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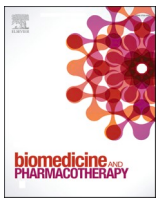

Review

Cancer cell-intrinsic PD-1: Its role in malignant progression and immunotherapy

Muhua Chen [a,*,1], Lei Bie [b,1], Jieer Ying [a,*]

[a] Department of Hepato-Pancreato-Biliary & Gastric Medical Oncology, Zhejiang Cancer Hospital, Hangzhou Institute of Medicine (HIM), Chinese Academy of Sciences, Hangzhou, Zhejiang 310022, China
[b] Department of Thoracic Surgery, Wuhan No.1 Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei 430030, China

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ABSTRACT

Programmed cell death protein-1 (PD-1), also called CD279, is coded by the *PDCD1* gene and is constitutively expressed on the surface of immune cells. As a receptor and immune checkpoint, PD-1 can bind to programmed death ligand-1/programmed death ligand-2 (PD-L1/PD-L2) in tumor cells, leading to tumor immune evasion. Anti-PD-1 and anti-PD-L1 are important components in tumor immune therapy. PD-1 is also expressed as an intrinsic variant (iPD-1) in cancer cells where it plays important roles in malignant progression as proposed by recent studies. However, iPD-1 has received much less attention compared to PD-1 expressed on immune cells although there is an unmet medical need for fully elucidating the mechanisms of actions to achieve the best response in tumor immunotherapy. iPD-1 suppresses tumorigenesis in non-small cell lung cancer (NSCLC) and colon cancer, whereas it promotes tumorigenesis in melanoma, hepatocellular carcinoma (HCC), pancreatic ductal adenocarcinoma (PDAC), thyroid cancer (TC), glioblastoma (GBM), and triple-negative breast cancer (TNBC). In this review, we focus on the role of iPD-1 in tumorigenesis and development and its molecular mechanisms. We also deeply discuss nivolumab-based combined therapy in common tumor therapy. iPD-1 may explain the different therapeutic effects of anti-PD-1 treatment and provide critical information for use in combined anti-tumor approaches.

1. Introduction

The number of cancer cases as well as that of cancer deaths is rapidly increasing worldwide. An estimated number of 19.3 million new cancer cases and almost 10.0 million cancer deaths have been reported for 2020, which exceeds that reported for 2018 [1,2]. Unfortunately, it is predicted that the global cancer burden will increase by 47 %, which translates into 28.4 million cases by 2040 [2]. Cancer is developing into a leading cause of death and reduces life expectancy [3]. Therefore, studies on the mechanism of malignant cancer progression and improvement of current therapeutic drug efficacy are critical with regard to global cancer control.

The discovery of immune checkpoints is considered a great breakthrough [4,5]. PD-1/PD-L1 and cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) are well known representatives of such molecules [4,6]. Furthermore, other immune checkpoints, such as Lymphocyte-activation gene-3 (LAG-3) [7,8], Mucin-domain containing-3 (TIM-3) [9,10], T cell immunoglobulin and ITIM domain (TIGIT)

Abbreviations: PD-1, Programmed cell death protein-1; PD-L1/PD-L2, Programmed death ligand-1/Programmed death ligand-2; NSCLC, Non-small cell lung cancer; HCC, Hepatocellular carcinoma; PDAC, Pancreatic ductal adenocarcinoma; TC, Thyroid cancer; GBM, Glioblastoma; TNBC, Triple-negative breast cancer; CTLA-4, Cytotoxic T lymphocyte-associated antigen-4; LAG-3, Lymphocyte-activation gene-3; TIM-3, Mucin-domain containing-3; TIGIT, T cell immunoglobulin and ITIM domain; VISTA, V-domain Ig-containing suppressor of T-cell activation; Siglec-15/7/9/10, short for sialic acid-binding immunoglobulin-like lectin 15/7/9/10; KIR, Killer-cell immunoglobulin-like receptors; HLA-G, Human leukocyte antigen-G; SIRPα, Signal regulatory protein alpha; SFRs, SLAM (signaling lymphocytic activation molecule) family receptors; HPA, Human Protein Altas; IHC, Immunohistochemistry; CCLE, Cancer Cell Line Encyclopedia; MMR, Mismatch repair; OS, Overall survival; ORR, Objective response rate; DCR, Disease control rate; HPD, Hyperprogressive disease; mTOR, Mammalian target of rapamycin; eIF4E, Eukaryotic initiation factor 4E; RPS6, Ribosomal protein S6; ICI, Immune checkpoint inhibitor; TKI, Tyrosine-kinase inhibitor; BTIC, Brain tumor–initiating cell; YB-1, Y-box binding protein 1; TME, Tumor microenvironment; APC, Adenomatous polyposis coli; PFS, Progression free survival.

* Corresponding authors.
E-mail addresses: chenmuhua2019@bjmu.edu.cn (M. Chen), jieerying@aliyun.com (J. Ying).
[1] These authors contributed equally.

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[11–13], V-domain Ig-containing suppressor of T-cell activation (VISTA) [14,15], short for sialic acid-binding immunoglobulin-like lectin 15/7/9/10 (Siglec-15/7/9/10) [16–20], a poliovirus receptor-like protein (CD112R) [21], Killer-cell immunoglobulin-like receptors (KIR) [22,23], C-type lectin-like receptor superfamily (NKG2A) [24,25], Human leukocyte antigen-G (HLA-G) [26,27], Immunoglobulin-like transcript 2/4 (ILT2/4) [28,29], Killer cell immunoglobulin-like receptor 2DL4 (KIR2DL4) [30,31], Signal regulatory protein alpha (SIRPα) [32], SLAM (signaling lymphocytic activation molecule) family receptors (SFRs) [33], CD47 [34,35], and Clever-1 [36,37] were discovered one after another. Targeted immune checkpoints monoclonal antibody drugs are being used like mushrooms after rain in pre-clinical, clinical trials and in clinical practice [38]. PD-1/PD-L1 inhibitors are still the most widely ones applicated so far [39]. As shown in Fig. 1, PD-1 expressed on the surface of immune cells and PD-L1 expressed on the surface of cancer cells, mediate the immune escape of cancer cells [40]. Thus, the blockade of PD-1/PD-L1 unleashes antitumor T cell responses [4]. T cell exclusion, immune privilege, and the tumor microenvironment are still severe obstacles for ICI therapy [41]. Recently, targeting PD-1/PD-L1 has achieved satisfactory results, especially in melanoma

