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REVIEW

Regulation of PD-1/PD-L1 Pathway in Cancer by Noncoding RNAs

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Abstract
Immune checkpoint blockade has demonstrated significant anti-tumor immunity in an array of cancer types, yet the underlying regulatory mechanism of it is still obscure, and many problems remain to be solved. As an inhibitory costimulatory signal of T-cells, the programmed cell death 1 (PD-1)/programmed cell death ligand 1 (PD-L1) pathway can paralyze T-cells at the tumor site, enabling the immune escape of tumor cells. Although many antibodies targeting PD-1/PD-L1 have been developed to block their interaction for the treatment of cancer, the reduced response rate and resistance to the therapies call for further comprehension of this pathway in the tumor microenvironment. MicroRNAs (miRNAs) and long noncoding RNAs (lncRNAs) are two main types of noncoding RNAs that play critical parts in the regulation of immune response in tumorigenesis, including the PD-1/PD-L1 pathway. Here we summarize the most recent studies on the control of this pathway by noncoding RNAs in cancer and hopefully will offer new insights into immune checkpoint blockade therapies.

Keywords PD-1/PD-L1 pathway · Immune checkpoint blockade · Noncoding RNA · microRNA

Introduction

The immune system is essential to the maintenance of homeostasis by discriminate "non-self" from "self" through immunological surveillance and elimination of aberrant and carcinogenic cells. However, multiple mechanisms have been elucidated to hinder anti-tumor immunity during tumorigenesis, making the ability to escape from the immune surveillance one of the hallmarks of cancer [1].

The Nobel Prize in Physiology or Medicine 2018 was awarded jointly to James P. Allison and Tasuku Honjo for their discovery and further study of cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) [2] and programmed cell death 1 (PD-1) [3], both of which are commonly referred to as immune checkpoints that function as the brakes of the immune system, and the overexpression of them and the PD-1 ligand, programmed cell death ligand 1 (PD-L1), in tumors or immune cells is one of the most studied causes that lead to T cell dysfunction, form immunosuppressive tumor microenvironment, bring about immune tolerance and eventually enable immune escape of tumor cells [4].

PD-1/PD-L1 Pathway and Precision Medicine

The PD-1 cDNA was first isolated by Tasuku Honjo [3] in 1992 while B7 Homolog 1 (B7-H1) was identified independently by Lieping Chen in 1999 [4, 5] and later known as PD-L1 to emphasize their ligand-receptor relationship [6]. PD-1 is a type I transmembrane glycoprotein consisting of an immunoglobulin V (IgV)-type extracellular domain, a transmembrane region, and an intracellular tail and mainly expressed on the surface of T-cells, B-cells and natural killer (NK) cells [7]. PD-L2 (B7-DC) is the other ligand of it besides PD-L1, which is also a member of the B7 family of transmembrane proteins [8].

To be fully activated, T cells must receive two sets of signals from antigen-presenting cells (APCs): the recognition of T cell receptor (TCR) mediated antigen-specific signal of complexes of major histocompatibility complex

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(MHC) with the antigen on the surface of APCs or tumor cells, and a second costimulatory signal mediated by interaction of CD28 on the T-cells with CD80 (B7–1) or CD86 (B7–2) on APCs [9]. While the interaction of CD28 with B7–1/B7–2 can activate T-cells, the engagement of PD-1 by PD-L1 and PD-L2 can efficiently paralyze T-cells by inhibiting T lymphocytes glucose consumption, proliferation, survival and cytokine production, leading to their malfunction and apoptosis [4, 10], which usually acts as a basic pattern to avoid host autoimmunity [11, 12].

PD-L1 is expressed on the surface of many cell types including T-cells, B-cells, APCs, epithelial cells and monocytes, and rapidly upregulated in response to proinflammatory cytokines like interferon-gamma (IFN-γ) and tumor necrosis factor-α (TNF-α) secreted by tumors [13] while the expression of PD-L2 is mainly restricted to APCs [8]. Also, unlike PD-L2, PD-L1 is a binding partner for B7–1 and competitively binds B7–1 with stronger affinity than CD28, thus impeding the activation of T-cells by B7–1/CD28 pathway [14]. As a result, the anti-tumor effect of PD-L2 is limited, and researchers attach much more importance to PD-L1 study.

Clinically, the PD-1/PD-L1 blockade has demonstrated notable anti-tumor immunity in various tumor types including melanoma [15, 16], non-small cell lung cancer (NSCLC) [17, 18], gastric cancer [19–21], colorectal cancer (CRC) [22, 23], renal cell carcinoma (RCC) [24], pancreatic cancer [25], breast cancer [26, 27], ovarian cancer [28, 29], bladder carcinoma [30] and Hodgkin's lymphoma [25]. In 2015, a miracle in cancer treatment history that the PD-1 inhibitor pembrolizumab (Keytruda®) [31] cured the 91-year-old American former president Jimmy Carter of metastatic melanoma (MM) ignited the enthusiasm of immune checkpoint blockade therapy investigators all over the world, as a result of which the precision medicine has become more and more popular.

