

Review

The Interaction of Programmed Cell Death Protein and Its Ligands with Non-Coding RNAs in Neoplasms: Emerging Anticancer Immunotherapeutics

Mahmoud Kandeel ^{1,2,*} , Duaa Althumairy ³, Ibrahim M. El-Sabagh ^{4,5}, Saad Shousha ^{1,6}, Yehia Hussin ^{7,8}, Ahmed M. A. Meligy ^{9,10} , Mohamed K. Zabady ^{7,11}, Khaled M. Zahran ^{12,13}, Nawal Elkhair ^{1,14}, Abdulrahman Hereba ^{15,16}, Mahmoud G. Elsebaei ^{1,17} , Aliya Elamin ¹⁸, Faiza Irshad ¹⁹, Muhammad Sufyan ²⁰, El-Awad M. El-Hassan ¹⁵ and Ibrahim Albokhadaim ¹

¹ Department of Biomedical Sciences, College of Veterinary Medicine, King Faisal University, Al-Ahsa 31982, Saudi Arabia

² Department of Pharmacology, Faculty of Veterinary Medicine, Kafrelsheikh University, Kafrelsheikh 33516, Egypt

³ Department of Biological Sciences, King Faisal University, Al-Ahsa 31982, Saudi Arabia

⁴ Central Biotechnology Laboratory, College of Veterinary Medicine, King Faisal University, Al-Ahsa 31982, Saudi Arabia

⁵ Department of Virology, Faculty of Veterinary Medicine, Cairo University, Giza 12211, Egypt

⁶ Department of Physiology, Faculty of Veterinary Medicine, Benha University, Benha 13518, Egypt

⁷ Department of Clinical Studies, College of Veterinary Medicine, King Faisal University, Al-Ahsa 31982, Saudi Arabia

⁸ Department of Forensic Medicine, Faculty of Veterinary Medicine, Alexandria University, Alexandria 5410012, Egypt

⁹ Central Lab. Department of Clinical Sciences, College of Veterinary Medicine, King Faisal University, Al-Ahsa 31982, Saudi Arabia

¹⁰ Department of Physiology, Agriculture Research Center (ARC), Giza 3725005, Egypt

¹¹ Department of Surgery, Faculty of Veterinary Medicine, Cairo University, Giza 12211, Egypt

¹² Department of Physical Education, College of Education, King Faisal University, Al-Ahsa 31982, Saudi Arabia

¹³ Department of Competitive Sport, College of Physical Education, Minia University, Minia 61511, Egypt

¹⁴ Department of Physiology, Faculty of Veterinary Medicine, University of Khartoum, Shambat 13314, Sudan

¹⁵ Department of Microbiology, College of Veterinary Medicine, King Faisal University, Al-Ahsa 31982, Saudi Arabia

¹⁶ Department of Biomedical Physics, Medical Research Institute, Alexandria University, Alexandria 5422031, Egypt

¹⁷ Department of Biochemistry and Chemistry of Nutrition, Faculty of Veterinary Medicine, Mansoura University, Mansoura 7650030, Egypt

¹⁸ Biomedical Sciences Department, College of Medicine, King Faisal University, Al-Ahsa 31982, Saudi Arabia

¹⁹ Institute of Botany, University of Punjab, Lahore 54590, Pakistan

²⁰ Department of Bioinformatics and Biotechnology, Government College University, Faisalabad 38000, Pakistan

* Correspondence: mkandeel@kfu.edu.sa



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Abstract: Recent studies have demonstrated that cancer cells can elude immune cells by creating a sanctuary within the tumor's microenvironment. Large amounts of immune-suppressing signaling proteins can be expressed by cancer cells. One of the most important mechanisms in this system is immune suppression caused by tumors and the modulation of the immune checkpoint. The immune checkpoint is modulated by both the programmed cell death protein 1 (PD-1) and its ligands, programmed death ligand 1 (PD-L1) and PD-L2. Non-coding RNAs (ncRNA), including the more well-known microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs), all play roles in the regulation of biological processes and extensive diseases such as cancer. Thus, the focus of this study is on the interactions between the programmed death protein and its ligands with miRNAs, lncRNAs, and circRNAs during tumorigenesis and tumor progression. Furthermore, some FDA-approved drugs for the treatment of various cancers were based on their interactions with PD-1, PD-Ls, and ncRNAs. This promising strategy is still in the production stages, with additional results and clinical trials being processed.

Keywords: cancer; noncoding RNA; immunotherapy; apoptosis; ligand

1. Introduction

The immune system plays a pivotal role in halting the progression of cancer. Cancer is a condition in which the immune system fails to recognize and eliminate abnormal cells and tissues. Tumor cells can evade the immune system in part because of the immunosuppressive qualities of the tumor microenvironment. It is commonly assumed that immunological checkpoints are negative modulators of the immune response due to their primary role in preventing tissue damage [1]. These checkpoints are frequently enhanced in response to the continuous activation of immune cells. When this checkpoint is engaged, the immune cell is prevented from launching a cytotoxic response. Therefore, the immunity cells are unable to kill other cells. To maintain the stability of the autoimmunity/self-tolerance balance, these checkpoint proteins are important. However, tumors may benefit from this network as they attempt to spread and grow.

Tumor cells may be able to avoid being destroyed by the immune system because of the immunosuppressive conditions brought about by immune checkpoint signaling [2]. Checkpoints are inhibitive in nature and comprise the cytotoxic T-lymphocyte-associated molecule-4, PD-1, and PD-L1 [3]. PD-1 is a costimulatory molecule that has a repressive function in adjusting T-cell stimulation in the periphery. PD-L1 and PD-L2 are ligands for PD-1, and both can bind to PD-1. PD-L1 is a type 1 transmembrane protein that plays a role in dampening the immune response to infection to prevent persistent tissue damage [4]. Because of its role, PD-L1 is extensively distributed throughout the body. PD-L2 is a ligand of PD-1 that has received very little research attention. It is mostly found on activated dendritic cells and macrophages, both of which participate in the suppression of the immune response against tumors [5].

In recent years, ncRNAs have been established as crucial participants in epigenetic gene regulation. It has been hypothesized that ncRNAs promote epigenetic modifications by recruiting chromatin-remodeling complexes that control transcription [6]. It has also been proven that a great number of ncRNAs act as negative regulators of transcription as well as transcription cofactors [7]. ncRNAs are also thought to have a role in the control of post-transcriptional processes such the splicing, transport, translation, and destruction of mRNAs [8]. In particular, miRNAs, lncRNAs, and circRNAs are the focus of several studies due to the likelihood that they play a role in the regulation of a wide range of cellular procedures, both normally and pathologically. In the milieu of tumor immunity, a substantial number of miRNAs and, to a lesser degree, lncRNAs and circRNAs, have been discovered as powerful regulators of tumor immunity through the direct control of genes that govern the equilibrium between immune stimulation and repression [9]. Using the current literature, we explored interactions between ncRNAs and PD-L1/-L2 within the context of human neoplasms. Additionally, we highlight existing and new notions within the fields of immunology and ncRNA research.

