



Review

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Tumor immune checkpoints and their associated inhibitors

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Abstract: Immunological evasion is one of the defining characteristics of cancers, as the immune modification of an immune checkpoint (IC) confers immune evasion capabilities to tumor cells. Multiple ICs, such as programmed cell death protein-1 (PD-1) and cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4), can bind to their respective receptors and reduce tumor immunity in a variety of ways, including blocking immune cell activation signals. IC blockade (ICB) therapies targeting these checkpoint molecules have demonstrated significant clinical benefits. This is because antibody-based IC inhibitors and a variety of specific small molecule inhibitors can inhibit key oncogenic signaling pathways and induce durable tumor remission in patients with a variety of cancers. Deciphering the roles and regulatory mechanisms of these IC molecules will provide crucial theoretical guidance for clinical treatment. In this review, we summarize the current knowledge on the functional and regulatory mechanisms of these IC molecules at multiple levels, including epigenetic regulation, transcriptional regulation, and post-translational modifications. In addition, we provide a summary of the medications targeting various nodes in the regulatory pathway, and highlight the potential of newly identified IC molecules, focusing on their potential implications for cancer diagnostics and immunotherapy.

Key words: Immune checkpoint; Immune checkpoint inhibitor; Programmed cell death-ligand 1 (PD-L1); Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4); Lymphocyte activation gene-3 (LAG-3); T-cell immunoglobulin and immunoreceptor tyrosine-based inhibitory motif (ITIM) domain (TIGIT); B7 family

1 Introduction

Interactions between the immune system and tumors are regulated by a complex network of biological modulators. Tumor cells can develop the ability to evade immune surveillance through immune editing, in which immune checkpoints (ICs) play an important role (Schreiber et al., 2011). ICs are molecules expressed on the surfaces of immune cells, regulating the immune response. Their normal function is to control immune homeostasis (Pardoll, 2012). However, the tumor activates ICs through ligands to suppress

T-cell function and develop the ability to circumvent immune recognition and evade immune response. Thus, tumor cells are supported by these ICs in the tumor microenvironment (TME) to inactivate tumor-infiltrating immune cells and achieve immune tolerance (Fig. 1) (Topalian et al., 2016).

The main idea of tumor immunotherapy is to reactivate the immune cells in the TME by blocking the immune suppressive effect of cancer cells (Fig. 1), leading to their destruction, eventually achieving the goal of oncology treatments and preventing tumor recurrence. Immunotherapy is a revolutionary innovation in cancer treatment, that has completely transformed oncology (Zhang and Zhang, 2020). It provides several advantages over traditional chemotherapy and targeted medicines, including more flexibility, higher long-term survival rate, and fewer side effects (Tan et al., 2020). In spite of tremendous advances

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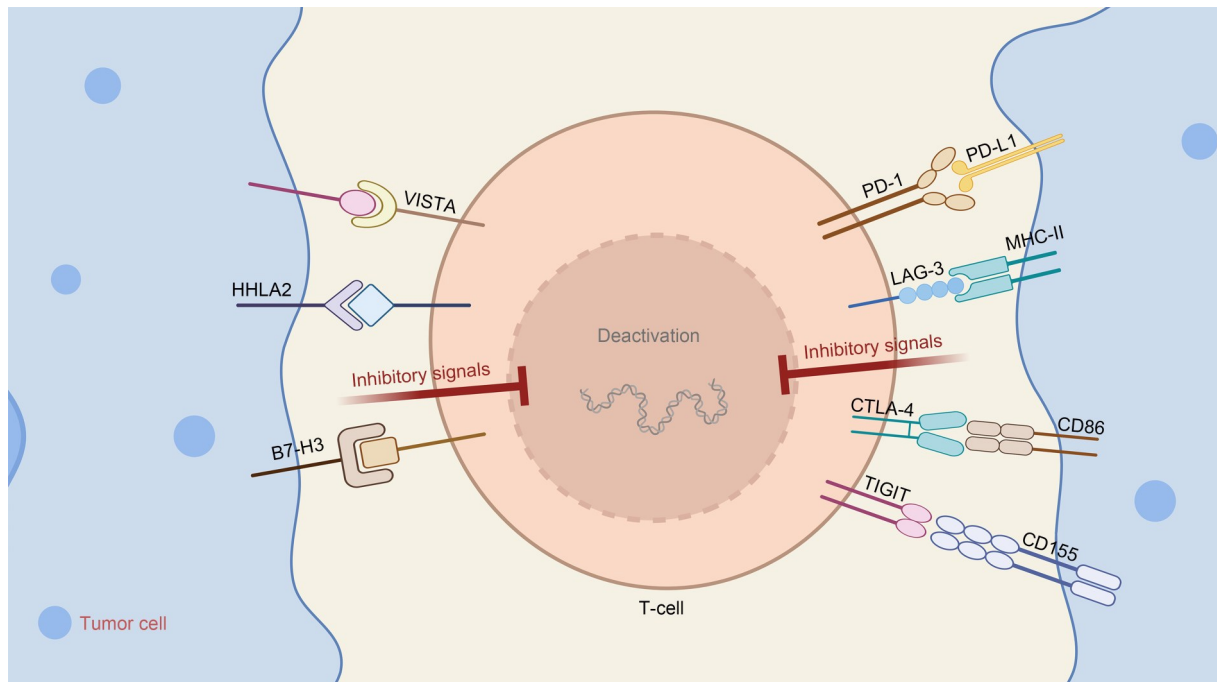


Fig. 1 Tumor microenvironment (TME) and immune checkpoints (ICs). In the TME, T-cell activation requires the presentation of tumor antigens to naive T-cells by the antigen-presenting cell (APC) and the binding of co-stimulatory molecules on their surface to the corresponding receptors on the T-cell surface. However, inhibitory molecules (ICs) are also present on the cell surface, and they are activated through ligands that can limit T-cell activation and proliferation, leading to the immune escape of tumor cells. VISTA: immunoglobulin V structural domain-containing T-cell activation suppressor; HHLA2: human endogenous retroviral H long terminal repeat-binding protein 2; B7-H3: B7 homolog 3 protein; PD-1: programmed cell death protein-1; PD-L1: programmed cell death-ligand 1; LAG-3: lymphocyte activation gene-3; MHC-II: major histocompatibility complex-II; CTLA-4: cytotoxic T-lymphocyte-associated antigen-4; CD: cluster of differentiation; TIGIT: T-cell immunoglobulin and immunoreceptor tyrosine-based inhibitory motif (ITIM) domain.

in immunotherapies, several obstacles exist, like the restricted response rates, the inability to forecast clinical efficacy, and the possibility of side effects, which cannot be overlooked (Hegde and Chen, 2020).

