




The nuclear transportation of PD-L1 and the function in tumor immunity and progression

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Received: 28 November 2021 / Accepted: 15 February 2022 / Published online: 5 March 2022
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Abstract

As the main immune checkpoint, PD-L1-PD-1 interaction plays a critical role in the dysregulation of effector T cells, which contributes to the failure of Chimeric Antigen Receptor T-cell (CAR-T) and other immunotherapies. Presently, most research focuses on the extracellular function of PD-L1. Membrane PD-L1 can interact with its receptor PD-1 and decrease T cell-induced cancer immunity. However, the function of PD-L1 in cancer cells is still unclear. Recent studies have shown the separated clinical significance of PD-L1 expression in various cancer types, showing the complexity of PD-L1 in cancer cell regulation. As a novel regulatory pathway, the nuclear translocation of PD-L1 in cancer cells receives more attention. Results of these preclinical studies demonstrated that nuclear PD-L1 has an essential role in cancer development and other immune checkpoint molecules transcription. Herein, we summarized the mechanisms involved in PD-L1 nuclear transportation and identify the key regulatory factors in this process. Furthermore, we also summarize the function of nuclear PD-L1 in cancer immunity. These findings suggested the novel PD-L1 regulation in cancer development, which showed that nuclear PD-L1 is a potential therapeutic target in future cancer therapy.

Keywords PD-L1 · Nuclear transportation · Immune escape · Transcriptional regulation · Cancer immunity and immunotherapy

Abbreviations

AP-1	Activator protein 1	GSDMC	Gasdermin C
BRCA	Breast cancer	HCC	Hepatocellular carcinoma
CAR-T	Chimeric antigen receptor T cell	HIP1R.	Huntingtin-interacting-protein-1-related
COAD	Colon cancer	IRF1	Interferon regulatory factor 1
CSN5	COP9 signalosome complex subunit 5	IFN	Interferons
EGF	Epidermal growth factor	IL	Interleukin
FDA	Food and drug administration	KPNs	Karyopherin
		KRTs	Keratins
		LADC	Lung adenocarcinoma
		LSCC	Lung squamous cell carcinoma
		HNSCC	Neck squamous cancer cells
		NSCLC	Non-small-cell lung cancer
		NF-κB	Nuclear factor kappa B
		NFAT	Nuclear factor of activated T-cells
		NLSs	Nuclear localization signals
		OS	Osteosarcoma
		PD-L1	Programmed cell death protein ligand 1
		PRAD	Prostate cancer
		RCC	Renal cell carcinoma
		STAT	Signal transducer and activator of transcription
		SRTFs	Stress-responsive transcription factors
		TCR	T cell receptor

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TRIM59	Tripartite motif-containing 59
TNF- α	Tumor necrosis factor alpha
VIM	Vimentin

Background

The development in immunologic research increases the attention in cancer immunotherapy. The therapeutic effect of immunotherapy relies on the activation of the T cell-based immune system [1]. The exposed antigen expressed on the surface of tumor cells promotes the functional activation of T cells by binding with T cell receptor (TCR). However, the tumor immunologic recognition and cytotoxicity induced by TCR is adjusted by the interaction of several co-expressed receptors and their ligands, such as immune checkpoints. They can synergistically stimulate or suppress the function and viability of T cells and alternate the magnitude and duration of T-cell immune response [2]. The immune checkpoints are a series of suppressant pathways through the receptor-ligand binding between T cell and target cells, including PD-L1/PD-1, CTLA-4/B7, CD47/SIRP- α , and LAG-3/MHC-II, which perform as an essential supervisor in physiologic immunity and prevent the occurrence of autoimmune diseases [3]. Unfortunately, the immune checkpoint-mediated immunologic inhibition also contributes to the T cell exhaustion in anti-tumor immunity and results in the immune escape of cancer cells [4, 5]. Among the immune checkpoint, programmed cell death protein ligand 1 (PD-L1) and its receptor become the center of attention by

researchers. The antibodies against PD-1/PD-L1 therapy is Food and Drug Administration (FDA) approved and promise as an exciting therapeutic effect in cancer immunotherapy [6–8]. However, the dominating investigation of PD-L1 focused on the membrane PD-L1 (mPD-L1). Recent studies proved that besides membrane expression, PD-L1 also has nuclear expression in cancer and normal cells, and the translocation of nuclear PD-L1 (nPD-L1) is involved in the immunologic variation of cancer cells [9–11]. In this review, we mainly summarized the nPD-L1 and the mechanism of nPD-L1 nuclear transportation (Table 1). Meanwhile, the functional differences between mPD-L1 and nPD-L1 are also discussed to clarify the PD-L1 regulation in tumor development and immunity, which may contribute to the therapeutic difference in the PD-L1/PD-1 targeted therapy.