2. Immune Checkpoints and Modulators

An organism's immune system acts as one of its three lines of defense, protecting it from potentially harmful outside agents. The skin and mucous membranes, which serve as a natural barrier, make up the first line of defense. Natural bactericidal substances, which serve as the "vanguard" of the immune response, make up the second line of defense. Finally, the immune organs and cells, which are responsible for generating specific immune responses, make up the third line of defense. The T-cell receptor (TCR) and the peptide-major histocompatibility complex (pMHC) on the surface of antigen-presenting cells (APCs) interact to produce the first signal, and an antigen-independent co-signaling molecule is required for the second signal [4].

T-cells must receive two different signals to fully activate. The interaction of the antigenic peptide with MHC on the surface of APCs produces signal one. It is significant to highlight the immunological checkpoints that can operate as co-stimulators or co-inhibitors and tightly modulate the stimulating T-cells. If the binding of costimulatory receptors, such as CD28, occurs concurrently with the binding of the antigen/MHC and TCR, then T-lymphocytes may multiply and move toward a particular antigen. On the other hand, the activation of T-cells would be prevented if coinhibitory receptors such as CTLA-4 were activated concurrently with the binding of antigen/MHC and TCR [10,11]. CTLA-4 is not present in naive T-cells; however, it is quickly increased when T-cells are activated. Its primary function is to govern the increase in T-cells through the early priming phase in lymphoid organs. Naive T-cells do not have CTLA-4. When CTLA-4 connects to B7 proteins, it interferes with the costimulatory signals that are being sent out by CD28, which ultimately helps to inhibit overactive immunity. This co-inhibitor aids in the fight against unwanted autoimmunity and limits damage to healthy tissues [12,13].

PD-1 is an essential component in the process of keeping peripheral tolerance intact. After Src homology-2 (SH2) domain-containing phosphatases 1/2 (SHP1/2) are recruited, the TCR-mediated regulation of T-cell proliferation and cytokine production can occur [14]. This happens because the engagement of PD-1 by its ligands causes the recruitment of SHP1/2. It has been shown that an increased expression of PD-L1 on tumors has a strong correlation with an advanced disease state and an unfavorable prognosis in several kinds of cancer.

Immune checkpoint medicines do not directly eliminate cancer cells; rather, they make use of the capacity of the immune system of the host to re-enhance the body's natural ability to fight tumors [15,16]. The development of immunotherapy with the use of immune checkpoint inhibitors (ICIs) has meaningfully enhanced the overall survival rate in a sizeable proportion of society [17], which has resulted in a revolution in the treatment of cancer. Since their discovery, ICIs have assumed the role of primary treatment for a variety of cancers. In general, the method by which ICIs exert their impact is to remove the inhibitory brakes on T-cells, resulting in an increased immunological response. Although T-cells constitute the foundation of an ICI-mediated immune response, ICIs also activate innate, adaptive, and peripheral immunological responses [18]. Because of the careful coordination of these processes, the anti-tumor immune response is much improved overall when mediated by ICIs.

The FDA has authorized three ICIs to date. The first antibody to be discovered was ipilimumab, which was an antagonist antibody against CTLA-4. It was given to people who had advanced melanoma. The second type of antibody acts by reducing the amount of PD-1 generated by T-cells. The FDA has approved pembrolizumab and nivolumab as PD-1 inhibitors (Figure 1). These drugs were approved for the treatment of melanoma; however, they are currently used to treat a variety of other cancers. The third class of pharmacological medications works by inhibiting PD-L1 expression in cancer cells. Drugs in this class include atezolizumab, durvalumab, and avelumab. These medications were originally given to treat advanced-stage melanomas; however, they are now approved for the treatment of other cancers [19,20].

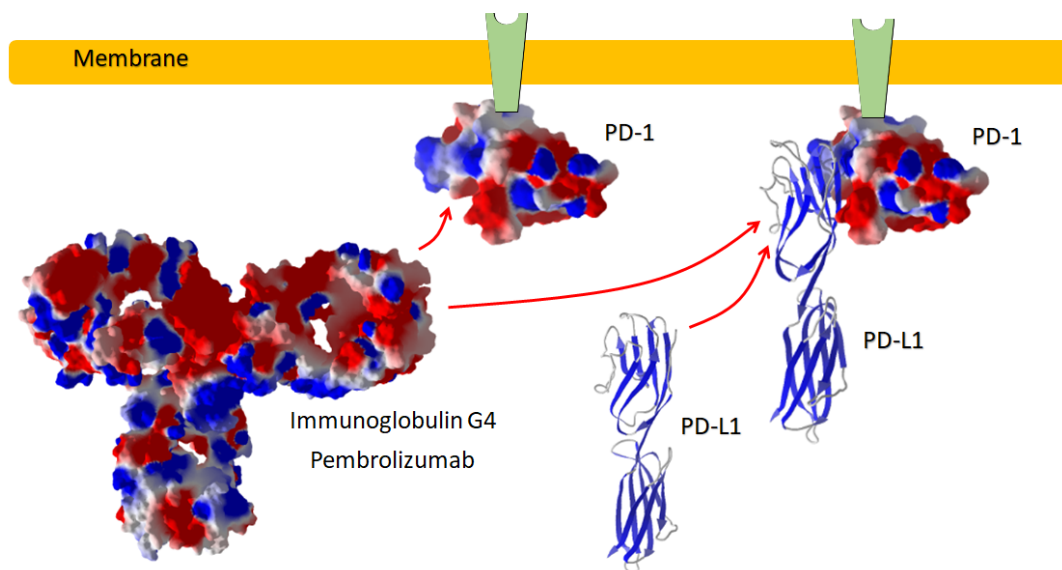


Figure 1. PD-1 inhibitor antibody. Pembrolizumab binds with the surface of the ectodomain of PD-1, preventing the immune-suppressive reaction by the binding of PD-L1 to its site on PD-1.

3. PD-L1 and PD-L2 in Cancer

In 1992, Tasuku Honjo and coworkers identified PD-1, and this molecule was shown to be involved with apoptosis (Figure 2) [21]. This finding emerged when the PD-1 gene was cloned from dying immune cell lines. By studying the immune responses of PD-1-deficient mice, scientists were able to demonstrate that PD-1 is synthesized for use as a negative modulator for immune responses [22]. Antigen-experienced memory T-cells in peripheral tissues express proteins at a higher level than B-cells, activated monocytes, dendritic cells (DC), or natural killer (NK) cells [23]. PD-1 is a member of the type II CD28 family of protein receptors. The extracellular region is structurally and functionally similar to immunoglobulin V and includes a transmembrane region, an intracellular region consisting of about 95 residues, and two phosphorylation sites located in the immunoreceptor tyrosine-based inhibitory motif (ITIM) and the immunoreceptor tyrosine-based switch motif (IgV). Src homology phosphatase-1 (SHP-1) and SHP-22 are phosphorylated, which can suppress TCR signaling [24,25].