The most notable advanced technique is IC blockade (ICB) therapy. ICB refers to the targeting of IC molecules by blocking their recognition of ligands or inhibiting their expression on tumor cells by IC inhibitors (ICIs). ICIs block this process in several ways to reactivate suppressed T-cells and enhance anti-tumor immunity (Clarke et al., 2018). Over the past few years, numerous clinical trials of checkpoint blockade in the lung, prostate, kidney, and other types of cancer have shown promising results, highlighting the great potential of this therapeutic strategy (Sharon et al., 2014) and promoting ICIs as one of the most potent therapeutic options in tumors (Robert, 2020). As classical IC molecules, programmed cell death protein-1 (PD-1)/programmed cell death-ligand 1 (PD-L1) and cytotoxic T-lymphocyte-associated

antigen-4 (CTLA-4) have garnered tremendous interest in the field of oncology (Robert, 2020). As demonstrated in these clinical studies, the blockade of different ICs activates the antitumor immune response of the immune system through different mechanisms and at various levels, which has transformed cancer therapeutics. Therefore, it is essential to consider the functions of inhibitors of numerous ICs. The clinical efficacy results of antibodies that inhibit receptors suggest that antitumor immunity can be enhanced on multiple levels, and that combinatorial methods can be rationally designed using molecular considerations and preclinical models (Pandey et al., 2022). Based on the discovery of ICs and the success of checkpoint blockade inhibitors, the new generation of tumor immunotherapies has recently entered the mainstream strategies of cancer treatment. However, some patients exhibit low response to these therapies, which could be attributed to the expression of ICs in the TME (Topalian et al., 2020). Therefore, it

is of considerable clinical and scientific importance to understand the molecular mechanisms behind the control of ICs and create novel techniques, such as combining ICI with other medications, or devising new immunotherapies for broader, more durable response and safer efficacy.

2 Classical IC molecules

2.1 PD-L1/PD-1

PD-1, also known as cluster of differentiation 279 (CD279), belongs to the CD28 superfamily and is a receptor protein expressed on the surface of immune cells. It is expressed at low levels on resting cells of the immune system and can also be expressed on activated T-cells, B-cells, natural killer (NK) cells, monocytes, dendritic cells (DCs), and tumor-infiltrating lymphocytes (TILs) (Table 1) (Agata et al., 1996; Norris et al., 2012; Thibult et al., 2013; Gros et al., 2014; Lim TS et al., 2016; Jiang, 2020). When PD-1 interacts with its ligands, the tyrosine residues of cytoplasmic immunoreceptors on T-cells will be phosphorylated and protein tyrosine phosphatases, including SH2-containing protein tyrosine phosphatase 1 (SHP1) and SHP2, will be recruited, thereby inhibiting costimulatory receptors such as the T-cell receptor (TCR) and CD28. This results in the dephosphorylation of key downstream kinases (Boussiotis, 2016; Borst et al., 2021), which counteracts activation signals induced by TCR-CD28 and inhibits the activation, proliferation, and cytokine production, and even the survival of T-cells (Boussiotis, 2016). The ligands of PD-1,

PD-L1 and PD-L2, can be expressed in a range of cell types, including antigen-presenting cells (APCs) and cancer cells, where the PD-L1/PD-1 axis is associated with immuno-inflammatory phenotypes (Cesano and Warren, 2018) and is involved in the immune escape of cancer cells (Wei et al., 2018). PD-L1, also known as CD274 and B7-H1, belongs to the B7 family and is highly expressed in melanoma, lung cancer, ovarian cancer, colon cancer, and many other human cancer tissues (Skafi et al., 2020). The overexpression of PD-L1 is closely related to poor clinical prognosis, and various regulatory factors and drugs can affect PD-L1 expression directly or indirectly at the DNA, RNA, and protein levels (Fig. 2) (Wu Q et al., 2021; Xiong et al., 2021; Yi et al., 2021; Yamaguchi et al., 2022).

2.1.1 Regulation of PD-L1 at the nucleic acid level

2.1.1.1 Epigenetic regulation

The hypomethylation of CpG sites leading to PD-L1 upregulation is the most prevalent epigenetic feature within cancer cells (Table 2) (al Emran et al., 2019). DNA methyltransferase inhibitors (DNMTis) are thought to stimulate interferon (*IFN*) genes and produce *IFN-γ* to induce PD-L1 expression by increasing the expression of endogenous retroviruses (ERVs) with hypermethylated DNA (al Emran et al., 2019). Drugs such as azacitidine and decitabine were found to enhance the efficacy of anti-PD-L1 antibodies by upregulating PD-L1 expression through DNA hypomethylation in mouse models of non-small cell lung cancer (NSCLC), colorectal cancer (CRC), gastric cancer (GC), and leukemia (Yang et al., 2014;

Table 1 Immune checkpoints and their main expressing cells

Checkpoint	Cells
PD-1	Activated T-cells, B-cells, NK cells, monocytes, DCs, and TILs
PD-L1	Melanoma, lung cancer, ovarian cancer, colon cancer, and many other human cancer tissues
CTLA-4	Activated T-cells, NK cells, and many other immune cell types
LAG-3	Activated CD4 ⁺ and CD8 ⁺ T-cells, Treg and NK cells, B-cells, and plasma cell-like DCs
TIGIT	T-cells and NK cells, and usually low expression on naive cells
B7-H3	Overexpression in CRC and many other human cancer tissues
VISTA	Hematopoietic stem cells, myeloid cells, lymphoid and myeloid DCs; Less on CD4 ⁺ and CD8 ⁺ T-cells and Treg cells, and also detected on TILs
HHLA2	Restricted except in epithelial cells of the intestine, kidney, gallbladder, breast, and trophoblast of the placenta

PD-1: programmed cell death protein-1; PD-L1: programmed cell death-ligand 1; CTLA-4: cytotoxic T-lymphocyte-associated antigen-4; LAG-3: lymphocyte activation gene-3; TIGIT: T-cell immunoglobulin and immunoreceptor tyrosine-based inhibitory motif (ITIM) domain; B7-H3: B7 homolog 3 protein; VISTA: immunoglobulin V structural domain-containing T-cell activation suppressor; HHLA2: human endogenous retroviral H long terminal repeat-binding protein 2; NK: natural killer; DCs: dendritic cells; TILs: tumor-infiltrating lymphocytes; CD: cluster of differentiation; Treg: regulatory T; CRC: colorectal cancer.

