Biomedicine & Pharmacotherapy 143 (2021) 112213

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha

Review

A scoping review on the potentiality of PD-L1-inhibiting microRNAs in treating colorectal cancer: Toward single-cell sequencing-guided biocompatible-based delivery

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ARTICLE INFO

Keywords:
MicroRNAs
PD-L1
Colorectal cancer
Single-cell sequencing
Biocompatible carriers
Personalized medicine

ABSTRACT

Tumoral programmed cell death ligand 1 (PD-L1) has been implicated in the immune evasion and development of colorectal cancer. Although monoclonal immune checkpoint inhibitors can exclusively improve the prognosis of patients with microsatellite instability-high (MSI-H) and tumor mutational burden-high (TMB-H) colorectal cancer, specific tumor-suppressive microRNAs (miRs) can regulate multiple oncogenic pathways and inhibit the de novo expression of oncoproteins, like PD-L1, both in microsatellite stable (MSS) and MSI-H colorectal cancer cells. This scoping review aimed to discuss the currently available evidence regarding the therapeutic potentiality of PD-L1-inhibiting miRs for colorectal cancer. For this purpose, the Web of Science, Scopus, and PubMed databases were systematically searched to obtain peer-reviewed studies published before 17 March 2021. We have found that miR-191–5p, miR-382–3p, miR-148a-3p, miR-93–5p, miR-200a-3p, miR-200c-3p, miR-138–5p, miR-140–3p, and miR-15b-5p can inhibit tumoral PD-L1 in colorectal cancer cells. Besides inhibiting PD-L1, miR-140–3p, miR-382–3p, miR-148a-3p, miR-93–5p, miR-200a-3p, miR-200c-3p, miR-138–5p, and miR-15b-5p can substantially reduce tumor migration, inhibit tumor development, stimulate anti-tumoral immune responses, decrease tumor viability, and enhance the chemosensitivity of colorectal cancer cells regardless of the microsatellite state. Concerning the specific, effective, and safe delivery of these miRs, the single-cell sequencing-guided biocompatible-based delivery of these miRs can increase the specificity of miR delivery, decrease the toxicity of traditional nanoparticles, transform the immunosuppressive tumor microenvironment into the proinflammatory one, suppress tumor development, decrease tumor migration, and enhance the chemosensitivity of tumoral cells regardless of the microsatellite state.

1. Introduction

Colorectal cancer is the third cause of cancer-related death worldwide [1]. Although the patients' five-year survival is above 65% in the most affluent countries, there is a need to develop a high efficacy therapy [2].

In solid cancers, the tumor microenvironment plays a critical role in determining the fate of anti-tumoral immune responses [3,4]. The PD-L1/programmed cell death protein 1 (PD-1) immune checkpoint axis, which can be established between effector immune cells and

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https://doi.org/10.1016/j.biopha.2021.112213
Received 2 August 2021; Received in revised form 13 September 2021; Accepted 15 September 2021
Available online 22 September 2021

tumoral cells, can suppress anti-tumoral immune responses and facilitate cancer development [5]. Besides immune evasion, tumor-intrinsic PD-L1 can stimulate oncogenic signaling pathways in colorectal cancer cells. It has been shown that PD-L1 expression can upregulate epidermal growth factor receptor (EGFR), leading to colorectal cancer development [6]. Furthermore, short hairpin RNA (shRNA)-mediated tumoral PD-L1 silencing has been associated with the increased rate of apoptosis and decreased expression of phosphatidylinositol-3 kinase (PI3K) and protein kinase B (Akt) both in vivo and in vitro [7]. In line with these, it has been reported that PD-L1 can stimulate the PI3K/Akt and MAPK/ERK kinase (MEK)/extracellular signal-regulated kinase (ERK) signaling pathways in colorectal cancer cells. Besides, PD-L1 knockdown has decreased the population of colorectal cancer cells with CD133 and CD44 [8]. Of interest, it has been shown that Akt activators can increase the population of colorectal cancer cells with CD133 + and CD44 +, and Akt inhibitors can inverse this process [9]. Also, inhibiting mechanistic target of rapamycin (mTOR), well-known downstream signaling of the PI3K/Akt pathway, has been associated with a remarkable decrease in CD44 and EGFR expression [10]. CD133 and CD44 are well-established stem cells markers implicated in the development of chemoresistance and tumor recurrence [11–13]. Besides these oncogenic pathways, recent findings have indicated that adenomatous polyposis coli (APC) mutation can liberate β-catenin to form β-catenin/transcription factor 4 (TCF4), which ultimately lead to PD-L1 expression in colorectal cancer cells [14]. Consistent with this, β-catenin inhibition/silencing has been associated with decreased PD-L1 expression in colorectal cancer stem cells, leading to impaired immune evasion of colorectal cancer stem cells [15]. Despite the promising efficacy of monoclonal immune checkpoint inhibitors in treating patients with MSI-H and TMB-H colorectal cancer, current immune checkpoint inhibitors are exclusively effective for patients with TMB-H and MSI-H colorectal cancer. Besides, these monoclonal antibodies do not remarkably regulate oncogenic pathways in colorectal cancer cells.