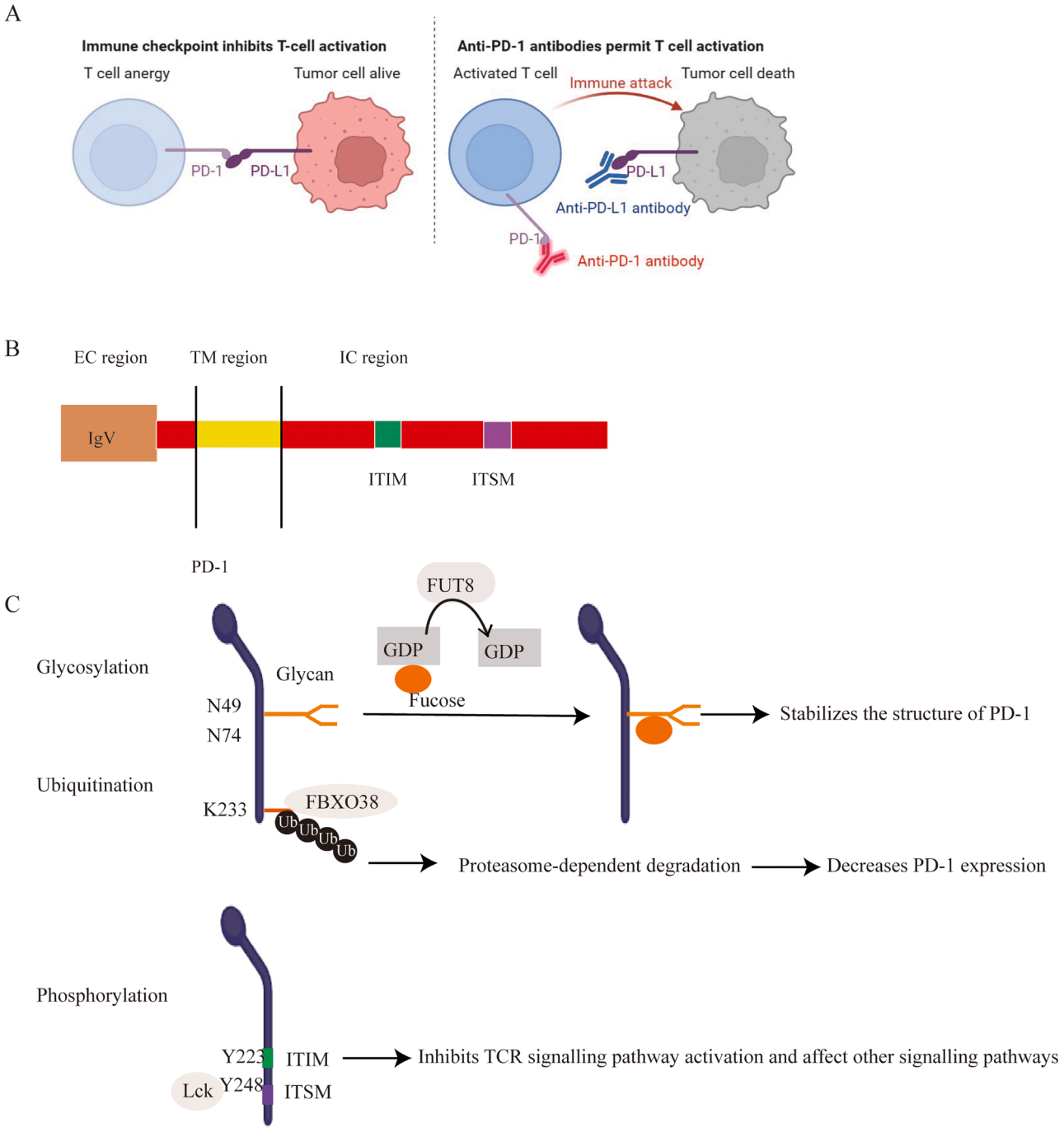

Fig. 1. Mechanism diagram of anti-PD-1 immunotherapy. (A) PD-1 receptor expressed on the surface of T cells and PD-L1 expressed on the surface of tumor cell mediate the immune escape of cancer cells in the tumor microenvironment. When anti-PD-1 antibody blocks the PD-1 of the T cell, activated T cells kill the tumor cell. (B) PD-1 functional domains: IgV, variable region of immunoglobulin; ITIM, immunoreceptor tyrosine-based inhibitory motif; ITSM, immunoreceptor tyrosine-based switch motif; EC region, extracellular region; TM region, transmembrane region; IC region, intracellular region. (C) PD-1 post-translational modifications and their biological effects.

[42], hepatocellular carcinoma (HCC) [43], and non-small cell lung cancer (NSCLC) [44]. However, there are still patients suffering from ineffective treatment outcomes, even from hyperprogression after immune therapy [45–48].

PD-1 comprises three functional domains: an extracellular region (EC), a transmembrane region (TM), and an intracellular region (IC). The variable region of the immunoglobulin domain (IgV) is the main functional domain of the EC. Immunoreceptor tyrosine-based inhibitory motif (ITIM) and immunoreceptor tyrosine-based switch motif (ITSM) are important domains of the IC (Fig. 1B). The extracellular IgV-like structure of PD-1 binds to its ligand, changes ITSM, recruits Src homology containing protein tyrosine phosphatase 2 (SHP2) signal and activates a downstream pathway [49].