The PD-1/PD-L1 Axis in cancer immunity

PD-L1, also called B7-H1 or CD274, has been regarded as a vital immune regulator in anti-cancer immunity, which can be recognized by PD-1 in T and NK cells and cause the exhaustion of these immune cells [12, 13]. Mediated by inflammation and different cytokines and growth factors, the expression of PD-L1 is regulated by two separated pathways, including transcription and post-transcription pathways. The ChIP-seq analysis indicated that the binding of NF- κ B1/p65 in the PD-L1 enhancer region is increased by paclitaxel-induced reactive oxygen species and further upregulate the expression of PD-L1 in tumor-associated macrophages [14].

Table 1 The overview of concerning nPD-L1 in various cancer researches

Cancer type	Condition	Binding site	Transcription	Function	Ref.
TNBC	Loss of Sororin	SMC1/SMC3/ SA2/SCC1/ PDS5B/WAPL	–	Sister chromatid cohesion	[89]
NSCLC	–	KPNB1/SP1	Gas6	Cell proliferation	[54]
BRCA	Deacetylation	HIP1R/KPNA2/ Vimentin	BIRC3/TRAF1/ RELB/HLA-A/ HLA-B/PD-L2/ VISTA/PD-L1/ PD-L2	Immune response enhancement	[9]
TNBC	Hypoxia	p-STAT3	GSDMC	Pyroptosis and necrosis	[10]
BRCA	Doxorubicin	p-AKT (prediction)	–	Anti-apoptosis	[44]
PRAD/BRCA/COAD/OS	Circulating tumor cells	Vimentin (prediction)	–	Overall-survival decrease	[19]
LADC/LSCC/RCC/HCC	–	–	–	Nuclear immunoreactivity	[46]
HNSCC	–	AKT-1	–	Radioresistant	[80]
ESCC	–	–	–	Invasion promotion	[45]
PRAD	Primary radiotherapy	–	–	Higher Gleason score and cT stage	[91]
CC	BRAF-mutated CRC cells	–	–	Promoting cell proliferation	[90]

TNBC Triple-Negative Breast Cancer, *NSCLC* Non-Small Cell Lung Cancer, *BRCA* Breast Cancer, *PRAD* Prostate Adenocarcinoma, *CC* Colorectal cancer, *COAD* Colon Adenocarcinoma, *OS* Osteosarcoma, *LADC* Lung Adenocarcinoma, *LSCC* Lung Squamous Cell Carcinoma, *RCC* Renal Cell Carcinoma, *HCC* Hepatocellular Carcinoma, *HNSCC* Neck Squamous Cell Carcinoma, *ESCC* Esophageal Squamous Cell Carcinoma

On the other hand, IL-27 can activate the JAK1 and JAK2 and promote the phosphorylation of STAT1 after binding with IL-27R α and IL-6R β . The phosphorylation of STAT1 leads to the nucleus transportation and enhances the PD-L1 transcription [15]. Meanwhile, Lin's researches suggested that the ERK-induced C/EBP β phosphorylation causes Bcl-2-associated athanogene-1 transcription and PD-L1 expression, which promotes the development of non-small cell lung cancer (NSCLC) [16]. These results showed the importance of NF- κ B, ERK, and STAT pathway in PD-L1 transcriptional expression.

The function of PD-L1 also requires post-transcription regulation, including Ubiquitination, N-Glycosylation, Phosphorylation, Palmitoylation, and so on. Post-translational modifications of PD-L1 can alternate the structure of PD-L1 and adjust the PD-L1 stability inside the cancer cells and prevent the proteasome-induced degradation [17]. Meanwhile, the intracellular localization of PD-L1 also requires post-translational modifications, such as in ER, Golgi, nucleus, and cytoplasm [18, 19]. However, the specific effect of its subcellular localization remains unknown.