As small noncoding RNAs, miRs can post-transcriptionally regulate the expression of their target mRNAs. It has been shown that epigenetic dysregulation of colorectal cancer cells can facilitate immune evasion and tumor development in colorectal cancer [16]. Indeed, miR dysregulation has been implicated in tumor growth, cancer therapy resistance, and tumor migration [17,18]. On the other side, growing evidence has indicated that specific tumor-suppressive miRs can inhibit PD-L1 expression and impede tumor development in colorectal cancer cells [19,20]. Since miRs are multi-targets and one miR can regulate multiple mRNAs, tumor-suppressive miRs can substantially decrease tumor development via regulating multiple oncogenic pathways. Although conventional monoclonal immune checkpoint inhibitors are predominantly effective for inhibiting the development of MSI-H and TMB-H colorectal cancer, PD-L1-inhibiting miRs has been shown to inhibit the development of both MSS and MSI-H colorectal cancer due to the multi-target nature of miRs [21]. For instance, Jiang et al. have reported that restoration of miR-140–3p, as a PD-L1-inhibiting miR, can substantially decrease tumor migration, suppress tumor proliferation, inhibit the clonogenicity of tumoral cells, stimulate apoptosis, and downregulate tumoral PD-L1 in SW480, a well-established MSS colorectal cancer cell line [22]. Also, Chen et al. have demonstrated that miR-93–5p, as another PD-L1-inhibiting miR, can decrease the migration and invasion of SW480 cells. Besides, this PD-L1-inhibiting miR has substantially upregulated the expression of interleukin (IL)-2, tumor necrosis factor (TNF)-α, and interferon (IFN)-γ and downregulated the expression of IL-1β, IL-10, and transforming growth factor (TGF)-β [23]. Therefore, identifying the PD-L1-inhibiting miRs and highlighting their overall effect on tumoral cell viability, migration, and tumor microenvironment can provide valuable insights for treating colorectal cancer regardless of the microsatellite state.

Herein, we aimed to shed light on these PD-L1 inhibiting miRs, review their overall effect on tumor development and tumor microenvironment, and determine their prognostic and clinical significance based on the data from TCGA-COAD. Moreover, we intended to highlight the recent advances in biocompatible and biodegradable nanoparticles and propose a novel strategy, i.e., single-cell sequencing-guided biocompatible-based miR delivery, for effective, safe, and specific delivery of PD-L1-inhibiting miRs. Indeed, our results and our proposed strategy for miR delivery, which is based on personalized medicine concepts, can serve as a roadmap for future miR-based gene therapy for colorectal cancer patients and change the landscape of colorectal cancer treatment.

2. Methods

For the scoping review part, the framework proposed by Arksey and O'Malley [24] and improved by Levac et al. [25] was adopted. The current study methodology consists of five steps, i.e., identifying the research question, identifying relevant studies, study selection, charting the data, and collating, summarizing, and reporting results. The current scoping review was also based on the preferred reporting items for systematic reviews and meta-analyses extension for scoping reviews (PRISMA-ScR) statements [26]. Also, we included a bioinformatic phase to shed light on the miR-signaling pathway cross-talk and the clinical significance of the identified PD-L1-inhibiting miRs in affected patients. Besides, we briefly discussed the recent advances in biocompatible and biodegradable nanoparticles and proposed new perspectives based on single-cell sequencing technologies to address the current challenges in miR delivery.

2.1. Identifying the research question

This scoping review is about to map the current knowledge regarding the therapeutic potentiality of PD-L1-inhibiting miRs for treating colorectal cancer.

2.2. Identifying relevant studies

The Web of Science, Scopus, and PubMed databases were systematically searched to obtain peer-reviewed records published before 17 March 2021. For this systematic search, the following keywords were used: ("miRNA" OR "miRNA" OR "miRNA-" OR "microRNA-" OR "miR-" OR "microRNA" OR "micro RNA" OR "miRNA-" OR "micro RNA-" OR "miR" OR "microRNAs") and ("programmed cell death 1 ligand 1" OR "cluster of differentiation274" OR "programmed death-ligand 1" OR "programmed death 1 ligand 1" OR "PD-L1" OR "PD L1" OR "B7-H1" OR "PDCD1 ligand 1" OR "B7 H1" OR "CD274" OR "cluster of differentiation 274" OR "B7H1" OR "CD 274" OR "B7 homolog 1" OR "PDCD1LG1" OR "PDCD1L1" OR "PDL1" OR "HPD-L1" OR "B7-H1 antigen") and ("cancer" OR "tumor" OR "tumour" OR "malignancy" OR "neoplasia" OR "neoplasm" OR "lesion" OR "malignant" OR "carcinoma" OR "cancerous" OR "tumoral" OR "tumoural" OR "neoplastic" OR "neoplasms" OR "adenocarcinoma") and ("colorectal" OR "colon" OR "rectum" OR "rectal" OR "colonic" OR "bowel"). We also used Emtree and MeSH terms to increase the sensitivity of our systematic search.

