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Review Article

Programmed Cell Death Ligand 1-Inhibiting MicroRNAs in Hepatocellular Carcinoma: A Systematic Review

Haleh Hamedifar[a,b], Parisa Lotfinejad[c], Zahra Asadzadeh[c], Nima Hemmat[c], Ali N. Kamali[a,b]*

[a] *CinnaGen Medical Biotechnology Research Center, Alborz University of Medical Sciences, Karaj, Iran.*
[b] *CinnaGen Research and Production Company, Alborz, Iran.*
[c] *Immunology Research Center, Tabriz University of Medical Sciences, Tabriz, Iran.*

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HIGHLIGHTS

- Cancer cells can use the PD-1/PD-1 axis to evade the anti-tumor response of immune cells.
- Increased PD-L1 expression is directly associated with poor prognosis in hepatocellular carcinoma.
- Several microRNAscan inhibit PD-L1 expression in HCC cells.

ABSTRACT

The Programmed cell death ligand-1 (PD-L1), an immune checkpoint molecule, is the ligand of Programmed cell death protein 1 (PD-1). They are crucial molecules in maintaining immune homeostasis. PD-L1/PD-1 axis regulates the initiation and maintenance of tolerance and protects tissues from autoimmune responses; however, cancer cells can use the PD-1/PD-1 axis to evade the anti-tumor response of immune cells. Increased PD-L1 expression is directly associated with poor prognosis in hepatocellular carcinoma (HCC). Although immunotherapy with immune checkpoint inhibitors (ICIs) are leading therapy in cancer treatment, using biomarkers to regulate immune checkpoints at the RNA level is considered a promising tool in novel therapeutic approaches. Increasing evidence has reported that miRNAs are critical regulators of tumor development. Hence, we performed a current systematic review to explore PD-L1 inhibiting miRNAs involved in hepatocellular carcinoma. Five databases were systemically searched to obtain the relevant original articles. Consequently, seventeen studies were included in the current systematic review. According to obtained literatures, some microRNAs, namely miR-194-5p, -675-5p, 194-5p, -1, -455-5p, -223-3p, -513, -195, -506, -329-3p, -424, -411-5p, -182-5p, -200, -378a-3p, -570, -200c, and -513a-5p can inhibit PD-L1 expression in HCC cells. These can ultimately reduce tumor proliferation, inhibit tumor migration, stimulate the chemosensitivity of cancer cells, and induce apoptosis in tumor cells. Moreover, the investigated miRNAs were further analyzed using miRNA target prediction online tools to highlight the future direction of their functions in HCC.

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H. Hamedifar: https://orcid.org/0000-0003-2308-8925
A. N. Kamali: https://orcid.org/0000-0002-6225-9726

**Corresponding Author:*
Email: kamalia@cinnagen.com , alin_kamali@yahoo.com (A. N. Kamali)

Introduction

Primary liver cancer is a high-risk malignant tumor with an expected incidence of 906,000 new cases in 2020 or

4.7% of all cancer cases. Hepatocellular carcinoma (HCC) is the most prevalent form of primary liver cancer, accounting for 75–85 percent of cases. HCC is the third biggest cause of cancer-related fatalities globally, with an estimated 830,000 deaths in 2020 (Lafaro et al., 2015; Bray et al., 2018). Unfortunately, the majority of patients are detected at a later or more severe stage, for which there is no effective treatment. Although many HCC-related risk factors, such as viral hepatitis, liver cirrhosis, and alcohol misuse, are generally well understood (Ng and Wu, 2012; White et al., 2012), the molecular mechanism underlying the formation and progression of HCC is mainly unclear. Thus, greater clarification of HCC tumorigenesis is required.

Immune checkpoint molecules, such as programmed cell death one and its ligand (PD-1 and PD-L1), are the most extensively researched and have the most significant therapeutic implications for treating human cancer. PD-L1 is expressed in immune cells and tumor cells, and tumor cells employ PD-L1 to attach to PD-1 of T cells to 'trick' the T cells and evade detection, allowing them to continue to spread throughout the body. The immune checkpoints, particularly the PD-1/PD-L1 signaling pathway, play a crucial role in this process (Shrestha et al., 2018). The expression of PD-L1 on HCC cells limits T cell function in the microenvironment of liver tumors. High PD-L1 expression on tumor cells was identified as a predictor of recurrence in HCC patients (Gao et al., 2009), which is not surprising. In addition to its connection with tumor aggressiveness and poor prognosis, analyses of HCC resection samples revealed a greater level of PD-L1 expression (Calderaro et al., 2016; Jung et al., 2017). It has been demonstrated that PD-L1 knockdown can significantly reduce HCC proliferation, promotes apoptosis, block migration, and enhance chemosensitivity (Shi et al., 2011; Liu et al., 2017; Dai et al., 2018, Mocan et al., 2019). To improve the efficacy of PD-L1/PD-1 blocking, it is required to have a deeper understanding of the mechanisms governing PD-L1 expression in HCC.