After engagement with PD-1 on T cells, PD-L1 induces the conformation change of PD-1 and promotes the phosphorylation of SHP-2 in the cytoplasmic tail of PD-1 [20, 21]. The PD-1-induced SHP-2 decreases the TCR signal pathway by LCK-induced ZAP70 phosphorylation and cause T cell dysfunction [22]. On the other hand, the interaction between PD-L1/PD-1 decreases the activation of PI3K/AKT and causes a series of cellular biological alternations, promoting p21Cip/p27Kip-induced proliferation inhibition and FOXO1-induced apoptosis [23]. Meanwhile, PD-L1/PD-1 pathway also interferes with the therapeutic effect of active immunotherapy such as chimeric antigen receptor (CAR)-T therapy and enhances the anti-tumor activity and safety profile [24]. Clinical researches have emerged that PD-1 gene disrupted CAR-T cells therapies have an attractive result by monoclonal antibody or CRISPR/Cas9 strategy [25, 26]. Thus, the PD-L1/PD-1 targeted therapy received a great deal of attention from cancer immunologic therapies.

Although multiple kinds of research have suggested the unfavorable prognosis in cancer with high expression of PD-L1 [27, 28], a part of the studies showed the different results of PD-L1 in some cancer types. Sideras and his colleagues found that the expression of PD-L1 indicated the higher survival probability in hepatocellular carcinoma (HCC), which can be the superior predictors of HCC mortality together with Galectin-9 and low CD8 + TIL [29]. Similarly, in advanced gastric cancer, the patients with better prognostic had a high grade of PD-L1 and a high density of CD8 + T cells [30]. Also, some other clinical prognosis data showed that high expression of PD-L1 is related to the favorable prognosis in certain cancer types, including NSCLC, HCC, BRCA, OS et.al, which challenge the

conventional opinion of PD-L1. Parts of relevant research have summarized in Table 2 [29–43]. These results suggested that PD-L1 has a disparate regulatory mechanism in cancer cell immunity and development.

The nPD-L1 in cancer cell

The nPD-L1 was first illustrated in 2010 in breast cancer cells. Ghebeh and his colleagues [44] found that the expression of nPD-L1 plays a role as the anti-apoptosis molecule. The depletion of PD-L1 significantly reduced the chemotherapy-induced cytotoxicity. In their research, the dose-dependent treatment of doxorubicin in breast cancer repressed the expression of mPD-L1 and increased the PD-L1 nuclear expression induced by phosphorylation of nuclear AKT, which suggested the chemotherapy-induced PD-L1 nuclear transportation. They also found that doxorubicin-induced nPD-L1 existed in heart tissues, indicating the non-tissue specific expression pattern of nPD-L1. As the poor prognostic biomarker, nPD-L1 also exists in invasive esophageal cancer [45]. Besides these findings, Parra and his colleagues [46] investigated the PD-L1 expression in malignant and nonmalignant cells and discovered that the nPD-L1 occurs in some other samples of lung adenocarcinoma (LADC), lung squamous cell carcinoma (LSCC), renal cell carcinoma (RCC), and hepatocellular carcinoma (HCC). Meanwhile, the immunofluorescence research also clarified the nPD-L1 expression in circulating tumor cells isolated from prostate cancer (PRAD), breast cancer (BRCA), colon cancer (COAD), and osteosarcoma (OS) patients [19]. These findings suggested that the nuclear transportation of PD-L1 is ubiquitous and has a critical regulatory function in cancer development.

Interestingly, the research from Polioudaki [47] found that the nuclear location of PD-L1 may result from the error of experimental operation. The immunostaining using standard conditions of fixation and permeabilization showed the nuclear-location of PD-L1 in MDA-MB-231 cell lines while the mild detergent and rigorous fixation conditions maintain the membrane localization of PD-L1, similar to the immunostaining pattern of CD24. Further research achieved no significant PD-L1 translocation with 24 h-treatment of doxorubicin, which is opposite to the data from Ghebeh. However, these results are still unverified in the following research. Nowadays, FDA has approved the application of three PD-L1 assessments, including PD-L1 IHC 22C3 PharmDx kit (Dako North America), the PD-L1 28–8 PharmDx kit (Dako North America), and the PD-L1 SP142 Ventana test (Ventana Medical Systems Inc). These PD-L1 test platforms have a high affinity with different PD-L1 domains [48]. So, cross-validation by diverse test platforms is necessary for the investigation of nPD-L1 expression in