Several known PD-1 post-translational modifications (PTMs) can affect its biological functions of which glycosylation, ubiquitination, and phosphorylation are common ones [50]. As a glycosyltransferase, α-1, 6-fucosyltransferase (FUT8) is responsible for the synthesis of core fucose. Glycosylation is crucial for PD-1 stability and membrane localization [51]. Ubiquitination is mediated by F-box-containing protein 38 (FBXO38) for proteasome-dependent degradation and decreases PD-1 expression [52,53]. When binding to PD-L1, ITSM and ITIM of PD-1 are induced to phosphorylation by the Src family kinases (SFKs), finally leading to T cell receptor (TCR) signaling pathway inhibition and affecting other signaling pathways.

Recent studies have shown that PD-1 can also be expressed in cancer cells, except for immune cells, however, its function independent of adaptive immune regulation remains to be further studied [54]. Cancer cell-intrinsic PD-1 receptor is definited as iPD-1 in this review. Hence, elucidating the potential mechanisms by which iPD-1 may regulate cancer growth will partly explain the unsatisfactory treatment outcomes. Therefore, we focus on elaborating the effect of iPD-1 in carcinogenesis and its associated clinical significance. This will be done from a new perspective with regard to the mechanisms of the PD-1/PD-L1 axis. In conclusion, the article elaborates widely-expressed PD-1 in tumor tissues and cancer cell lines, reviews the role of iPD-1 in tumor malignant progression and its mechanisms, and summarizes the recent research progress of nivolumab-based clinical trials.

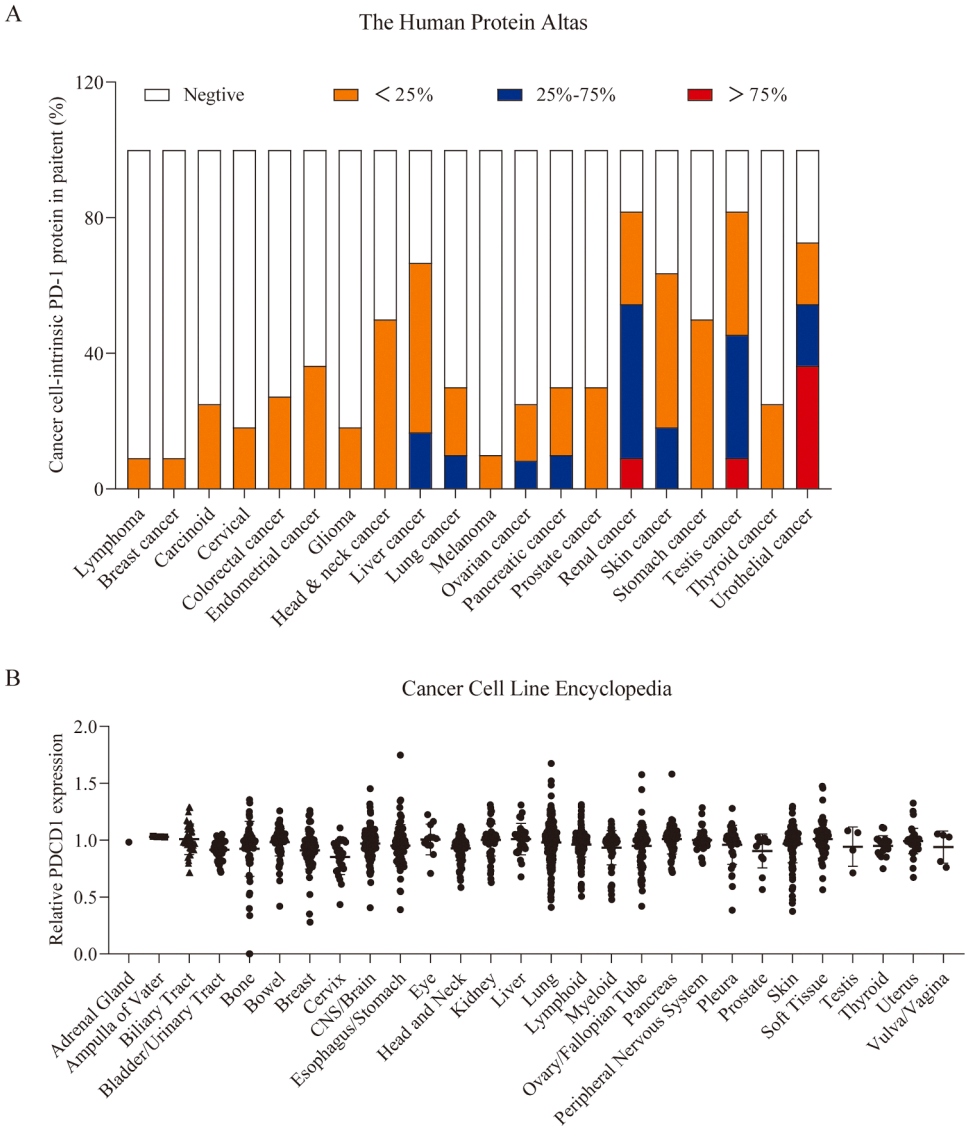

Fig. 2. iPD-1 is widely expressed in cancer tissues and cancer cell lines. (A) PD-1 protein expression analysis in different tumor tissues using immunohistochemistry from the human protein atlas database (www.proteinatlas.org). The quantity of PD-1 protein was divided into negative, < 25 %, 25–75 %, > 75 % groups. (B) PD-1 mRNA expression in cancer cells based on data from the Cancer Cell Line Encyclopedia (CCLE).