MicroRNAs (miRs), a highly conserved class of tiny non-coding RNAs with an average length of 18 to 24 nucleotides, regulate gene expression at the transcriptional level by interacting with the promoters of their target genes (Janowski et al. 2007; Khraiwesh et al., 2010) and at the post-transcriptional level by deleting their target mRNAs and/or blocking their translation by binding to the 3′-untranslated region (3′UTR) of those (Hutvagner and Zamore, 2002; Kozomara et al., 2019). A single miR may regulate hundreds of target mRNAs with the same tiny recognition region, and most mRNAs contain multiple miR binding sites in their 3′-UTR. Since the discovery of the first miR, lin-4, in 1993 (Lee et al., 1993; Hammond, 2015; Sidhu et al., 2015), more than 2000 microRNAs that regulate one-third of the human genome have been found. All malignancies exhibit differential miR expression because tumor-suppressor miRs are often downregulated, and oncogenic miRs are typically enriched (Ali Syeda et al., 2020). Epithelial-mesenchymal transition (EMT), angiogenesis, drug resistance, and autophagy are all regulated by miRs in the development and metastasis of HCC (Khare et al., 2013; Xu et al., 2018; Pratama et al., 2019). MiRs can also modify immune system players to influence innate and adaptive immune responses. It appears that targeted therapy using miRs can be beneficial in malignancies, including HCC, as the complimentary interaction between miRs and PD-L1 has been demonstrated to modulate PD-L1 expression (Chen et al., 2014; Zhao et al., 2016; Fan et al., 2021).

Here, the current systematic review aims to find studies that mostly focus on the ability of an individual or a cluster of miRNAs to express PD-L1 and the further alterations in cancer features such as proliferation, metastasis, immune escape, and others, in HCC.

Materials and Methods

The current systematic review study is performed according to the PRISMA statements (Moher et al., 2009).

Search strategy

We searched Scopus, PubMed, Web of Science, ProQuest, and Ovid databases up to 29 July 2022. The search terms used in mentioned databases included combinations of the following keywords: ("miRNA" OR "microRNAs" OR "miR" OR "micro RNA" OR "microRNA" OR "miRNA") AND ("CD274" OR "programmed death-ligand 1" OR "programmed cell death ligand 1" OR "programmed cell death ligand-1" OR "death ligand-1" OR "PD-L1" OR "PDL1" OR "B7-H1" OR "PDCD1LG1" OR "B7 H1" OR "B7H1" OR "HPD-L1" OR "cluster of differentiation 274" OR "PD L1" OR "CD 274" OR "B7 homolog 1" OR "PDCD1 ligand 1" OR "PDCD1L1" OR "B7-H1 antigen" OR "programmed death 1 ligand 1") AND ("hepatocellular carcinoma" OR "HCC" OR "liver cancer" OR "hepatic cancer" OR "advanced hepatocellular carcinoma" OR "liver hepatocellular carcinoma").

Eligibility

The following records met the requirements for inclusion in this analysis: (1) Articles in English. (2) Original research papers on cell lines from hepatocellular carcinoma. (3) Research projects that evaluated miRNAs and PD-L1. (4) Research on the

correlation between PD-L1 expression and miRNA expression and HCC cell line migration, treatment resistance, and apoptosis. Papers that did not match the inclusion criteria listed above, human studies, review articles, conference abstracts, and case report studies, were all eliminated from this study.

Data Extraction

Two authors independently reviewed all identified records. Data from each included study was independently extracted. The following information was extracted from the included studies: the first author, the publication year, the studied miRNAs, the effect of studied miRs on PD-L1 expression, and the studied HCC cell lines.

In silico investigation

After the investigated miRNAs were analyzed to find the probable targeting using miRWalk v3.0 (Sticht et al., 2018), the resulting miRNA-mRNA interactions were evaluated by miRTarBase (Huang et al., 2020) to find experimentally validated ones. Finally, the predicted targets of each miRNA were functionally enriched by Enrichr (Kuleshov et al., 2016), and the results were illustrated using Cytoscape v3.9.1 (Shannon et al., 2003).

Results

Included studies

The method of choosing studies is described in (Fig. 1).

There were 643 possibly relevant records in total as a consequence of the thorough systematic search. Three hundred thirty duplicate records were eliminated during the initial screening. In addition, 251 papers were disregarded after their titles and abstracts were examined. The entire texts of the remaining 62 papers were evaluated, and 44 articles were removed for the following reasons: studies using human samples, publications in which PD-L1 expression was evaluated in different cells, and studies in which there was no examination of the relationship between mRNAs and PD-L1. There were then just 17 studies left (Guo et al., 2015; Sun et al., 2018; Cao et al., 2020; Zhang et al., 2020; Fan et al., 2021; Li et al., 2021; Liu et al., 2021; Samir et al., 2021; Wang and Cao, 2021a; Yan et al., 2021; Zeng et al., 2021; Kong et al., 2022; Li et al., 2022a; Sun et al., 2022; Zhang et al., 2022).

Study characteristics

The main characteristics of the included studies in the current systematic review are summarized in Table 1. Included studies were published between 2015 and 2022. We have found that the presence of miR-194-5p, -675-5p, -1, -455-5p, -223-3p, -513, -195, -506, -329-3p, -424, -411-5p, -182-5p, -200, -378a-3p, -570, -200c, and -513a-5p can considerably downregulate PD-L1 expression in HCC cell lines (Fig. 2).