Table 2 The overview of the research indicating the favorable prognosis in PD-L1 high expression cancer

Cancer type	Item	Subtype condition	Detection methods	Ref.
Colorectal cancer	OS	Mismatch repair proficient	IHC	[31]
Nasopharyngeal carcinoma	OS/PFS	–	IHC	[32]
Endometrial carcinoma	OS	–	IHC	[33]
Non-Metastatic Nasopharyngeal carcinoma	LRFFS	Intensity-modulated radiation therapy	IHC	[34]
Bladder squamous cell carcinoma	OS/DSS	Radical cystectomy	IHC	[35]
Non-Small Cell Lung Cancer	PFS	Immunotherapy	IHC	[36]
Advanced lung adenocarcinoma	PFS	Pemetrexed maintenance therapy	IHC	[37]
HER2-positive invasive breast cancer	OS	–	IHC	[38]
Skin cutaneous melanoma & Clear cell renal cell carcinoma	OS/PFS	–	RNA-Seq	[39]
Hepatocellular carcinoma	DSS	–	IHC	[29]
High-grade serous carcinoma	PFS	–	IHC	[40]
Esophageal squamous cell carcinoma	OS/PFS	–	IHC	[41]
Advanced gastric cancer	OS	–	IHC	[30]
Osteosarcoma	OS	–	RT-qPCR	[42]
Non-Small Cell Lung Cancer	OS	Adjuvant therapy Squamous cell pT2-4 (tumor size) Positive lymph node status	IHC	[43]

OS Overall survival, PFS Progression free survival; loco-regional failure-free survival (LRFFS), DSS Disease specific survival, IHC Immunohistochemistry, RNA-Seq RNA Sequencing, RT-qPCR Real-time quantitative PCR

cancer cells. In this regard, we should consider the authenticity in the research of nPD-L1, and the experimental methods of PD-L1 detection require further improvement.

Initiation of nPD-L1

As the special regulation in cancer cells compared to the mPD-L1 function, the initiation of nPD-L1 requires a specific cancer microenvironment. Hou and his colleagues investigated different nPD-L1 initiation conditions including PD-L1 antibody, small molecule drugs, cytokines, autophagy, and cell stress, and found that hypoxia is the most effective initiation factor of nPD-L1 in a hypoxia-inducible factor-1 α (HIF-1 α)- independent manner [10]. Gao and his colleagues [9] also found that the HDAC2-dependent PD-L1 deacetylation initiates its internalization, which can be reversed by p300/CBP-dependent PD-L1 acetylation. However, the acetylation-dependent nPD-L1 transportation remains unclear. Acetyl-CoA, one of the key products in aerobic metabolism, is essential in the p300/CBP-dependent PD-L1 acetylation. Hypoxia can suppress the activation of Acetyl-CoA Synthetase and cause the decline of Acetyl-CoA [49], which may play a crucial role in the process of PD-L1 acetylation and nuclear transportation. Meanwhile, the research found that Epidermal Growth Factor (EGF)

enhances the Lysine acetylation of PD-L1, which can be detected by Acetyl lysine binding beads [50]. In this process, EGF promotes the p300 phosphorylation at the Ser1834 site induced by PI3K/AKT signaling pathway after binding with EGFR[51]. These results indicate that the absence of EGF can promote the nuclear transportation of PD-L1.

The mechanisms of nPD-L1 transportation

The PD-L1 nuclear transportation is a complicated process and requires accurate adjustment. Until now, a few factors elucidated to participate in nPD-L1 regulation, including Karyopherin protein family (nuclear transportation recognizer), Vimentin (nPD-L1 carrier), and STAT3 and AKT pathway (co-transcription factor). We will discuss them in the following sections.