2. PD-1 is widely expressed in tumor tissues and cancer cell lines

Advances in sequencing technologies and genomics have facilitated the analysis of PD-1 expression in tumors [55–57]. We analyzed the expression of cancer cell-intrinsic PD-1 protein in the Human Protein Altas (HPA) database (www.proteinatlas.org) [58]. PD-1 protein is widely expressed in tumors, except immune cells in the tumor microenvironment, and can be detected by immunohistochemistry (IHC). Especially, the quantity of PD-1 protein is greater than 25 % in a part of the patients suffering from liver, lung, urothelial, ovarian, skin, pancreatic, renal, and testis cancer (Fig. 2**A**). Moreover, we analyzed the expression of PD-1 mRNA with the help of the Cancer Cell Line Encyclopedia (CCLE) dataset based on cancer cell lines and thus without the influence of a complex tumor microenvironment, especially immune cells [59]. 28 tumor types and 1671 cancer cell lines were included in our research. The vast majority of tumors exhibit a high expression of PD-1 mRNA (Fig. 2**B**). Undeniably, PD-1 is widely expressed in tumor tissues and cancer cell lines. Cancer cell-intrinsic PD-1 affected the therapeutic effect of immune checkpoint inhibitors (ICIs) [60,61], thus the functions of iPD-1 need to be explored in depth.

3. iPD-1 suppresses tumorigenesis

3.1. Non-small cell lung cancer (NSCLC)

A PD-1/PD-L1 inhibitor monotherapy or a combination with chemotherapy has become the first-line treatment of advanced NSCLC [62] (Fig. 3). Nivolumab vs. docetaxel demonstrated a survival benefit of NSCLC patients and a proportion of the patients had a long-term overall survival (OS) and durable responses (CheckMate 017/057, CA209-003 Study) [63,64]. However, quite a few patients develop disease progression after a standard-of-care treatment. In 2017, Du et al. presented a first-time report of iPD-1 expression in a NSCLC patient whose cancer rapidly progressed upon initiation of anti-PD-1 therapy (NCT02318771) [45]. Due to this result, they further investigated the effect of a PD-1 knockout or antibody blockade of PD-1 resulting in an enhanced viability of M109 cells, a mouse lung cancer cell line. PD-1 blockade accelerated the growth of M109-xenograft tumors in immune-deficient mice [45]. Knockdown of PD-1 or PD-L1 promoted NSCLC cell proliferation and colony formation in vitro and tumor growth in vivo mainly through activating downstream pathways of PD-1/PD-L1 including the protein kinase B (PKB) and extracellular signal-regulated kinase 1/2 (ERK1/2) pathways [60]. Later, Cao et al. could show that iPD-1 is a direct target of p53 and that p53-mediated PD-1 transcription was regulated by p53 acetylation at K120/164. Acetylated p53 selectively facilitated PD-1 transcription by enhancing local chromatin acetylation [65].

However, the role of iPD-1 in NSCLC is complex and potentially heterogeneous. New studies have shown that PD-1 expression was enhanced in NSCLC stem-like pneumospheres, capable of inhibiting chemo-surviving NSCLC cells which is therefore exploitable to prevent disease relapses following chemotherapy [66]. These results suggest that iPD-1 plays an important role in NSCLC and that it is necessary to elucidate the mechanism of how iPD-1 regulates tumor development in NSCLC.

3.2. Colon cancer

In mismatch repair-deficient (dMMR) and MMR-proficient (pMMR) early stage colon cancer patients, nivolumab plus ipilimumab led to