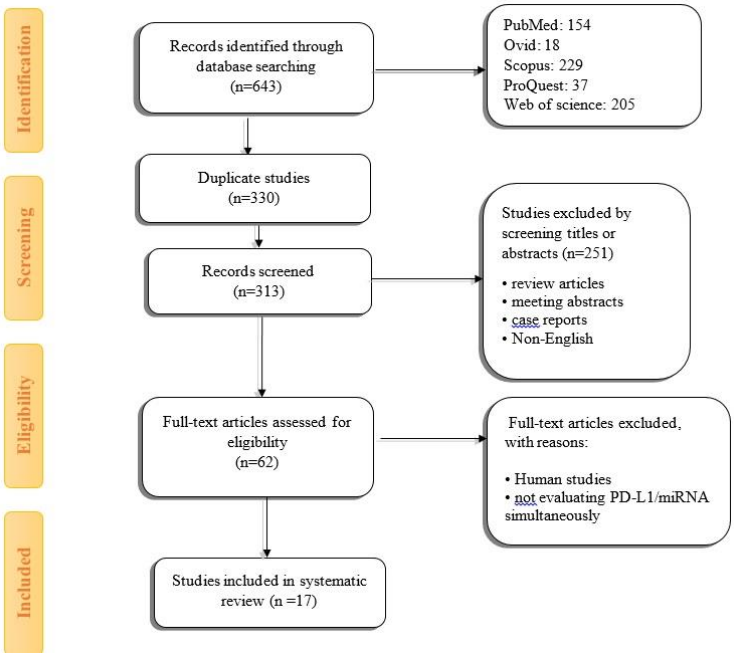

Figure 1. Process of study selection.

Table 1. PD-L1 inhibiting miRNAs in HCC cells

No	First Author /Year	microRNA	Axis of action	Mechanism of action
1	Fei Fan, 2020 (Fan et al., 2021)	miR-194-5p	PCED1B-AS1/ miR-194-5p/PD-L1-PD-L2	MiR-194-5p increased the expression of PD-Ls by sponging miR-194-5p, which negatively correlates with PD-L1 and the long non-coding RNA PCED1B -AS1.
2	Zongcai Liu, 2021 (Liu et al., 2021)	miR-675-5p	EGFR-P38 MAPK/ miR-675-5p/PD-L1	MiR-675-5p is prevented by EGFR activation, and miR-675-5p mimics prevent PD-L1 accumulation and higher PD-L1 mRNA stability brought on by EGFR activation.
3	Dong Li, 2020 (Li et al., 2020)	miR-1	NRF-2/miR-1/PD-L1	Loss of miR-1 contributes to increased proliferation of hepatoma cells; mir-1 inhibits tumorigenicity of sorafenib-resistant hepatoma cells via PD-L1 inhibition.
4	Cheng Zeng, 2021 (Zeng et al., 2021)	miR-455-5p	HOXA-AS3/miR-455-5p/PD-L1	HOXA-AS3 elevates PD-L1 through the miR-455-5p sponge.
5	Suihui Li, 2022 (Li et al., 2022a)	miR-223-3p	circ_0048674/miR-223-3p/PDL1	Hsa_circ_0048674 serves as the miR-223-3p sponge in PD-L1 expression. circ_0048674/miR-223-3p/PDL1 axis has an oncogenic effect on HCC by promoting tumor cell growth, migration, and angiogenesis and inhibiting apoptosis.
6	Guoqiang Sun, 2022 (Sun et al., 2022)	miR-513	miR-513/PD-L1	Olaparib, a PARP inhibitor, causes HCC cells to upregulate PD-L1 via inhibiting miR-513.
7	Yihe Yan, 2021 (Yan et al., 2021)	miR-195	IRF-1/CHK1/miR-195/PD-L1	IRF-1 downregulates CHK1 through miR-195 to upregulate PD-L1 expression via STAT3 phosphorylation and increased apoptosis in HCC cells
8	Junli Zhang, 2020 (Zhang et al., 2020)	miR-506	KCNQ1OT1/miR-506/PD-L1	miR506 expression is low in sorafenib-resistant HCC cells. KCNQ1OT1 controls the expression of PDL1 via sponging miR506. miR506 specifically targets PDL1.
9	Y. Wang, 2021 (Wang and Cao, 2021)	miR-329-3p	KDM1A/ miR-329-3p/ PD-L1	In HCC cells, miR-329-3p suppresses PD-L1 expression by downregulating KDM1A.
10	Xinling Cao, 2020 (Cao et al., 2020)	miR-424	LINC00657/ miR-424/PD-L1	LINC00657 controlled the expression of PD-L1 by sponging miR-424. MiR-424 mimic significantly decreased PD-L1 mRNA and protein expression.
11	X. Zhang, 2022 (Zhang et al., 2022)	miR-411-5p	MAIT/miR-411-5p/STAT3/PD-L1	MIAT negatively regulates the expression of miR-411-5p, upregulates STAT3, and eventually increases the expression of PD-L1.
12	Amany Samir, 2021 (Samir et al., 2021)	miR-182-5p	XIST & MALAT1/ miR-182-5p/PD-L1	Following transfection with a mimic of miR-182-5p and silencing of MALAT1, the expression of PD-L1 was decreased.
13	S. Guangshun, 2022 (Guangshun et al., 2022)	miR-200	MicroRNA-200/PD-L1	Meloxicam may upregulate the amount of PD-L1 by silencing the production of COX2, which lowers microRNA-200 in tumor cells.
14	Yaqin Li, 2022 (Li et al., 2022b)	miR-378a-3p	miRNA-378a-3p/STAT3/PD-L1	miR-378a-3p is downregulated in HCC and correlates adversely with PD-L1 levels.
15	Wei Guo, 2015 (Guo et al., 2015)	miR-570	miR-570/PD-L1	miR-570's target gene is PD-L1. By inhibiting PD-L1, miR-570 suppresses HCC cell growth and metastasis.
16	Cheng Sun, 2018 (Sun et al., 2018)	miR-200c	STAT3/SALL4/miR-200c/PD-L1	Overexpression of miR-200c or injection of miR-200c mimics can directly suppress PD-L1 expression by hepatocytes. miR-200c is downregulated in HCC.
17	Xiangyi Kong, 2022 (Kong et al., 2022)	miR-513a-5p	GUSB/ miR-513a-5p/PD-L1	GUSB inhibits PD-L1 expression by increasing miR-513a-5p expression.

