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REVIEW
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Tumor-Intrinsic PD-L1 Signaling in Cancer Initiation, Development and Treatment: Beyond Immune Evasion

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Although the role of PD-L1 in suppressing the anti-tumor immune response is extensively documented, recent discoveries indicate a distinct tumor-intrinsic role for PD-L1 in modulating epithelial-to-mesenchymal transition (EMT), cancer stem cell (CSC)-like phenotype, metastasis and resistance to therapy. In this review, we will focus on the newly discovered functions of PD-L1 in the regulation of cancer development, describe underlying molecular mechanisms responsible for PD-L1 upregulation and discuss current insights into novel components of PD-L1 signaling. Furthermore, we summarize our current understanding of the link between PD-L1 signaling and the EMT program as well as the CSC state. Tumor cell-intrinsic PD-L1 clearly contributes to cancer stemness, EMT, tumor invasion and chemoresistance in multiple tumor types. Conversely, activation of OCT4 signaling and upregulation of EMT inducer ZEB1 induce PD-L1 expression in cancer cells, thereby suggesting a possible immune evasion mechanism employed by cancer stem cells during metastasis. Our meta-analysis demonstrated that *PD-L1* is co-amplified along with *MYC*, *SOX2*, *N-cadherin* and *SNAI1* in the TCGA endometrial and ovarian cancer datasets. Further identification of immune-independent PD-L1 functions and characterization of crucial signaling events upstream or downstream of PD-L1 in diverse cancer types and specific cancer subtypes, would provide additional targets and new therapeutic approaches.

Keywords: PD-L1, CD274, metastasis, EMT, cancer stem cells, microRNA

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INTRODUCTION

In cancer, the epithelial-to-mesenchymal transition (EMT) is a phenotypic process that promotes the acquisition of a mesenchymal features of epithelial tumor cells, reduces cell polarity and cell-cell adhesion, and enables them to migrate and invade more efficiently, by switching off the expression of epithelial markers, such as E-cadherin, and turning on mesenchymal markers, including N-cadherin and Vimentin (1, 2). Epithelial tumor cells undergoing EMT are shown to contribute to tumorigenesis, invasion, metastasis, and resistance to chemotherapy, radiation and small-molecule-targeted therapy (3).

Cancer stem cells (CSCs) represent a fraction of undifferentiated cancer cells that are the seeds of tumor recurrence, have the ability to self-renew and exhibit significant resistance to conventional

chemo- and radiotherapy (4). Emerging evidence has revealed an association between EMT and the acquisition of CSC-like properties (5). The induction of EMT program is a critical regulator of the CSC phenotype (6, 7). On the other hand, tumors cells that exhibit the CSC phenotype also express genes associated with the EMT features and show enhanced metastatic ability, thus representing a novel mechanism contributing to cancer metastasis (8).

The mutual interactions between tumor cells and the tumor microenvironment are essential for tumorigenesis, tumor progression, metastasis and resistance to drug therapy (9). Tumor microenvironment consists of extracellular matrix and diverse cell populations such as T cells, NK cells, macrophages, dendritic cells, fibroblasts, and endothelial cells (10). Progression of cancer to an advanced or metastatic disease usually suggests a failure or insufficiency of the ongoing immune response. Tumors not only effectively escape immune recognition, they also actively inhibit T-cell-mediated normal anti-tumor activity to promote further tumor growth and metastasis by modulating immune checkpoints, which mediate immune tolerance and inhibit the anti-tumor immune response (11). Multiple checkpoint molecules, such as PD-1/PD-L1, CTLA4, BTLA, B7H3, B7H4, HHLA2, IDO1, Tim-3, CD28, CD40, CD47, CD70, CD137, VISTA, LAG-3, and TIGIT, have been reported (11). Among them, B7H3 has been identified as a critical promoter of tumor cell proliferation, migration, invasion, EMT, cancer stemness, and drug resistance (12).

PD-L1 (also known as CD274 or B7H1) is expressed in tumor cells and plays a crucial role in tumor immune escape and the formation of a permissive immune microenvironment, through at least three mechanisms: (i) tolerizing or anergizing tumor-reactive T cells by binding to its receptor PD-1; (ii) rendering tumor cells resistant to $CD8^+$ T cell and Fas ligand-mediated lysis; and (iii) tolerizing T cells by reverse signaling through T cell-expressed CD80 (13, 14). In addition, PD-L1 is also expressed by tumor-associated myeloid-derived suppressor cells and macrophages, which are the major factors responsible for tumor-associated immune deficiencies (15).

