Interplay between programmed death-ligand 1 and non-coding RNAs

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Programmed death-ligand 1 (PD-L1) is a transmembrane protein with essential roles in the suppression of adaptive immune responses. As an immune checkpoint molecule, PD-L1 can be exploited by cancer cells to evade the anti-tumor attacks initiated by the immune system. Thus, blockade of the PD1/PD-L1 axis can eliminate the suppressive signals and release the antitumor immune responses. Identification of the underlying mechanisms of modulation of the activity of the PD1/PD-L1 axis would facilitate the design of more efficacious therapeutic options and better assignment of patients for each option. Recent studies have confirmed the interactions between miRNAs/lncRNAs/circ-RNAs and the PD1/PD-L1 axis.

Abbreviations: CRC, Colorectal Cancer; CC, Cervical cancer; OC, Ovarian Cancer; EC, Endometrial Cancer; HCC, Hepatocellular Carcinoma; EAC, Esophageal Adenocarcinoma; GC, Gastric Cancer; PC, Pancreatic Cancer; LUAD, Lung Adenocarcinoma; NSCLC, Non-Small Cell Lung Cancer; BCa, Breast Cancer; IP, Intraperitoneal; PARP, Polymerase; OIP5-AS1, OPA-Interacting Protein 5 Antisense Transcript 1; TAMs, Tumor-Associated Macrophages; HK2, Hexokinase 2; EGFR, Epidermal Growth Factor Receptor; SPOP, Cullin 3-Speckle Type POZ Protein; IV, Intravenous; FGD5-AS1, FGD5-Antisense 1; Grhl2, Grainy Head-Like 2; HIF1A-AS2, Hypoxia-Inducible Factor-1 Alpha Antisense RNA-2; CHK1, Checkpoint Kinase 1; IRF-1, Interferon Regulatory Factor 1; HUVECs, Human Umbilical Vein Endothelial Cells; CIK, Cytokine-Induced Killer; HUSMC, Human Uterine Smooth Muscle Cells; HDLEC, Human Dermal Lymphatic Endothelial Cells; HESCs, Human Embryonic Stem Cells; PTEN, Chromosome Ten; MMP-1, Metalloproteinase-1; NPs, Nanoparticles; CAFs, Cancer-Associated Fibroblasts; NRF-2, Nuclear Factor E2-Related Factor 2; TRAIL, Tumor Necrosis Factor-Related Apoptosis-Inducing Ligand; dMMR, Mismatch Repair Deficiency; BLNK, B-cell linker; PBLs, Peripheral Blood Lymphocytes.
the current review, we give a summary of interactions between these transcripts and PD-L1 in the context of cancer. We also overview the consequences of these interactions in the determination of the response of patients to anti-cancer drugs.

**KEYWORDS**

PD-L1, IncRNA, miRNA, expression, cancer

**Introduction**

Programmed death-ligand 1 (PD-L1), alternatively named as CD274 or B7-H1, is a transmembrane protein with essential roles in the suppression of adaptive immune responses. The reaction of the adaptive immune system to external or internal danger signals leads to the expansion of antigen-specific CD8+ and/or CD4+ T cell clones (1). However, when PD-L1 binds to the PD-1 checkpoint, an inhibitory signal is transmitted which decreases the proliferation of antigen-specific T-cells in lymph nodes and at the same time reduces apoptosis of regulatory T cells. PD-1/PD-L1 axis mainly acts at the late stage of induction of T-cell immune responses in peripheral tissues (2).

Immune checkpoint pathways are exploited by cancer cells so as to evade the anti-tumor attacks initiated by the immune system (3). Thus, the blockade of immune checkpoints can eliminate the suppressive signals and release the antitumor immune responses. PD-1 and PD-L1 have been used as key drug targets for the development of immune checkpoint blockade treatment modalities (2). Several PD-1/PD-L1 targeted therapies have been approved for the treatment of several types of malignancies (2). At least three human IgG1 antibodies anti-PD-L1 antibodies have been approved for clinical application (4). While atezolizumab and durvalumab have been designed to eliminate FcγR-binding and effector function, avelumab retains the intact function of Fc (5). BMS-936559 is another PD-L1-targeting antibody that is distinctive from the mentioned approved PD-L1 antibodies since it is an IgG4 mAb with S228P mutation (5). In addition, the fusion protein KN035 contains a distinct domain of the humanized anti-PD-L1 antibody and the Fc of an IgG1 (6). Meanwhile, PD-L1-targeting agents can be prescribed in the form of a prodrug. An example is the agent CX-072 which can be activated by a protease (7). Due to incomplete success and drawbacks of using PD-L1-targeting drugs, assessment of expression of PD-L1 is regarded as a marker for prediction of response and identification of patients who gain a favorable clinical response from this type of therapy (4).

The expression of genes can be regulated at the transcriptional and posttranscriptional levels by functional RNA molecules known as non-coding RNAs (8, 9). The expression of ncRNAs, which primarily regulate oncogenes and tumor suppressor genes, is altered in several kinds of human malignancies (10, 11). Recent studies have confirmed the interplay between a variety of non-coding RNAs and the PD1/PD-L1 axis. In fact, several microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs) have been shown to modulate the activity of this axis. Identification of molecular mechanisms that modulate the activity of the PD1/PD-L1 axis would facilitate the design of more efficacious therapeutic options and better assignment of patients for each option. In the current review, we give a snapshot of interactions between these transcripts and PD-L1 in the context of cancer. We also overview the consequences of these interactions in the determination of the response of patients to anti-cancer drugs.

