

Figure 1. Illustrates the mechanism by which drug resistance is generated through the suppression of the tumor microenvironment.

In the treatment strategies for cancer cell resistance, in the future, it can be achieved through the prediction of new tumor markers and their combined use with co-stimulatory molecule agonists, interferon gene agonists, fecal microbiota transplantation, epigenetic regulators, new chemotherapy drugs, metabolic regulators, or in combination with radiotherapy.

4. Summary and Prospect

This study examines biological therapeutics that use immune checkpoints and immune checkpoint inhibitors for cancer treatment, with a focus on hepatocellular carcinoma. It evaluates their biological functions, mechanisms of action, current drug applications in clinical settings, and explores the mechanisms and strategies for overcoming resistance. It also conducts an in-depth summary and induction of PD-1/PD-L1, which is currently more widely used.

Currently, the drug regimens using immune checkpoint inhibitors for the treatment of hepatocellular carcinoma are not comprehensive, and many issues urgently require resolution. Therefore, there is a necessity to expedite the research and clinical trials of immune checkpoint inhibitors beyond PD-1/PD-L1 Immune Checkpoint, while further delving into the mechanisms of PD-1/PD-L1 checkpoints and developing new drug designs.

During the discovery and development of new targets, it is also needed to enhance the clinical trials and formulation of combined drug strategies, striving to further improve the safety of immune checkpoint inhibitors in the treatment of hepatocellular carcinoma in the future and reduce the drug resistance that occurs in patients during the medication process.

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Conflicts of Interest

The authors declare no competing interests.

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