Although PD-L1 is widely implicated in tumor immune evasion, the tumor-intrinsic roles of PD-L1 and the mechanisms by which PD-L1 regulates EMT, the acquisition of tumor-initiating potential and resistance to anti-tumor drugs, as well as the ability to disseminate and metastasize in human cancers are currently less well defined. As will be discussed in more detail below, the identification of tumor-intrinsic PD-L1 signaling may provide critical targets for the development of cancer therapies.

PD-L1 DYSREGULATION AND PROGNOSIS IN CANCER

An increasing number of studies suggested that PD-L1 is highly expressed in solid tumors, including colorectal cancer (16), lung cancer (17), pancreatic carcinoma (18), hepatocellular carcinoma (19), gastric cancer (20), ovarian cancer (21), endometrial cancer (22, 23), and cervical cancer (24, 25). High expression of PD-L1 was associated with significantly worse overall survival in cervical cancer (25), non-small cell lung cancer (26), gastric cancer (27), esophageal cancer (28), glioma (29), ovarian cancer (30), and other cancers (31). However, the prognostic value of PD-L1 for certain types of cancer is still controversial. Some studies reported that high PD-L1 could predict favorable prognosis (32, 33). In cervical cancer, squamous cell carcinomas tended to express more PD-L1 than adenocarcinomas (34). The possible reasons for these inconsistent results might include cancer type (or subtypes), tumor heterogeneity, sample size, clinical stage, different intervention, the time point of PD-L1 measurement as well as the different methodology used in research (such as detection methods and procedures).

MECHANISMS OF PD-L1 ACTIVATION IN CANCER

The tumor-intrinsic PD-L1 signaling pathway is inappropriately activated in many cancers. Mechanisms underlying aberrant PD-L1 activation mainly include genomic alterations (including copy number amplification and 3'-UTR disruption), constitutive oncogenic signaling activation, extrinsic factors and epigenetic mechanisms, such as upregulation of oncogenic microRNAs (miRNAs), downregulation of tumor suppressor miRNAs, aberrant DNA methylation, and histone modifications (**Figure 1**).

Copy Number Gain and 3′-UTR Disruption

Small-cell lung cancer (35), squamous cell carcinoma of the oral cavity (36), cervical cancer (37), ovarian cancer (38), breast cancer (39), melanoma, bladder cancer, head and neck cancer, soft tissue sarcoma and prostate cancer (40) exhibit increased copy number of chromosome 9p24, on which CD274 resides. Here, we investigated the frequency of elevated PD-L1 in ovarian cancer and endometrial cancer in The Cancer Genome Atlas (TCGA) data portal. Analysis of TCGA data by cBioPortal (41) demonstrated that overall, PD-L1 was highly expressed in these two cancers, mainly including gene amplification and mRNA up-regulation (**Figure 2A**). Moreover, analyses of U133A and U133Plus2 datasets in the GENT (gene expression across normal and tumor tissue) database (42) revealed that *PD-L1* was highly overexpressed in many tumor tissues (**Figure 2B**). Furthermore, analysis of the TCGA dataset was performed by using the MethHC browser (43). *PD-L1* mRNA expression was consistently upregulated across various cancers (**Figure 2C**). In addition, disruption of the 3' region of the *PD-L1* increases mRNA stability, leading to a marked elevation of aberrant *PD-L1* transcripts in multiple cancers (44).

Constitutive Oncogenic Signaling Activation

Loss of PTEN expression, activation of PI3K/AKT pathway, activation of RAS/MAPK pathway, inhibition of p53 signaling, upregulation of reprogramming factors (Oct4, Sox2, and c-Myc)