**Gastrointestinal cancers**

In colorectal cancer (CRC) samples, over-expression of SETDB1 expression has been associated with the expression of PD-L1. Mechanistically, SETDB1 can down-regulate miR-22 levels by decreasing the expression of FOSB. On the other hand, miR-22 down-regulates PD-L1 levels by targeting BATF3. SETDB1 knockdown has enhanced the cytotoxic effects of T cells on tumor cells by influencing the FOSB/miR-22/BATF3/PD-L1 axis, thus hindering the growth of CRC tumors in mice. Cumulatively, the effects of SETDB1 on the activity BATF3/PD-L1 axis leads to immune evasion of CRC tumors (12). miR-124 is another miRNA with a possible regulatory role on PD-L1. Expression of miR-124 is significantly decreased in CRC, and its under-expression has been correlated with the up-regulation of PD-L1 (13). The luciferase assay has validated PD-L1 targeting by miR-124 (13). miR-124 mimics could significantly reduce the expression of PD-L1 at the transcript, protein, and cell surface levels (13). Moreover, this miRNA could inhibit Tregs in co-culture models by influencing levels of IL-10, IL-2, TNF-α, TGF-β, and IFN-γ. Up-regulation of miR-124 could also decrease the proliferation of CRC cells and induce cell cycle arrest at G1 via down-regulating c-Myc. Moreover, this miRNA could induce intrinsic and extrinsic apoptotic pathways, down-regulate CD44 and MMP-9 expression levels, and suppress cell migration and invasion (13). STAT3 signaling has also been suppressed by miR-124 (13). miR-93-5p (14) and miR-140-3p (15) are two other miRNAs that can target PD-L1 in CRC cells. Meanwhile, a number of lncRNAs and circRNAs have...
been found to affect CRC progression by influencing the expression of miRNAs and enhancing the expression of PD-L1. For instance, MIR17HG lncRNA promotes the progression of CRC by influencing the expression of miR-17-5p (16). Besides, KCNQ1OT1 lncRNA released by CRC cells-originated exosomes can mediate immunity through the regulation of PD-L1 ubiquitination via miR-30a-5p/USP22 (17). Hsa_circ_0136666 is also involved in Treg-mediated immune escape through modulation of miR-497/PD-L1 axis (Figure 1A) (18). Cancer-associated fibroblasts have been shown to secrete circEIF3K in their exosomes to enhance progression of CRC through miR-214/ PD-L1 axis (19).

In hepatocellular carcinoma (HCC), suppression of PARP has enhanced the efficacy of immune checkpoint therapy via influencing the miR-513/PD-L1 axis. Thus, combined administration of the PARP inhibitor olaparib and anti-PD1 has been suggested as a treatment modality in HCC (20). In this type of cancer, HOXA-AS3 lncRNA has been found to promote proliferation and migratory potential through miR-455-5p/PD-L1 axis (21). Another study in HCC has shown a correlation between expressions of PD-L1 and PD-L2. Moreover, this study has demonstrated the up-regulation of PCED1B-AS1. Expression of PCED1B-AS1 has been positively correlated with expression levels of PD-L1 and PDL-2 while being negatively correlated with hsa-miR-194-5p. Mechanistically, PCED1B-AS1 increases expressions of PD-L1 and PD-L2 through sequestering hsa-miR-194-5p, thus inducing PD-L1/PD-L2-mediated immunosuppressive effects on T cells (22). Table 1 shows the interactions between non-coding RNAs and PD-L1 in gastrointestinal cancers.

**Lung cancer**

In lung cancer samples, expression of PD-L1 has been correlated with the T stage. Treatment with PD-L1 inhibitor has decreased the expression of PD-L1 and diminished T stage in patients suffering from PD-L1-positive lung cancer. In this group of patients, over-expression of PD-L1 or decreased serum exosomal level of miR-16-5p has been correlated with longer survival upon treatment with a PD-L1 inhibitor. Moreover, this kind of treatment reduced the quantity of exosomes in the sera of PD-L1-positive patients and enhanced serum exosomal levels of miR-16-5p. High exosomal levels of miR-16-5p could depress cell proliferation and migration in cell cultures, and induce apoptosis, particularly in cells treated with a PD-L1 inhibitor. Cumulatively, the miR-16-5p content of serum exosomes possibly inhibits tumor growth and can be used as a marker for PD-L1 inhibitor therapy (41). miR-155-5p (42) and miR-326 (43) are two other miRNAs that suppress PD-L1 expression and attenuate immune escape in lung cancer by targeting PD-L1. In addition, miR-138-5p has been found to affect the activity of the PD-1/PD-L1 axis, inhibit tumor growth and activate the immune system in this type of cancer (44). A number of oncogenic lncRNAs and circRNAs, namely OIP5-AS1, MALAT1, Circ_0000284, Circ-CPA4 and Circ-CHST15 have

![Figure 1](https://example.com/figure1.png)

**FIGURE 1**

A graphical representation of the ways in which programmed death ligand 1 (PD-L1) and non-coding RNAs interact with one another in gastrointestinal and gynecological cancers.
### TABLE 1 Interactions between non-coding RNAs and PD-L1 in gastrointestinal cancers.