The concept of precision medicine is based on the fundamental hypothesis that some specific molecular variations can be regarded as pathogeny of a given malignancy and identifying it will lead to therapeutics that are more discriminating and personized than traditional cancer treatment approaches such as chemotherapeutics and radiotherapeutics. As mentioned above, CTLA-4 and PD-1/PD-L1 are widely studied for their function as brakes of the immune system, especially the anti-tumor immunity. As a result, investigations on checkpoint blockade are in the ascendant and multiple anti-CTLA-4 and anti-PD-1/PD-L1 antibodies have been developed and clinically analyzed for the treatment of all kinds of malignant tumors, showing promising outcomes [25, 32].

The use of immune checkpoint antibodies in treating solid tumors was first established in 2010 when a CTLA-4 inhibitor, ipilimumab, showed to prolong patients' survival in MM and later approved by the US Food and Drug Administration (FDA) for the treatment of melanoma [33]. On December 22, 2014, the nivolumab of Bristol-Myers Squibb (BMS) became the first FDA approved PD-1 antibody for the treatment of melanoma, and the pembrolizumab mentioned above was approved on September 4, 2014 for treating MM [34].

NSCLC, accounting for 85% of all lung cancer diagnoses [35], has been a significant concern where numerous checkpoint blockade researches take place besides melanoma. As most of NSCLC patients are diagnosed at an advanced stage when the tumor is no longer operable, and chemoradiotherapy is not competent enough, more efficient therapies are incredibly urgent to develop [17, 36, 37]. It was not until March 2015 when FDA approved nivolumab for squamous NSCLC treatment, and eventually for all patients with advanced NSCLC progressing after platinum-based chemotherapy on October 9, 2015. Pembrolizumab was also approved on October 2, 2015 for PD-L1-positive NSCLC treatment. So far, both nivolumab and pembrolizumab have been approved by FDA and used for treatment in melanoma, NSCLC, head and neck cancer, RCC and Hodgkin lymphoma with more and more new drugs under clinical trials both domestically and abroad [38–43]. The latest PD-1/PD-L1 related drugs that are launched in the market or currently under clinical trials are listed below (Table 1).

Notwithstanding all the promising results achieved in checkpoint immunotherapies, failure of response to the PD-1/PD-L1 checkpoint blockade therapies makes them inefficacious, and the drug resistance also makes the treatment tougher [44]. The molecular mechanisms making tumors sensitive or not to the PD-1/PD-L1 blockade therapies and under which this pathway is regulated are barely understood. Therefore, further understanding of the underlying regulatory mechanisms of the PD-1/PD-L1 pathway is of noteworthy significance and may provide the basis for the development of more practical and effective targeted anti-cancer therapies.

PD-1/PD-L1 Pathway and Noncoding RNAs

PD-1 is absent on resting T-cells and found initially only in activated mouse T-cells upon TCR engagement [45], yet its expression is commonly upregulated in patients with various cancer types and usually implies a poor prognosis [46–49]. Likewise, PD-L1 mRNA can be found broadly in various tissues under normal physiological conditions while its protein is only expressed in specific tissue types such as placenta, tonsil and a small proportion of macrophage-like cells in lung and liver [4], suggesting that the expression of PD-1 and PD-L1 is regulated post-transcriptionally, which is typically mediated by noncoding RNAs.

Noncoding RNAs refer to RNAs that have no protein-coding ability, and the most studied types are microRNAs (miRNAs) with a length of about 22 nucleotides and long

Table 1 The latest PD-1/PD-L1-related drugs that are launched in the market or under clinical trials