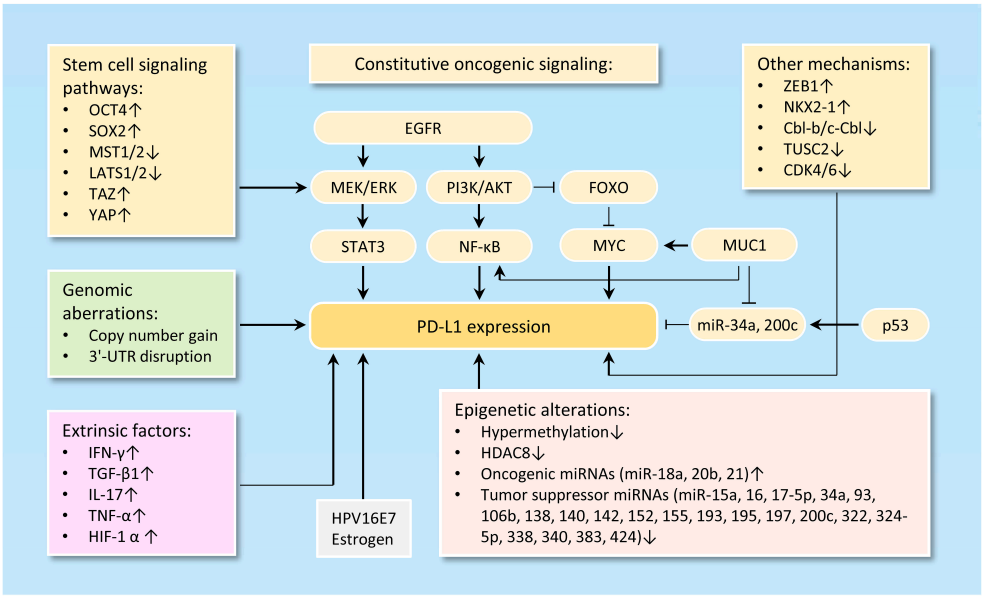

FIGURE 1 | Mechanisms of PD-L1 activation in cancer. The diagram illustrates the diverse mechanisms of PD-L1 activation in cancer, including genetic alterations to *PD-L1* (such as gene amplification, 3'-UTR disruption, or dysregulated transcription) and a wide range of epigenetic mechanisms (including upregulation of oncogenic microRNAs, downregulation of tumor suppressor microRNAs, aberrant DNA methylation and histone modifications).

and upregulation of ZEB1 (an inducer of EMT) are clearly linked to the activation of PD-L1 signaling pathway (45, 46) (**Figure 1**).

PD-L1 expression could be regulated via the PI3K/AKT and/or RAS/MAPK pathways in different tumor cell types (47–49). PD-L1 expression is suppressed by the tumor suppressor gene PTEN. Deletion of PTEN gene results in elevated PD-L1 expression at the translational level by activating the PI3K/AKT signal pathway (50, 51). FOXOs inhibit the expression of PD-L1 through repressing Myc or Wnt/β-catenin signaling pathways in tumor cells (52). MUC1 elevates *PD-L1* transcription by recruitment of MYC and NF-κB (a downstream effector of PI3K/AKT pathway (53) to the *PD-L1* promoter in breast cancer (54). Also, MUC1 was shown to increase PD-L1 levels via downregulation of miR-34a and miR-200c, two direct suppressors of PD-L1 (55–57).

Abnormal activation of stem cell signaling pathways has been implicated in the regulation of PD-L1. OCT4 is a key regulatory gene that maintains the self-renewal properties of CSC and promotes tumorigenesis of cervical cancer cells by miR-125b/BAK1pathway (58). We recently reported that, OCT4 promotes cervical cancer invasion and proliferation by enhancing PD-L1 expression through a miR-18a-dependent mechanism, by which miR-18a upregulates PD-L1 by targeting *PTEN*, *WNK2* and *SOX6* to activate the PI3K/AKT, MEK/ERK and Wnt/β-catenin pathways and inhibit the p53 pathway (25). In addition, SOX2, a transcription factor that controls tumor initiation and cancer stem-cell functions, can directly bind to the *PD-L1* promoter and transactive its expression, contributing to the increased proliferation of hepatocellular carcinoma cells (59). The upstream kinases of the Hippo pathway MST1/2 and LATS1/2 suppress PD-L1 expression, while TAZ and YAP enhance PD-L1 levels in breast and lung cancer cells (60).

Tumor cells undergoing EMT are shown to share a variety of capabilities with experimentally defined CSC (61). In lung cancer, PD-L1 expression was significantly higher in patients with EMT phenotypes (such as increased SNAI1 and Vimentin expression) compared with those with epithelial phenotypes (62). siRNA-mediated ZEB1 knockdown suppressed PD-L1 expression but promoted E-cadherin expression in esophageal squamous cell carcinoma (63). In agreement with these reports, cBioportal analysis of data on somatic copy number variation and mRNA level using TCGA endometrial and ovarian cancer dataset demonstrated that *PD-L1* is indeed co-amplified along with *MYC*, *SOX2*, *N-cadherin* and *SNAI1* in both cancer types (**Figure 2A**).