PD-L1 and PD-L2 are the two PD-1 ligands; they belong to the B7 family of transmembrane proteins and function as type I receptors. The human B7-H1 gene was identified and cloned in 1999 by Lieping Chen and colleagues, who also found that it suppressed T-cells via generating IL-10 [26]. The finding that PD-1 interacted with B7-H1 led to the molecule being renamed PD-L1. The CD274 gene, located on human chromosome 9, encodes the 290-amino-acid protein receptor known as PD-L1 [27]. It consists of a transmembrane region, an intracellular region, and two extracellular regions that are structurally comparable to those of IgV and IgC. With only 30 amino acids, the PD-L1 intracellular domain is extremely short and seemingly useless. Multiple cell types, such as antigen-presenting cells, T-cells, B-cells, monocytes, and epithelial cells, might exhibit this immunological checkpoint. The protein is also upregulated in some cells in response to stimulation by pro-inflammatory cytokines, such as interferon-gamma (IFN- γ) and interleukin 4 (IL-4), by the transcription factors signal transducer and activator of transcription 1 (STAT1) and IFN regulatory factor 1 (IRF1) [28–30].

PD-L2 is encoded by the *Pdcd1lg2* gene, which is located 42 kilobase pairs (kb) from the *Cd274* gene in the human genome. It is composed of 7 exons and 273 amino acid residues split between cytoplasmic, transmembrane, IgV-like, and IgC-like domains. Bone-marrow-derived DCs, macrophages, and mast cells do not naturally produce PD-L2 but can be induced to do so [31,32].

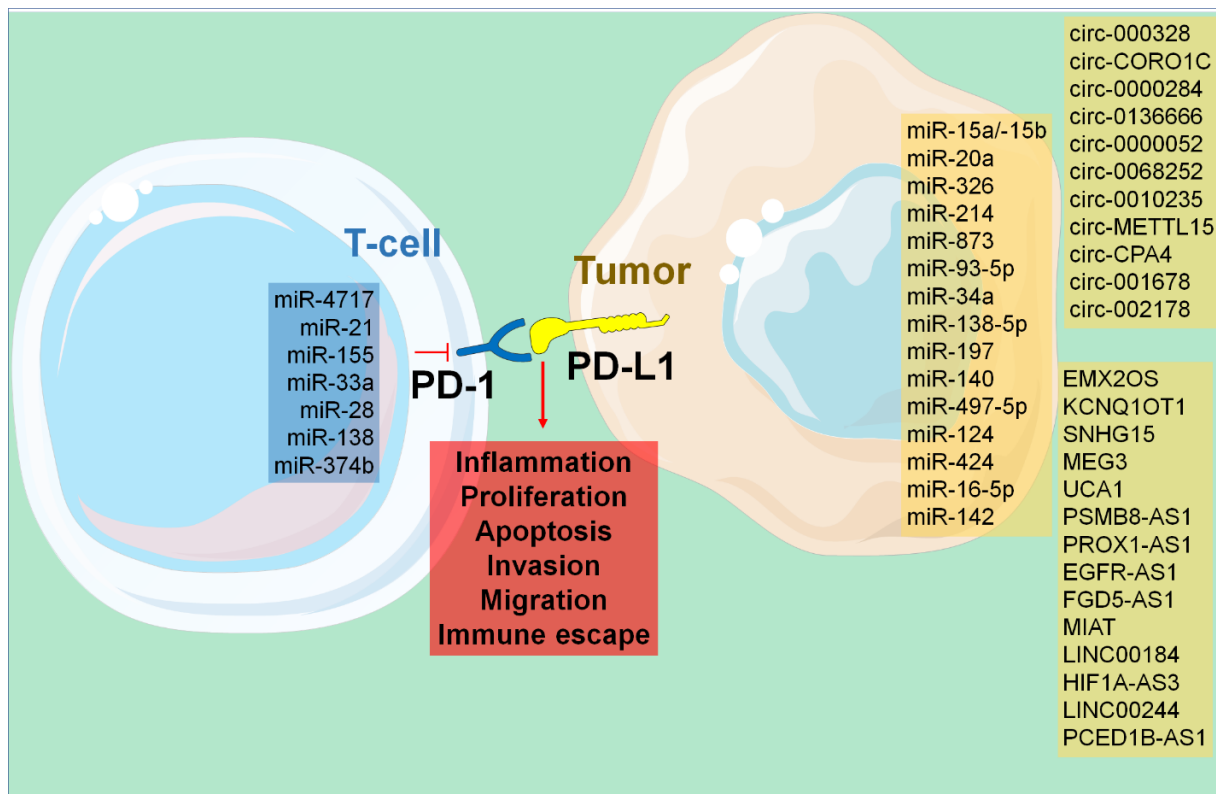


Figure 2. Cellular processes governed by the activation of PD-1/-L1 and -L2.

4. ncRNAs and Cancer

For several decades, the relatively small section of the genome that is responsible for protein coding was the primary focus of medical research. The decoding of the human genome revealed that fewer than 2% of our genes eventually code for proteins, and many scientists concluded that the other 98% of our genome was nothing more than non-functional “junk” [33,34]. Regardless, the ENCODE research discovered that the section of the genome that does not code for proteins is replicated in hundreds of RNA molecules. These RNA molecules appear to have an essential role in the whole spectrum of human illness, including cancer, besides modulating essential biological processes such as growth, development, and organ function [35,36]. The overall length of an ncRNA may be used to categorize it into one of many distinct types. The miRNAs, transfer RNA-derived small RNAs (tsRNAs), and Piwi-interacting RNA (piRNAs) are examples of the tiny ncRNAs that play an essential role in cancer. On the other end of the size spectrum are the lncRNAs, which are untranslated RNAs that are longer than 200 nucleotides and comprise subclasses such as pseudogenes and circRNAs [37].

4.1. miRNAs

The family of ncRNAs known as microRNAs (miRNAs, miR) has been researched the most, since it is responsible for negatively influencing the expression of up to 60% of protein-coding genes [38]. One of the most significant characteristics of miRNAs is their ability to target several mRNA molecules at once. For example, a single miRNA may target up to 200 distinct mRNAs, and many miRNAs can modify the same mRNA target [39]. The synthesis of miRNA starts in the nucleus with the transcription of a long hairpin transcript called pri-miRNA (Figure 3).