Target	Name (Code)	Corporation	Clinical Indications	Status
PD-1	Nivolumab	Bristol-Myers Squibb/ Ono	Unresectable melanoma (2014); Squamous and non-squamous NSCLC, advanced RCC (2015); Hodgkin's lymphoma, RCC, recurrent or metastatic head and neck cancer (2016); Unresectable or metastatic UC, HCC, metastatic CRC (2017)	Launched-2014
	Pembrolizumab	Merck	Unresectable or metastatic melanoma (2014); NSCLC (2015); Squamous head and neck cancer, metastatic NSCLC (2016); CRC, Hodgkin's lymphoma, Gastric Cancer (2017)	Launched-2014
	Cemiplimab	Sanofi/Regeneron	Metastatic CSCC; NSCLC; Cervical cancer	Pre-Registered
	Tislelizumab	BeiGene	Unresectable HCC	Phase 3
	REGN2810	Regeneron Pharmaceuticals	NSCLC	Phase 3
	Niraparib	ARCAGY/ GINECO GROUP	Ovarian Cancer; Endometrial Cancer	Phase 2/Phase 3
	Camrelizumab	Jiangsu Hengrui	Non-squamous NSCLC and squamous esophageal Cancer	Phase 2
	IBI-308	Innovent Biologics	NSCLC	Phase 2
	Spartalizumab	Novartis	Advanced melanoma	Phase 2
	MGA-012	Incyte/ MacroGenics	Metastatic CRC; metastatic Merkel cell Cancer	Phase 2
	AGEN-2034	Agenus	Cervical Cancer	Phase 2
	Sym-021	Symphogen	Solid tumors; lymphomas	Phase 2
	LZM-009	Livzon	Solid tumors	Phase 2
	BI-754091	Boehringer Ingelheim	Solid tumors	Phase 2
	XmAb-20,717	Xencor	Solid tumors	Phase 2
	MGD-013	MacroGenics	Solid tumors; hematologic neoplasms	Phase 2
	TSR-042	Tesaro/ AnaptysBio	Solid tumors	Phase 2
	AMP-224	GlaxoSmithKline/ MedImmune	CRC	Phase 2
	Atezolizumab	Oslo University Hospital	NSCLC	Phase 2
	SHR-1210	Shanghai Zhongshan Hospital	Gastric Cancer	Phase 2
	CV301	Bavarian Nordic	Bladder Cancer	Phase 2
	eFT508	Effector Therapeutics	Solid Tumors	Phase 2
	JNJ-63723283	Janssen Research & Development, LLC	Multiple Myeloma; Castration-Resistant Prostatic Neoplasms; UC	Phase 1/ Phase 2
	TTI-622	Trillium Therapeutics Inc.	Lymphoma; Myeloma	Phase 1
	HLX10	Henlix, Inc	Solid Tumor	Phase 1
	PF-06801591	Pfizer	Solid tumors; lymphomas; Prostatic Cancer; Melanoma; Ovarian Cancer; Sarcoma; Hodgkin lymphoma	Phase 1
PD-L1	Atezolizumab	Roche	Locally advanced or metastatic UC and NSCLC	Launched-2016
	Durvalumab	AstraZeneca	Locally advanced or metastatic UC (2017) and NSCLC (2018)	Launched-2017
	Avelumab	Merck/ Pfizer	Metastatic Merkel cell Cancer and locally advanced or metastatic UC	Launched-2017
	M-7824	Merck	Advanced solid tumors	Phase 2
	CX-072	CytomX Therapeutics	Solid tumors, lymphomas	Phase 2
	MSB-2311	MabSpace Biosciences	Solid tumors	Phase 2
	FS-118	F-star/ Merck	Advanced cancer	Phase 2
	FAZ-053	Novartis	Advanced cancer	Phase 2
	KN-035	Suzhou Alphamab	Solid tumors	Phase 2
	LY-3300054	Lilly	Solid tumors	Phase 1

noncoding RNAs (lncRNAs) which are longer than 200 nucleotides [50, 51].

miRNAs are a class of small single-stranded RNAs that post-transcriptionally modulate gene expression by binding to the mRNA 3′-untranslated region (3′UTR) of target genes, causing mRNA degradation or repression of translation [52]. Currently, it is well-known that miRNAs can be aberrantly expressed in various human cancers [53, 54], as a result of

which the majority of studies on miRNAs have focused on their function as oncogenes or tumor suppressors [55–59].

LncRNAs are recognized to play vital roles in the regulation of numerous biological processes such as cell proliferation, RNA splicing, gene expression, and apoptosis, which are altered during cancer development and progression [51]. Due to their highly cell-specific and time-dependent expression patterns, lncRNAs are mainly studied as cellular address code and gene expression modulators, which are often realized by interaction with other noncoding RNAs [60–63].

Emerging evidence has revealed the pervasive involvement of noncoding RNAs in the regulation of the host immune response, especially in the tumor microenvironment [64–71]. Here we summarize the most recent studies on the regulation of the PD-1/PD-L1 pathway by noncoding RNAs in cancer and aim to contribute to further understanding of the immune checkpoint blockade and precision medicine in cancer immunotherapies.

Regulation of the PD-1/PD-L1 Pathway by Noncoding RNAs in Cancer

Regulation of PD-1/PD-L1 by miRNAs

miRNAs exert their functions mostly by interaction with the 3′UTR of their target genes' mRNA, which has been a consensus in miRNA study [72]. Elevated PD-L1 expression caused by structural variations disrupting its mRNA 3′UTR uncovered a novel genetic mechanism of immune escape in multiple cancers [73]. Likewise, variant single nucleotide polymorphisms (SNPs) at the binding sites of miRNAs in the PD-L1 3′UTR obstructed the interaction between miRNAs and PD-L1 mRNA, leading to increased risk of cancers [74]. For example, a guanine-to-cytosine mutation at the 3′UTR of PD-L1 mRNA which was further confirmed to locate at the "seed region" of the binding sites of miR-570 was frequently observed in gastrointestinal cancers, as a result of which the interaction between miR-570 and PD-L1 mRNA was hindered, consequently leading to the overexpression of PD-L1 [75].