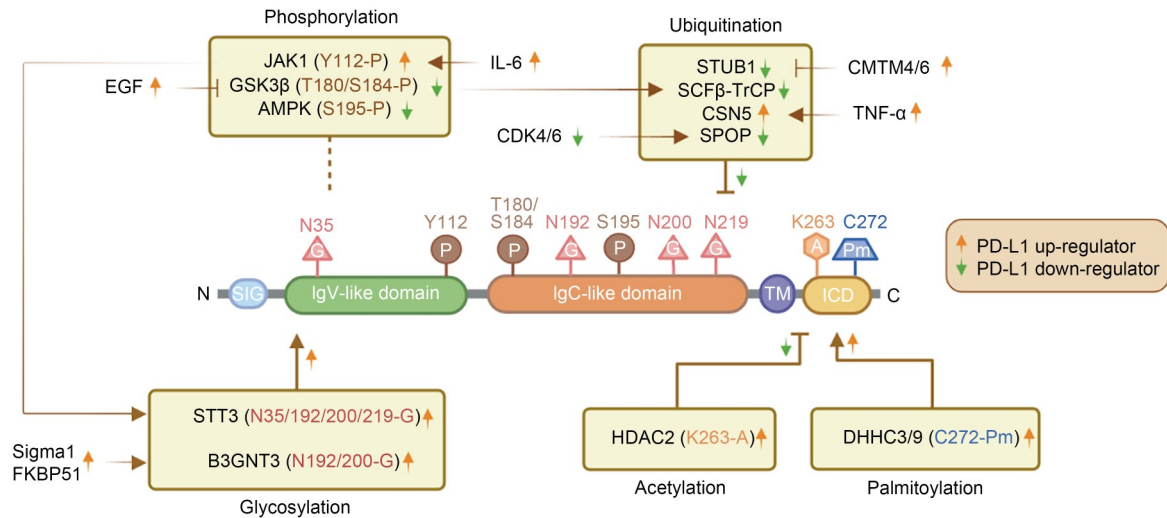


Fig. 2 Post-translational modifications (PTMs) of PD-L1. As a protein molecule, the activity and stability of PD-L1 are regulated by various PTMs. Glycosylation can affect the stability of PD-L1, that is, the interaction between PD-L1 and PD-1. Palmitoylation can also increase the stability of PD-L1. Conversely, poly-ubiquitination is a negative regulation that induces the degradation of PD-L1. Phosphorylation regulates PD-L1 levels by cross-talk through glycosylation and polyubiquitination. PD-1: programmed cell death protein-1; PD-L1: programmed cell death-ligand 1; EGF: epidermal growth factor; JAK1: Janus tyrosine kinase 1; GSK3β: glycogen synthase kinase 3β; AMPK: AMP-activated protein kinase; IL-6: interleukin-6; CDK4: cyclin-dependent kinase 4; CMTM: CMTM-like MARVEL transmembrane domain-containing; TNF-α: tumor necrosis factor-α; STUB1: STUB1 homology and U-box-containing protein 1; SCFβ-TrCP: SKP1-cullin-F-box (β-transducin repeat-containing protein); CSN5: COP9 signalosome 5; SPOP: speckle type BTB/POZ protein; FKBP51: FK506-binding protein 51; STT3: dolichyl-diphosphooligosaccharide-protein glycosyltransferase subunit STT3; B3GNT3: β-1,3-N-acetylglucosaminyltransferase 3; HDAC2: histone deacetylase 2; DHHC: DHHC-type palmitoyltransferase; SIG: signal peptide; IgV: immunoglobulin variable; IgC: immunoglobulin constant; TM: transmembrane domain; ICD: intracellular domain; Pm: palmitoylation; G: glycosylation; P: phosphorylation; A: acetylation.

Zhang et al., 2017; Franzen et al., 2018; Huang et al., 2020; Zhu et al., 2020), providing a more significant antitumor effect than anti-PD-L1 treatment alone (Zhu et al., 2020). In addition, tri-methylation of lysine 4 on histone H3 (H3K4me3) was found to be a histone modifier reflecting the transcriptional activation status of the gene (Howe et al., 2017). Mixed lineage leukemia 1 (MLL1), the binding protein of PD-L1 promoter, could catalyze H3K4me3 and thus promote PD-L1 transcription (Lu et al., 2017). In contrast, verticillin A attenuated the mediating ability of MLL1, thereby downregulating PD-L1 expression at the transcriptional level (Lu et al., 2017). Besides, T-cell responses can be inhibited in the GC microenvironment rather than through the membrane by lysine-specific demethylase 1A (LSD1), inducing the accumulation of PD-L1 in exosomes, which may provide a new target for immunotherapy (Shen et al., 2022). In fact, the LSD1 inhibitor (ORY-1001) combined with an anti-CD47/PD-L1 monoclonal antibody inhibits tumor growth more effectively than a single blocking strategy (Xu et al., 2021).

2.1.1.2 Transcriptional regulation

2.1.1.2.1 Inflammatory signaling

PD-L1, a negative feedback regulator molecule of multiple inflammatory signals, can be induced to be upregulated by multiple inflammatory factors, such as IFN-α, IFN-β, IFN-γ, interleukin-6 (IL-6), IL-4, tumor necrosis factor-α (TNF-α), and transforming growth factor-β (TGF-β) (Table 2), among which IFN-γ is thought to be the main stimulator promoting PD-L1 expression (Zerdes et al., 2018). IFN-γ binds to type II IFN receptors and activates the Janus tyrosine kinase (JAK)-signal transducer and activator of transcription 1 (STAT1) signaling pathway (Yao et al., 2015; Garcia-Diaz et al., 2017), subsequently leading to the upregulation of several transcription factors, especially IFN response factors (IRFs). IFN-γ-induced PD-L1 upregulation through membrane requires cyclin-dependent kinase 5 (CDK5), which inhibits the expression of PD-L1 transcriptional repressors, namely the IFN regulatory factor 2 (IRF2) and IRF2-binding protein 2 (IRF2BP2), which may lead to increased PD-L1 expression in tumors (Dorand et al., 2016).

Table 2 Regulators of PD-L1

Regulatory type	Regulator	PD-L1	Cancer type	Inhibitors	References
Epigenetic	Methylation at CpG sites	Downregulation	Melanoma, NSCLC, HNSCC, CRC, GC, leukemia	Azacitidine, decitabine	Yang et al., 2014; Goltz et al., 2017; Marwitz et al., 2017; Shin et al., 2017; Zhang et al., 2017; Franzen et al., 2018; Micevic et al., 2019; Huang et al., 2020; Zhu et al., 2020
	H3K4me3	Upregulation	Pancreatic cancer and breast cancer	Verticillin A	Howe et al., 2017; Lu et al., 2017; Darvin et al., 2019
Transcriptional	IFN- α	Upregulation	Melanoma		Garcia-Diaz et al., 2017
	IFN- β	Upregulation	Melanoma		Garcia-Diaz et al., 2017
	IFN- γ	Upregulation	Sarcoma, colon cancer, melanoma, and NSCLC	Tofacitinib, ruxolitinib, fedratinib, silvestrol, vertiporfin	Yao et al., 2015; Ikeda et al., 2016; Bu et al., 2017; Garcia-Diaz et al., 2017; Noguchi et al., 2017; Cerezo et al., 2018; Chang et al., 2018; Chen et al., 2018; Shao et al., 2019
	IL-6	Upregulation	Prostate cancer, HCC, GBM, NSCLC, lung cancer		Shen et al., 2017; Shin et al., 2017; Xu et al., 2018; Lamano et al., 2019; Zhang et al., 2020
	IL-4	Upregulation	RCC, kidney cancer		Quandt et al., 2014
	TNF- α	Upregulation	Kidney cancer		Quandt et al., 2014
	TGF- β	Upregulation	NSCLC, lung cancer		Ni et al., 2012; David et al., 2017
	EGFR		NSCLC and LUAD		Akbay et al., 2013; Gainor et al., 2016
	PI3K-AKT-mTOR	Upregulation	GC, NSCLC, CRC, glioma, melanoma, HNSCC, CRC, and Her2-amplified cancer	Buparlisib, Worman penicillin, trimethimidine phosphate, rapamycin	Jiang et al., 2013; Mittendorf et al., 2014; Lastwika et al., 2016; van Rensburg et al., 2018; Peng et al., 2019; Du et al., 2020; Fiedler et al., 2020
	MAPK	Upregulation	Multiple human cancer	Selumetinib	Stutvoet et al., 2019; Yuan et al., 2020
	AP-1	Upregulation	Hodgkin's lymphoma		Green et al., 2012; Chen et al., 2013
	HIF-1	Upregulation	LUAD, RCC		Barsoum et al., 2014
	Myc	Upregulation	Melanoma, NSCLC, ESCC, leukemia, lymphoma, and pancreatic cancer		Casey et al., 2016; Atsaves et al., 2017; Kim et al., 2017; Wang et al., 2017; Cheng et al., 2019; Pan et al., 2019; Liang et al., 2020; Wang J et al., 2020
ALK	Downregulation	NSCLC, lymphoma, LUAD		Marzec et al., 2008; Yamamoto et al., 2009; Ota et al., 2015; Koh et al., 2016; Shen et al., 2020	
Met	Upregulation	NSCLC		Demuth et al., 2017; Albitar et al., 2018; Ahn et al., 2019; al Emran et al., 2019; Peng et al., 2019	
RNA-level	ZNF36	Downregulation		Adriamycin	Coelho et al., 2017
	MiR-148a-3p	Downregulation	CRC		Ashizawa et al., 2019
	MiR-34a	Downregulation	AML and lymphoma		Wang et al., 2015; Anastasiadou et al., 2019
	MiR-200 family	Downregulation	NSCLC and GC		Chen et al., 2014; Xie et al., 2017
	MiR-142-5p	Downregulation	Pancreatic cancer		Jia et al., 2017
	MiR-424	Downregulation	Ovarian cancer		Xu et al., 2016