| Cancer     | miRNA/IncRNA | Sample                                                                 | Cell Line | PD-L1 Expression | Target                  | Function                                                                                       | Ref |
|------------|--------------|------------------------------------------------------------------------|-----------|------------------|-------------------------|-------------------------------------------------------------------------------------------------|-----|
| CRC        | miR-22 (-)   | 36 pairs of CRC and paratumoral tissues, BALB/c nude mice              | CRL-1831, SW480, FHC, CCL-22, LS174T, CL-188,    | Up                | BATF3, FOSB              | Histone Methyl-transferase SETDB1 via BATF3/ PD-L1 axis by decreasing miR-22 could enhance immune evasion. | (12) |
| CRC        | miR-124-3p (Down-regulated) | 20 pairs of CRC and paratumoral tissues                               | HCT-116, HT29, SW480, 293T, PBMCs               | Negative correlation with miR-124-3p | MMP-9, c-Myc, Bcl-2, Bax, Caspase-3/8/9, STAT3 | miR-124-3p via targeting STAT3 can decrease PD-L1 expression and block tumorigenesis in CRC cells. | (13) |
| CRC        | miR-93-5p (Down-regulated) | 125 pairs of CRC and paratumoral tissues                              | HCTT16, SW480, PBMCs                          | Up                | MMP12/19, IL-2/1/β/10, IFN-γ, TGF-β, AKT | miR-93-5p via targeting PD-L1 could modulate the progression of CRC. | (14) |
| CRC        | miR-140-3p (Down-regulated) | 31 pairs of CRC and paratumoral tissues, BALB/c-nude mice              | HCTT16, SW480, NCM460                         | Up                | PD-L1, PI3K, AKT         | miR-140-3p via targeting PD-L1 could induce apoptosis and decrease cell growth in CRC. | (15) |
| CRC        | MIR17HG (Up-regulated), miR-17-5p | Cohort study, RELA mice, nude mice                                      | HCTT15, HCTT16, SW480, SW620, HT29, DLD-1, IRO, LoVo | PD-L1/2, PD-L1 had positive correlation with MIR17HG | BLNK, TIM3, CTLA-4, NF-kB | miR-17-5p is transcribed from MIR17HG and reduces expression of the tumor suppressor B-cell linker. MIR17HG can also upregulate the expression of PD-L1. | (16) |
| CRC        | KCNQ1OT1 (Up-regulated), miR-30a-5p | 20 pairs of CRC and paratumoral tissues, BALB/c nude mice              | FHC, 293T, SW480, PBMCs SW1463, HT-29, CT26   | –                 | USP22, ALIX, Vimentin, E/N-cadherin, Bax, Bcl-2 | LncRNA KCNQ1OT1 via miR-30a-5p/USP22 axis by regulating PD-L1 could promote CRC immune escape. | (17) |
| CRC        | Hsa_circ_0136666 (Up-regulated), miR-497 | nude mice                                                              | HCTT16, SW480, SW620, HT29, HCT8, FHC         | Up                | IL-2/10/1β, TGF-α, TGF-β, AKT, mTOR, ERK1/2, PTEN | Hsa_circ_0136666 via targeting miR-497/PD-L1 axis could enhance Treg-mediated immune escape of CRC. | (18) |
| CRC        | Circ-EIF3K (-), miR-214 | TCGA database, NOD-SCID mice                                           | HCTT16, SW620, FHC, 293T, HDLEC               | Up                | –                        | Exosomal circ-EIF3K from cancer-associated fibroblast via modulating the miR-214/PD-L1 axis could enhance CRC progression. | (19) |
| CRC        | Circ-CDR1-AS (-), miR-7 | BALB/c nude mice                                                        | 293T, SW620, Caco2, HUVECs                   | Positive correlation with Circ-CDR1-AS | CMTM4/6 | Overexpression of circ-CDR1-AS via enhancing cell surface PD-L1 levels could increase the immune escape of CRC cells. | (20) |
| HCC        | miR-513 (-) | C57BL/6 mice                                                           | Hep-3b, YY-8103                              | –                 | PARP2                     | Habitation of PARP via miR-513/PD-L1 axis in HCC could potentiate immune checkpoint therapy. | (21) |
| HCC        | HOXA-AS3 (Up-regulated), miR-455-5p | TCGA database                                                          | Hep3B, SNU-387, Li-7, HuH-7, L-02, 293T     | Up                | –                        | Overexpression of IncRNA HOXA-AS3 10 by targeting the miR-455-5p/PD-L1 axis could contribute to cell invasion. | (22) |
| HCC        | PCEIDB-A51 (Up-regulated), hsa-miR-194-5p (Down-regulated) | 45 pairs of HCC and paratumoral, nude mice                            | Hep-7, HepG2, 293T                           | PD-L1/2, Positive correlation with PCEIDB-A51 | LRP6, AKT, STAT3, NotCH-1 | LncRNA PCEIDB-A51 via sponging miR-19 by promoting PD-L1 and PD-L2 function could induce immunosuppression in HCC. | (23) |
| HCC        | miR-195 (-) | 30 pairs of HCC and paratumoral tissues                                | Hepa1-6, Huh-7, Hep3B, HepG2                | –                 | CHK1, IRF-1               | IRF-1 via targeting miR-195 by modulating PD-L1 could increase apoptosis of HCC cells. | (24) |