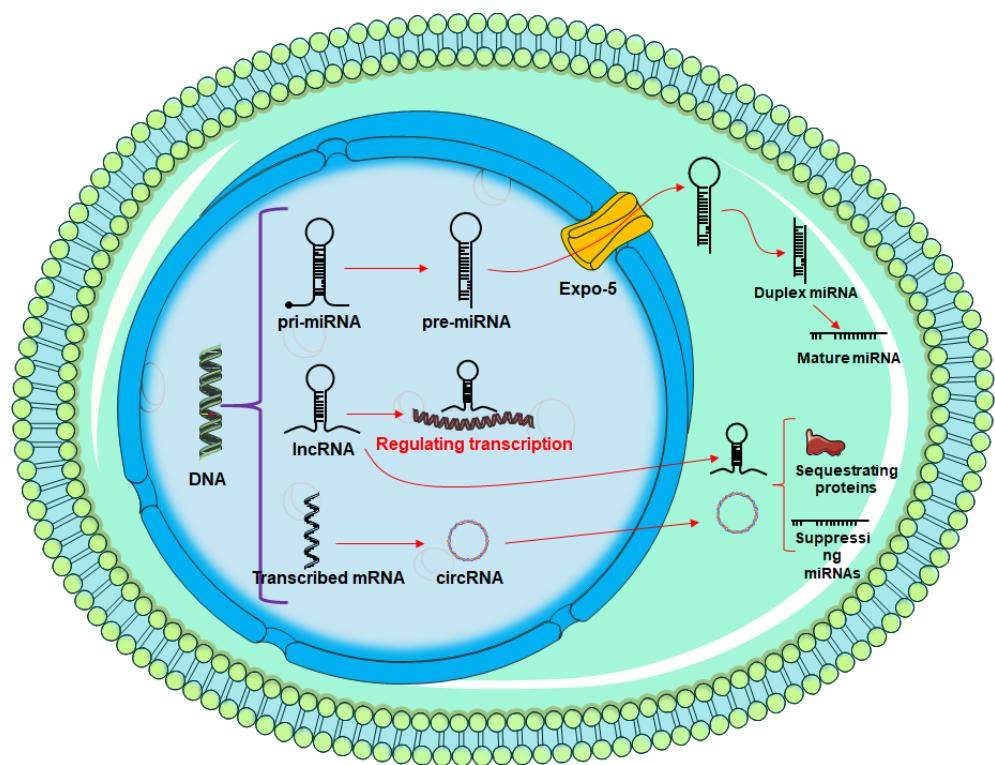


Figure 3. Overview of miRNA and circRNA production. The process is initiated in the nucleus, then exported to the cytoplasm for downstream activities.

The length of the pri-miRNA transcript can range from hundreds to thousands of nucleotides. In addition, RNA polymerase III Drosha and DGCR8 catalyze an enzymatic mechanism that converts pri-miRNA to pre-miRNA, a shorter transcript (DiGeorge syndrome critical region 8). Approximately 70 nucleotides make up this pre-miRNA transcript. Once pre-miRNA has been transported to the cytoplasm by nuclear receptor exportin 5, it is further processed by the Dicer complex, which first forms a mature miRNA duplex of around 22 nucleotide lengths before finally reducing it to a single-stranded miRNA. As a result of sequence complementarity, typically in the 3' untranslated region (UTR), mature miRNA loaded onto AGO2 and the RNA-induced silencing complex (RISC) will direct the targeting of certain mRNA transcripts, resulting in translational repression or mRNA destruction [40].

Changes in the expression of miRNA caused by physiological processes are critical components in the regulation of complex genomic networks and, as a consequence, cellular signaling cascades. As part of the pathological cellular alterations that can occur as a result of various diseases [41], reformed miRNA expression has a vital impact on the modification of protein expression in many disease situations. These short RNAs offer therapeutic potential for the focused modification of cell processes that are critical to a disease phenotype [42], in addition to the diagnostic potential of changed miRNA expression levels.

4.2. LncRNAs

A transcript that is longer than 200 nucleotides is referred to as a lncRNA. There are around 16,000 lncRNA genes in the human genome [43]. lncRNAs are classified into one of five different types, each of which is determined by the relative position of the protein gene and the lncRNA within the genome [44]. Sense lncRNAs, antisense lncRNAs, bidirectional lncRNAs, intronic lncRNAs, and intergenic lncRNAs all fall into this category (also known as long intergenic ncRNAs [lincRNAs]). lncRNAs have recently been found to play an important role in a wide variety of biological processes through regulating gene expression

in several distinct types of cancer. Furthermore, invasion, metastasis, and chemotherapy resistance have all been linked to the abnormal expression of lncRNAs [45,46].

4.3. CircRNAs

CircRNAs are a specific kind of ncRNA that are single-stranded and are found in very large quantities in human cells. Back-splicing is one of the processes that can lead to exon shuffling, and it is the mechanism that is responsible for the production of the vast majority of circRNAs. Because of their covalently-closed loop structure, lack of open terminals, and resistance to digestion by exonucleases and RNase R [47], circRNAs are more stable and better-conserved over evolutionary time than linear RNAs. Since circRNAs do not have any free terminals, they are not easily broken down by enzymes such as RNase R or exonucleases. Many different functions of circRNAs have been discovered in recent years. These functions include scavenging for miRNAs, regulating transcription, connecting proteins, and facilitating translation [48].

5. Regulation of PD-L1 and PD-L2 in Cancer by ncRNAs

Below is the information about the ability of ncRNAs to modify the activity of PD-L1/L2 in cancers (Table 1). There is a special focus on the interaction of miRNAs and PD-L1, which is shown in Figure 4.

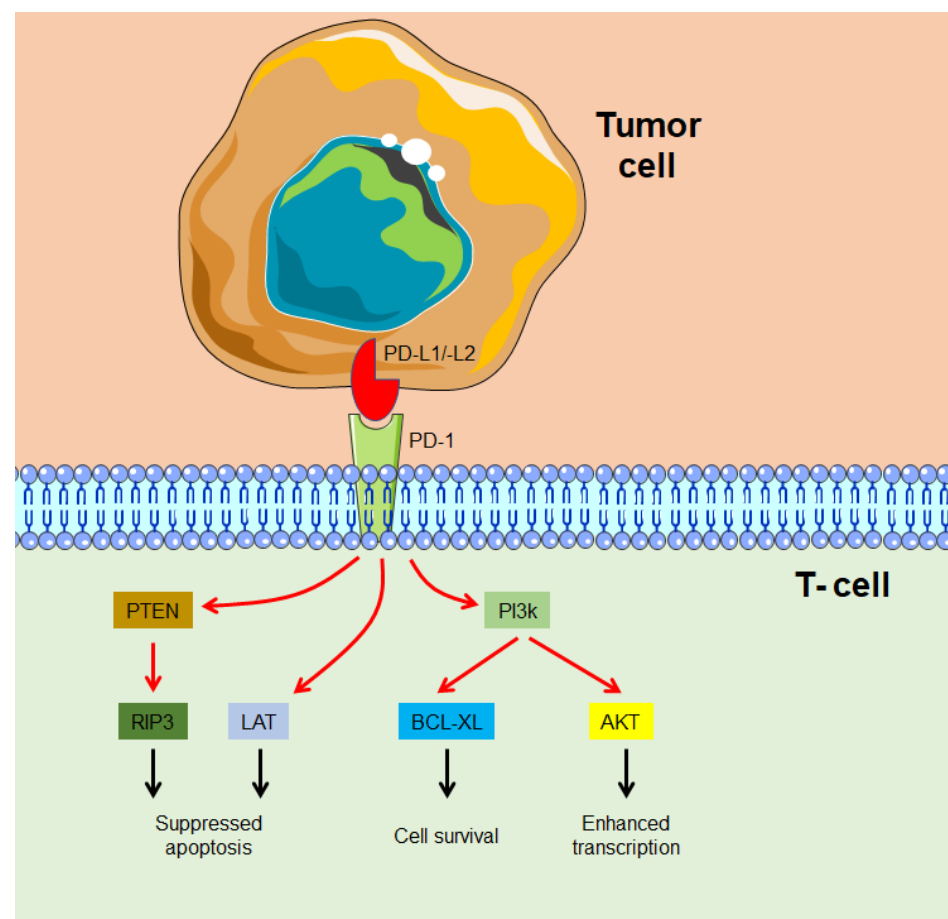


Figure 4. An overview of miRNAs with the ability to target PD-1/PD-L1 in human malignancies.