Abbreviations: PCED1B-AS1: PCED1B Antisense RNA 1, EGFR: Epidermal Growth Factor Receptor, XIST: X-Inactive Specific Transcript, HOXA-AS3: HOXA Cluster Antisense RNA 3, PARP: Poly (ADP-ribose) polymerase, IRF-1: Interferon Regulatory Factor 1, KCNQ1OT1: KCNQ1 Opposite Strand/Antisense Transcript 1, MIAT: Myocardial Infarction Associated Transcript, MALAT1: Metastasis-Associated Lung Adenocarcinoma Transcript, COX2: Cyclooxygenase 2.

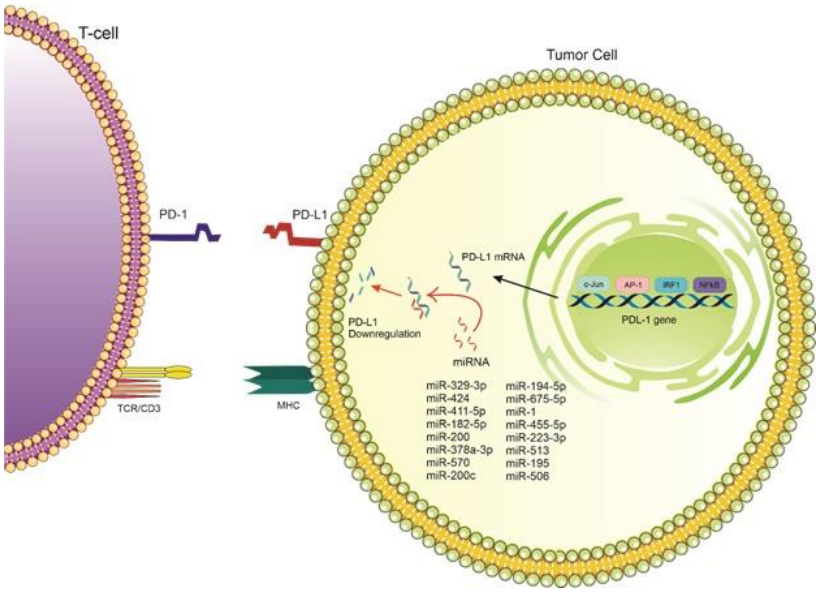

Figure 2. PD-L1 expression down regulated by miRNAs. Several transcription factors, including NF-κB, IRF-1, AP-1 and c-Jun, are involved in PD-L1 expression. As a result, the PD-L1 gene is amplified in tumor cells. This leads to the upregulation of PD-L1 mRNA transcription. miRNAs, by targeting the 3' untranslated region (UTR) of PD-L1, downregulate PD-L1 expression.

In silico investigation

The obtained results predicted that miR-182-5p mostly plays a role in regulating apoptosis. Furthermore, miR-200c, -424, and -195 are mainly enriched in regulating the cell cycle and subsequent proliferation. miR-182-5p and -506 could significantly take part in the stemness. miR-223-3p and -378a-3p are two of the most important orchestrators of the FOXA2 pathway, which consequently promote cell proliferation and maintain cancer stem cells. In addition, the latter, along with miR-194-5p, might modulate TCR signaling and activation of T cells (Fig. 3).

Discussion

The immune system typically acts as a cancer suppressor by preventing the spread of cancer and destroying cancerous cells. However, cancer cells can elude immune monitoring, which promotes carcinogenesis and the spread of cancer. Immune checkpoints significantly aid the immunological evasion of cancer cells. A wide range of cells express PD-L1, and aberrant PD-L1 expression in malignancies has been found to reduce T-cell anti-tumor activity, protecting cancers from killing T-cells (Yi et al., 2021). Recent research suggests that miRs are strongly linked to regulating PD-L1 expression in HCC and directly target the 3'UTR of PD-L1 to suppress expression (Wang et al., 2021a). Here, we emphasize the therapeutic potential of these PD-L1-inhibiting miRs in preventing the growth of HCC.