To be continued

Table 2 (continued)

Regulatory type	Regulator	PD-L1	Cancer type	Inhibitors	References
	MiR-214	Downregulation	Lymphoma		Sun et al., 2019
	MiR-497-5p	Downregulation	RCC		Qu et al., 2019
	MiR-140	Downregulation	NSCLC		Xie et al., 2018
Post-translational modification					
Modification cite	Tyr112	Phosphorylation	HCC		Chan et al., 2019
	Ser195	Phosphorylation	Breast cancer		Cha et al., 2018; Dai et al., 2021
	Asn192/200/219	Glycosylation	Breast cancer		Li et al., 2016
	Cys272	Palmitoylation	Breast cancer and colon cancer	Competitive inhibitor	Yang et al., 2019; Yao et al., 2019
Modification enzyme	GSK3 β	Phosphorylation	Breast cancer	Olaparib	Li CW et al., 2016; Jiao et al., 2017; Li H et al., 2019
	STT3	Glycosylation	Cancer stem cell	Etoposide	Hsu et al., 2018; Li et al., 2018; Ruan et al., 2020
	B3GNT3	Glycosylation	Breast cancer		D'Arrigo et al., 2017
	CMTM4	Ubiquitination	NSCLC and melanoma		Mezzadra et al., 2017
	CMTM6	Ubiquitination	Melanoma, NSCLC, CRC, thyroid cancer, pancreatic cancer, breast cancer		Burr et al., 2017; Mezzadra et al., 2017; Wu et al., 2019
	CSN5	Ubiquitination	Breast cancer		Lim SO et al., 2016
	CDK4/6	Ubiquitination	Cervical cancer and breast cancer		Zhang et al., 2018

PD-L1: programmed cell death-ligand 1; NSCLC: non-small cell lung cancer; HNSCC: head and neck squamous cell carcinoma; CRC: colorectal cancer; GC: gastric cancer; H3K4me3: tri-methylation of lysine 4 on histone H3; IFN: interferon; IL: interleukin; HCC: hepatocellular carcinoma; GBM: glioblastoma multiforme; RCC: renal cell carcinoma; TNF- α : tumor necrosis factor- α ; TGF- β : transforming growth factor- β ; EGFR: epidermal growth factor receptor; LUAD: lung adenocarcinoma; MAPK: mitogen-activated protein kinase; AP-1: activator protein-1; HIF-1: hypoxia-inducible factor-1; ESCC: esophageal squamous cell carcinoma; ALK: anaplastic lymphoma kinase; ZNF36: zinc finger protein 36; AML: acute myeloid leukemia; GSK3 β : glycogen synthase kinase 3 β ; B3GNT3: β -1,3-*N*-acetylglucosaminyltransferase 3; CMTM: CKLF-like MARVEL transmembrane domain-containing; CSN5: COP9 signalosome 5; CDK4: cyclin-dependent kinase 4; PI3K: phosphatidylinositol 3 kinase; AKT: protein kinase B; mTOR: mammalian target of rapamycin; STT3: dolichylidiphosphooligosaccharide-protein glycosyltransferase subunit STT3.

Research has speculated that CDK5 may regulate PD-L1 through protein post-translational modification (Gao et al., 2021), whereas the role of CDK5 in regulating PD-L1 expression remains to be determined. Tofacitinib, ruxolitinib, and fedratinib (small molecule JAK inhibitors) have been shown to downregulate PD-L1 expression in triple-negative breast cancer (TNBC), NSCLC, nasopharyngeal carcinoma (NPC) cells (Ikeda et al., 2016; Chen et al., 2018), and several cancer models, in which the ability to inhibit STAT1 expression by silvestrol also reduced PD-L1 expression (Ikeda et al., 2016; Bu et al., 2017; Cerezo et al., 2018). Besides, vertiporfin blocked IFN- γ -induced STAT1-IRF1 interactions, leading to the downregulation of PD-L1 transcription. In addition to IFN- γ , the type I IFNs, IFN- α and IFN- β , can

stimulate PD-L1 expression, but the regulation of PD-L2 by type I IFNs is more pronounced compared to PD-L1 (Garcia-Diaz et al., 2017). Apart from IFNs, ILs are also important cytokines that regulate PD-L1 expression. The IL-6-JAK-STAT3 pathway can promote PD-L1 expression and thus lead to the immune escape ability of cancer cells (Shin et al., 2017). Furthermore, in lung cancer, PD-L1 expression derived by IL-6 is associated with multiple pathways, especially the mitogen-activated extracellular signal-regulated kinase (MEK)-extracellular signal-regulated kinase (ERK) signaling pathway (Shen et al., 2017). IL-4 and TNF- α can induce PD-L1 transcription in kidney cancer cells by synergistically activating signaling molecules, such as nuclear factor- κ B (NF- κ B), inhibitor of NF- κ B (I κ B), and STAT6 (Quandt et al., 2014).

TGF- β can upregulate PD-L1 in DCs in lung cancer (Ni et al., 2012) and upregulate PD-L1 expression in NSCLC through Smad-binding elements (David et al., 2017). However, it has also been proven that TGF- β can inhibit PD-L1 expression in monocytes or renal tubular epithelial cells (Starke et al., 2007; Ou et al., 2012).

2.1.1.2.2 Oncogenic signaling

The epidermal growth factor receptor (EGFR) is upstream of various key signaling pathways that regulate PD-L1 activity, including phosphatidylinositol 3 kinase (PI3K)-protein kinase B (AKT)-mammalian target of rapamycin (mTOR), rat sarcoma (RAS)-rapidly accelerated fibrosarcoma (RAF)-MEK-ERK, JAK-STAT, and glycogen synthase kinase 3 (GSK3) (Table 2). Among them, the PI3K-AKT-mTOR pathway can transcriptionally regulate PD-L1 expression through activator protein-1 (AP-1), STAT3, Yes-associated protein 1 (YAP1)/tafazzin (TAZ), and others. PD-L1 expression can be upregulated by regulatory factors such as AP-1, STAT3, and YAP1/TAZ (Jiang et al., 2013; van Rensburg et al., 2018; Peng et al., 2019; Du et al., 2020), and inhibitors based on different components of this pathway all have regulatory effects on PD-L1 expression, such as buparlisib and wortmannin (PI3K inhibitors) in head and neck squamous cell carcinoma (HNSCC) or breast cancer (BC) cells (van Rensburg et al., 2018; Fiedler et al., 2020), or trimethidine phosphate (AKT inhibitor, LY294002) and rapamycin (mTOR inhibitor) in NSCLC cells (Lastwika et al., 2016). RAS-RAF-MEK-ERK signaling through AP1 and STAT3 can also upregulate PD-L1 transcription. The mitogen-activated protein kinase (MAPK) pathway is a broad pathway of carcinogenesis, accounting for nearly 40% of human cancer cases (Yuan et al., 2020). The MEK inhibitor selumetinib inhibited the epidermal growth factor (EGF)- and IFN-stimulated upregulation of PD-L1 messenger RNA (mRNA) and protein by blocking the MAPK signaling pathway (Stutvoet et al., 2019). In addition, mutations in hypoxia-inducible factor-1 (HIF-1) (Barsoum et al., 2014), Myc (Casey et al., 2016; Kim et al., 2017; Pan et al., 2019; Liang et al., 2020), anaplastic lymphoma kinase (ALK) (Ota et al., 2015), and mesenchymal-epithelial transition factor (Met) (Demuth et al., 2017; al Emran et al., 2019) are also oncogenic factors that affect PD-L1 expression.