Meanwhile, PD-L1 expression was induced by IFN-γ and *Cryptosporidium parvum* in Cholangiocytes through the downregulation of miR-513 [76, 77] while suppressed by miR-155 induction via TNF-α and IFN-γ in primary human cells [78, 79]. A miRNA cluster, the miR-25-93-106b cluster, was also demonstrated to regulate bone marrow metastasis and immune invasion via modulation of PD-L1 in bone marrow (BM) stromal niche [80].

As previously mentioned, most of the studies on noncoding RNAs are focused on the roles they played during the tumorigenesis and development. As NSCLC, melanoma and gastrointestinal cancers are the primary causes of cancer-related deaths worldwide [35], they have undoubtedly drawn much attention. Hereunder, we will mainly discuss the study progress of the PD-1/PD-L1 pathway regulation mechanisms by noncoding RNAs in NSCLC, melanoma, gastrointestinal cancers, and many other cancers.

NSCLC

The role of miRNAs in NSCLC carcinogenesis was indicated as early as in 2004 since the relatively low expression of several miRNAs was demonstrated in lung cancer cell lines [81, 82]. The number of functional studies focusing on the miRNAs' role in NSCLC has increased and several independent researches revealed the pro- or anti-cancer functions of miRNAs including miR-150 [83], miR-34a [84, 85], miR-486-5p [86–89], miR-18a [90, 91] and miR-146a [92, 93].

The emergence of numerous predictive bioinformatics tools has offered us unprecedented opportunities and convenience for noncoding RNA function prediction and analysis. miR-140-3p, for example, is predicted to have the potential to bind to the 3′UTR of PD-L1 mRNA in many cancers [94], which was further verified in osteosarcoma [95] and NSCLC [96]. Similarly, the high expression of miR-33a was found to be associated with low PD-1 expression and more prolonged survival of patients in lung adenocarcinoma exploiting The Cancer Genome Atlas (TCGA) database and further confirmed with patients' tissue samples [97].

miRNAs that share the same seed alignment and consensus secondary structures are considered to belong to a miRNA family [98], and the family members are often found to work synergistically to maximize their function in the biological processes [99]. The miR-34 family has been reported to be a suppressor in various cancer types by targeting the Notch, c-Myc, c-Met, Bcl-2, Src, and p53 [100]. miR-34a especially has shown clinical significance in the treatment of MM [101] and NSCLC [85]. p53 is one of the most commonly mutated genes in cancers and crucial in regulating apoptosis, cell division, DNA damage and repair, senescence, and modulating the immune response [102]. A p53/miR-34/PD-L1 axis was demonstrated in NSCLC, where p53 regulated PD-L1 via the miR-34 family.

Moreover, in vivo administration of MRX34 (a liposomal formulation complexed with miR-34a mimic) alone or in combination with radiotherapy could reduce PD-L1 expression in the tumor and liberate T cell from exhaustion, showing a promising anti-tumor potential of miRNAs [103].

miR-200 family is another well studied miRNA family in various malignancies, including acute myeloid leukemia (AML), ovarian cancer, colorectal cancer, and lung cancer [104–106]. The miR-200/ZEB1 (zinc-finger E-box-binding homeobox 1) axis has been reported to regulate tumor metastasis through epithelial-to-mesenchymal transition (EMT) progress, and PD-L1 was found to be under the regulation of

this miR-200/ZEB1 axis in NSCLC, which subsequently led to debility of $CD8^+$ T-cells in the tumor microenvironment, connecting the $CD8^+$ tumor-infiltrating lymphocytes (TILs) exhaustion with EMT and revealing the significance of immune-suppression to tumor metastasis [107].

Besides directly binding with the 3′UTR of PD-1/PD-L1 mRNA, miRNAs are also found to exert their regulation on PD-1/PD-L1 through their upstream and downstream pathways.

As drug resistance and chemoresistance are the main obstacles affecting the treatment of NSCLC, it seems essential to focus on reversing the resistant state of tumors to sensitive ones. In chemoresistant NSCLC, a miR-197/cyclin-dependent kinases regulatory subunit 1 B (CKS1B)/ signal transducers and activators of transcription 3 (STAT3)-mediated PD-L1 network was revealed in which the downregulation of miR-197 was associated with chemoresistance and worse overall survival [108]. PD-L1 was regulated by STAT3, which was a pivotal target downstream of the miR-197/CKS1B pathway and proved to have the potential of relieving lung cancer drug resistance and tumor progression. On the contrary, miR-3127-5p was found to promote STAT3 phosphorylation and subsequently induced the expression of PD-L1 in NSCLC and eventually resulted in immune escape and chemoresistance [109].