Another study reported that transcription factor NKX2-1 bound to the locus of *PD-L1* and induced its expression in mucinous lung cancer cells (64). In non-small cell lung cancer cells, the ubiquitin ligases Cbl-b and c-Cbl inhibit PD-L1 expression by inactivating STAT, AKT, and ERK signaling (65), and overexpression of tumor suppressor gene TUSC2 downregulated PD-L1 expression (66). CDK4 and CDK6 kinase destabilize PD-L1 protein via cullin 3–SPOP, leading to the downregulation of PD-L1 in cancer cells (67).

Regulation of PD-L1 Expression by Epigenetic Mechanisms

The expression of cancer-associated genes can occur by epigenetic mechanisms, including DNA methylation (68),

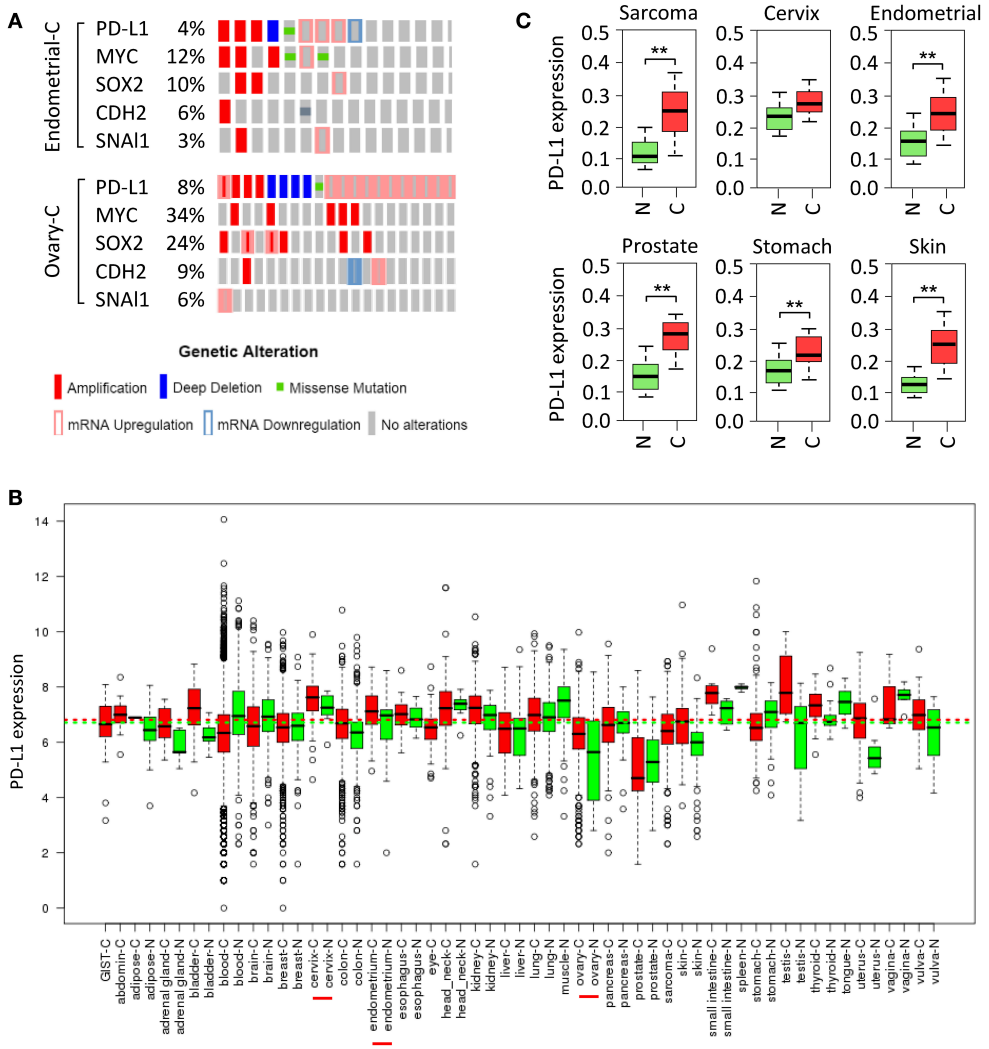

FIGURE 2 | Amplification and upregulation of PD-L1 and genes co-amplified with PD-L1 in TCGA data. **(A)** The Cancer Genome Atlas (TCGA) datasets in the cBioPortal database (www.cbioportal.org) was used to investigate molecular alterations (RNA expression, copy number variation, and mutation). Shown are OncoPrint outputs where each bar represents a tumor that was found to contain an alteration (amplification, deletion, mutation, upregulation, and downregulation, as indicated) in *PD-L1*, *MYC*, *SOX2*, *N-cadherin* (*CDH2*), and *SNAI1* gene in samples of endometrial cancer (upper panel) and ovarian cancer (lower panel) based on TCGA data. **(B)** *PD-L1* mRNA expression pattern was analyzed in a panel of cancer (red) vs. normal (green) tissues from the GENT database. **(C)** *PD-L1* expression pattern was determined in multiple cancer microarray datasets available in the MethHC database. N, normal; C, cancer. $^{**}P < 0.005$.