2.1.1.3 Regulation of RNA levels

Zinc finger protein 36 (ZFP36) can downregulate PD-L1 by destabilizing mRNA (Coelho et al., 2017), and although ZFP36 has no direct activator, ZFP36 can be phosphorylated and inactivated by a variety of MAPKs in the RAS-MAPK signaling pathway (Table 2) (Coelho et al., 2017). Besides, the *N*⁶-methyladenosine (*m*⁶A) methylation regulator may be crucial for PD-L1 expression (Guo et al., 2021). PD-L1 mRNA is a direct target of *m*⁶A modification, and its levels are regulated by AlkB homolog 5 (ALKBH5), an important *m*⁶A demethylase. The deletion of ALKBH5 enriches the 3' untranslated region (UTR) of PD-L1 mRNA with *m*⁶A modifications, thereby promoting its degradation in a YTH *m*⁶A RNA-binding protein 2 (YTHDF2)-dependent manner (Qiu et al., 2021). In addition, adriamycin can induce ZFP36 expression, and all of these mechanisms may be the means of inhibition of the indirect pathway. Meanwhile, tumor-derived microRNAs (miRNAs) are also important post-transcriptional regulators of PD-L1. For instance, PD-L1 mRNA is a direct target of miR-148a-3p, and lowering miR-148a-3p can elevate PD-L1 mRNA (Ashizawa et al., 2019). Thus far, many miRNAs have been identified as direct targets of PD-L1 mRNA, such as miR-34a, the miR-200 family, miR-142-5p, miR-424, miR-214, miR-497-5p, and miR-140 (Table 2) (Chen LM et al., 2014; Wang et al., 2015; Xu et al., 2016; Jia et al., 2017; Sun C et al., 2018; Xie et al., 2018; Anastasiadou et al., 2019; Qu et al., 2019; Sun JR et al., 2019; Chen C et al., 2020).

2.1.2 Post-translational modifications of PD-L1

2.1.2.1 Phosphorylation and glycosylation

IL-6-activated JAK1 promotes the phosphorylation of PD-L1 (Tyr112), and the phosphorylated PD-L1 in turn recruits STT3A (*N*-glycosyltransferase) to catalyze the glycosylation of PD-L1 (Chan et al., 2019), which can improve the stability of PD-L1 (Table 2). Etoposide can reduce PD-L1 *N*-glycosylation and its expression in mouse models by inhibiting the expression of STT3 (Hsu et al., 2018; Ruan et al., 2020). Meanwhile, it has been reported that the inhibition of other key molecules mediating PD-L1 glycosylation modifications, such as β -1,3-*N*-acetylglucosaminyltransferase 3 (B3GNT3) (Li et al., 2018), Sigma1 (Maher et al., 2018) and spliced isoform of FK506-binding protein 51 (FKBP51s) (D'Arrigo

et al., 2017), can also reduce the expression level of PD-L1 (Table 2). However, metformin-activated AMP-activated protein kinase (AMPK) can promote the phosphorylation of PD-L1 (Ser195), leading to aberrant PD-L1 glycosylation, disrupting the translocation of PD-L1 from the endoplasmic reticulum to the Golgi apparatus, and impeding it at the cell membrane, while also promoting the degradation of endoplasmic reticulum-associated PD-L1 (Cha et al., 2018; Dai et al., 2021). In addition, GSK3 β can reduce PD-L1 levels by promoting phosphorylation-dependent proteasomal degradation (Li CW et al., 2016; Li H et al., 2019). Several drugs have been used clinically to indirectly modulate GSK3 β activity, thereby affecting PD-L1 stability. For example, olaparib (a poly(ADP-ribose) polymerase inhibitor) induced GSK3 β inactivation, which increased PD-L1 expression in cancer cells (Jiao et al., 2017). Glycosylation of the Asn192/200/219 site inhibits the formation of the GSK3 β - β -transducin repeat-containing protein (β -TrCP)-PD-L1 complex and stabilizes PD-L1; EGF induces GSK3 β glycosylation by promoting inactivation to increase PD-L1 expression (Table 2) (Li et al., 2016).

2.1.2.2 Ubiquitination

Ubiquitination has been commonly associated with proteasome-mediated protein degradation (Table 2). In a variety of cancer cells, CKLF-like MARVEL transmembrane domain-containing 6 (CMTM6) prolongs PD-L1 half-life by reducing PD-L1 ubiquitination (Mezzadra et al., 2017; Wu et al., 2019), while CMTM4 also has the same function (Mezzadra et al., 2017). Upon the knockdown of CMTM6, the E3 ubiquitin ligase STIP1 homology and U-box-containing protein 1 (STUB1) induces PD-L1 polyubiquitination (Burr et al., 2017; Mezzadra et al., 2017). In addition, the TNF- α -NF- κ B pathway inhibits PD-L1 ubiquitination by upregulating COP9 signalosome 5 (CSN5) (Lim SO et al., 2016). Meanwhile, cytokinin-dependent kinase 4 (CDK4) indirectly promotes PD-L1 ubiquitination by phosphorylating speckle type BTB/POZ protein (SPOP) (an E3 ubiquitin ligase cullin 3 of PD-L1), which inhibits PD-L1 expression (Zhang et al., 2018). On this basis, CDK4/6 inhibitors can block the degradation of PD-L1 by inhibiting CDK4. To this end, several clinical trials evaluated the efficacy of CDK4/6 inhibitors in combination with anti-PD-L1/PD-1 antibodies (Petroni et al., 2020; Sun et al., 2021; Wu YQ et al., 2021; Zhu et al., 2021).

2.1.2.3 Palmitoylation

Palmitoylation is a widely studied lipid modification at the Cys272 site that enhances PD-L1 stability by counteracting ubiquitination (Table 2) (Yang et al., 2019; Yao et al., 2019). Since DHHC-type palmitoyltransferase 3 (DHHC3) can catalyze the Cys272 palmitoylation reaction of PD-L1, silencing DHHC3 enhances the antitumor immune responses both in vivo and in vitro (Yao et al., 2019), while DHHC9 plays the same function in BC. By combining a cell-penetrating peptide with the palmitoylation motif of PD-L1, a competitive inhibitor of PD-L1 palmitoylation was produced, which was subsequently proven to diminish PD-L1 palmitoylation and expression (Yang et al., 2019; Yao et al., 2019).