(Continued)
| Cancer | miRNA/IncRNA | Sample | Cell Line | PD-L1Expression | Target | Function | Ref |
|--------|--------------|--------|-----------|-----------------|--------|----------|-----|
| HCC    | miR-675-5p   | wild-type C57BL/6 mice | SMMC-7721, HepG2, PBMCs | – | PARP, STAT3 | – |
|        | miR-424     | 152 HCC tissue samples, BALB/c nude mice | – | HK2, HLA-ABC, EGFR, MAPK | EGFR-P38 MAPK axis via miR-675-5p and HK2 by decreasing HLA-ABC could enhance PD-L1 in HCC cells. | (25) |
| HCC    | LINC00657 (Up-regulated), miR-145 | 60 pairs of HCC and paratumoral tissues, BALB/c nude mice | HepG2, Huh7, SMMC-7721, HCCL63, L02 | Up | E/Cadherin, AKT | Knockdown of IncRNA LINC00657 via targeting miR-424 by regulating PD-L1 could attenuate HCC cell progression. | (26) |
| HCC    | hsa_circ_003288 (Up-regulated), miR-145 | 40 pairs of HCC and paratumoral tissues, BALB/c nude mice | HepG2, Huh7, SMMC-7721, Bel-7402, L02 | Up | E/Cadherin, AKT | hsa_circ_003288 could induce EMT through modulating the miR-145/PD-L1 axis in HCC cells. | (27) |
| EAC    | miR-145-5p   | 30 pairs of EAC and paratumoral tissues, BALB/c nude mice | OE33, FLO-1, HET-1A, PBL | – | SPOP, c-Myb, IFN-γ, IL-2/4/10, MMP-3/9, E/Cadherin | c-Myb via targeting miR-145-5p/SPOP/PD-L1 axis could facilitate immune escape. | (28) |
| GC     | miR-1290     | 81 pairs of GC and paratumoral tissues, C3H mice | GEC-1, MGC-803, BGC-823, MFC, 293T | – | Ghrh2, ZEB1, TSG101, IL-2, INF-γ | Tumor-derived extracellular vesicles containing miR-1290 via Ghrh2/ZEB1/PD-L1 axis could promote the escape of cancer cells. | (29) |
| GC     | miR-16-5p    | 68 pairs of GC and paratumoral tissues, BALB/c mice, NOD/SCID mice | AGS, NCI-N87, 293T, PBMCs | – | hNOS, HSP70, IL-2, TNF-α, INF-γ | miR-16-5p via activation of T cell immune response by regulation PD-L1 could inhibit GC progression. | (30) |
| GC     | miR-105-5p   | 368 GC tissue samples | AGS, NCI-N87, SNU-719, SNU-216, MKN-74, 293T, PBMCs | – | F922, IFN-γ, IL-2 | DNA methylation via controlling miR-105-5p could decrease PD-L1 expression and increase immunogenicity in GC cells. | (31) |
| GC     | miR-15a/16   | 6 pairs of GC and paratumoral tissues, BALB/c nude mice | SGC7901, 293T | Up | TSG101, ALIX | miR-15a/16 via modulating PD-L1 could decrease the immune escape of GC cells. | (32) |
| GC     | miR-502-5p   | 25 pairs of GC and paratumoral tissues, nude mice | SGC-7901, BGC823, MGC803, GE1-1 | Up | STAT3 | miR-502-5p by modulating PD-L1 could enhance GC progression and invasion. | (33) |
| GC     | PROX1-AS1 (Up-regulated), miR-877-5p | 30 pairs of GC and paratumoral tissues | AGS, MGC-803, SGC-7901, SNU-1, GE1-1 | Negative correlation with miR-877-5p | Cyclin-D1, p21, Bax, Bcl-2, Caspase-3/9, Cox-2, MMP-2/9 | LncRNA PROX1-AS1 via targeting miR-877-5p/PD-L1 axis could accelerate GC progression and invasion. | (34) |
| GC     | HIF1A-AS2 (Up-regulated), miR-429 | 50 pairs of GC and paratumoral tissues, BALB/c nude mice | SNU-5, HGC-27, MKN45, AGS | Up | – | LncRNA HIF1A-AS2 via targeting miR-429/PD-L1 axis could enhance metastasis of GC cells. | (35) |
| GC     | SNHG15 (Up-regulated), miR-141 | 9 pairs of GC and paratumoral tissues | GE1-1, HGC-27, PBMCs | – | – | LncRNA SNHG15 via targeting the miR-141/PD-L1 axis could contribute to the immune-escape of GC cells. | (36) |
| PC     | miR-194-5p   | C57BL/6 mice | 293T, Panc02, Panc1 | Up | N/Cadherin, Vimentin, | miR-194-5p via targeting PD-L1 could regulate the immune escape of PC cells. | (37) |
been shown to act as molecular sponges for PD-L1-targeting miRNAs, thus increasing levels of PD-L1 (Figure 2A) (Table 2).

**Gynecological cancers**

The impact of non-coding RNAs on the expression of PD-L1 has been assessed in ovarian cancer (OC), cervical cancer (CC), and endometrial cancer (EC). In OC, miR-92 has been reported to block the functions of immune cells by modulating the expression of PD-L1 via the LATS2/YAP1 axis (51). Moreover, the sponging effect of EMX2OS on miR-654-3p has been shown to result in the induction of cell proliferation, invasive properties, and sphere formation in OC through regulation of the AKT3/PD-L1 axis (52). In addition, the Lnc-OC1/miR-34a axis has a crucial role in the pathogenesis of EC through the modulation of PD-L1 (53). Conversely, another study has shown that PD-L1 has a tumor suppressor role in aggressive EC and its expression is influenced by MEG3/miR-
Table 2 Interaction between non-coding RNAs and PD-L1 in lung cancer.

| miRNA/LncRNA  | Sample                                                                 | Cell Line                | PD-L1 Expression | Target Functions                                                                 | Ref |
|---------------|------------------------------------------------------------------------|--------------------------|------------------|-----------------------------------------------------------------------------------|-----|
| miR-16-5p (-) | 60 LUAD patients and 20 healthy controls, BALB/C nude mice             | BEAS-2B, A549, PC9, HCC827| –                | Calnexin, TSG101                                                                  | (41) |
| miR-155-5p (Up) | 9 pairs of LUAD and paratumoral tissues                                | A549, H1650              | –                | miR-155-5p via suppressing PD-L1 expression could modulate the immune response in LUAD. | (42) |
| miR-326 (Down-regulated) | 50 LUAD tissue samples, BALB/c nude mice                              | A549, H1975, H1734, Calu-3, BEAS-2B, 293T, PBMCs | Negative correlation with miR-326 | miR-326 by modulating PD-L1 and B7-H3 could attenuate immune escape and prevent metastasis in LUAD cells. | (43) |
| miR-138-5p (-) | 5 NSCLC tumor tissue samples, C57BL/6 mice, nude mouse                 | A549, 3LL, 293T          | PD-L1/CD1          | Cyclin-D3, MCM2                                                                  | (44) |
| miR-142-5p (Up, regulated) | 20 NSCLC tissue samples and 20 normal tissue samples, serum samples | A549, 293T, PBMCs        | Down              | IFN-γ, Caspase-3/9, CCL-17/22, PTEN, PI3K, AKT                                  | (45) |
| OIP5-AS1 (Up-regulated), miR-34a | 68 NSCLC patients                                                     | H522, H22, H23           | –                | LncRNA OIP5-AS1 via binding to miR-34a could upregulate oncogenic PD-L1 in NSCLC. | (46) |
| MALAT1 (-), miR-200a-3p | 113 NSCLC tissue samples                                               | A549, CAL-12T            | Positive correlation with MALAT1 | LncRNA MALAT1 via modulating miR-200a-3p/ PD-L1 axis could contribute to NSCLC progression. | (47) |
| Circ_0000284 (Up-regulated), miR-377-3p | 60 pairs of NSCLC and paratumoral tissues, BALB/c nude mice         | MRC-5, A549, H82         | –                | E-cadherin, Fibronectin, MMP9, HIPK3                                              | (48) |
| Circ-CPA4 (Up-regulated), miR-let-7 | 50 pairs of NSCLC and paratumoral tissues, nude mice                  | A549, H1299, SK-MES-1, Calu-3, HBE, PBMCs | Up                | Oct-4, SOX2, Nanog, N-cadherin, Vimentin, Bax, IL-4/10, IFN-γ                    | (49) |
| Circ-CHST15 (Up-regulated), miR-155-5p, miR-194-5p | 90 pairs of LC and paratumoral tissues, BALB/c nude mice           | 16HBE, H1299, H23, H1359, H1435, A549, H358, PC-9, BNCC341852, GMF-167 | Positive correlation with Circ-CHST15 | Circ-CHST15 via sponging miR-155-5p and miR-194-5p could enhance the invasion and migration of LC cells mediated by PD-L1. | (50) |