5.1. miRNAs

According to a recent study, miR-15a/miR-15b is responsible for the degradation of PD-L1 mRNA. The RNA-induced silencing complex and the 3'-UTR play a role in this phenomenon. Additional evidence suggests that miR-15a/miR-15b promotes neuroblastoma-

specific CD8+T-cell activation and cytotoxicity in vitro. In addition, the injection of miR-15a-overexpressing murine cells reduced tumor growth and vasculature and enhanced CD8+T and NK cell activation and infiltration into tumors in vivo. The anti-PD-L1 antibody has also been demonstrated to interfere with miR-15a/miR-15b-induced CD8+T and NK cell-regulated anti-cancer responses [49]. NSCLC cells were more likely to proliferate when miR-20a was present because it reduced the amount of PTEN that was expressed and increased the amount of PD-L1 [50].

Shao and colleagues found that the expression of miR-326 in LUAD tissue had a negative correlation with PD-L1/B7-H3. The change in the cytokine profile of CD8+ T-cells and the reduced migratory capacity of tumor cells are both brought about as a result of the inhibition of PD-L1 and B7-H3 expression, due to the overexpression of miR-326. At the same time, the downregulation of miR-326 facilitated the migration of tumor cells. In addition, inhibiting PD-L1 and B7-H3 had a dampening impact on the effect that the miR-326 inhibitor had on stimulating tumor growth. After miR-326 was overexpressed in tumor-bearing mice, there was a considerable increase in the infiltration of CD8+ T-cells, as well as a significant enhancement in the production of both TNF- α and IFN- γ , both of which contributed to the growth of the tumor [51].

In diffuse large B-cell lymphoma (DLBCL) tissues and cell lines, miR-214 was found to be downregulated, whilst PD-L1 was found to be increased. This was in comparison with normal neighboring tissues or normal B-cells. This suggested that there was an inverse relationship between the expression levels. The overexpression of miR-214 in OCI-Ly3 cells led to the triggering of apoptosis, as well as the inhibition of cell viability and invasion. In addition to this, it was discovered that miR-214 targets PD-L1 mRNA by binding to the 3'-untranslated region. OCI-Ly3 cells had a less malignant behavior after PD-L1 expression was knocked down. Targeting PD-L1 in vivo with an overexpression of miR-214 was shown to limit the development of tumors [52].

When PD-L1 was overexpressed, it activated the PI3K/Akt and ERK1/2 pathways, which in turn caused breast cancer cells to become resistant to chemotherapy and exhibit stem cell characteristics. A correlation between PD-L1 expression and stemness marker expression provided proof of this. Reduced PD-L1 expression and PI3K/Akt/ERK1/2 signaling [53] were responsible for miR-873's effects on breast cancer stemness and chemoresistance. Mechanistically, miR-873 bound to the 3'-UTR of PD-L1 and inhibited its expression, hence repressing its production. MiR-93-5p has been definitively linked to tumor growth and immune regulation in breast cancer, and it directly targets PD-L1 and CCND1 to accomplish its goals [54]. Wang et al. analyzed miR-34a and PD-L1 expression in 44 AML specimens (AML). An unfavorable correlation between PD-L1 and miR-34a expression was observed. The overexpression of miR-34a inhibited PD-L1 expression and reduced surface PD-L1 expression in HL-60 and Kasumi-1 cells. It was observed that miR-34a was a possible binding partner for the PD-L1-3'UTR region. In a similar vein, miR-34a was able to reverse the increase in PD-L1 surface expression that had been induced by chemotherapeutic medications, and was also able to reduce PD-L1-specific T-cell death after transfection. In addition, it was found that PD-L1 expression and AKT activation form a positive feedback loop [55].

MiR-138-5p, a tumor suppressor in CRC, works by reducing levels of the protein PD-L1. PD-L1 and miR-138-5p may be used as CRC biomarkers for optimum treatment selection and clinical outcome prediction [56], as patients with low miR-138-5p and high PD-L1 had shorter overall survival. In their study, Fujita et al. reported that PD-L1 is a possible biomarker of the miR-197-mediated CKS1B/STAT3 axis, which, in turn, regulates the expression of several oncogenic genes such as Bcl-2, c-Myc, and cyclin D1. Increased chemoresistance, tumorigenicity, and pulmonary metastasis are seen both in vitro and in vivo when miR-197 is downregulated in platinum-resistant NSCLC [57]. Furthermore, Xie and coworkers found that, whereas NSCLC cells expressed high amounts of PD-L1 and cyclin E, they expressed low levels of miR-140. In A549 and NCI-H1650 cells, miR-140 overexpression suppressed cell growth, and this effect was correlated with decreased cyclin

E expression. The direct binding of miR-140 to the 3' untranslated region of PD-L1 was responsible for its downregulation (UTR). Inhibiting PD-L1 had a comparable effect on cyclin E expression, resulting in a decrease in its levels independent of miR-140 levels [58]. It was discovered that an increase in PD-L1 expression was connected to a decrease in the level of miRNA-497-5p. The downregulation of miRNA-497-5p was connected not only with an increase in PD-L1 expression but also with a decreased chance of survival. In two different cell lines derived from renal cell carcinoma, PD-L1 served as a direct target for miRNA-497-5p. In addition, this miRNA increased apoptosis while inhibiting cell proliferation, clone formation, and migration in in vitro experiments, and this was the case despite the fact that it suppressed cell proliferation [59].

It was also shown that miR-124 expression is drastically lower in CRC tissues compared with almost normal samples, and that this reduction is correlated negatively with PD-L1. Additional research showed that transfecting HT29 and SW480 cells with miR-124 mimics significantly reduced PD-L1 mRNA, protein, and cell surface expression. Interleukin (IL)-10, IL-2, tumor necrosis factor (TNF), and transforming growth factor (TGF) beta expression were all downregulated in coculture models, with the additional effect of suppressing Tregs [60]. Based on research into the underlying mechanisms, it was revealed that miR-424(322) suppressed the production of PD-L1 and CD80. The inhibition of the PD-L1 immunological checkpoint is observed concurrently with the reversal of chemoresistance that results from the restoration of miR-424(322) expression. This synergistic impact of chemotherapy and immunotherapy is linked to the proliferation of functional cytotoxic CD8+ T-cells, as well as the suppression of myeloid-derived suppressive cells (MDSCs) and Tregs [61]. In addition to this, it was shown that the expression of miR-224-5p was considerably elevated in the urine extracellular vesicles (EVs) of renal cell carcinoma (RCC) patients in comparison with healthy volunteers. The overexpression of miR-224-5p was found to be responsible for the inhibition of RCC cell growth as well as the induction of cell cycle arrest. Through a combination of prediction and confirmation, the cyclin D1-encoding gene, CCND1, was found to be a direct target of the miRNA known as miR-224-5p. In addition to this, the expression of miR-224-5p in RCC cells led to an increase in both their invasiveness and their capacity to metastasize. It is interesting to note that, by reducing CCND1, miR-224-5p was also able to boost the stability of the PD-L1 protein. This impact had the potential to be conveyed by EVs and further increased the resistance of RCC cells to toxicity dependent on T-cells [62].