2.1.2.4 Acetylation

Acetylation can regulate the stability, subcellular localization, and functional activity of proteins (Table 2). At present, the function of PD-L1 acetylation is unclear. Interestingly, Lys263 acetylation suppresses PD-L1 nuclear translocation, during which unacetylated PD-L1 is transferred to the nucleus via lattice-protein-mediated endocytosis, and nuclear PD-L1 can bind directly to DNA and regulate a variety of immune response-related expression (Gao et al., 2020). The use of histone deacetylase 2 (HDAC2) inhibitors to upregulate Lys263 acetylation, or the introduction of the proposed acetylated Lys263Gln mutation into PD-L1, disrupts its interaction with huntingtin-interacting protein 1-related (HIP1R), thereby blocking PD-L1 relocation in the nucleus, reprogramming the expression of immune-response-related genes, and enhancing the antitumor response to PD-1 blockade (Gao et al., 2020; Hou et al., 2020).

2.2 CTLA-4

CTLA-4, also known as CD152, is mainly expressed on activated T-cells and NK cells, and it is also expressed on the surface of many immune cells as a receptor protein (Table 1), capable of binding CD80 (B7-1)/CD86 (B7-2) and inhibiting T-cell activation through multiple mechanisms. Because of its high homology with CD28 and its higher affinity for the binding sites of B7 molecules of APCs than CD28 (Rotte, 2019), it can inhibit T-cell function. At the same time, CTLA-4 is also expressed on regulatory T (Treg) cell membranes, and it enhances Treg activity and differentiation to inhibit T-cell activation. In addition, CTLA-4 can directly interfere with DCs, thereby

promoting immunosuppression in the TME (Iñarrairaegui et al., 2018). Interestingly, PD-L1 is also able to bind to CD80 to mediate the suppression of T-cell activation (Butte et al., 2007), a mechanism that is one of the few direct overlapping functions of PD-1/PD-L1 and CTLA-4 (Korman et al., 2006). Similar to PD-L1, the intracellular localization of CTLA-4 can specifically regulate the anticancer response (Rowshanravan et al., 2018); therefore, an understanding of the regulators of CTLA-4 and their regulatory mechanisms can help identify patients who respond well to anti-CTLA-4 therapy and continuously improve the corresponding anticancer strategies.

2.2.1 Regulation of CTLA-4 at the nucleic acid level

2.2.1.1 Epigenetic regulation

Currently, those studies are rather focused on CTLA-4 and its related molecules, but little is known about their epigenetic regulation, which is essential for the development of predictive biomarkers of immunotherapy response. It has been reported that the altered expression of HDACs can promote tumorigenesis, and the alteration of the HDAC structural domain of transcription factor 1 (Tcf1) can promote CTLA-4 expression in follicular helper T-cells (TFH) (Table 3) (Li et al., 2021). Meanwhile, the methylation modification of DNA on CpG sites can also inhibit CTLA-4 expression (de Vos et al., 2020). For

instance, in normal tissue, the DNA methylation of CpG sites where the CTLA-4 promoter is located was negatively connected with mRNA expression, whereas in tumor tissue, the connection was either positive or negative, depending on the specific CpG site (de Vos et al., 2020). In addition, the methylation of CpG site in the CD28 promoter region was inversely linked not only with CD28 mRNA but also with CTLA-4 mRNA expression (de Vos et al., 2020). Therefore, it has been postulated that DNA methylation could serve as a biomarker for predicting PD-1 and CTLA-4 ICB responses (Table 3) (Goltz et al., 2018).

2.2.1.2 Transcriptional regulation

Thus far, research on the transcriptional regulation of CTLA-4 has been relatively limited. The nuclear factor of activated T-cells (NFAT) binds to the CTLA-4 promoter to elevate CTLA-4 transcription, and mutations in the NFAT locus disrupt the activity of the CTLA-4 promoter; hence the treatment of inhibitors of NFAT leads to the downregulation of CTLA-4 transcription (Gibson et al., 2007). In addition, NFAT can interact with Forkhead box P3 (Foxp3) and bind to another promoter of CTLA-4 to activate its transcription (Wu et al., 2006). Meanwhile, IL-1 α , IFN- γ , IL-2, and the inhibition of CD28 have all been shown to promote CTLA-4 expression (Table 3) (Nagaraju et al., 1999). However, IL-4, IL-6, IL-7, and IL-12 showed only limited induction (Alegre et al., 1996).

Table 3 Regulators of CTLA-4

Regulatory type	Regulators	CTLA-4	References
Nucleic acid level			
Epigenetic	Methylation at CpG sites	Downregulation	de Vos et al., 2020
	HDACs	Upregulation	Li et al., 2021
Transcriptional	NFAT	Downregulation	Gibson et al., 2007
	IL-1 α	Upregulation	Nagaraju et al., 1999
	IFN- γ	Upregulation	Nagaraju et al., 1999
	IL-2	Upregulation	Alegre et al., 1996; Nagaraju et al., 1999
	CD28	Downregulation	Nagaraju et al., 1999; Oyewole-Said et al., 2020
RNA level	MiR-487a	Downregulation	Chang et al., 2017; Wang MM et al., 2020
	MiR-9	Downregulation	Jebbawi et al., 2014
Cellular localization	AP-1	Upregulation	Schneider et al., 1999
	AP-2	Upregulation	Linsley et al., 1996; Shiratori et al., 1997
	GTPases, PLD-1, PLD-2, ARF-1	Upregulation	Mead et al., 2005
	Ca ²⁺	Upregulation	Linsley et al., 1996

CTLA-4: cytotoxic T-lymphocyte-associated antigen-4; HDACs: histone deacetylases; NFAT: nuclear factor of activated T-cells; IL: interleukin; IFN- γ : interferon- γ ; CD: cluster of differentiation; AP: activator protein; GTPases: guanosine triphosphatases; PLD: phospholipase D; ARF: ADP ribosylation factor.

2.2.1.3 Regulation of RNA levels

MiRNAs are important vectors for regulating CTLA-4 expression (Table 3). To date, several different miRNAs have been shown to directly regulate the expression of CTLA-4. For example, miR-105 directly binds to the 3' UTR of the mutated allele of CTLA-4 instead of binding to the wild-type allele to regulate its expression. MiR-487a acted as a tumor suppressor in prostate cancer but an oncogenic factor in other cancer types (Chang et al., 2017; Wang MM et al., 2020), where miR-487a-3p can directly target CTLA-4 and reduce its expression. MiR-9 was also found to directly target CTLA-4, and the downregulated expression of this miRNA in Treg cells may correlate with the upregulation of CTLA-4 therein (Jebbawi et al., 2014).

2.2.2 Cellular localization of CTLA-4

The localization analysis of CTLA-4 provides important information because CTLA-4 is mainly localized in the cytoplasm rather than the cell surface. AP-1 binds to the GVVVKM motif of CTLA-4 to maintain a stable intracellular expression level of CTLA-4 (Schneider et al., 1999). Similarly, once AP-2 binds to the YVKM or FVKM motif of CTLA-4, CTLA-4 accumulates rather inside the cell than on the surface (Linsley et al., 1996; Shiratori et al., 1997). Reports have shown that CTLA-4 T-cell surface localization requires the involvement of activated guanosine triphosphatases (GTPases), phospholipase D-1 (PLD-1), PLD-2, and ADP ribosylation factor-1 (ARF-1) (Mead et al., 2005). Similarly, the rapid upregulation of calcium ions (Ca^{2+}) elevates CTLA-4 expression on the cell surface (Table 3) (Linsley et al., 1996).