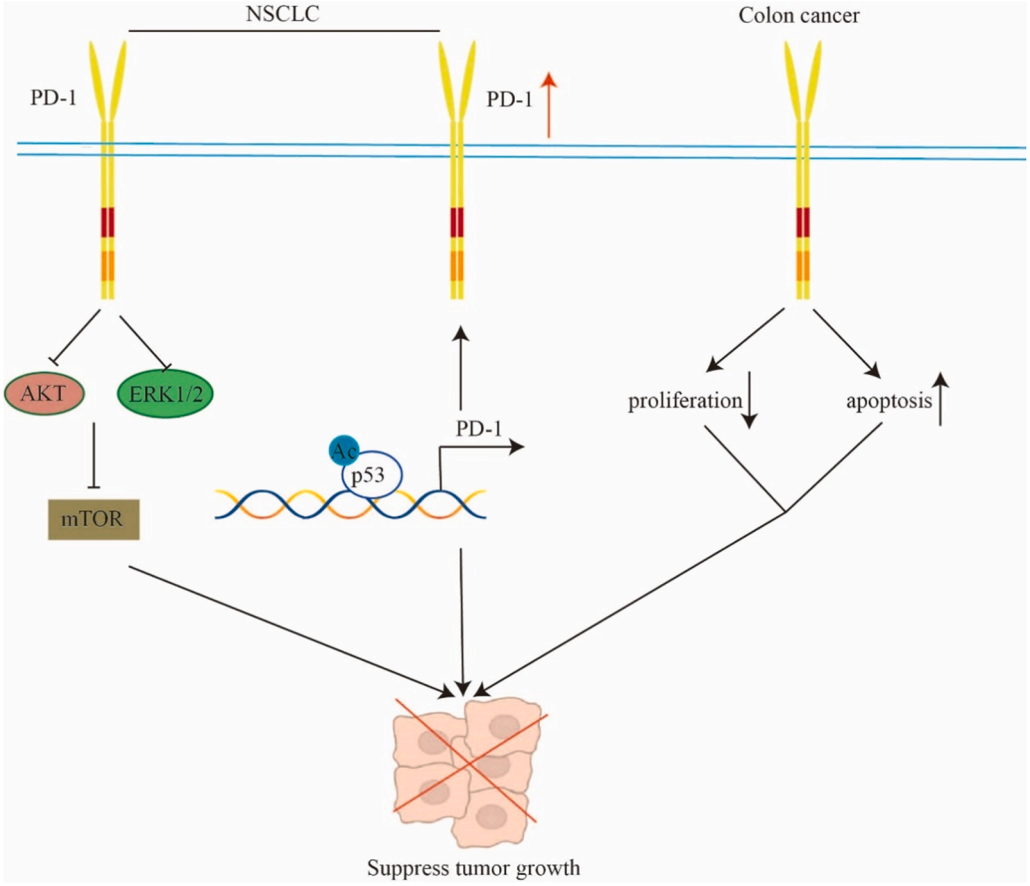

Fig. 3. iPD-1 suppresses tumorigenesis. NSCLC-intrinsic PD-1 inhibits the mTOR pathway, whereas colon cancer cell-intrinsic PD-1 inhibits proliferation and promotes apoptosis. NSCLC, non-small cell lung cancer.

pathological responses (NCT03026140) [67]. In one reported case a microsatellite-unstable/instability (MSI)-high colon cancer patient with anticancer drug-resistance received a postoperative ICI treatment and displayed a pathologically complete response (pCR) [68]. Moreover, in human colon cancer cells (HT29, HCT116 and LoVo), iPD-1, which is not regulated by IFN-α/γ and PD-1 signaling, significantly decreased proliferation and promoted apoptosis [69]. However, nivolumab promotes survival and was able to protect tumor cells from chemotherapy and radiotherapy [69]. In addition, 22.9 % of human colon cancer biopsies expressed PD-1 which is significantly associated with lower pathologic T (pT) stage [69]. Although larger cohort studies are needed, the iPD-1/total PD-1 expression ratio may represent a potential biomarker for anti-PD-1 therapy in colon cancer patients. Therefore, it may be promising to analyze the iPD-1 levels of those patients who do not respond to conventional therapies.

4. iPD-1 promotes tumorigenesis

4.1. Melanoma

Some melanoma cells have been shown to express PD-1 and this expression was able to promote tumor growth (Fig. 4). In established melanoma xenografts and clinical tumor specimens, preferentially, tumorigenic ATP-binding cassette sub-family B member 5^{+} ($ABCB5^{+}$) malignant melanoma initiating cell subpopulations expressed PD-1 and B7.2 [70]. The co-expression of PD-1 and B7.2 might confer additional immunoevasive and protumorigenic properties on $ABCB5^{+}$ subpopulations for T-cell anergy [70]. Therefore, anti–PD-1 antibodies, such as nivolumab, could have a direct antitumor effect, even in immunodeficient patients. Recently, a study reported that inhibition of melanoma-PD-1 reduces tumor growth by modulating downstream mammalian target of rapamycin (mTOR) signaling, independently of adaptive immunity [71]. BRAF and MEK inhibitors (BRAF/MEKi) increase the ratio of $PD\text{-}1^{+}$ melanoma cells that may sustain tumor relapse, thus BRAF/MEKi and anti–PD-1 antibody combination strategies may have a synergistic effect in anti-melanoma therapy [72]. In addition, in human melanoma xenograft, the C-X-C receptor 4 (CXCR4) antagonist Peptide R54 potentiates the inhibition of cell-intrinsic PD-1 [73]. Combining anti-PD-1 and CXCR4 antagonist Peptide R54 may enhance the anti-tumor efficacy (Table 1). In conclusion, anti–PD-1 antibody-based combination therapy may be a new approach for melanoma treatment.