Karyopherin protein family

Karyopherin (KPNs) family protein, also called Importin, is a series of nuclear import proteins, which controls the nucleocytoplasmic transport progress by forming the

heterodimer of importin α and β subunits [52]. During the nuclear-transportation process, the protein-containing nuclear localization signals (NLSs) are identified by importin α and then orientated to the nuclear pore complex with the assistance of importin β [53]. The studies have suggested that KPNs engage in the regulation of the nuclear translocation of PD-L1. The mass spectrometry assay in Du's research demonstrated that PD-L1 has the highest binding capacity with the β 1 subunits of Karyopherin (KPNB1). The abrogation of KPNB1 causes the downregulation of nPD-L1 in NSCLC. The KPNB1-induced PD-L1 nuclear transportation enhances the activation of Sp1 and promotes the transcription of Gas6 as well as Mertk pathway [54]. Gao and his colleagues [9] also found that the deacetylation of PD-L1 leads to the bond with importin- α 1 (KPNA1), which carries the PD-L1 through nuclear pore complexes into the nucleus. These two studies showed that the nuclear transportation of PD-L1 requires the synergetic interaction of importin α and β .

However, the research in human head and neck squamous cancer cells (HNSCC) revealed that the suppression of KPNB1 inhibited the expression of PD-L1 on the surface of cancer cells induced by radiotherapy [55]. This result is opposite to the phenomenon of mPD-L1 decrease in condition of KPNs-induced mPD-L1 internalization. The reduction of PD-L1 induced by KPNB1 knock-down may result from the interaction between KPNB1 and interferons (IFNs)-related pathway. The Interferon Regulatory Factor 1 (IRF1) contains the NLS structure, which can be recognized and carried into nuclear by KPNA2 after being activated by IFNs [56, 57]. The depletion of KPNB1 reduced the nuclear location and transcription activation of IRF1, consequently diminishing the IRF1-related PD-L1 expression [58]. Furthermore, the employment of KPNB1 inhibitor, importazole, diffuses the nuclear localization of IRF1 and causes the downregulation of PD-L1 after irradiation therapy, confirming the pivotal role of IRF1 in KPNB1-induced IRF1 and PD-L1 nuclear transportation [59]. Second, the KPNs are also responsible for the activation of stress-responsive transcription factors (SRTFs), including Nuclear Factor Kappa B (NF- κ B), Activator Protein 1 (AP-1), Nuclear Factor of Activated T-cells (NFAT), and Signal Transducer and Activator of Transcription 1 alpha (STAT-1 α), and dominate the cytokines and chemokines-mediated proinflammatory response [60]. Lim and his colleagues have illustrated that the expression of PD-L1 is related to the macrophage-secreted inflammatory cytokines induced by Tumor Necrosis Factor alpha (TNF- α) [61]. These findings reveal that the KPNs-induced SRTFs pathway promotes the expression of PD-L1. The role of KPNs in nPD-L1 and mPD-L1 will be also discussed in the next section.

STAT3 pathway

In response to the stimulation of cytokines including IFNs, EGF, Interleukin (IL)-6, Transducer and Activator of Transcription 3 (STAT3) facilitates the formation of heterodimers by kinases-induced phosphorylation, which moves into the nuclear and transduces the signal from receptor to nuclear [62–64]. Hou and his colleagues found that the Y705 phosphorylation of STAT3 enhances the nuclear aggregation of PD-L1 and regulates the transcription of gasdermin C (GSDMC) [10]. Coincidentally, it is reported that KPNs participate in the nuclear transportation of STAT3. The knock-down of KPNA2 impaired the expression of STAT3 in nuclear in pancreatic ductal adenocarcinoma cells [65]. The Ma's data elucidated that KPNA5 and KPNA7 have a similar function in binding with STAT3, rather than KPNA1 or KPNA3. These results suggested the complicity in PD-L1 and STAT3 transportation [66]. On the other hand, the nuclear relocation of STAT3 induced by EGFR also requires the interaction between KPNA5 and phosphorylated Tripartite Motif-containing 59 (TRIM59), a ubiquitin ligase, in glioblastoma, suggested the TRIM59 in PD-L1 transportation [67]. In this regard, we hypothesize that the complex of PD-L1 translocator consists of KPNs, STAT3, and TRIM59 in the PD-L1 regulation in nuclear.