miR-194-5p

According to Fan et al., the hsa-mir-194-5p inhibitor increases PD-L1 protein levels, whereas the hsa-mir-194-5p mimic decreases PD-L1 protein levels. These findings imply that PD-L1 is a target of hsa-mir-194-5p, which inhibits its expression in HCC. Additionally, they discovered that lncRNA PCED1B-AS1 is a key regulator of PD-L1 expression and promotes PD-L1 expression and function by sponging miR-194-5p to cause immunosuppression in HCC (Fan et al., 2021). Additionally, it has been discovered that overexpressing miR-194-5p significantly lowers the amount of FOXA1 in HepG2 cells and suppresses the development of HCC (Wang et al., 2019a). According to research by Bao et al. (2015), miR-194 abundance was reduced in HCC tissue, and a low miR-194 abundance was associated with a higher incidence of vascular invasion. Furthermore, the motility and invasiveness of HCC cells in vitro and metastatic seeding in mice were inhibited by overexpressing miR-194. Besides, our *in silico* investigation predicted that this miRNA could play a role in the cell cycle, hedgehog signaling pathway, and response to oxidative damage.

Figure 3. The functional enrichment analysis. The majority of investigated miRNAs could interact with signaling pathways involved in the proliferation, metastasis, and stemness of malignant cells.

miR-675-5p

EGFR activation in HCC tissues has been found to have a positive correlation with the expression of PD-L1 and a negative correlation with the expression of HLA-ABC, according to a study carried out by Liu et al. In HCC cells, EGF may cause EGFR signaling activation, which can then upregulate PD-L1 and downregulate HLA-ABC. This can potentially have a functionally important effect, which the EGFR inhibitor gefitinib can successfully eliminate. Hexokinase-2 up-regulation increased aerobic glycolysis and then mediated the decrease in HLA-ABC expression, while MiR-675-5p down-regulation increased PD-L1 mRNA stability possibly via 3'-UTR and subsequently caused PD-L1 accumulation. On the other hand, PD-L1 accumulation was caused by hexokinase-2 up-regulation. This is the mechanism behind the enhanced activation of P38 MAPK. (Liu et al., 2021). This research uncovered a previously unknown signaling network that has the potential to suppress the immune response in HCC cells. In addition, the results of our research conducted *in silico* revealed that this miRNA could be engaged primarily in the process of DNA replication as well as the miRNA control of the p53 signaling pathway.

miR-1

According to Li et al. findings, miR-1 exerts its tumor-suppressing effects on drug resistance and other malignant properties in sorafenib-resistant hepatoma cells by partially inhibiting PD-L1. This occurs both in vitro and in vivo. They postulated that an NRF-2/miR-1/PD-L1 regulatory axis contributes to establishing and maintaining drug resistance in sorafenib-resistant hepatoma cells and other tumorigenic traits (Li et al., 2020). This was done in the context of hepatoma cells. Compared to a normal human liver cell line, the levels of the miR-1-3p present in the HCCLM3, Hep3B, Bel-7404, and SMMC-7721 cell lines are significantly lower. Overexpression of miR-1-3p in HCC cells caused them to undergo apoptosis and significantly limited their capacity for cell division. SOX9 is a direct target of miR-1-3p in HCC cells and inhibition of SOX9 results in a significant reduction in cell proliferation (Zhang et al., 2019).

miR-455-5p

In the HCC cell lines, Zeng et al. discovered a high level of HOXA-AS3 expression. Overexpression of HOXA-AS3 increased migration, invasion, and proliferation in HCC cells while also modulating the cell cycle and delaying apoptosis. These effects were achieved while also inhibiting apoptosis. Additionally, a binding site for miR-455-5p was found in the HOXA-AS3 sequence. Through the process of miR-455-5p sponging, HOXA-AS3 was able to increase the expression of PD-L1 (Zeng et al., 2021).

Additionally, blocking PD-L1 and overexpressing miR-455-5p was also shown to be effective in reversing the effects of HOXA-overexpression AS3s on cell proliferation and invasion (Zeng et al., 2021). In addition, Hu and colleagues found that the expression of miR-455-5p was significantly downregulated in the tumor tissues and cell lines of HCC patients. This downregulation was related to a poorer prognosis for the patients. Overexpression of the microRNA 455-5p led to a decrease in cell proliferation, colony formation, migration, and invasion in Huh7 and HepG2 cell lines. They tested whether or not this miRNA might directly bind to the 3′-untranslated region of the insulin growth factor receptor (IGF-1R), therefore preventing HCC cells from producing IGF-1R (Hu et al., 2019). Our data also revealed that this miRNA could mainly act as a regulator of the immune system by interfering with CTLA-4 function, IL-9, and IL-7 signaling pathways, TCR and co-stimulatory signaling, as well as PI3K/AKT/mTOR signaling pathway.

miR-223-3p

Li et al. found that the hsa circ 0048674/miR-223-3p/PDL1 axis promotes tumor cell proliferation, migration, invasion, and angiogenesis while blocking apoptosis, which results in an oncogenic effect on HCC. To change the expression of PDL1, Hsa-circ-0048674 acted as a sponge for miR-223-3p (Li et al., 2022a). Additionally, it has been demonstrated that miR-223 acts as a tumor suppressor and is essential for preventing carcinogenesis and encouraging apoptosis in HCC via the mTOR signaling pathway (Dong et al., 2017). In HCC cells treated with celastrol, Si et al. showed that CXCR4 is a direct and practical target of miR-223-3p. They also mentioned how circ-SLIT3 sequesters miR-223-3p to defend against CXCR4 suppression (Si et al., 2021). Moreover, our *in silico* data predicted that this miRNA could significantly impact the FOXA2 signaling pathway and mediate proliferation and stemness.