Melanoma

The promising results achieved by anti-PD-1/PD-L1 therapies have inspired more and more studies in checkpoint blockade in melanoma treatment as the low 5-year survival rate and inadequate response to traditional chemotherapies are two main obstacles facing the treatment of melanoma.

PD-L1 expression was upregulated in tissue biopsies after resistance to BRAF or mitogen-activated extracellular signal-regulated kinase (MEK) inhibitors (BRAFi or MEKi) treatment arose in a cohort of 80 MM patients, consequently leading to increased invasiveness and worse prognosis. Plasmatic miR-17-5p levels showed to be inversely correlated with that of PD-L1, which was further verified to be post-transcriptionally regulated by miR-17-5p. Together, these results revealed that miR-17-5p might be used as inverse indicators of PD-L1 levels by the tumor, along with PD-L1 a marker for the aggressiveness of melanoma and a predictor of response to BRAFi or MEKi treatment [110].

miR-28, likewise, through silencing of PD-1, restored the impaired secretion of cytokines interleukin 2 (IL-2) and TNF-α by liberating the exhausted T-cells in melanoma in vivo, thus providing a novel target in melanoma immunotherapies [111].

Tumor-associated macrophages (TAMs) are the dominant and most abundant leukocytic infiltrate in many tumor types that participate in tumor angiogenesis, invasion, metastasis and almost every process during tumor progression. It is commonly acknowledged that TAMs have two dominant distinctive phenotypes: the immunosuppressive, tumor-promoting M2 macrophage and pro-inflammatory and tumoricidal M1 macrophage [112–114].

MiRNAs have long been studied for their regulation of host immuno-inflammatory responses [115]. miR-21 and miR-4717 are among the first ones found to modulate host immune response through regulation of PD-1 in virus-induced inflammation and liver diseases [116, 117]. As one of the first identified miRNAs, miR-21 has been reported to be a key regulator of oncogenesis in gastric [118–121], renal [122, 123], esophageal [124–126], colon [127–129], lung [130–132], prostate [133–135], breast cancer [136, 137] and melanoma [138]. By downregulating Janus kinase 2 (JAK2) and signal transducers and activators of transcription 1 (STAT1), miR-21 inhibited the IFN-γ-induced STAT1 signaling pathway, which is required for macrophage M1 polarization. miR-21 depletion was thus confirmed to facilitate tumoricidal inclination through participating in the STAT1-mediated activation of anti-tumor immunity and improved PD-1 immunotherapy [6, 139, 140], which was verified in vivo in melanoma xenografts.

Gastrointestinal Cancers

Gastric cancer and colorectal cancer (CRC) are the two main types of gastrointestinal cancers, which are among the most prevalent cancers in the general population [141]. While *Helicobacter pylori (H. pylori)* infection is the most common cause of gastric cancer, a novel mechanism was revealed through which *H. pylori* promotes gastric cancer development by upregulating PD-L1 expression via inhibition of the miR-200b and miR-152 expression, causing immune escape [142]. PD-L1 was further verified to be a target gene of miR-152, and overexpression of the latter could increase immune response via PD-L1 inhibition [143].

In CRC, miR-138-5p expression was downregulated in tissue samples and inversely connected with advanced cancer stage, lymph node metastasis, and overall survival. Moreover, miR-138-5p could bind to PD-L1 mRNA 3′UTR, leading to CRC cell growth suppression in vitro and tumorigenesis inhibition in vivo [144]. Also, in advanced CRC, a PTEN (phosphatase and tensin homolog)-inhibition-induced PD-L1 upregulation was mediated by miR-20b, 21 and -130b, where the PD-L1 overexpression was induced by the inhibition of PTEN, as has been reported before [145], and PTEN silencing was regulated by overexpression of miR-20b, 21 and -130b [146].

Other Cancers

Targeted therapies are showing extraordinary effectiveness in treating all kinds of cancers in this era of precision medicine. As a result, studies on immune checkpoint blockade are also carried out in various malignant tumors.

Acute myeloid leukemia (AML) is a fatal hematological malignancy that features a highly immunosuppressive microenvironment [147]. As the incidence rate of the disease is rapidly growing through the decades, a more profound understanding of its genetic underpinnings is urgent. miR-34a was verified to regulate PD-L1 through interaction with its 3′UTR and could further reduce the PD-L1-induced IL-10 production, sensitizing the PD-L1-overexpressing tumor cells to T cell killing in AML [148]. miR-200c and miR-34a were also identified as crucial regulators of PD-L1 in AML, which is mediated by the heterodimeric oncoprotein MUC1, which could regulate the processing of miRNA. Herein the silencing of MUC1 caused a marked increase in mature miR-200c and miR-34a levels, and a decrease in PD-L1 protein level consequentially [149].