4.2. Hepatocellular carcinoma (HCC)

Immunotherapy and targeted therapy are the main systematic

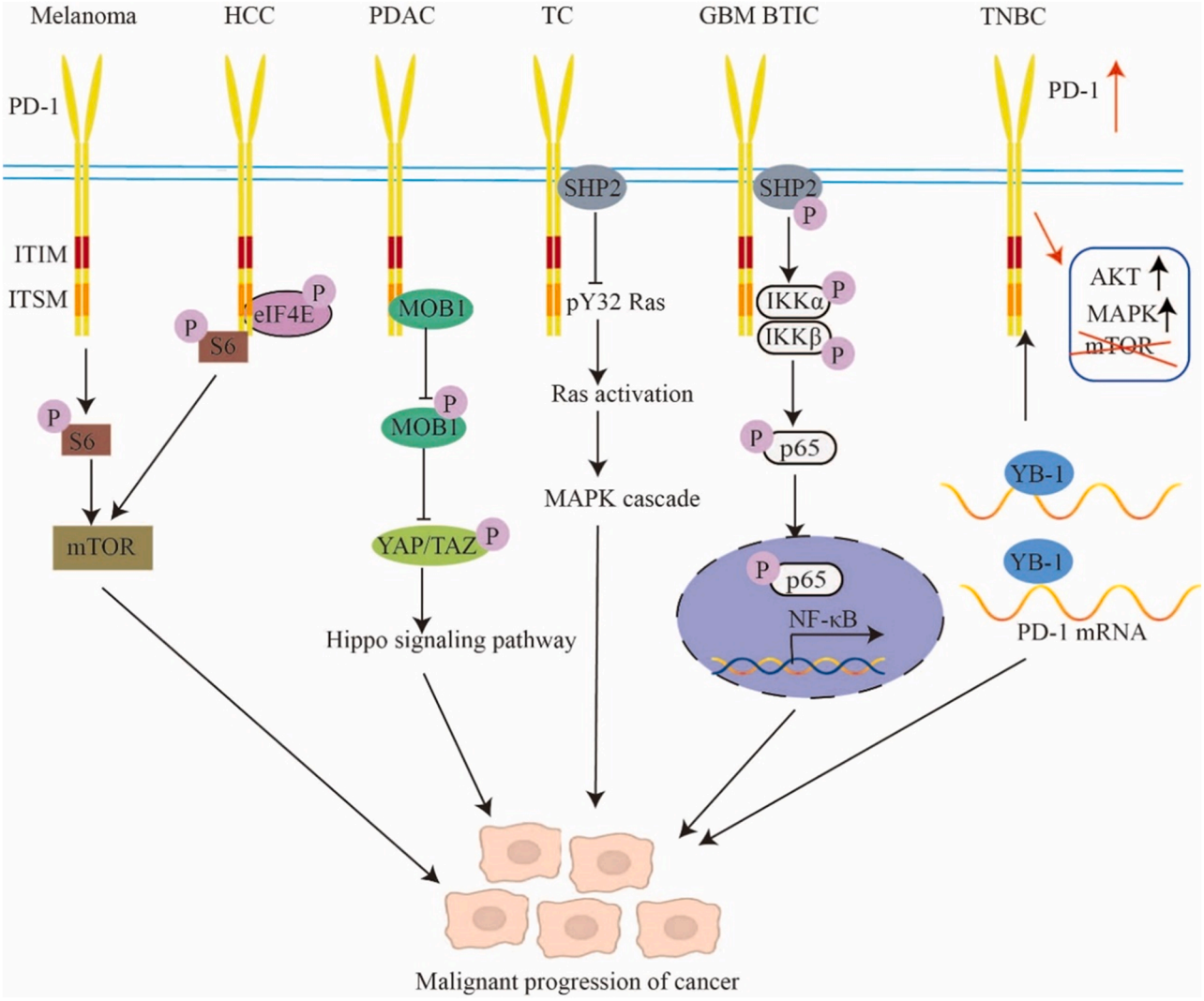

Fig. 4. iPD-1 promotes tumorigenesis. HCC, hepatocellular carcinoma; PDAC, pancreatic ductal adenocarcinoma, TC, thyroid cancer, GBM BITC, glioblastoma brain tumor–initiating cell; TNBC, triple-negative breast cancer.

Table 1
Preclinical studies of PD-1 antibodies-based combination therapy for tumors.

Tumor types	Combined therapy	Effect	Ref.
Melanoma	BRAF and MEK inhibitors	Synergistic effect	[1]
	CXCR4 antagonist Peptide R54	Synergistic effect	[2]
HCC	mTOR inhibitors	Synergistic effect	[3]
PDAC	Hippo pathway inhibitors	Synergistic effect	[4]

therapies against innate HCC resistance to chemotherapy and radiotherapy [74]. In the CheckMate 040 randomized clinical trial, nivolumab plus ipilimumab had a manageable safety profile, a promising objective response rate, and durable responses [75]. The FDA has approved atezolizumab plus bevacizumab in HCC first-line treatment to improve overall survival (OS) relative to sorafenib (IMbrave150, NCT03434379) [76]. In the phase III HIMALAYA study (NCT03298451), durvalumab plus tremelimumab was associated with a better overall survival compared to sorafenib [77,78]. In unresectable HCC patients in China those patients treated with PD-1 inhibitors plus lenvatinib, had a longer survival time and a considerably better objective response rate (ORR) as well as a disease control rate (DCR) [79]. However, only a portion of HCC patients benefit from anti-PD-1 therapy [80]. In a fraction of advanced HCC patients, even hyperprogressive disease (HPD) occurs during PD-1 blockade [81]. The mechanisms and biomarkers causing HPD are yet unknown. It was reported that some HCC cell lines and clinical HCC tissues frequently overexpressed PD-1 and that PD-1 overexpression in HCC enhances HCC growth independently of adaptive immunity, mainly through binding to and phosphorylating the downstream mammalian target of rapamycin (mTOR) effectors eukaryotic initiation factor 4E (eIF4E) and ribosomal protein S6 (RPS6) [61]. Hence, anti-PD-1 therapy combined with mTOR inhibitors provides a significantly better anti-tumor efficacy (Table 1).

4.3. Pancreatic ductal adenocarcinoma (PDAC)

PDAC is known as one of the most common malignancies with high incidence and mortality. 90 % of PDAC are diagnosed at a late stage after they have spread beyond the pancreas, with systemic metastases in more than 50 % [82]. No matter how strong a treatment regimen, PDAC inevitably progresses rapidly. Thus, exploring the mechanisms of PDAC malignant progression is extremely urgent. Although PD-1 monotherapy showed amazing effects in some cancers, less than 20 % of all cancer patients respond to immune checkpoint inhibitors (ICIs) as single agents [83]. Moreover, PDAC is an immunogenically "cold" tumor because they lack natural infiltration of effector T cells [84]. Even so, anti-PD-1 therapy is one of the main treatments of PDAC. It has recently been discovered that PDAC iPD-1 promotes proliferation by targeting the cysteine-rich angiogenic inducer 61 (CYR61)/connective tissue growth factor (CTGF) via the hippo pathway [85]. Therefore, anti PD-1 therapy plus hippo pathway inhibitors may improve the anti-tumor efficacy in PDAC patients (Table 1).

4.4. Thyroid cancer (TC)

TC is the most common endocrine malignancy [86]. The genomic landscape of TC shows that the most frequent mutations and chromosomal rearrangements occur in tyrosine kinase receptors, including the mitogen-activated protein kinase (MAPK)/phosphatidylinositol-4, 5-bisphosphate 3-kinase (PI3K) signaling pathway [86–88]. Therefore, tyrosine-kinase inhibitor (TKI) treatments become the most effective therapeutic choice for TC to weaken the activation of MAPK/PI3K. Moreover, it has been shown recently that TC cell lines and 47 % of human TC specimens displayed a PD-1 expression [89] and that this was significantly correlated with the tumor stage and lymph node metastasis. PD-1 overexpression promoted TC cell proliferation and migration and triggered the MAPK cascade mainly through enhancing Ras activation by dephosphorylating SHP2's inhibitory tyrosine 32 [89]. Thus, blocking PD-1 may have the functions of both immune response reconstitution and direct anti-tumor effects.