histone modification (69), chromatin remodeling, and non-coding RNAs (70). The anti-PD-1 therapy could induce PD-L1 promoter methylation and decrease PD-L1 levels in patients with non-small cell lung cancer (71). The class I histone deacetylase HDAC8 acts as an epigenetic inhibitor of PD-L1 expression in melanoma cells via modulating HOXA5 and STAT3 (72). Numerous miRNAs, including miR-15a/miR-16 (73), miR-17-5p (74), miR-93/106b (75), miR-138-5p (76), miR-140/miR-142/miR-340/miR-383 (25), miR-152 (77), miR-155 (78), miR-193 (73), miR-195 (73), miR-324-5p/miR-338 (79) and miR-322/miR-424 (80), have been shown to directly target and inhibit PD-L1 expression in tumor cells. In chemo-resistant non-small-cell lung cancer cells, miR-197 indirectly inhibits PD-L1 expression by regulating the CKS1B/STAT3 axis (81). On the other hand, oncogenic miR-20b and miR-21 inhibited PTEN expression, resulting in PD-L1 overexpression in colorectal cancer (82). Our recent data established that an oncogenic OCT4-miR-18a pathway serves as the key upstream activator of PD-L1 in cervical cancer (27).

Extrinsic Factors Influencing the Expression of PD-L1

The main regulators of PD-L1 are the interferon-γ (83), inflammatory cytokines such as IL-17 (84) and TNF-α (84), TGF-β1 (85), and HIF-1α (86). Of note, overexpressing HPV16E7 oncoprotein increased PD-L1 protein expression, and knockdown of HPV16E7 resulted in a reduction in

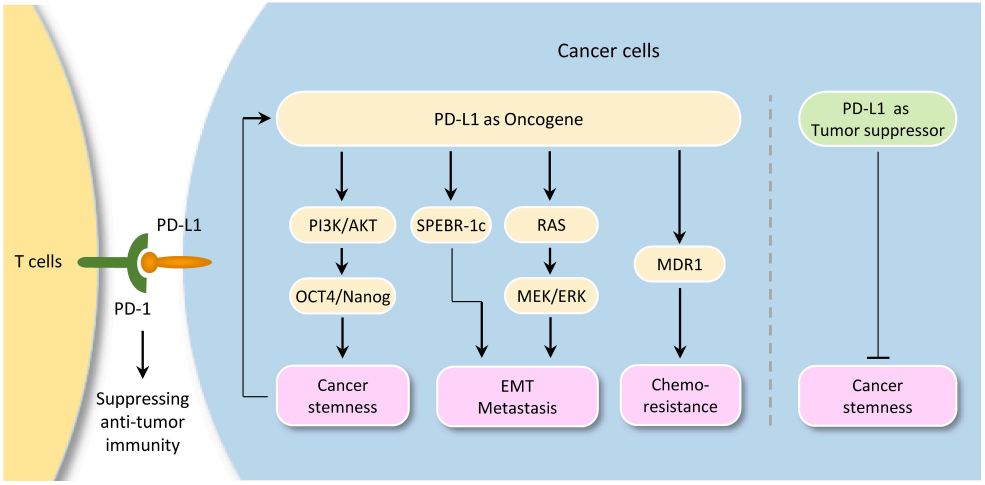

FIGURE 3 | Tumor-intrinsic PD-L1 signaling in cancer initiation and development. The diagram illustrates signaling events downstream of PD-L1 activation in cancer. Although PD-L1 could serve as a tumor suppressor by inhibiting cancer stem cell properties in cholangiocarcinoma, it plays a pivotal role in promoting cancer stemness, EMT, tumor invasion, and chemoresistance in several tumor types. Importantly, activation of OCT4 signaling induces PD-L1 expression in cancer cells, thereby suggesting a possible immune evasion mechanism employed by cancer stem cells during metastasis.