2.2.3 CTLA-4-related antitumor drug development

Ipilimumab and tremelimumab were approved by the United States Food and Drug Administration (FDA) in 2011 and 2015 for the treatment of advanced melanoma and malignant mesothelioma, respectively. Ipilimumab upregulates the antitumor activity of T-cells by binding to the MYPPPY motif of CTLA-4 and blocking its interaction with CD80/CD86; meanwhile, tremelimumab binds to CTLA-4 and blocks its binding to the B7 ligand, thereby inhibiting the decrease in T-cell activity mediated by B7-CTLA-4. Currently, there are still significant limitations in the

monotherapy of ipilimumab and tremelimumab, although combination therapy regimens related to them are under investigation. Ipilimumab has been approved as a combination with nivolumab (PD-1 inhibitor) for the treatment of unresectable (advanced) melanoma, renal cell carcinoma (RCC), and MSI-h (metastatic microsatellite instability high), or mismatched (repair-deficient) CRC (Klein et al., 2021). In addition, a synthetic peptide p344 was shown to bind to the MYPPPY motif of CTLA-4 and block its interaction with the B7 ligand (Podlesnykh et al., 2021).

3 Roles of novel IC molecules in immune escape

3.1 LAG-3

Lymphocyte activation gene-3 (LAG-3), also known as CD223, is mainly expressed on activated $CD4^+$ and $CD8^+$ T-cells, Treg and NK cells, as well as B cells and plasma cell-like DCs (Table 1). LAG-3 has a similar molecular structure to CD4 and binds more strongly to major histocompatibility complex-II (MHC-II). Upon binding, it transmits negative regulatory signals through the TCR-CD3 complex, thereby inhibiting T-cell proliferation and cytokine production. It also binds other ligands including galectin-3, liver sinusoidal endothelial cell lectin (LSEctin), α -synuclein, and fibrinogen-like protein 1 (FGL1), thus inducing immune cell depletion and reducing cytokine secretion (Baixeras et al., 1992; Huard et al., 1994; Kouo et al., 2015; Anderson et al., 2016; Baumeister et al., 2016; Mao et al., 2016; Wang J et al., 2019). To date, more than 20 drug designs and clinical trials targeting LAG-3 have been established. IMP321 is the first LAG-3Ig fusion protein developed as a vaccine immune adjuvant, which binds to MHC-II molecules on naive DCs to promote their maturation and thus antigen presentation to tumor cells while upregulating co-stimulatory molecules and increasing IL-12 production to enhance antitumor immune responses. LAG525 is a human anti-LAG-3 monoclonal antibody that interferes with the binding of MHC-II molecules to LAG-3 (Nguyen and Ohashi, 2015). Other LAG-3 inhibitory antibodies are under experimental evaluation, such as AVA-017 (LAG-3 antagonist), MK-4280, REGN3767, Sym022, and relatlimab.

3.2 TIGIT

T-cell immunoglobulin and immunoreceptor tyrosine-based inhibitory motif (ITIM) domain (TIGIT), also known as Washington University Cell Adhesion Molecule (WUCAM), is mainly expressed on T-cells and NK cells, and usually has a low expression on naive cells (Table 1). However, some studies have demonstrated that TIGIT appears to be upregulated on both activated T-cells and NK cells (Harjunpää and Guillerey, 2020). The TIGIT ligands are mainly CD155, CD112, and CD133, with CD155 having a higher affinity, which is highly expressed on the tumor surface. Once TIGIT binds to CD155, the antitumor effects will be inhibited, which include the inhibition of NK cell-mediated tumor killing, the induction of immunosuppression, the inhibition of CD8 T-cell initiation and differentiation, and the blocking of CD8 T-cell-mediated killing (Buisson and Triebel, 2005; Li et al., 2014; Fuhrman et al., 2015; Kurtulus et al., 2015; Liu et al., 2015; Kourepini et al., 2016). Currently, various TIGIT monoclonal antibodies are being evaluated in clinical trials as therapeutic agents for refractory solid tumors, either as single drugs or in combination with other agents, such as BMS-986207, domvanalimab (AB-154), ASP-8374, and COM902.

3.3 B7 family (B7-H3, B7-H4, VISTA, and HHLA2)

At present, there are at least ten members of the B7 family species, of which the B7 homolog 3 protein (B7-H3, CD276), immunoglobulin V structural domain-containing T-cell activation suppressor (VISTA, B7-H5), and human endogenous retroviral H long terminal repeat-binding protein 2 (HHLA2, B7-H7) are the highest mRNA-expressing checkpoint molecules in CRC (Wang CG et al., 2020). Meanwhile, the B7-H4 is also abnormally expressed in tumors, inflammation and autoimmune diseases (Greenwald et al., 2005; Ceeraz et al., 2013).

In most normal tissues, B7-H3 commonly exhibits relatively low protein expression (Sun et al., 2002; Flem-Karlsen et al., 2020). B7-H3 is overexpressed in most human cancers (Table 1), which correlates with poor patient prognosis (Castellanos et al., 2017). In T-cell regulation, B7-H3 is considered to be a conflicting co-repressor and co-stimulatory molecule, selectively enhancing IFN- γ production and promoting cellular immunity in the presence of TCR signaling (Chapoval et al., 2001; Zhang et al., 2004);

however, a growing body of evidence suggests that B7-H3 plays a negative regulatory role in antitumor immunity (Chapoval et al., 2001; Suh et al., 2003; Zhang et al., 2004; Mahnke et al., 2007; Leitner et al., 2009; Lee et al., 2017).

B7-H4 mRNA can be detected in most non-hematopoietic tissues, while protein expression is more limited and confined to the induced expression on APCs as well as cancer cells. It has been associated with poor clinical and pathological features (Emaldi and Nunes-Xavier, 2022) and identified as a novel marker or therapeutic target for the treatment of tumors (Wang and Wang, 2020) by studies assessing the level of soluble B7-H4 in the serum (Shi et al., 2014; Radichev et al., 2016). Mounting evidence suggests that B7-H4 negatively regulates T-cell immune response by inhibiting T-cell proliferation, cytokine secretion, and the cell cycle, thereby promoting immune escape (Sica et al., 2003; Ou et al., 2006; Luan et al., 2009; Xu et al., 2014; Paiva et al., 2016).

VISTA is a negative immunomodulatory factor identified in recent years and expressed mainly on hematopoietic stem cells, with its highest expression level on myeloid cells, lymphoid and myeloid DCs, and lower levels on CD4⁺ and CD8⁺ T-cells and Treg cells (Table 1) (Liu et al., 2015). VISTA is also expressed on TILs (Wang JH et al., 2019), acting as a suppressor of CD4⁺ and CD8⁺ T-cells and directly inhibiting T-cell activation both in vitro and in vivo (Ni and Dong, 2017). VISTA has also been discovered to reduce Toll-like receptor (TLR)-mediated activation of MAPK/AP-1 and inhibitor of NF- κ B kinase (IKK)/NF- κ B signaling cascades, which controls myeloid cell-mediated inflammation and immunosuppression.