4.5. Glioblastoma (GBM)

GBM is the most frequent and fatal primary brain malignancy in adults [90]. Clinical trial results of PD-1 blockade therapies have not shown survival benefits (CheckMate 143, NCT02017717). However, 7.8 % of the patients responded to nivolumab and patient response proved more durable for nivolumab (11.1 months) vs. bevacizumab (5.3 months) [91]. To shed some light on these findings, Yong and his colleagues examined human GBM specimens with regard to the immune checkpoint axis and observed that about 8 % of the cells across samples coexpressed PD-1 in addition to one of the brain tumor–initiating cell (BTIC) markers [92]. Tumor-intrinsic PD-1 promoted proliferation and self-renewal of BTICs by recruiting Src homology 2–containing phosphatase 2 and activating the nuclear factor kB in BTICs through phosphorylation of tyrosines within the cytoplasmic tail of PD-1 [92]. Thus, intrinsic PD-1 plays a critical role in BTIC.

4.6. Triple-negative breast cancer (TNBC)

TNBC is the most aggressive breast cancer subtype and has only limited treatment options [93]. Compared with other breast cancer subtypes, chemotherapy has a lower efficacy in TNBC due to chemoresistance [94]. Immunotherapy is playing an increasingly important role in TNBC [95]. Although most studies on PD-1 expression have focused on immune cells, Yang et al. revealed that intrinsic PD-1 in TNBC cells significantly facilitated tumor growth and metastasis in vitro and in vivo [96]. Moreover, PD-1 is a critical effector of Y-box binding protein 1 (YB-1) in TNBC [96].

4.6.1. The advantage of tumor cells overexpressing PD-1

With more and more in-depth studies, iPD-1 has been revealed. Recent studies indicate that PD-1 is expressed in NSCLC, colon cancer, melanoma, HCC, PDAC, TC, GBM, and TNBC cells. PD-1 on cancer cells is constitutively expressed, however, further studies are needed to elucidate the role of iPD-1, which is different from the one of inducible PD-L1 expression [97–100]. PD-1 is an important protein that regulates biological functions of tumor cells. However, the potential functions are largely unclear so that future in-depth investigations on iPD-1 may provide additional insights into the unexpected effects.

5. The key factors that may influence the role of iPD-1 in tumor progression

Previous studies have revealed that iPD-1 plays an important role in tumor progression, independent of adaptive immunity. As discussed earlier, iPD-1 suppresses tumorigenesis in NSCLC and colon cancer cells, whereas it promotes tumor progression in melanoma, HCC, PDAC, TC, GBM, TNBC. Understanding the recent findings associated with the converse effects of iPD-1 is therefore of major concern. The tumor microenvironment, tumor heterogeneity, and signaling pathways may be involved in this interplay.

The tumor microenvironment (TME) is a significant factor in some tissue settings since lung and colon communicate with the external environment, while liver, brain, thyroid, and pancreas are not. Tumor microenvironment may influence the function of iPD-1. For example, historical findings linked cancer and microbes already as early as four millennia ago. Utilizing spatial multi-omic tools for in-depth functional analyses, microbial-immune-cancer cell mechanistic interactions may be elucidated [101]. Moreover, the tumor microenvironment could be simply classified into cold or hot on the basis of T cell infiltration [102]. The balance between T cell activation and tumor cell growth upon PD-1/PD-L1 blockade is critical in the clinical outcome of

immunotherapy [60].

Second, the internal drive factors vary widely among tumors of different origin. For example, Adenomatous polyposis coli (APC) is mutated in most of the colorectal cancers [103], whereas the p53-R249S mutation is a common phenomenon in hepatocellular carcinoma [104]. Cao et al. identified iPD-1 as a direct target of the tumor suppressor p53. Acetylated p53 preferentially recruited acetyltransferase cofactors onto the PD-1 promoter, selectively facilitating PD-1 transcription by enhancing local chromatin acetylation [65]. Therefore, we assume that these main mutated oncogenes and tumor suppressor genes may be upstream regulatory genes of iPD-1, thereby influencing the role of iPD-1 in tumor progression.

Third, selective signaling pathways may be involved. T-cell anergy is due to the SHP1 and SHP2 phosphatases, the downstream of PD-1/PD-L1 signaling [105]. Kleffel et al. reported growth suppression by PD-1 blockade in PD-1-expressing melanoma cells. They hypothesized that the differential effects of PD-1 blockade on T-cells vs. melanoma were due to the differences in SHP2 signaling in two cell types expressing melanoma [71]. iPD-1 has a pro-tumor effect on melanoma and HCC via activation of the mTOR signaling pathway, independently of adaptive immunity. However, PD-1 is a tumor suppressor that suppresses the canonical signaling pathways, such as the PKB and ERK1/2 pathways, in NSCLC in vitro and in vivo systems [60]. PD-1 blockade instead promotes cell proliferation and activates the PKB and ERK1/2 signaling pathways in both NSCLC and colon cancer cells [60,69].