PD-L1 protein expression in cancer cells (87). Consistent with this data, PD-L1 protein expression was significantly higher in the normal cervical tissues with HPV infection than those normal cervical tissues without HPV infection (53). Estrogen is a well-known oncogenic driver of endometrial and breast cancer, and it upregulates PD-L1 protein expression in ERα-positive endometrial and breast cancer cells (88).

THE ROLE OF PD-L1 IN STIMULATING OR INHIBITING CANCER

A tumor-intrinsic role for PD-L1 in promoting cancer initiation, metastasis, development, and resistance to therapy is emerging (**Figure 3**). For instance, knockdown of PD-L1 expression in gastric cancer cells could significantly suppress cell proliferation, migration and invasion (89). Also, knockout of PD-L1 expression by CRISPR/Cas9 inhibits the spheroid formation of osteosarcoma cells (90). PD-L1 was shown to promote EMT in esophageal cancer (91). Knockdown of PD-L1 expression significantly suppressed tumor growth in nude mice in gastric cancer (92) and cervical cancer model (27).

Interestingly, a link between PD-L1 expression and EMT/CSC-like phenotypes has been reported. For example, bladder cancer cells with surface expression of PD-L1 exhibited signatures of immune evasion as well as increased stemness (93). PD-L1 has been shown to be preferentially expressed on $CD44^{high}$ CSCs in lung cancer cells (94). Selective expression of PD-L1 was observed on $CD44^{+}$ head and neck tumor cells compared with $CD44^{-}$ tumor cells (95). $CD133^{+}$/$PD\text{-}L1^{+}$ colorectal CSC cells showed the characteristic of EMT (96). Tumor cell-intrinsic PD-L1 promotes tumor-initiating cell generation in melanoma and ovarian cancer (97). Similarly, PD-L1 promotes OCT4 and Nanog expression in breast CSCs through the activation of PI3K/AKT pathway (98).

Moreover, PD-L1 overexpression promotes EMT and invasion in glioblastoma multiforme via RAS/ERK/EMT activation (99). RNA-sequencing analysis of glioblastoma multiforme revealed that PD-L1 significantly altered the expression of genes, which were enriched in cell growth/migration/invasion pathways (99). PD-L1 induced EMT via activating SREBP-1c in renal cell carcinoma (100). CRISPR/Cas9 system-mediated *PD-L1* disruption increased drug sensitivities for doxorubicin and paclitaxel (90). The interaction of PD-L1 with PD-1 induced phosphorylation of AKT and ERK, resulting in the activation of PI3K/AKT and MAPK/ERK pathways and increased MDR1 expression in breast cancer cells (101).

However, depletion of PD-L1 expression by shRNA in cholangiocarcinoma cells enhances their tumorigenicity and increases ALDH activity, and patients with lower PD-L1 expression shows poorer prognosis when compared with those with higher PD-L1 expression (102), indicating that PD-L1 may also have anti-tumor effects by inhibiting cancer stemness under certain circumstances.

CONCLUSIONS

It is becoming clear that, although PD-L1 could serve as a tumor suppressor by inhibiting cancer stem cell properties in cholangiocarcinoma, tumor cell-intrinsic PD-L1 plays a pivotal role in promoting cancer stemness, EMT, tumor invasion, and chemoresistance in several tumor types. Importantly, activation of OCT4 signaling and upregulation of EMT inducer ZEB1 induce PD-L1 expression in cancer cells, thereby suggesting a possible immune evasion mechanism employed by cancer stem cells during metastasis. The continued

characterization of immune-independent PD-L1 functions and identification of crucial signaling events upstream or downstream of PD-L1 in diverse cancer types (or specific cancer subtypes), would provide additional targets and new therapeutic approaches.

AUTHOR CONTRIBUTIONS

PD and HW provided direction. PD, YX, and HW wrote the manuscript. JY and SH made significant revisions to the manuscript. All authors read and approved the final manuscript.

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