216a axis (Figure 1B) (54). Table 3 shows the interactions between non-coding RNAs and PD-L1 in gynecological cancers.

Breast cancer

At least four studies have assessed interactions between non-coding RNAs and PD-L1 in the context of breast cancer (BCa) (Table 4). Two down-regulated miRNAs in BCa, namely miR-383-5p (55) and miR-424-5p (56) have been reported to affect the expression of PD-L1 (Figure 2B). Moreover, exosomes secreted by BCa-associated fibroblasts have been shown to assist in the suppression of immune cell function through the transfer of PD-L1 inhibiting miRNA miR-92 (57). Finally, expression of GATA3-AS1 has been found to be markedly increased in triple-negative BCA tissues and cells parallel with a reduction in the proportion of CD8+ T cells. GATA3-AS1 silencing has suppressed the growth of tumor cells and decreased the half-life of the PD-L1 protein. GATA3-AS1 has been shown to induce PD-L1 deubiquitination via miR-676-3p/COPS5 axis.
Thus, this lncRNA contributes to the progression of triple-negative BCa and immune evasion via enhancing the stability of PD-L1 protein and inducing GATA3 degradation (58).

Renal cancer

miR-497-5p is a putative tumor suppressor miRNA in renal cancer whose down-regulation leads to the over-expression of PD-L1 in this type of cancer (59). Moreover, urinary extracellular vesicles (EVs) have been found to contain miR-224-5p. Expression of miR-224-5p has been higher in urinary EVs of patients with renal cell carcinoma compared to healthy controls. Over-expressed miR-224-5p could inhibit proliferation and induce cell cycle arrest by targeting CCND1. Besides, miR-224-5p has a role in the induction of invasive and metastatic properties of renal carcinoma cells. Remarkably, miR-224-5p has a role in the enhancement of PD-L1 stability through the suppression of CCND1 (60). Finally, SNHG1 has been found to regulate

### TABLE 3 Interaction between non-coding RNAs and PD-L1 in gynecological cancers.

| Cancer | miRNA/LncRNA | Sample | Cell Line | PD-L1 Expression | Target | Function | Ref |
|--------|--------------|--------|-----------|------------------|--------|----------|-----|
| OC     | miR-92       | 40 OC tissue samples | SKOV3 | – | LATS2, YAP1 | miR-92 via LATS2/YAP1/PD-L1 signaling overexpression could suppress immune cell function in OC cells. (51) |
| OC     | EMX2OS       | 50 pairs of OC and paratumoral tissues, BALB/c nude mice | SKOV-3, ES-2, OVCA3, A2780, CAOV3, IOSE-80 | Up | SOX2, AKT3, Oct-4, Nanog, Caspase-3 | LncRNA EMX2OS through modulating miR-654-3p/akt3/PD-L1 axis could induce metastasis of OC cells. (52) |
| EC     | Lnc-OC1      | 28 pairs of EC and paratumoral tissues | HESCs, Ishikawa | – | – | Lnc-OC1 by targeting miR-34a and suppressing PD-L1 could induce cell apoptosis in EC. (53) |
| EC     | MEG3         | 65 EC tissue samples and 18 normal endometrium samples | HEC-50, HeLa, HOUA1, HEC-1, EM, SPAC-1-L | Down | Caspase-3/7, MCL-1, ZO-1, E-cadherin, EMT, Vimentin, Snail | LncRNA MEG3 via repressing miR-216a and by increasing PD-L1 expression could inhibit cell invasion. (54) |

Thus, this lncRNA contributes to the progression of triple-negative BCa and immune evasion via enhancing the stability of PD-L1 protein and inducing GATA3 degradation (58).

### TABLE 4 Interaction between non-coding RNAs and PD-L1 in breast cancer.

| miRNA/LncRNA | Sample | Cell Line | PD-L1 Expression | Target | Function | Ref |
|--------------|--------|-----------|------------------|--------|----------|-----|
| miR-383-5p   | 24 pairs of BCa and paratumoral tissues | MDA-MB-231, PBMGs, MDA-MB-468, MCF-7, SK-BR-3 | Up | Caspase-3/9, Bcl-2, Bax, MMP-2/3/9, Vimentin, IL-2, IL-10, INF-γ, TNF-α/β, AKT, PI3K, mTOR | miR-383-5p via inhibition of PD-L1 can induce apoptosis and decrease metastasis of BCa cells. (55) |
| miR-424-5p   | 35 pairs of BCa and paratumoral tissues | MDA-MB-231, PBMGs, MDA-MB-468, SKBR-3, MCF-7 | Up | VEGF, c-Myc, Caspase-3, Bcl-2, Bax, p53, p27, Beclin-1, IL-2/10, INF-γ, PTEN, PI3K, AKT | miR-424-5p via targeting PD-L1 could decrease the progression of BCa cells. (56) |
| miR-92       | 34 BCa tissues and 34 normal tissues, BALB/c mice | MA-782, MC77, NK-92 | Up (in cancer cells treated with CAF-derived exosomes) | Vimentin, A-SMA, ALIX, YAP1, LATS2 | CAFs via targeting the miR-92/PD-L1 axis could suppress immune cell function in BCa cells. (57) |
| GATA3-AS1    | 68 pairs of TNBC and paratumoral tissues | MDA-MB-468, MDA-MB-436, MDA-MB-231, HCC1937, MCF-10A | – | CSN5, COP55, CBP, GATA3 | GATA3-AS1 via stabilizing PD-L1 and degrading GATA3 contributes to TNBC progression and immune evasion. (58) |
immune escape in this type of cancer through targeting miR-129-3p and subsequently activating STAT3 and PD-L1 (61). Table 5 shows the interaction between non-coding RNAs and PD-L1 in renal cancer.