6. Nivolumab-based clinical studies

Up to now, as shown in Table 2, there are a lot of clinical trials for tumor combination therapy based on Nivolumab, one representative of a PD-1 antibody. These combination drugs/treatments include ipilimumab (a CTLA-4 inhibitor)[106–113], NKTR-214 (bempegaldesleukin, a CD122-preferential interleukin-2 pathway agonist) [114–119], CMP-001 (a virus-like particle containing a TLR9 agonist) [120], BMS-986205 (an immunosuppressive enzyme indoleamine 2,3-dioxygenase (IDO) inhibitor) [121,122], Relatlimab (a new anti-LAG-3 blocking antibody) [123–127], Avadomide (CC-122, a cereblon E3 ligase modulator (CELMoD) agent) [128–130], Oncolytic Virus HF10 and Pexa-Vec [131], External Beam Radiotherapy [132], Nab-paclitaxe[133], Metformin Hydrochloride [134], Tumor Infiltrating Lymphocytes [135], Gemcitabine [136], Carotuximab (TRC105, an antibody against endoglin) [137], JNJ-64041757 (JNJ-757, a live, attenuated, double-deleted *Listeria monocytogenes*-based immunotherapy expressing human mesothelin) [138,139], Cabozantinib (a multi-target small molecule tyrosine kinase inhibitor) [140], TAK-659 (an inhibitor of Spleen Tyrosine Kinase) [141], Abemaciclib (the CDK4/6 inhibitor) [142,143], CC-122 (a novel pleiotropic pathway modifier compound) [144], BMS-813160 (a potent and selective CCR2/5 dual antagonist) [145], Cabiralizumab (a CSF1R inhibitor) [146,147], DC Vaccines [148], Tumor Treating Fields (TTF) [149,150], Short-course Radiotherapy [151,152], ONC201 (a caseinolytic protease activator) [153,154], TAS-102 (a combination of trifluridine and tipiracil) [155,156]. Although the results of some clinical trials showed that cancer patients failed to experience a clinical benefit from nivolumab-based combined therapies [111,156], there are a lot of clinical trials suggested a survival benefit in a subset of patients [110,112,113,116,118,119,157]. These suggest that combination therapy is the inevitable trend in cancer therapy. No matter which combination therapy approach, be it ICI, chemotherapy, radiotherapy, biological agents or others, this treatment approach is expected to improve overall outcomes, including but not limited to OS, progression-free survival (PFS), overall response rate (ORR) and disease control rate (DCR).

Table 2
Clinical trials of Nivolumab-based combination therapy in common tumors.

Combined therapy	Tumor types	NCT-ID
Ipilimumab	Melanoma	NCT01928394
	Lung cancer	NCT02538666、NCT03043599、NCT02659059、NCT03256136
	Breast cancer	NCT03789110
	CRC	NCT03693846
NKTR-214	Melanoma	NCT02983045、NCT03635983、NCT02905266、NCT03068455、NCT02599402、NCT01844505、NCT01621490
CMP-001	Melanoma	NCT03618641
BMS-986205	Melanoma	NCT03329846
Relatlimab	Melanoma	NCT03470922、NCT02656706、NCT01585194、NCT03903640
Avadomide (CC-122)	Melanoma	NCT03834623
HF10 Oncolytic Viral Therapy	Melanoma	NCT03259425、NCT03903640、NCT02970981、NCT02731729、NCT01927419
Oncolytic Immunotherapy Pexa-Vec	HCC	NCT03071094
External Beam Radiotherapy	Melanoma	NCT02659540、NCT02714218
Nab-paclitaxe	Lung cancer	NCT02967133
Metformin Hydrochloride	Lung cancer	NCT03048500、NCT02998528
Tumor Infiltrating Lymphocytes	Lung cancer	NCT03215810
Gemcitabine	Lung cancer	NCT03662074
Carotuximab (TRC105)	Lung cancer	NCT03181308
JNJ-64041757	Lung cancer	NCT03371381
Cabozantinib	Breast cancer	NCT03316586
TAK-659	Breast cancer	NCT02834247
Abemaciclib	HCC	NCT03781960
CC-122	HCC	NCT02859324
BMS-813160, Gemcitabine and Nab-paclitaxel	PDAC	NCT03496662
Cabiralizumab	Brain cancer	NCT02526017
DC Vaccines	Brain cancer	NCT02529072
Tumor Treating Fields (TTF; Optune) plus Ipilimumab	GBM	NCT03430791
Ipilimumab and Short-course Radiotherapy	GBM	NCT03367715
ONC201	CRC	NCT03791398
TAS-102	CRC	NCT02860546

7. Developing small molecular inhibitors of PD-1

In addition to the high affinity PD-1 antibodies we're talking about, small molecular inhibitors of PD-1 are also developed for oral administration [158,159]. They are easier to transport and store in clinical treatments [160]. Small molecule inhibitors not only can better suppress tumor growth and migration than antibodies, but also display a higher biosafety [160]. Thus, small molecule inhibitors may replace antibody drugs or serve as supplementary medicines in the near future. Methylene blue (MB) is an effective PD-1 inhibitor that reduces the recruitment of SHP2 by PD-1 and enhances the cytotoxicity of cytotoxic T lymphocytes (CTLs) both in vitro and in vivo [161]. A lot of studies have shown that MB is clinically safe [162,163]. Lu et al. found that CH-4.7, a small molecule inhibitor of PD-1, effectively inhibits the PD-L1/PD-1 interaction [164]. Cancer patients may benefit from these highly effective small molecule inhibitors specifically targeting PD-1.

8. Conclusion and prospect

To overcome cancer, there is still a long way to go. Clinical data show

that some cancer patients fail to respond to immunotherapy or even display a hyperprogression of the disease. We believe the discovery of iPD-1 is a breakthrough that can help explain some of the therapy failures. Furthermore, an in-depth elucidation of the precise molecular and cellular mechanisms of iPD-1 in tumor progression should be the focus of future studies. For instance, how is the expression of iPD-1 regulated, what are the iPD-1 regulated signaling pathways, and what role does iPD-1 play in tumor immunity, metabolism, metastasis, and drug resistance? Finding answers to these questions will provide new insights and set new standards for the precision treatment of cancer patients.

CRediT authorship contribution statement

M.H.C. and L.B. collected related literature and finished the manuscript. M.H.C., L.B. and J.E.Y. participated in the design of this review. All authors read and approved the final version of the manuscript.

Declaration of Competing Interest

The authors declare no conflict of interest.

Data Availability

The data that has been used is confidential.

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