miR-513a

Since the immunosuppressive factors, PD-L1 and PARP2, have a negative correlation, according to Sun et al., treating HCC with PARP inhibitors and PD1 monoclonal antibodies may be more effective. They detected that Olaparib could raise HCC cells' PD-L1 levels. Furthermore, they verified that Olaparib

stimulates the transcription of PD-L1 by inhibiting miR-513 to understand why PARP inhibitors increase PD-L1 in HCC cells. These findings define the precise mechanism by which Olaparib and PD1 monoclonal antibodies are used to treat HCC (Sun et al., 2022). In addition, our results showed that this miRNA might take part in regulating the p53 transcriptional gene network and TGF-β signaling pathway.

miR-195

By encouraging miR-195 binding to the 3'UTR of the CHEK1 mRNA, Yan et al. showed that IRF-1 suppresses CHK1 through a post-transcriptional mechanism that blocks translation—upregulated IRF-1 blocks CHK1, which causes HCC cells to undergo apoptosis. In HCC tumors, CHK1 inhibition also increases cellular death. A higher infiltration of NK cells into the tumor may be the cause of this impact. However, through enhanced STAT3 phosphorylation, IRF-1 expression or CHK1 inhibition increases PD-L1 expression (Yan et al., 2021). According to reports, miR-195 was often downregulated in HCC tissues and cell lines. Also, ectopic expression of miR-195 significantly reduced the ability of HCC cells to form in vitro colonies and to grow tumors in naked mice. Besides, research on miR-195's gain- and loss-of-function properties shows that it might obstruct the G1/S transition. Cyclin D1, CDK6, and E2F3 were identified as additional G1/S transition-related molecules that miR-195 directly targets (Xu et al., 2009). Furthermore, it has been proposed that miR-195 plays a crucial role in controlling HCC lung metastasis. Targeting the angiogenesis-related genes FGF2 and VEGFA may mediate this action (Wang et al., 2015). Yu et al. prove that miR-195 may suppress YAP to reverse EMT in HCC. Their findings showed that miR-195 expression was highly downregulated in HCC and that this lowered expression was related to the patient's poor clinical characteristics (Yu et al., 2017). In addition, our data demonstrated that this miRNA could function in regulating the cell cycle and G1 to S cell cycle control, as well as the hedgehog signaling pathway.

miR-506

To better understand the functions of KCNQ1OT1 and miR-506 in the proliferation, apoptosis, and metastasis of sorafenib-resistant HCC cells, Zhang et al. examined the levels of KCNQ1OT1, miR-506, and PD-L1 in sorafenib-resistant HCC tissues and cells. In HCC tissues and cells that were resistant to sorafenib, it was shown that KCNQ1OT1 expression had significantly risen. Additionally, it was discovered that the PD-L1-mediated apoptosis of T cells and the susceptibility of HCC cells to sorafenib are both strongly influenced by the KCNQ1OT1/miR-506 axis. In HCC tissues and cells resistant to sorafenib, PD-L1 was noticeably elevated. Additionally, PD-L1 prevented T-cell activation, which was critical in the immunological escape of malignancies. Through targeting miR-506, KCNQ1OT1 knockdown improves sorafenib sensitivity, causes apoptosis, and prevents the metastasis of sorafenib-resistant HCC cells. Furthermore, sorafenib-resistant HCC cells' ability to bypass the immune system may be regulated by the KCNQ1OT1/miR-506 axis (Zhang et al., 2020). Also, it has been discovered that miR-506 inhibits the formation of tumors and the proliferation of cells in HCC by targeting ROCK1 (Deng et al., 2015). According to a recent study, miR-506 lowers tumor development in vivo and decreases proliferation, migration, and invasion when it is forcedly expressed in cells.

On the other hand, miR-506 suppression positively impacted tumor development in vivo and in vitro, as well as proliferation, migration, and invasion. Furthermore, it has been demonstrated that miR-506 binds to the 3'UTR of F-spondin 1 (SPON1) and that miR-506 expression is driven to reduce SPON1 accumulation (Dai et al., 2015). Moreover, the *in silico* analysis showed that this miRNA could mainly act as the regulator of carbon and estrogen metabolism, suggesting its involvement in drug response and probable resistance.

miR-329-3p

By causing MEF2D demethylation, Wang et al. demonstrated a novel method of PD-L1 regulation. By lowering MEF2D methylation, KDM1A encourages PD-L1 abundance and boosts immunosuppressive action in HCC. In contrast, miR-329-3p strengthens the response to the cytotoxic impact caused by T cells in HCC cells by targeting KDM1A and suppressing PD-L1 expression (Wang and Cao, 2021). Additionally, a recent study found that the expression of miR-329-3p is considerably lower in HCC tissue. MiR-329-3p mimics suppressed HepG2 cell growth and migration. By blocking the USP22-Wnt/β-Catenin pathway, miR329-3p has been shown to limit HepG2 cell proliferation and migration (Xin et al., 2020). Our results showed that this miRNA might participate in regulating several paths, including MAPK, EMT, and B cell receptor signaling pathways.