**Other cancers**

The interaction between non-coding RNAs and PD-L1 has also been investigated in laryngeal cancer, anaplastic thyroid carcinoma, osteosarcoma, and diffuse large B-cell lymphoma (DLBCL) (Table 6). In laryngeal cancer, miR-217 by repressing the AEG-1/PD-L1 axis could inhibit metastasis (62). In thyroid carcinoma, UCA1 has been found to affect the miR-148a/PD-L1 axis to attenuate the cytotoxic effects of CD8+T cells (63). In osteosarcoma, miR-200a through promoting PTEN-mediated PD-L1 up-regulation could increase immunosuppression (64). Moreover, LINC00657 via targeting miR-106a could promote metastasis through the activation of PD-L1 (65). Finally, MALAT1 by sponging miR-195 could enhance tumorigenesis and immune escape of DLBCL (67).

**TABLE 5 Interaction between non-coding RNAs and PD-L1 in renal cancer.**

| miRNA/IncRNA | Sample | Cell Line | PD-L1 Expression | Target Function | Ref |
|---------------|--------|-----------|------------------|-----------------|-----|
| miR-497-5p (Down-regulated) | 30 pairs of ccRCC and paratumoral tissues, TCGA-KIRC databases | Caki-2, ACHN | Up | miR-497-5p suppressing could enhance PD-L1 expression in ccRCC. | (59) |
| miR-1-3p, miR-150-5p, miR-224-5p (Up-regulated) | 35 pairs of RCC and paratumoral tissues, 6 RCC urine samples, and 6 control urine samples | 297T, 769-P, 786-O, Caki-1, OS-RC-2, ACHN, 293T, PBMCs | – | miR-224-5p containing in urinary extracellular vesicle expression by suppressing Cyclin-D1 could regulate PD-L1 in RCC cells. | (60) |
| SNHG1 (Up-regulated), miR-129-3p | 20 pairs of RCC and paratumoral tissues, nude mice | ACHN, A498, 786-O, Caki-1, PBMCs | Down (after SNHG1 knockdown) | LncRNA SNHG1 via targeting miR-129-3p by activation STAT3 and PD-L1 could modulate the immune escape of RCC cells. | (61) |

**TABLE 6 Interaction between non-coding RNAs and other cancers.**

| Cancer | miRNA/IncRNA | Sample | PD-L1 Expression | Other Targets | Function | Ref |
|--------|--------------|--------|------------------|--------------|----------|-----|
| Laryngeal Cancer | miR-217 (Down-regulated) | 29 pairs of LC and paratumoral tissues, BALB/C nude mice | Hep2, HUVEC | AEG-1 | miR-217 by repressing AEG-1/PD-L1 axis expression could inhibit metastasis. | (62) |
| Anaplastic Thyroid Carcinoma | UCA1 (Up-regulated), miR-148a | 10 pairs of ATC and paratumoral tissues, NOG mice | 8505C, Hh74, 293T, PBMCs | IFN-γ, TNF-α | LncRNA UCA1 via targeting miR-148a/PD-L1 axis could attenuate the killing effect of cytotoxic CD8+T cells. | (63) |
| Osteosarcoma | miR-200a (-) | 32 OS tissue samples, Mice | 143B, MG63, HOS, U2OS, K7, K7/M2, DUNN, PBMCs | Positive correlation with high levels of miR-200a | PD-L1, PTEN | miR-200a could increase immunosuppression. | (64) |
| Diffuse large B-cell lymphoma (DLBCL) | LINC00657 (-), miR-106a | – | MG63, U2OS, HDLEC, 293T | Up | LINC00657 via targeting miR-106a could promote metastasis. | (65) |
| MALAT1 (-), miR-195 | 20 pairs of DLBCL and paratumoral tissues | OCI-Ly-10, 293T, PBMCs | Up | IFN-γ, TNF-α, IL-10 | Overexpression of miR-195 by targeting PD-L1 could attenuate the immune escape of DLBCL. | (66) |
| MALAT1 (-), miR-195 | 37 DLBCL patients | OCI-Ly10, PBMCs | Positive correlation with MALAT1 | Slug, E/N-cadherin, Vimentin, EBIK/2 | LncRNA MALAT1 by sponging miR-195 could enhance tumorigenesis and immune escape of DLBCL. | (67) |
Interactions between non-coding RNAs and PD-L1 in response to chemotherapeutic agents

The interaction between non-coding RNAs and PD-L1 can also affect the response of cancer cells to anti-cancer modalities. Moreover, anti-cancer drugs can affect these interactions (Table 7). Cisplatin is the mostly assessed drug in this regard. Cisplatin via modulation of miR-181a expression could negatively regulate PD-L1 expression in NSCLC (68). Meanwhile, miR-3127-5p via regulating STAT3 could up-regulate PD-L1-associated chemoresistance in NSCLC cells (69). Besides, miR-526b-3p through inhibiting STAT3-promoted PD-L1 expression could decrease cisplatin resistance and metastasis (70). miR 576-3p by affecting PD-L1 and cyclin D1 expression could enhance the cisplatin sensitivity of OC cells (74).