Interestingly, the activation of STAT3 is also involved in the IFNs-induced transcription diversity of PD-L1 and reduces of immunotherapy effect in multiple cancer types [68–70]. Xiang and his colleagues also elucidated that the dexamethasone inhibits the nuclear translocation of GR/STAT3 complex and suppresses the expression PD-L1, decreasing the cancer cell immune evasion [71]. Meanwhile, together with p65, the activation of STAT3 promotes the transcription of COP9 signalosome complex subunit 5 (CSN5), which functions as the deubiquitin enzyme and reduces ubiquitination-induced PD-L1 degradation [70]. So, it is easy for us to get the hypothesis that the nPD-L1-induced STAT3 activation can in turn feedback the transcription of PD-L1 and increase the mPD-L1-induced immune escape. The hypothesis indicates the close relationship between nPD-L1 and mPD-L1, which has been elucidated in Gao's research [9]. The expression of KPNs and STAT3 engage in the acceleration of the membrane-nuclear-membrane expression loop of PD-L1, which plays an essential role in the rotation of cell death and tumor immunity in cancer cells.

AKT pathway

The activation of AKT is related to cell viability, apoptosis, and proliferation, which manipulates the development of various cancer types and can be the therapeutic target in

cancer treatment [72, 73]. The research has emerged that AKT plays a crucial role in PD-L1 regulation. The investigation showed that phosphorylation of AKT promotes immune escape by driving the expression of PD-L1 [74, 75]. Meanwhile, the stimulation from c-MET amplification, the HGF, and EGFR-T790M mutation caused the activation of PI3K and sequentially improved the phosphorylation of AKT, increasing the transcription of PD-L1 [76]. These results revealed the crucial role of an inside-out regulator in PD-L1 expression.

On the other side, AKT also controls the outside-in transportation of PD-L1. The phosphorylation of AKT increased after the treatment of doxorubicin, along with the enhancement of nPD-L1 expression in breast cancer cells [44]. 112-480aa fragment of AKT is the fundamental structure that can recognize 128-237aa fragment of PD-L1 with the stimulation of starvation and facilitates glioma cell invasion [77]. However, the specific mechanism of AKT in PD-L1 nuclear transportation is still unclear. Jeong's research provided an explanation that phosphorylation of AKT promotes nuclear translocation by enhancing the binding and transportation ability of importin α , which facilitates the PD-L1 nuclear translocation [78]. On the other hand, The AKT and its phosphorylation contribute to the phosphorylation of STAT3, suggesting the sequential activation from AKT to STAT3 in nPD-L1 transportation [79]. Moreover, Schulz and his colleagues [80] proved that PD-L1 can directly bind with AKT-1, especially in the radio-resistant neck squamous cancer cells. The irradiation enhanced the binding capacity between PD-L1 and AKT-1 with the time extension. Different from the previous result, the higher binding affinity between AKT and PD-L1 reveals the lower nuclear enrichment of nPD-L1 in radio-resistant neck squamous cancer cells. Their results indicated that the AKT has various function in nPD-L1 expression in different cells, which requires further research.

Vimentin

Encoding a type III intermediate filament protein, Vimentin (VIM) intermediate filaments (VIFs) network is widely distributed from the nucleus surface to the plasma membrane [81]. VIM acts as one of the crucial components of the cytoskeleton to retain its stability, which monitors cell migration, adhesion, and differentiation [82, 83]. High expression of VIM has a positive relationship with PD-L1 expression and promotes the epithelial-mesenchymal transition (EMT) [83, 84]. Meanwhile, as the marker of circulating tumor cells, the cells with positive VIM expression on the cell surface showed a higher nPD-L1 expression in multiple cancer types, which indicates the regulatory function of VIM in PD-L1 nuclear location [19]. In addition, the mass

spectrometry data has also illustrated that PD-L1 connected several cytoskeleton proteins by its C-terminal, including VIM and Keratins (KRTs). The depletion of VIM caused the down-regulation of PD-L1 accumulation in nuclear and cytoskeletal [9]. The VIM-induced PD-L1 binding to the cytoskeleton is associated with the functional PD-L1 interaction with Huntingtin-interacting-protein-1-related (HIP1R) protein, which is an essential factor in PD-L1 lysosomal degradation [9, 85]. These results implied that the nuclear import and export of PD-L1 depends on the route along with the cytoskeleton.