miR-424

By sponging miR-424, Cao et al. found that LINC00657 controls PD-L1 expression, impacting the progression of HCC (Cao et al., 2020). Additionally, it has been shown that low levels of serum miR-424 expression are linked

to advanced clinical stages and a poor prognosis for HCC (Yao et al., 2015). Additionally, it was discovered that miR-424-5p was down-regulated in HCC cells and that it might stop HCC cells from proliferating by preventing them from entering the G1 phase. Conversely, E2F7 upregulation could encourage the growth of HCC cells. To further investigate the mechanism of the miR-424-5p/E2F7 regulatory axis in HCC, dual-luciferase assay and rescue studies were carried out. According to the findings, miR-424-5p inhibited the growth of HCC by targeting E2F7 (Zhao et al., 2020). Yang et al. showed that the expression of miR-424 was remarkably downregulated in HCC tissues and six liver cancer cell lines. Significantly, the tumor size, the number of nodules, vein invasion, TNM stage, and overall survival of HCC were linked with the expression levels of this gene. They discovered that increased miR-424 inhibited the growth of HCC cells both in vivo and in culture. The pRb-E2F pathway was repressed by miR-424, according to multi-pathway reporter arrays. The fact that ectopic miR-424 expression decreased the expression of Akt3 and E2F3 consistently established Akt3 and E2F3 as miR-424 targets (Yang et al., 2015). The current *in silico* study showed that this miRNA could play a role in pRb regulation and response to DNA damage.

miR-411-5p

Zhang et al. found a connection between PD-L1, STAT3, miR-411-5p, and MIAT. They discovered that MIAT controlled PD-L1 expression, and both MIAT and PD-L1 were markedly increased in HCC tissues. The reduction of MIAT improved T cells' ability to kill HCC cells. From the transcriptional level, MIAT upregulated STAT3, raised miR-411-5p, and eventually enhanced PD-L1 expression. In HCC cells, the suppression of miR-411-5p restored STAT3 and PD-L1 expression that had been reduced by MIAT knockdown (Zhang, Pan et al. 2022). MiR-411-5p mimics were able to reverse the oncogenic characteristics brought on by circ-001569. Circ-001569 has been shown to have carcinogenic effects in HCC via sponging miR-411-5p. As a result, circ 001569/miR-411-5p regulatory signaling may aid in developing and spreading HCC (Liu, Xue et al. 2018). Through the miR-411-5p/KPNA2/AKT axis, KDM4A-AS1 supported the development and metastasis of HCC. In HCC, KPNA2 elevated HIF-1 levels by triggering the AKT pathway, creating a KDM4A-AS1/KPNA2/HIF-1α positive feedback loop (Chen, Liu et al. 2021). The results of the *in silico* study predicted that this miRNA could be significantly involved in the disruption of translation factors.

miR-182-5p

According to Samir et al., PD-L1 expression was elevated relative to that of mock cells after transfection of miR-182-5p mimics and suppression of the lncRNA XIST (tumor suppressor). However, PD-L1 expression was found to be significantly downregulated after transfection with miR-182-5p mimic and knockdown of Tsix (a negative regulator of lncRNA XIST), and PD-L1 expression was also found to be downregulated after transfection with miR-182-5p mimic and silencing of lncRNA MALAT1 (Samir et al., 2021). MiR-182-5p overexpression was seen in HCC tissues as well as HCC cell lines. By targeting the 3′-UTR of the mRNA at the 72-79 position, miR-182-5p adversely regulates FOXO3a. Furthermore, by turning on Wnt signaling, miR-182-5p promotes HCC metastasis and HCC development in both in-vitro and in-vivo. Additionally, miR-182-5p overexpression promotes HCC cell proliferation by suppressing FOXO3a and activating AKT/FOXO3a signaling (Cao, You et al. 2018). According to a recent study, miR-182-5p downregulation might prevent HCC cells from proliferating and increase their likelihood of dying. They demonstrated that LINC01018 suppressed tumor growth and proliferation while promoting apoptosis by increasing FOXO1 expression through sponging miR-182-5p (Wang et al., 2019b). It has also been shown that miR-182 might specifically target NPTX1 in HCC cells. In HCC cells, hsa-circ-0070269 overexpression boosts NPTX1 expression; however, miR-182 mimics counteract the effects (Su et al., 2019). Our results demonstrated that this miRNA might interact with the p53 network, Kit receptor signaling pathway, ERK pathway, and modulation of apoptosis.