HHLA2 is a newly discovered member of the B7 family, and its mRNA is widely expressed in human tissues (Wang B et al., 2019); however, it has very limited protein levels except in epithelial cells of the intestine, kidney, gallbladder, breast, and trophoblast of the placenta (Table 1) (Janakiram et al., 2015). HHLA2 may control intestinal inflammation, and this phenomenon is usually considered to occur through the expression of HHLA2 in the intestine (Janakiram et al., 2015). Moreover, HHLA2 has been reported to bind to CD28H on T-cells and promote T-cell proliferation and cytokine production through an AKT-dependent signaling cascade (Zhu et al., 2013).

3.4 Co-immunotherapy against novel ICs

It was found that the blockade of LAG-3 alone did not restore T-cell depletion, but the combination of LAG-3 with PD-L1 was able to achieve a significant reduction in tumor size (Woo et al., 2012). For example, efitilagimod α (LAG-3-Fc fusion protein) and pembrolizumab (anti-PD-1 monoclonal antibody) could be combined for NSCLC and HNSCC (Peguero et al., 2019). To this end, BI754111 (anti-LAG-3 monoclonal antibody) and BI754091 (anti-PD-1 monoclonal antibody) were combined for the treatment of refractory solid tumors.

Several studies have shown that TIGIT and PD-1 are co-expressed and interrelated (Johnston et al., 2014; Chauvin et al., 2015), suggesting the presence of potential mechanisms to amplify the immune response to enhance antitumor activity, which provides the theoretical foundation for the combination of TIGIT and PD-1 as blockade therapy. In January 2021, tiragolumab, a novel cancer immunotherapy agent targeting the combination of TIGIT, was designated by FDA as breakthrough therapy for the proposed use as a combination with atezolizumab (a PD-L1 antibody) for the treatment of patients with metastatic NSCLC with high PD-L1 expression and no EGFR or ALK genomic tumor aberrations. In addition, various other anti-TIGIT antibodies are in the process of development and clinical trials, such as vibostolimab (MK-7684) in combination with pembrolizumab (PD-L1 antibody) for melanoma, and ociperlimab (BGB-A1217) in combination with an anti-PD-1 antibody.

B7-H3 is a potential target molecule for targeted therapeutic agents because of its wide overexpression on cancer cells and tumor-infiltrating vessels in many tumor types, while it is undetectable in normal tissues. For example, enoblituzumab (MGA271), an anti-B7-H3 monoclonal antibody with antibody-dependent cytotoxicity (ADCC), has been investigated in a variety of solid tumors, including pediatric tumors. It is currently used as a monotherapy agent, or in combination with anti-PD-1 antibodies (revansumab or pembrolizumab) or anti-CTLA-4 antibodies (ipilimumab).

It has been reported that B7-H4, an actionable IC protein, plays a role in current treatment-resistant cases of advanced kidney cancer in combination with targeted therapy (Emaldi and Nunes-Xavier, 2022). However, most of the antibodies used to identify B7-H4 protein expression are not commercially available

(Podojil and Miller, 2017). With the exception of classical monoclonal antibodies such as 1D11 (Leong et al., 2015), recombinant single-chain variable fragments (scFvs) against B7-H4 have been reported, which completely reverse the B7-H4-induced inhibition of T-cell function (Dangaj et al., 2013).

Notably, VISTA (PD-1H), a homolog of PD-1, has a similar structural domain to PD-1, except that it lacks the classical ITIM or the immunoreceptor tyrosine transition motif (ITSM) in the cytoplasmic structural domain (Flies et al., 2011). Currently, there are few anti-VISTA antibodies in clinical trials, even though their similar but non-overlapping properties make them ideal therapeutic agents to overcome immunosuppression.

HHLA2 is widely expressed in PD-1-negative NSCLC patients, suggesting that it may be a promising therapeutic target when PD-1 pathway blockade is ineffective in some patients (Cheng et al., 2018). To date, there have been few studies on HHLA2, which may be related to its underexpression in experimental mice. HHLA2 is highly expressed at the mRNA and protein levels in certain cells, making it a potential immunotherapeutic target for CRC patients.

4 Perspectives

Thus far, the clinical values of drugs such as inhibitors and antibodies to PD-1/PD-L1 and CTLA-4 have been demonstrated in many cancer patients, and novel ICs such as LAG-3, TIGIT, B7-H3, and their combination therapies have greatly enriched the options of cancer immunotherapy. Meanwhile, for a large proportion of patients, the currently known ICIs do not seem to work. Thus, more details of the mechanisms and strategies of immunomodulation, cancer, and cancer patients need to be understood. In addition, ICIs face numerous problems and challenges, including immune-related side effects, the development of ICI resistance, and the lack of effective biomarkers.

In response, many studies have been published on the expression of IC molecules in TME, and accumulating evidence demonstrates that different oncogenic signaling pathways are involved at the transcriptional, post-transcriptional, and post-translational levels, that is, multiple potential mechanisms lead to the abnormal expression of IC molecules, such as PD-L1

and CTLA-4, in various malignancies. These expression abnormalities are often associated with the immune escape of cancer cells. Therefore, it is important to study the regulation of IC molecule expression during the development of immunotherapies for cancer. In the immune evasion of tumor cells, these regulatory mechanisms and molecules form a complex network, controlling immunological checkpoint molecules at multiple levels. Nonetheless, a number of questions remain unanswered. Firstly, although the tasks performed by these regulatory molecules and processes at their respective nodes have been clarified, the correlations among them, such as the presence of compensatory or synergistic mechanisms between distinct pathways, have not yet been clarified. Clarifying the relationships between these regulatory elements will have significant theoretical implications for the development of combination immunotherapy targets and medicines. Secondly, as a continuation of the preceding topic, the composition of the TME differs significantly between cancer types and even between patients, which in part influences the heterogeneity of tumor immune escape regulatory mechanisms and IC regulation mechanisms. With the development of cutting-edge technologies such as single-cell sequencing, the identification of major IC molecules that mediate immune evasion in various cancer species, as well as the identification of new IC molecules, is expected to emerge as a vital area of immunotherapy research. In the meantime, the pursuit to identify the primary regulators of IC regulation under varying conditions has major clinical implications and may yield novel ideas for combating immunotherapy resistance. Finally, research on the regulation mechanisms of opposing immunological checkpoints has led to the development of a number of small-molecule and antibody-based therapies. The majority of them have demonstrated promising outcomes in animal research; nevertheless, their performance in clinical therapies, particularly their potential toxicity, remains to be evaluated (Huang et al., 2021). Due to the complexity and interconnectedness of the human immune system, even a minor effect might have undesired effects.

Despite the current challenges, we anticipate that as research on ICs continues, we will eventually obtain a deeper and more systematic understanding of tumor immune escape and immunological checkpoints. More specific and improved regulatory systems will be

elucidated, and the continued development of new medications and cures will take place. From the past to the future, all discoveries of spectacular regulating mechanisms of immunological checkpoints will be of considerable importance.

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Author contributions

Aifu LIN determined the topic of the article and proposed this program. Zerui GAO, Xingyi LING, Chengyu SHI, and Ying WANG collected the literature. Zerui GAO and Xingyi LING summarized and drew a diagram of the mechanism. Zerui GAO, Xingyi LING, Chengyu SHI, and Aifu LIN wrote the manuscript. All authors have read and approved the final manuscript.

Compliance with ethics guidelines

Zerui GAO, Xingyi LING, Chengyu SHI, Ying WANG, and Aifu LIN declare that they have no conflict of interest.

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