Thalidomide has been shown to suppress angiogenic process and immune evasion of NSCLC cells by influencing the

| Type of Diseases | Drug | Non-coding RNAs | Sample | Cell line | PD-L1 Expression | Other Targets | Function | Ref |
|------------------|------|----------------|--------|-----------|-----------------|--------------|----------|-----|
| NSCLC Cisplatin  | miR-181a | (-) | C57BL6/J mice | A549R, H69R (A549, H69, LL/2); treated with 10 µg/ml cisplatin for 24 h | Up (in CDDP-resistant) | ATM, c-FOS | Cisplatin via affecting miR-181a expression could negatively regulate PD-L1 expression in NSCLC. (68) |
| NSCLC Cisplatin  | miR-3127-5p | (-) | 64 pairs of NSCLC and paratumoral tissues | A549, NCI-H1299, A549/DDP, 293T, PBMCs | Up | LC3, P62, STAT3 | miR-3127-5p via regulating STAT3 could up-regulate PD-L1-associated chemoresistance in NSCLC cells. (69) |
| NSCLC Cisplatin  | miR-526b-3p | (-) | 100 NSCLC patients, BALB/c nude mice | BEAS-2B, H1975, A549, PC-9 | PD-L1, MDR1, c-Myc, STAT3 | miR-526b-3p through suppression of STAT3-promoted PD-L1 could decrease cisplatin resistance and metastasis. (70) |
| NSCLC Thalidomide | FGDS-AS1 (Up-regulated), miR-454-3p | (-) | 45 pairs of NSCLC and paratumoral tissues, BALB/c nude mice; treated with 200 mg/kg Thalidomide twice a week for 3 weeks | A549, SPC-A1, H1299, PC-9, H226, 16HBE, 293T, HUVECs; treated with 100 µM thalidomide for 24 h | Up | PD-1, ZEB1, VEGFA, E/N-cadherin | Thalidomide affects FGDS-AS1/miR-454-3p/ZEB1 axis and expressions of VEGFA and PD-1/PD-L1. (71) |
| NSCLC Nobiletin  | miR-197 | (-) | – | A549, H292, H460; treated with 200 µM Nobiletin for 48 h | PD-L1, p53, MDM2, STAT3, EGFR, JAK2 | Nobiletin by regulating STAT3-mediated PD-L1 expression and via p53-independent PD-L1 downregulation could inhibit tumor progression. (72) |
| LUAD Cisplatin   | FGDS-AS1, miR-142-5p | (-) | 46 LUAD tissue samples | A549/DDP, HCC827/ DDP, A549, HCC827 | Up (in DDP-resistant cells) | – | FGD5-AS1 via targeting miR-142-5p/PD-L1 axis could enhance cisplatin resistance of LUAD cells. |
| OC Cisplatin     | miR-576-3p (down) | (-) | BALB/c nude mice; treated with 10 mg/kg cisplatin, IP, twice a week for 3 weeks | SKOV3/DDP and A2780/DD, 293T, SKOV3, A2780; treated with 1, 2, 4, 8 µM cisplatin for 48 h | Up (in DDP-resistant cells) | Cyclin-D1, MDR1, PARP, Caspase-3 | miR-576-3p by affecting PD-L1 and cyclin D1 expression could enhance the cisplatin sensitivity of OC cells. (74) |
| OC Cisplatin     | miR-145 (Down-regulated) | (-) | 73 OC tissue samples | A2780, PBMCs, (A2780/DDP); pretreated with 100 µg/ml cisplatin for 24 h | Up (in treated cells with DDP) | c-Myc | Cisplatin-mediated miR-145 downregulation via targeting c-Myc by modulating PD-L1 could contribute to cisplatin resistance in OC cells. (75) |
| Epithelial Ovarian Cancer | Olaparib, Radiation | miR-200c-3p | (-) | 5 EOC tissue samples | SKOV3; treated with 1.5 and 5 µM Olaparib after 48 h post-Olaparib treatment, irradiated 4 Gy | PD-L1, c-Myc, β-catenin | miR-200c-3p by combinatorial therapies could contrast the induction of PD-L1 and via downregulating the c-Myc/β-catenin could decrease cell proliferation. (76) |
**TABLE 7 Continued**