miR-200 family

Meloxicam, a COX2 inhibitor with great anti-HCC potential, is verified by Guangshun et al. to reduce the development of HCC and improve the sensitivity to immunotherapy through the microRNA-200/PD-L1 pathway. MicroRNA-200 in tumor cells drastically decreased when COX2 expression was knocked down, which could be a method through which meloxicam increases PD-L1 levels (Guangshun, Guoqiang et al. 2022). Additionally, Sun et al. demonstrated that over-expression of miR-200c reverses antiviral CD8+ T cell fatigue by directly targeting the 3'-UTR of PD-L1 and inhibiting HBV-mediated PD-L1 production. Over-expression of miR-200c can stop hepatocytes from expressing PD-L1 and make CD8+ T cells in vivo functional again. Additionally, HBV may interfere with the activity of miR-200c by reactivating the

transcriptional repressor SALL4 through the STAT3 pathway, increasing the expression of PD-L1 (Sun, Lan et al. 2018). It has been shown that miR-200b/200c/429 subfamily overexpression prevented HCC cell migration. It turns out that the Rho/ROCK-mediated cell cytoskeletal rearrangement and cell-substratum adhesion are modulated by the miR-200b/200c/429 subfamily, which in turn inhibits HCC cell migration. Re-expression of miR-200b dramatically reduced the ability of HCC cells to metastasize to the lungs (Wong, Wei et al. 2015). According to a study by Feng et al., HCC patients with low miR-200a expression have a considerably poorer prognosis than those with high miR-200a expression. They demonstrated miR-200a's inhibitory effect on MACC1 in HCC and partially clarified a putative molecular mechanism by which miR-200a contributes to tumor aggressiveness (Feng, Wang et al. 2015). Our data suggested that miR-200c could considerably function in regulating the cell cycle, especially in G1 to S cell cycle control.

miR-378a-3p

According to Li et al., miR-378a-3p levels in HCC showed a declining trend and a negative correlation with PD-L1 levels. MiR-378a-3p-PD-L1 axis seems to control the development of CD25+ Foxp3 + Treg cells in in vitro tests (most of the inhibitory T cells). Given the decline in the number of Tregs in the model following transfection of miR-378a-3p mimics, miR-378a-3p may be detrimental to the induction of Tregs and the suppression of the HCC immune system. Additionally, miR-378a-3p mimic transfection into HCC cells led to the overexpression of IFN-γ, IL-2, and TNF-α, suggesting the activation of effector T cells and the downregulation of IL-10 and TGF-β (Li et al. 2022b). In HCC patients, the low miR-378a-3p expression has been linked to worse survival outcomes and greater microvascular density. By increasing TRAF1 and NF-κB signaling, it has been discovered that DNA hypermethylation-induced silencing of miR-378a-3p promotes HCC angiogenesis (Zhu, Chen et al. 2021). Additionally, by targeting SKP2 and lowering tumorigenesis and angiogenesis in HCC cells, miR-378a-3p demonstrated an anti-oncogenic activity (Ji, Yang et al. 2021). *In silico* analysis also revealed that this miRNA might act in the FOXA2 pathway and regulate proliferation as well as stemness. Besides, it could interfere with the AMPK signaling pathway.

miR-570

MiR-570 targets PD-L1, which Gua et al. found to decrease proliferation and metastasis in HCC. In HepG2 cells, the transfection of miR-570 mimics led to the enhancement of cell death and the suppression of cell proliferation and migration by suppressing the production of PD-L1 at both the mRNA and protein levels (Guo et al., 2015). In recent work, SMMC7721 cells were transfected with miR-570 mimics and a negative control before being injected subcutaneously into the right flank of naked mice. Compared to the negative control, miR-570 mimics decreased tumor development and tumor weight and volume reductions. While the Bcl-2 level was dramatically downregulated, the Bax level was significantly upregulated. In addition, miR-570 dramatically boosted the ratio of CD^{8+} T cells while decreasing the ratio of CD4+ T cells, showing that it supports immunological function and may prevent HCC cells from evading the immune system (Lin et al., 2018).

miR-513a-5p

In HCC, Kong et al. showed that GUSB promotes miR-513a-5p, which suppresses PD-L1 expression and results in primary resistance to anti-PD1 therapy (Kong et al., 2022). Amoxapine, a GUSB inhibitor, increases the sensitivity of anti-PD1 therapy by decreasing GUSB. In a study by Xu et al., USP4 was identified as a direct target of miR-513a-5p. Additionally, they looked into the possibility that LINC01234 is overexpressed in liver cancer and that LINC01234 knockdown might prevent liver cancer cells from growing, migrating, and invading by modulating the miR-513a-5p/USP4 axis (Xu et al., 2020). Our data suggested that this miRNA could affect cellular proliferation by interacting with the p53 and TGF-β signaling pathways.

Conclusion

Overall, the current systematic review highlighted the role of PD-L1 inhibitory miRNAs on the progression of HCC. PD-L1 expression in HCC cells can be inhibited by many microRNAs, including miR-194-5p, -675-5p, 194-5p, -1, -455-5p, -223-3p, -513, 195, -506, -329-3p, -424, -411-5p, -182-5p, -200, -378a-3p, -570, and -513 This can ultimately stop tumor growth, prevent tumor spread, increase cancer cells' chemosensitivity, and cause tumor cells to die. Additionally, the miRNAs were further examined using online miRNA target prediction tools to suggest a potential direction for their roles in HCC. These results also highlighted the ability of the investigated miRNAs in cancer progression.

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Ethical Statement

This study did not contain any animal or human studies.

Competing Interests

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Authors Contribution

All authors contributed to the study conception and design. Search strategy designing, data collection, and data extraction were performed by H. Hamedifar, P. Lotfinejad, and Z. Asadzadeh. The first draft of the manuscript was written by H. Hamedifar, N. Hemmat, and A. N. Kamali. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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