The results of a recent study suggest that M1 macrophages had a negative association with the advancement of gastric cancer (GC), which shed light on the anti-tumor role that M1 macrophages play. Exosomal miR-16-5p can be produced by M1 macrophages, and this miR-16-5p can precisely target and inhibit PDL1 expression on GC cells. Blocking the PD1/PDL1 checkpoint may result in T-cell activation and the suppression of GC proliferation [63]. Furthermore, Zhao et al. found that miRNA-3127-5p promotes STAT3 phosphorylation by restricting autophagy; autophagy may preserve pSTAT3 into the nucleus in miRNA-3127-5p knockdown cells; and immune escape driven by high doses of PD-L1 leads to lung cancer chemoresistance [64]. Increasing miR-142-5p levels has been shown to slow the development of pancreatic cancer in animal and human studies. MiR-142-5p overexpression on tumor cells downregulates PD-L1 expression, which in turn increases the number of CD4+ and CD8+ T lymphocytes, decreases the percentage of PD-1+ T lymphocytes, and boosts the amount of IFN- γ and TNF- α in tumor microenvironments. Consequently, inhibiting the PD-L1/PD-1 pathway is one mechanism through which upregulating miR-142-5p expression can boost anti-tumor immunity [65]. Over-expression of the let-7 family was also found to inhibit immune evasion in head and neck squamous cell carcinoma (HNSCC) through suppressing TCF-4 expression, -catenin/STT3-mediated PD-L1 glycosylation, and PD-L1 stability, while simultaneously helping PD-L1 ubiquitination and degradation, as well as the T-cell recognition of HNSCC cells [66]. Furthermore, miR-140-3p has been demonstrated to be a tumor suppressor in colorectal cancer via directly

reducing PD-L1 and deactivating the PI3K/AKT pathway, indicating that miR-140-3p may be a promising marker for CRC diagnostics and therapy [67].

5.2. lncRNAs

The existence of lncRNAs affects a wide range of epigenetic regulatory mechanisms. The bulk of carcinogenesis and progression cannot be studied in isolation from the function that lncRNAs play in their regulation. When EMX2OS was knocked out, almost all of the cancerous characteristics of ovarian cancer cells were hindered; however, when EMX2OS was overexpressed, the same activities were promoted. In an in vivo xenograft model of human ovarian cancer, EMX2OS hastened tumor development. AKT3, a direct target of miR-654, was overexpressed due to the fact that EMX2OS may independently bind to miR-654 and suppresses its production. The overexpression of miR-654 or knockdown of EMX2OS was found to negatively affect cell proliferation, invasion, and sphere formation; however, restoring AKT3 was proven to rescue the cells from this fate. Moreover, PD-L1 was identified as the key oncogenic component in ovarian cancer cells, where it operated downstream of AKT3. The ectopic expression of PD-L1 prevented the anti-cancer effects of EMX2OS knockdown and AKT3 silencing in ovarian cancer cells [68]. Additionally, lncRNA KCNQ1OT1 acts as a sponge for miR-15a, which then allows it to enhance immune evasion and the advancement of malignant prostate cancer by up-regulating PD-L1 [69].

Dang and colleagues illustrated that SNHG15 and PD-L1 could be positively associated with one another. The upregulation of SNHG15 in gastric cells led to a reduction in the expression of miR-141, an inhibitor of PD-L1. This led to an increase in PD-L1 expression, which in turn enabled gastric cancer cells to be resistant to immune responses [70]. In addition, Xu et al. discovered that the amount of PD-L1 protein in invasive endometrial cancer cells might be controlled via the activity of miR-216a, which directly reduced PD-L1. They also discovered a mechanism by which the lncRNA MEG3 represses the production of miR-216a, which ultimately results in enhanced PD-L1 expression and a considerable reduction in cell motility and invasion [71].

The levels of expression of the lncRNAs UCA1 and PD-L1 were shown to be higher in anaplastic thyroid cancer (ATC) tissues and cells. The knocking down of UCA1 and PD-L1 led to an increase in the cytotoxic CD8⁺ T-cells' ability to destroy ATC cells. UCA1 acted as a negative regulator of the production of miR-148a, which in turn caused miR-148a to target PD-L1 and reduce the expression of that gene. In addition, it was shown that UCA1 inhibited the killing function of cytotoxic CD8⁺ T-cells and decreased the release of cytokines by working in conjunction with PD-L1 and miR-148a. Restoring the reduction in the lethal impact of CD8⁺ T-cells in vivo was achieved by silencing either UCA1 or PD-L1 in ATC cells [72]. Furthermore, it has been shown that the lncRNA PSMB8-AS1 promotes the proliferation and metastasis of pancreatic cancer (PC) cells by sponging up miR-382-3p, thereby increasing STAT1 expression. One plausible therapeutic target for PC is the PSMB8-AS1/miR-382-3p/STAT1/PD-L1 axis [73]. PC may benefit from targeting this axis with therapy because STAT1 transcriptionally upregulated PD-L1 and its stability.

Recent research found that the GC cell ectopic expression of miR-877-5p suppressed cell growth, reduced invasion, and induced cell death. Furthermore, it was shown that PD-L1, which is a target of miR-877-direct 5p, was negatively regulated. PD-L1 serves as a target for miR-877-5p. Several tests showed that miR-877-5p has a direct correlation with PD-L1, and several related experiments were carried out. It has been demonstrated that knocking down the lncRNA PROX1-AS1 reduced cell proliferation and that an increase in invasion ability was brought about by an inhibitor of miR-877-5p. However, a consequence of this inhibitor of miR-877-5p was later recovered by depleting the PD-L1 protein [74]. In addition, it was revealed that EGFR-AS1 increased PD-L1 expression in leiomyosarcoma cells by way of the EGFR/MYC pathway. This, in turn, suppresses T-cell infiltration and contributes to immunological escape [75]. Moreover, Zhang et al. [76] showed that silencing lncRNA FGD5-AS1 increased PD-L1 via sponging miR-497-5p, hence reducing malignant behaviors in colon cancer cells in vitro and in vivo. Proliferation, viability, invasion, migration, and

EMT are all facets that fall under this category. Furthermore, it was found that MIAT was responsible for controlling the expression of PD-L1, and that both MIAT and PD-L1 were significantly upregulated in HCC tissues. T-cell cytotoxicity toward HCC cells increased after MIAT was inhibited. At the transcriptional level, MIAT was able to reduce miR-411-5p expression, increase STAT3 activity, and then increase PD-L1 expression [77].