In epithelial ovarian carcinoma (EOC), one leading cause of death in women with gynecological malignancies, miR-424 activated cytotoxic T lymphocytes (CTLs), reduced regulatory cytokine secretions and eventually reversed chemoresistance by downregulating PD-L1 and CD80, as the immune checkpoint was blocked and T cell immune response activated [150]. As a matter of fact, miR-424 belongs to the miR-15/−16/−195/−424/−497/−503 family, whose another two members, miR-16 and miR-195, were also found to be able to enhance radiotherapy in prostate cancer by targeting PD-L1, which subsequently activated T-cells through proliferation of cytotoxic $CD8^+$ T-cells and inhibition restraint of myeloid-derived suppressor cells (MDSCs) and regulatory T-cells (Tregs) [151].

miR-374b [152], miR-375 [153], miR-138 [154], miR-142-5p [155], miR-574-3p [156], miR-195 [157] and miR-873 [158] were also demonstrated to regulate the PD-1/PD-L1 pathway and cancer immune response in liver cancer, head and neck squamous cell carcinoma (HNSCC), glioma, pancreatic cancer, spinal chordoma, diffuse large B cell lymphoma (DLBCL) and breast cancer respectively (Table 2).

Regulation of PD-1/PD-L1 by Other Noncoding RNAs

Besides the miRNAs, other types of noncoding RNAs were also found to be involved in PD-1/PD-L1 pathway regulation in cancers.

Actin filament-associated protein one antisense RNA 1 (AFAP1-AS1), for example, was found to be co-expressed with PD-1 in nasopharyngeal carcinoma (NPC) [159]. Also, the high expression of AFAP1-AS1 and PD-1 was strongly associated with distant metastasis and poor prognosis, revealing a novel marker and candidate target for clinical trials. Another lncRNA, small nucleolar RNA host gene 20 (SNHG20), has been demonstrated recently to promote cell growth and metastasis in esophageal squamous cell carcinoma (ESCC) via modulating ATM (ataxia telangiectasia–mutated kinase)-JAK-PD-L1 pathway [161]. The noncoding RNAs that regulate the PD-1/PD-L1 pathway indirectly are shown in Table 3.

HY4, a member of a newly discovered ncRNA category, Y RNA, is found to be enriched in chronic lymphocytic leukemia (CLL)-derived exosomes. Uptake of hY4 triggered PD-L1 upregulation and cytokine secretion in monocytes, which was further verified to be mediated via Toll-like receptor 7 (TLR7) signaling [160]. Since circulatory noncoding RNAs are mainly transported to the plasma in exosomes to avoid degradation by nuclease, exosomes are widely studied in order to search for novel biomarkers and targets in cancer diagnoses and treatment. This work uncovered a new kind of noncoding RNA participating in cancer immune response regulation and provided new insights into the cancer diagnoses and treatment [162]. The potential role of noncoding RNAs in PD-1/PD-L1 pathway regulation is shown in Fig. 1.

Conclusion and Perspective

As personalized cancer therapies are becoming more and more popular around the world, antibodies targeting different genes in various cancer types are studied and developed, of which the anti-PD-1/PD-L1 antibodies are doubtlessly the most high-profile and successful ones, with several of each kind approved by FDA for treatment of many cancer types [162, 163].

As PD-L1 is often induced by cytokines secreted by cancer cells like TNF-α and IFN-γ to evade the attack by activated T-cells via the interaction between PD-1 and PD-L1, the PD-1/PD-L1 checkpoints blockade therapies regulate the immune response at the tumor sites and fix ongoing immune processes unlike previous immune therapeutic agents that boost systemic immune responses against cancer in the first place. In other words, blockade of the PD-1/PD-L1 interaction can not only ameliorate the host immune response by activating the macrophages or promoting the secretion of anti-tumor cytokines, it can also remove the exhausted T-cells at the tumor sites, thus promoting the proliferation of the T cells and stimulate them to kill the cancer cells, which makes the anti-PD-1/PD-L1 therapies unique and far more effective and powerful than traditional immune therapeutic agents.

Meanwhile, apart from liberating T cells from exhaustion phenotype, PD-1/PD-L1 blockade has also demonstrated a significant impact on reversing the resistance of patients to traditional cancer treatments including chemotherapy and radiotherapy [103, 108–110, 150, 151]. Here we can see that once the PD-1/PD-L1 pathway is blocked by miRNA-mediated PD-L1 silencing, the T-cell immune response will be activated and thus reversing the resistance to traditional chemotherapies or radiotherapies or enhancing the efficacy of the therapies. On the contrary, the miRNA-mediated PD-L1 upregulation will often lead

Table 2 Noncoding RNAs regulating PD-1/PD-L1 pathway directly and their functions in cancer