| Type of Diseases | Drug | Non-coding RNAs | Sample | Cell line | PD-L1 Expression | Other Targets | Function | Ref |
|------------------|------|-----------------|--------|-----------|------------------|--------------|----------|-----|
| CRC              | Polydatin | miR-382 (-)       | CS7BL/6 mice       | 293T, (Caco-2, HCT 116); treated with 50, 100, 150 µM Polydatin | Down       | PCNA, Caspase-3 | Polydatin could induce an antitumor effect by targeting the miR-382/PD-L1 axis in CRC cells. | (77) |
| Esophageal Cancer | Sevoflurane | Circ-VIM (Up-regulated), miR-124 | 20 pairs of EC and paratumoral tissues, BALB/C nude mice, treated with 40 mg/kg Sevoflurane, IV, for every 2 days | PBMCs, 293T, HET-1A, TE-10, TE-11, (KYSE-150, Eca-109); treated with 1% to 4% sevoflurane for 6 h | Up        | Slug, Fibronectin, E/N-cadherin, Ras, ERK1/2 | Circ-VIM silencing has a synergic effect with sevoflurane by regulating the miR-124/PD-L1 axis. | (78) |
| GC               | Cisplatin | NUTM2A-AS1 (Up-regulated), miR-376a | NOD-SCID mice | – |– | – | LncRNA NUTM2A-AS1 via targeting miR-376a by regulating TET1 and HIF-1A could enhance GC tumorigenesis and drug resistance. | (79) |
| GC               | TRAIL | miR-429 (-)       | – | MKN45, BGC823, SGC7901, HGC27; treated with 100 ng/ml TRAIL for 6 days | PD-L1       | AKT, Caspase-3, EGFR, mTOR | miR-429-mediated regulation of PD-L1 affects the sensitivity of GC cells to TRAIL. | (80) |
| HCC              | Sorafenib (SR) | miR-1 (Up) | SPF BALB/c nude mice | Hep3B, HepG2, 293T, HepG2/SR and Hep3B/SR | Up (in cells treated with SR) | NRF-2, P-gp, MRP1, mTOR | NRF-2/miR-1/EGFR regulatory axis via targeting PD-L1 contributes to the development and maintenance of drug resistance. | (81) |
| HCC              | SR | KCNQ1OT1 (Up), miR-506 | SR-sensitive (n=25) and SR resistant (n=38) HCC tissue samples | SK-HEP-1, Huh-7, SK-HEP-1/SR, Huh-7/SR; treated with 1-3 µM Sorafenib for 48 h | Positive correlation with KCNQ1OT1 | TNF-α, IFN-γ, IL2/10, TGF-β | LncRNA KCNQ1OT1 via sponging miR-506 could contribute to SR resistance and PD-L1-mediated immune escape in HCC cells. | (82) |
| BCa              | Oleuropin | miR-194 (-)       | 21 pairs of BC and paratumoral tissues | MDA-MB-231; treated with 200 µM Oleuropin for 72 h | Up       | XIST | Oleuropin via modulating the miR-194/XIST/PD-L1 axis could repress BCa progression. | (83) |
| BCa              | Adriamycin (ADR) | miR-3609 (Down-regulated) | 47 BCa tissue samples and 19 paratumoral tissues | 293T, HBL-100, MCF-7, MDA-MB-231, MDA-MB-468 (MCF-7/ADR); treated with 0.001, 0.01, 0.1, 1, 10, 100 µg/mL ADR for 48 h | Up (in treated cells with ADR) | – | miR-3609 by blocking the PD-L1 immune checkpoint could sensitize BCa cells to ADR. | (84) |
| Gliona           | Paclitaxel | miR-34a (Down-regulated) | 21 glioma patients | U251, U87-MG, U87/P, treated with 0-200 nM Paclitaxel for 24-72 h | Up       | Caspase-3 | miR-34a via targeting PD-L1 could attenuate glioma cell invasion and chemoresistance. | (85) |

expression of VEGFA and PD-1/PD-L1 via affecting FGDS-AS1/miR-454–3p/ZEIB1 axis (71). Moreover, nobiletin has been shown to regulate PD-L1 expression through the modulation of STAT3, thus inhibiting the progression of NSCLC (72). Meanwhile, miR-34a via targeting PD-L1 could attenuate glioma cell invasion and their chemoresistance (85).

**Discussion**

PD-L1 has been found to participate in the tumorigenesis process via induction of Tregs and inhibition of antitumor immune responses. Besides, several non-coding RNAs can act as regulators of gene expression, particularly at the posttranscriptional level to affect the expression of PD-L1. In fact, a delicate interactive network exists between non-coding RNAs that in regulators of gene expression, particularly at the posttranscriptional level to affect the expression of PD-L1. In fact, a delicate interactive network exists between non-coding RNAs that in affecting FGD5-AS1/TGF-β3 axis (85). Moreover, nobiletin has been shown to regulate PD-L1 expression through the modulation of STAT3, thus inhibiting the progression of NSCLC (72). Meanwhile, miR-34a via targeting PD-L1 could attenuate glioma cell invasion and their chemoresistance (85).
MALAT1/miR-200a-3p, circ_000284/miR-377-3p, circ-CPA4/miR-let-7, circ-CHST15/miR-155-5p, circ-CHST15/miR-194-5p, EMX2OS/miR-654-3p, Lnc-OC1/miR-34a, MEG3/miR-216a, GATA3-AS1/miR-676-5p, LINC00657/miR-654-3p, Lnc-OC1/miR-34a, MEG3/miR-216a, MALAT1/miR-106a and MALAT1/miR-195 are examples of these modules.

In addition to the above-mentioned PD-L1-interacting non-coding RNAs, several non-coding RNAs can indirectly affect the activity of the PD-1/PD-L1 pathway (86). For instance, the up-regulated IncRNA in diffuse large B cell lymphoma SNHG14 adsorbs miR-5590-3p to enhance expression levels of ZEB1, thus activating the PD-1/PD-L1 pathway and inducing immune evasion (87).

The interactions between non-coding RNAs and PD-L1 are also involved in the response of patients to several anti-cancer modalities. These interactions can also be affected by the administration of several treatment modalities. Cisplatin, Adriamycin, Paclitaxel, Thalidomide, Nobiletin, Olaparib, Sevoflurane, Sorafenib, and Oleuropein are examples of drugs that can affect/be affected by such interactions.

Most importantly, several PD-L1-related non-coding RNAs have been found to be secreted in exosomes originated from tumor cells’ microenvironment residing cells. This finding not only shows the extensive impacts of these non-coding RNAs in tumor progression or modulation of the tumor microenvironment but also potentiates these transcripts as biomarkers for the early detection of cancer using biofluids.

The promising results of clinical trials of anti-PD-L1 during recent years have encouraged researchers to find better treatment modalities to enhance the clinical response to these modalities. Non-coding RNAs are putative modulators of PD-L1 expression and activity, and thus can be used as therapeutic targets in this regard. Moreover, expression levels of PD-L1-associated non-coding RNAs can be used as predictive markers for response to PD-L1 inhibitors. In fact, the lack of appropriate response to this type of therapy can be attributed to the levels of expressions of PD-L1-associated non-coding RNAs. Thus, modulation of expression of these transcripts using siRNA or antisense oligonucleotides can enhance clinical response to anti-PD-L1 therapy. Application of these methods needs a prior identification of the pattern of expression of PD-L1-associated non-coding RNAs in patients’ samples and the functional network between these transcripts and PD-L1. This can be achieved using high throughput sequencing methods with a system biology approach. Future studies are needed to propose tissue-specific panels of non-coding RNAs for this purpose.

Data availability statement

The analyzed data sets generated during the study are available from the corresponding author upon reasonable request.

Author contributions

SG-F wrote the manuscript and revised it. MT and GS supervised and designed the study. HS, YP and BH collected the data and designed the figures and tables. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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