Docetaxel resistance and a poor prognosis in prostate cancer were both discovered to be connected with the gene LINC00184. In prostate cancer cells, this gene influenced docetaxel resistance as well as the immunological response mediated by T-cells. The adsorption of miR-105-5p led to the induction of LINC00184, which then negatively regulated miR-105-5p and, as a consequence, decreased the expression level of PD-L1 [78]. HIF1A-AS2 is an oncogene that regulates the miR-429/PD-L1 axis to promote the proliferation and metastasis of GC cells; it is also a strong predictor of malignancy and prognosis in GC [79]. In addition, HIF1A-AS3 predicts the likelihood of survival in GC patients. A recent study found that HOXA-AS3 was significantly upregulated in HCC cells, and that it controlled PD-L1 expression by sponging miR-455-5p. The miR-455-5p/PD-L1 axis was also targeted by HOXA-AS3 overexpression, contributing to HCC cell invasion and proliferation [80]. Through a process known as the downregulation of PD-L1 expression, LINC00244 was able to reduce the proliferation, invasion, and metastasis of HCC. In addition, the decreased expression of LINC00244 triggered pathways that are involved in the epithelial–mesenchymal transition (EMT), which accelerated the fast development and metastasis of HCC cells [81]. In addition, PCED1B-AS1 and miR-194-5p were increased in head and neck cancer. In this cancer, PCED1B-AS1 had a positive correlation with PD-Ls (PD-L1 and PD-L2); however, it had a negative correlation with miR-194-5p. PCED1B-AS1 had an interaction with miR-194-5p, which resulted in the suppressed expression of PD-Ls. Through the process of sponging miR-194-5p, PCED1B-AS1 was able to increase the expression of PD-Ls. PCED1B-AS1 is responsible for the immunosuppression mediated by PD-Ls in co-cultured T-cells. Exosomes containing PCED1B-AS1 were produced by HCC cells, and these exosomal PCED1B-AS1 molecules boosted the expression of PD-Ls in receipt head and neck cancer cells while inhibiting the expression of PD-Ls in receipt T-cells and macrophages. PCED1B-AS1 suppressed apoptosis while simultaneously promoting cancerous features and in vivo tumor development in nude mice that had been xenografted with human tumor cells [82].

5.3. circRNAs

Growing amounts of data suggest that circRNAs have functional roles in cellular procedures such as miRNA sponging, transcription regulation, and gene expression regulation. It has been proven that hsa-circ-0003288 increased EMT and invasion of HCC by way of the PI3K/Akt pathway via the hsa-circ-0003288/miR-145/PD-L1 axis [83]. Wu et al. found a new circRNA, which they named circCORO1C. HCC patients and cell lines were discovered to have significantly higher expression of this circRNA. The proliferation and metastasis of hepatocellular carcinoma are mediated by CircCORO1C [84]. This is accomplished by increasing the expression of PD-L1 via the NF-κB pathway. Furthermore, circ 0000284 was shown to be upregulated in NSCLC, and can be used to indicate a bad prognosis for individuals with NSCLC. The downregulation of circ-0000284 inhibited the development of NSCLC tumors in both in vitro and in vivo experimental settings. In addition, circ-0000284 was a miRNA target of miR-377-3p, which targeted PD-L1 [85].

When compared with a normal colon epithelial cell line, the findings of a recent study revealed that the levels of PD-L1 and circ-0136666 were up in colorectal cancer cells; however, miR-497 was shown to be at a lower level in colorectal cancer cells. It was determined that circ-0136666 specifically targets miR-497, which controls PD-L1 by binding to its 3'UTR. Circ-0136666 was able to control cell proliferation and death by targeting miR-497 and modulating the expression of PD-L1. It is noteworthy that circ-0136666 can activate Treg cells via the miR-497/PD-L1 axis and its downstream signal pathway in Treg cells [86]. When it comes to regulating cell proliferation, migration, invasion, and

clonogenicity in HNSCC, the overexpression of PD-L1 is essential on both the clinical and fundamental biological levels. Signaling via IFN- γ /JAK2/STAT1 plays a significant role in the process that leads to the induction of PD-L1 overexpression.

It has been established that increased circ-0000052 is responsible for PD-L1 overexpression. It does this by binding competitively to miR-382-3p and reducing the suppressive impact that miR-382-3p has on PD-L1 [87]. Additionally, it was shown that a high level of circ-0068252 was associated with a poor prognosis of non-small cell lung cancer as well as cisplatin resistance. It is possible that knocking down the circ-0068252 gene will make cisplatin more effective in treating cisplatin-resistant NSCLC cells. In addition, knocking down circ-0068252 was able to regulate the immunological microenvironment, and this regulation was mediated by CD8⁺ T-cells. By absorbing miR-1304-5p, circ 0068252 has the potential to stimulate the expression of PD-L1 [88]. Circ-0010235 was elevated in lung cancer, and via sponging miR-636 and upregulating PD-L1, circ-0010235 accelerated lung cancer development and immune escape [89]. In addition, inhibiting Circ-METTL15 activity in lung cancer cells led to an upsurge in the rate of apoptosis, as well as a reduction in some cancerous characteristics, including immune evasion. Because it acted as a sponge for miR-1299, Circ-METTL15 was able to exert a regulatory influence on lung cancer via miR-1299. In addition, PD-L1 was shown to be a functional target of miR-1299, and research found that miR-1299 prevented the growth of lung cancer cells by lowering PD-L1 expression [76].

A recent study discovered that inhibiting circ-CPA4 using a knock-down strategy reduced levels of PD-L1 both inside and outside of cells via targeting let-7 miRNA. On the one hand, PD-L1 acted as a regulator of proliferation, motility, stemness, and chemoresistant properties in NSCLC cells that were treated with cisplatin. On the other hand, PD-L1 secreted inactivated CD8⁺ T-cells to promote immune evasion. This was accomplished by triggering extracellular and intracellular pathways that facilitated death in impaired cells [90]. Circ-001678 might act as a sponge for miR-326 and boost ZEB1 expression. Treatment with an anti-PD-L1/PD-1 antibody combination might counteract the effects of circ-001678 on tumor growth. The stimulation of the PD-1/PD-L1 pathway by circ-001678 led to the promotion of CD8⁺ T-cell death, which resulted in the induction of NSCLC cell immune escape via control of the miR-326/ZEB1 axis. These results suggest that circ-001678 functions as a sponge for miR-326, which then upregulates ZEB1 expression and induces the PD-1/PD-L1 pathway-dependent immune escape, hence aiding the formation of malignant tumors in NSCLC [78]. In addition, Wang and colleagues discovered that circ-002178 was considerably elevated in lung adenocarcinoma tissues, the cells and exosomes of cancer cells, and blood from patients. Through the process of sponging miR-34 in cancer cells, circ-002178 has the potential to increase PD-L1 expression. Additionally, circ-002178 might be transported into T-cells through the exosomes that are released by cancer cells in order to enhance PD1 expression. This would be accomplished by sequestering miR-28-5p [91].

Table 1. ncRNAs and their mechanisms to regulate PD-Ls.