The function of nPD-L1 in cancer cell

Although the canonical modification of PD-L1 has been widely investigated in a series of research, which is considered as the criminal in anti-tumor immunity, the reverse signaling of PD-L1 in cancer cell regulation is still unknown [86]. The activation of PD-L1 induced by PD-1 reduced the susceptibility to apoptosis induced by Fas ligation or staurosporine [87]. Meanwhile, the antibody-induced PD-L1 blocking inhibited mTOR and reprogramed the metabolic process in tumor cells in a T cell-independent manner [88]. However, the current PD-L1 concerned research focuses on the effect in the tumor microenvironment, especially in the cancer cell-T cell interaction. The regulatory function of PD-L1 in cytoplasm and nuclear cancer cells remains unclear.

The function of PD-L1 in various cancers partly results from the nPD-L1-induced cell remodeling. Yu and his colleagues found that nPD-L1 replaces the role of Sororin and engaged in the formation of sister chromatid cohesion by binding to PDS5B. The abolishment of PD-L1 downregulated the proliferation, colony formation of cancer cells in vitro, and tumor growth in vivo [89]. On the other hand, nPD-L1-induced Gas6 expression is recognized by MerTK and enhanced cell proliferation with the activation of ERK and AKT signaling pathways [54]. The nPD-L1-induced proliferation promotion results from the increasing expression of cell cycle regulator BUB1 via thyroid hormone receptor-associated protein 3 (THRAP3), thereby accelerating cell cycle progression and enhancing cell proliferation [90]. Moreover, the nuclear transportation of PD-L1 increases the transcription of immunosuppressive molecules such as PD-L2, VISTA, and B7H3 and decrease the T cell-induced anti-tumor immunity [9]. Shim and his colleagues found that the high-level expression of nPD-L1 predicted the higher Gleason score and cT stage in the prostate cancer patients with the treatment of primary radiation therapy, which suggested the higher malignancy and poor prognosis [91]. Similarly, the research in HNSCC also showed upregulated nuclear distribution of PD-L1 in radiotherapy-resistant

cancer cells as well as the cells post-radiation treatment [80]. In this regard, cancer cells enhance cell proliferation and the resistance of radiotherapy and immunotherapy via PD-L1 nuclear relocation.

However, the expression of nPD-L1 enhanced the STAT3-induced transcription of the GSDMC gene. GSDMC is a member of the conserved proteins family that includes gasdermin A, B, C, D, E, and DFNB59 [92]. Cleaved by Caspase family, GSDM family generates an N-terminal pore-forming fragment and gathers in the plasma membrane, forms the gasdermin pore and causes cell pyroptosis [93]. Hou's research found that nPD-L1-induced GSDMC expression accelerates the TNF α -induced tumor necrosis and promotes the chemotherapy-mediated pyroptosis in breast cancer in hypoxia condition [10, 94]. The knockdown of PD-L1 reduces the function of PD-L1/STAT1 binding complex and suppresses the hypoxia-induced pyroptosis [95]. These results indicated that nPD-L1 increases the response to the cell death signal and causes the better prognosis after chemotherapy. This research explained the results from Schmidt and his colleagues, which elucidated that the PD-L1 positive cancer patients who received adjuvant therapy have a higher survival rate while it has no prognostic significance in whole patient analysis [43]. Meanwhile, two studies from BRAF^{V600E}-induced human colon cancer cells showed that tumor intrinsic PD-L1 enhances chemotherapy-induced apoptosis [96, 97]. Knockout of tumor intrinsic PD-L1 reduces pro-apoptotic BIM and BIK, which cause the resistance to drug-induced apoptosis and show the better prognosis. These results suggested that the PD-L1 nuclear transportation has a different function in cancer development, which improves the sensibility of chemotherapeutic and prolong the survival time.