Target	Noncoding RNA	Host	Expression	Function	Reference
PD-1	miR-4717	HBV-associated liver diseases	Up-regulated	Increase the production of TNF-α and IFN-γ, affects the susceptibility and disease course of chronic HBV infection	[117]
	miR-21	HSV-Induced Inflammation; Melanoma	Up-regulated	miR-21 depletion promotes tumoricidal polarization and enhances PD-1 immunotherapy	[116, 138, 140]
	miR-155	Experimental autoimmune encephalomyelitis	Down-regulated	/	[79]
	miR-33a	Lung adenocarcinoma	Up-regulated	miR-33a high levels were associated with low PD-1 expression and longer survival of patients	[97]
	miR-28	Melanoma	Up-regulated	Convert the exhaustive status of T cells	[111]
	miR-138	Glioma	Up-regulated	In vivo miR-138 treatment demonstrated marked tumor regression and an associated decrease in PD-1 expression	[154]
	miR-374b	Liver cancer	Down-regulated	Enhance the tumor-targeting capacity of cytokine-induced killer cells, inhibit liver cancer progression	[152]
	AFAP1-AS1	NPC	Up-regulated	Promote the formation and development of NPC, predict poor prognosis in NPC	[159]
PD-L1	miR-513	Cholangiocytes	Down-regulated	Reduce IFN-γ-stimulated B7-H1 expression and consequently influence B7-H1-associated apoptosis in cocultured T cells	[76, 77]
	miR-155	Human primary cells	Up-regulated	/	[78]
	miR-25-93-106b	BM stromal niche	Up-regulated	Inhibit recruitment and invasion of bone marrow cells	[80]
	miR-140	NSCLC; Osteosarcoma	Down-regulated	Inhibit cell proliferation and cell cycle; suppress osteosarcoma tumor growth	[94–96]
	miR-34	NSCLC; AML	Down-regulated	Increase tumor-infiltrating CD8+ cells and reduce the PD-1+ T-cells and macrophages; inhibit tumor growth	[103, 148]
	miR-200	NSCLC; Gastric cancer; AML	Down-regulated	Determine the abundance and function of CD8+ TILs and tumor metastatic potential	[107, 142]
	miR-17-5p	Melanoma	Down-regulated	miR-17-5p levels in MM patients inversely correlate with PD-L1 expression and may predict sensitivity to BRAFi	[110]
	miR-152	Gastric cancer	Down-regulated	Improve T cells proliferation and function	[142, 143]
	miR-570	Gastric cancer	Up-regulated	/	[75]
	miR-138-5p	CRC	Down-regulated	Suppress CRC cell growth in vitro and inhibit tumorigenesis in vivo	[144, 154]
	miR-142-5p	Pancreatic cancer	Down-regulated	Inhibit mice pancreatic cancer growth and enhance anti-tumor immunity	[155, 164]
	miR-195	DLBCL; Prostate Cancer	Down-regulated	Promote IFN-γ and TNF-α levels and decrease IL-10 and the ratio of PD-1+ T cells; Enhance radiotherapy via T cell activation in the tumor microenvironment	[151, 157]
	miR-574-3p	Spinal chordoma	Down-regulated	/	[156]
	miR-375	HNSCC	Down-regulated	Increase T cell responses	[153]
	miR-424	Epithelial ovarian carcinoma	Down-regulated	Reverse chemoresistance by T cell immune response activation in vitro and in vivo	[150]
	miR-16	Prostate Cancer	Down-regulated	Enhance radiotherapy via T cell activation in the tumor microenvironment	[151]
	hY4	CLL	Down-regulated	Induce cytokine secretion and immunosuppressive molecules in monocytes	[160]

to resistance [109] (Table 4). In a sense, miRNAs can function analogously with PD-1/PD-L1 antibodies in cancer treatment to achieve a better outcome, which implies better exploitation of miRNAs in clinical trials.

Table 3 Noncoding RNAs regulating PD-1/PD-L1 pathway indirectly and their functions in cancer

Target	Noncoding RNA	Host	Expression	Direct Target	Function	Reference
PD-L1	miR-197	NSCLC	Down-regulated	CKS1B	Promote pulmonary metastasis and lead to chemoresistance	[108]
	miR-3127-5p	NSCLC	Down-regulated	STAT3	Upregulate PD-L1 inducing chemoresistance	[109]
	miR-20b-21-130b	CRC	Up-regulated	PTEN	/	[146]
	SNHG20	ESCC	Up-regulated	ATM	Promote growth and metastasis	[161]

Despite the success that anti-PD-1/PD-L1 antibodies achieved in clinical, there are still much unknown about the PD-1/PD-L1 pathway and the associated immune responses including the regulation of their expression in different tissues and tumor types, the mechanism of resistance to the blockade therapies and the pathways related in their functions on tumor immunity. At this moment through the work of the regulation of the PD-1/PD-L1 pathway by noncoding RNAs, we can take a glance at the mechanism underlying the expression pattern of the PD-1/PD-L1 pathway in the tumor microenvironment.