ncRNA	Name	Target	Role	Reference
miRNA	miR-15a/-15b	PD-L1	Induces activation and cytotoxicity in CD8+T and NK cells against neuroblastoma	[49]
	miR-20a	PD-L1	Reduces the amount of PTEN and PD-L1	[50]
	miR-326	PD-L1	Change in the cytokine profile of CD8+ T-cells and the reduced migratory capacity of tumor cells	[51]
	miR-214	PD-L1	Induction of apoptosis as well as repressing cell viability and migration	[52]
	miR-873	PD-L1	Chemoresistance and stemness-like features in breast cancer cells via activating PI3K/Akt and ERK1/2 pathways	[53]
	miR-93-5p	PD-L1	Affects tumor growth and immune modulation in breast cancer	[54]
	miR-34a	PD-L1	Inhibited PD-L1 expression	[55]
	miR-138-5p	PD-L1	A tumor suppressor in CRC	[56]
	miR-197	PD-L1	Mediates CKS1B/STAT3 axis tumor growth	[57]
	miR-140	PD-L1	Represses cellular proliferation, related to lower expression of cyclin E and inactivating the PI3K/AKT pathway	[58]
	miRNA-497-5p	PD-L1	Increases apoptosis while inhibiting cell proliferation, clone formation, and migration	[59]
	miR-124	PD-L1	Suppresses Tregs by altering IL-10, IL-2, TNF, and TGF- β	[60]
	miR-424	PD-L1	Increase the proliferation of functional cytotoxic CD8+ T-cells, MDSCs and Tregs	[61]
	miR-16-5p	PD-L1	T-cell stimulation and suppression of tumor proliferation	[62]
	miR-142-5p	PD-L1	Growth in the number of CD4+ and CD8+ T lymphocytes, a reduction in the percentage of PD-1+ T lymphocytes, and an upsurge in the quantity of IFN- γ and TNF- α in TME	[63]
lncRNAs	EMX2OS	PD-L1	Directly interacts with miR-654 and suppresses its expression	[68]
	KCNQ1OT1	PD-L1	Sponging miR-15a	[69]
	SNHG15	PD-L1	Reduction in the expression of miR-141, an inhibitor of PD-L1.	[70]
	MEG3	PD-L1	Represses the production of miR-216a, which ultimately results in enhanced PD-L1 expression	[71]
	UCA1	PD-L1	Sponging miR-148a which could target PD-L1	[72]
	PSMB8-AS1	PD-L1	Sponging miR-382-3p in order to increase STAT1 expression	[73]
	PROX1-AS1	PD-L1	Inhibits miR-877-5p, which could target PD-L1	[74]
	EGFR-AS1	PD-L1	Suppresses T-cell infiltration and contributes to immunological escape	[75]
	FGD5-AS1	PD-L1	Elevates PD-L1 via sponging miR-497-5p	[76]
	MIAT	PD-L1	Suppresses the expression of miR-411-5p, boosts the activity of STAT3, and finally raises the level of PD-L1 expression	[77]
	LINC00184	PD-L1	Negatively regulates miR-105-5p and, as a consequence, decreases the expression level of PD-L1	[78]
	HIF1A-AS3	PD-L1	Sponges miR-455-5p	[79]
	LINC00244	PD-L1	Represses PD-L1 expression	[81]
	PCED1B-AS1	PD-L1/-L2	Sponges mir-194-5p	[82]

Table 1. Cont.

ncRNA	Name	Target	Role	Reference
circRNAs	circ-0003288	PD-L1	Increases EMT and invasion of HCC by way of the PI3K/Akt pathway	[83]
	circCORO1C	PD-L1	Increasing the expression of PD-L1 via the NF- κ B pathway	[84]
	circ-0000284	PD-L1	Is a miRNA target of miR-377-3p, which targets PD-L1	[85]
	circ-0136666	PD-L1	Directly targets miR-497, which also regulates PD-L1	[86]
	circ-0000052	PD-L1	Signaling via IFN- γ /JAK2/STAT1	[87]
	circ-0068252	PD-L1	By absorbing miR-1304-5p, this circRNA has the potential to stimulate the expression of PD-L1	[88]
	circ-0010235	PD-L1	Sponging miR-636 and upregulating PD-L1	[89]
	circ-METTL15	PD-L1	Acts as a sponge for miR-1299	[76]
	circ-CPA4	PD-L1	Targeting let-7 miRNA	[90]
	circ-001678	PD-L1	Sponge for miR-326 and boosts ZEB1 expression	[78]
	circ-002178	PD-L1	Sequesters miR-28-5p	[91]

6. FDA-Approved Drugs

FDA-approved immunotherapies targeting PD-1/PD-L1 signaling might help stimulate long-lasting anti-tumor immune responses in certain patients with advanced malignancies [92–94]. This has led to immunotherapies becoming the first-line treatment for specific kinds of neoplasms. There is a correlation between the overexpression of PD-L1 and PD-1 on tumor cells and tumor-infiltrating lymphocytes, respectively, and a poor prognosis of illness in some human malignancies. Certain cancer cells have the potential to produce inhibitory ligands, which have the capability of binding co-inhibitory receptor molecules. Consequently, normal anti-tumor immune responses are suppressed, which contributes to immune evasion. Therefore, blocking these immunological targets might cause the patient's immune system to mount an attack against the tumor.

Three anti-PD-L1 antibodies have been granted FDA approval: atezolizumab (IgG4 mAb), durvalumab (IgG1 mAb), and avelumab (IgG1 mAb) [95]. Patients with locally advanced or metastatic urothelial carcinoma have access to atezolizumab, the first PD-L1 inhibitor licensed by the FDA [96]. In addition, patients with metastatic non-small-cell lung cancer (NSCLC), whose illness progressed while they were receiving platinum-containing medications for chemotherapy, have been approved to utilize this antibody [97]. Furthermore, the FDA has authorized the use of the combination of the antiangiogenic medications atezolizumab and bevacizumab for the treatment of persons with unresectable or metastatic hepatocellular carcinoma (HCC) [98]. BRAF V600E mutation-positive unresectable or metastatic melanoma patients may utilize atezolizumab in conjunction with cobimetinib, an inhibitor of the mitogen-activated extracellular kinase (MEK), and vemurafenib, a repressor of the B-Raf enzyme [99]. Locally progressed or metastatic urothelial carcinoma and Merkel cell carcinoma (MCC), a rare but lethal form of skin cancer, were the initial indications for the use of durvalumab [100,101]. Patients with advanced NSCLC may benefit from first therapy with durvalumab in addition to etoposide and carboplatin or cisplatin [102]. This treatment schedule has been given the green light. In 2017, the FDA approved avelumab for the treatment of MCC and metastatic urothelial carcinoma [101,103]. FDA approval was received in 2019 for the use of avelumab in combination with the tyrosine kinase inhibitor axitinib as a first-line therapy for patients with advanced renal cell carcinoma (RCC) [104].

7. Conclusions and Future Perspectives

NcRNA and PD-L1/PD-L2 interactions determine how well patients respond to anti-cancer medications. The therapeutic techniques employed may also have an impact on

these connections. The most surprising discovery of this research was the presence of several ncRNAs connected to PD-L1/L2 in exosomes discharged into the environment by tumor cells. This finding lends credence to the idea that these transcripts could be used as biomarkers for the early identification of neoplasia using biofluids, and it also draws attention to the crucial roles played by these lncRNAs during tumor development and in the regulation of the tumor microenvironment. Due to the promising outcomes seen in recent years from clinical trials with anti-PD-L1/-L2 medicines, scientists are now looking into alternative therapeutic approaches. Considering their potential role as modulators of PD-L1/PD-L2 expression and activity, ncRNAs could be exploited as therapeutic targets in this context. Additionally, ncRNAs associated with PD-L1/-L2 can be used to predict a patient's response to PD-L1/-L2 inhibitors. The apparent lack of response to this medication may be due to the expression levels of PD-L1/-L2-associated ncRNAs. As a result, antisense oligonucleotides or siRNA can be used to modulate the synthesis of these transcripts to enhance the therapeutic response to anti-PD-L1/-L2 treatment. High-throughput sequencing tools and a bioinformatics approach can be used to achieve this. This objective, however, cannot be achieved without further investigation into the idea of tissue-specific panels of ncRNAs.

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