Conclusion

Separated from PD-L1/PD-1 interaction in the canonical immune checkpoints pathway, the expression of PD-L1 in nuclear reveals the novel transcription regulation in cancer development and immune escape. The nPD-L1 promotes cell proliferation by chromatin remodeling, while the nuclear translocation of PD-L1 induced by hypoxia shows a higher sensibility to pyroptosis and enhances the therapeutic effect. Moreover, the nuclear-translocation of PD-L1 also promotes the expression of immune checkpoint

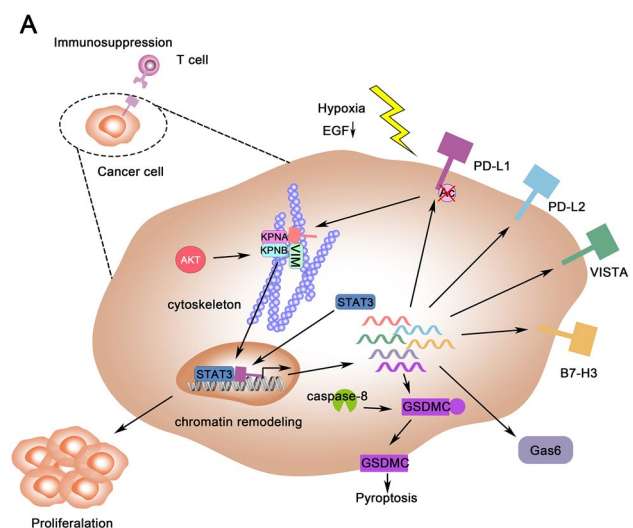


Fig. 1 The overview of nPD-L1 in cancer cells. **A** The PD-L1 was deacetylated in hypoxia condition and start the process of nuclear transportation regulated by a series of factors including KPNs, STAT3, AKT and VIM. nPD-L1 regulates the cancer cells in these four aspects: (1) promote the proliferation of cancer cells; (2) enhance the transcription of GMDSC and facilitate pyroptosis; (3) increase the secretion of Gas6 and (4) upregulation the expression of immune check-point molecules such as PD-L1, PD-L2, VISTA and B7-H3 and cause the immune escape

ligands such as PD-L1, PD-L2, VISTA and B7-H3. These immune checkpoint ligands interact with their receptors and cause the exhaustion of immune cells, further promoting the cancer immune escape (Fig. 1). These finding suggested that cancer cell with nPD-L1 expression has higher proliferation by cell cycle promoting. nPD-L1 also increase immunosuppression ability of cancer cells by further expression of immune check-point markers. However, these cells also facilitate the pyroptosis and show a higher sensibility to chemotherapy. This bidirectional regulation could contribute to the difference of prognosis in PD-L1 expression cancer patients (Fig. 2). The patients with nPD-L1⁺ cancer should consider the reinforce of chemotherapy and radiotherapy and have the higher frequency of follow-up. Thus, nPD-L1 is expected to be the biomarker of cancer development and therapeutic effect in future cancer treatment.

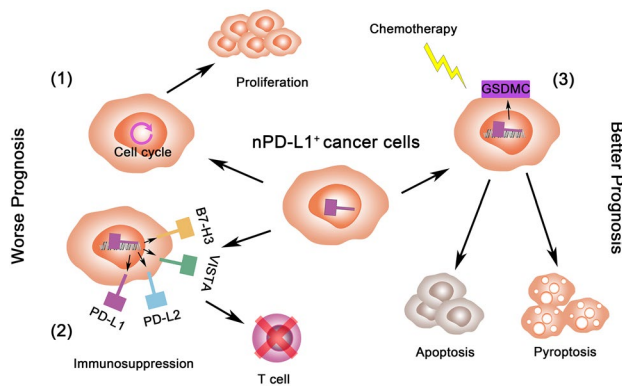


Fig. 2 The nPD-L1-induced cancer prognosis regulation. High expression of nPD-L1 (1) causes the higher proliferation by cell cycle promoting; (2) enhances immunosuppression by immune check-point marker expression; (3) increase the sensibility to chemotherapy by cell pyroptosis

Acknowledgements None.

Author contributions LQ, JJ and JL drafted most of the manuscript. CQ, JL and AX participated in the modification of the manuscript. BL and MZ mainly drawing the schematic diagram. HT and WY participated in the review design. All authors read and approved the final manuscript.

Funding This study was supported by grant from the National Natural Science Foundation of China (NO. 81872181), the program of Zhejiang medical and health technology (2019KY079), Natural Science Foundation of Zhejiang Province (NO. LY20H160025, LY21H160034 and LY21H060003) and Zhejiang Xinmiao Talents Program (2020R401234).

Data availability Not applicable.

Declarations

Conflict of interests The authors declare that they have no competing interests.

Ethics approval Not applicable.

Consent for publication Not applicable.

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