Although the function of lncRNAs in different biological activities have been studied comprehensively and understanding of them have been thriving, apparently there are still much unknown about their roles in immune checkpoint regulation. The studies focusing on the regulation of the PD-1/PD-L1 pathway by noncoding RNAs mostly revealed microRNA-mediated mechanisms, leaving much work for investigation of other unrevealed noncoding RNAs, especially lncRNAs. It must be admitted that there is still a long way ahead of us to achieve a full understanding of this pathway and the role it plays in the tumor immunology. Much more work is needed to reveal the complete picture of these critical immune checkpoints, which will facilitate the discovery and design of novel clinically applicable approaches in cancer immunotherapies.

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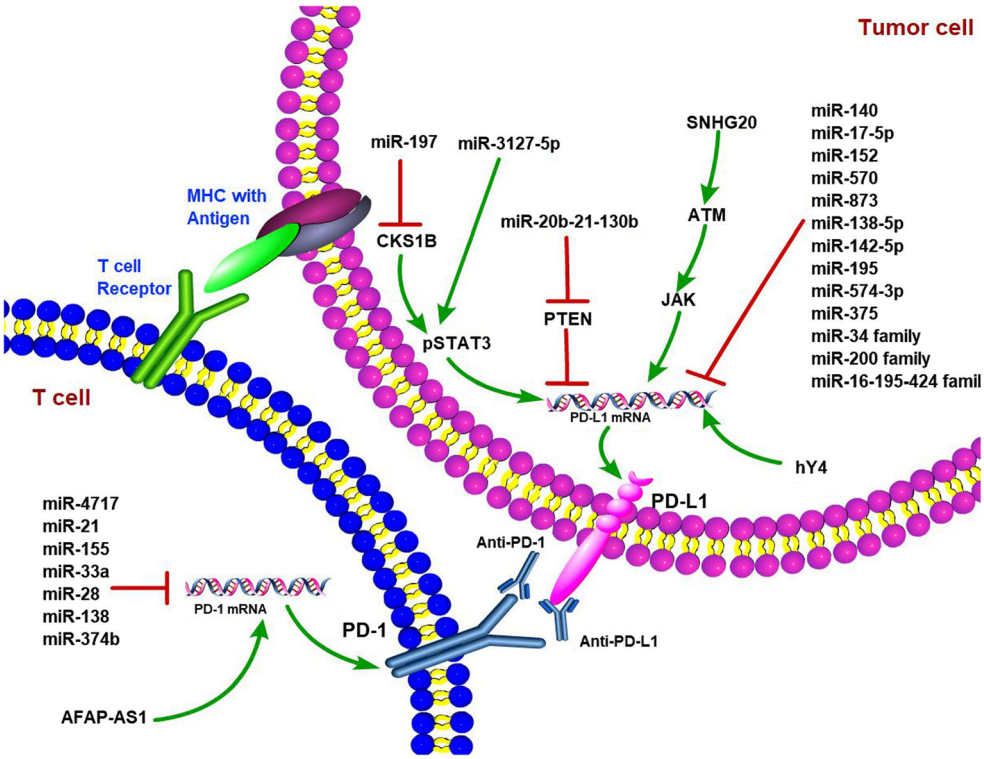

Fig. 1 Noncoding RNAs that are involved in regulation of the PD-1/PD-L1 pathway in cancer. The PD-1 is expressed on the surface of T cells, while PD-L1 is usually elevated in tumor cells in response to cytokines secreted by tumors. The PD-1/PD-L1 pathway are under regulation of many noncoding RNAs post-transcriptionally directly or indirectly, most of which are miRNAs. The use of PD-1/PD-L1 antibodies can specifically bind with PD-1 or PD-L1 and block the pathway, after which the T-cells will be activated again to kill the tumor cells

Table 4 miRNAs involved in regulating resistance to chemotherapy and radiotherapy

Noncoding RNA	Host	Treatment	Effect	Reference
miR-197	NSCLC	Platinum-based chemotherapy	Overexpression of miR-197 sensitized the drug response of Cis-diaminodichloroplatin (CDDP) and paclitaxel (TXL) in vitro	[108]
miR-3127-5p	NSCLC	Cisplatin chemotherapy	Upregulate PD-L1 expression, leading to chemoresistance	[109]
miR-17-5p	Melanoma	BRAF or MEK inhibitors (BRAFi or MEKi) treatment	Downregulated miR-17-5p in melanoma caused PD-L1 up-regulation, leading to resistance to BRAFi or MEKi	[110]
miR-424	EOC	Cisplatin chemotherapy	miR-424 reversed chemoresistance by silencing PD-L1 and T cell activation	[150]
miR-34	NSCLC	Radiotherapy	MRX34 delivery enhanced efficacy of radiotherapy	[103]
miR-195-16	Prostate cancer	Radiotherapy	Restoration of miR-195 and miR-16 expression enhanced radiotherapy via T cell activation in the tumor microenvironment by blocking PD-L1 expression.	[151]

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Compliance with Ethical Standards

Ethical Approval and Consent to Participate Not applicable.

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