2.3. Study selection

After the systematic search, the obtained records were reviewed in two phases. In phase I, two authors (M.A.S and Z.A) independently screened the retrieved records based on their titles and abstracts. In phase II, the same authors independently reviewed the full text of papers, along with their supplementary data. Any disagreements were resolved via consulting with B.B.

Studies with the following eligibility criteria were included in this study: (1) original papers published in English and (2) studies investigating the effect of miR on PD-L1 expression in colorectal cancer. According to the following criteria, these records were excluded from the systematic study: (1) studies that failed to meet the above-mentioned

inclusion criteria, (2) the studies that their data were solely based on bioinformatics, (3) studies that investigated the pro-tumoral miRs, and (4) and studies that did not investigate the miR restoration in colorectal cancer cells, rather in the cells residing in the colorectal tumor microenvironment.

2.4. Charting the data

The following data were extracted from the included studies: the first author, publication year, studied miR(s), colorectal cell line, the clinical significance of the studied miR(s), the number of patients with stage I, II/III, and IV, and the hazard ratio (HR) of the studied miR(s).

2.5. Collating, summarizing, and reporting the results

Besides reporting the findings of the included studies, we discussed the findings of included studies with other investigations to provide a more comprehensive picture of their therapeutic potentiality for treating colorectal cancer, proposed by Levac et al. [25].

2.6. In silico investigation

The data from TCGA-COAD was analyzed to investigate the prognostic values of the PD-L1-inhibiting miRs in affected patients. Besides, the TCGA-COAD data were used to determine the expression levels of the PD-L1-inhibiting miRs in patients with lymphatic and venous invasion. Furthermore, the data from the WikiPathways was obtained to study the effect of these PD-L1-inhibiting miRs on the biological pathways. For this purpose, the data from the miRPathDB v2.0 (https://mpd.bioinf.uni-sb.de/) were analyzed as previously described [27]. Briefly, we adjusted on the strong experimental evidence and a minimum of two significant miRs per pathway.

3. Results

3.1. Selected studies

Our systematic search retrieved 127 records. After removing duplication records, 76 studies remained. In phase I, two authors independently reviewed the remaining papers and excluded 56 studies. In phase II, the same authors independently reviewed 20 remaining studies, along with their supplementary data. Based on reviewing those 20 studies, 10 papers were included in the current systematic review. The exclusion reasons for those 10 excluded studies are shown in Table 1. The flowchart of literature selection is demonstrated in Fig. 1.

3.2. Study characteristics

The 10 included studies were published between 2016 and 2020. Most of the studies evaluated the studied miR(s) both at the cellular level and in clinical samples. One study only used clinical samples to study miRs. However, some studies only assessed the association between their studied miR(s) and PD-L1 at the cellular levels. Based on the study by Ahmed et al., we provided the microsatellite state of studied colorectal cancer cell lines [38]. Our results have indicated that miR-191–5p, miR-382–3p, miR-148a-3p, miR-93–5p, miR-200a-3p, miR-200c-3p, miR-138–5p, miR-140–3p, and miR-15b-5p can decrease the expression of PD-L1 in colorectal cancer cells. Also, miR-140–3p, miR-382–3p, miR-148a-3p, miR-93–5p, miR-200a-3p, miR-200c-3p, miR-138–5p, and miR-15b-5p can inhibit tumor development in colorectal cancer. The summary of the clinical and preclinical studies is present in Table 2 and Table 3.

Table 1
The excluded studies in phase II and the reasons for their exclusion.

First author and the year of publication	Reason for exclusion
Ronghua Liu 2018 [28]	PD-L1 was not sufficiently investigated and discussed.
Jiajia Xi 2018 [29]	They investigated in non-tumor cells.
Eri Tanaka 2019 [30]	They investigated other noncoding RNAs.
Lijun Xu. 2021 [31]	Their data were solely based on bioinformatics.
Z Saleh, 2019 [32]	Their data were solely based on bioinformatics.
Xiaoli Chen 2020 [33]	Their data were solely based on bioinformatics.
Changling Tu 2021 [34]	They investigated pro-PD-L1 miRs.
Jianjie Zhu, 2014 [35]	They investigated pro-PD-L1 miRs.
Jie Xu, 2019 [36]	They investigated pro-PD-L1 miRs.
Lei Wang, 2019 [37]	They investigated B7-H3.

3.3. Bioinformatic results

Our results indicate that the high expression levels of miR-200c-3p and miR-15b-5p are significantly associated with improved disease-specific survival of affected patients (P-value = 0.01601 and P-value = 0.007638 respectively) (Fig. 2D and Fig. 2H, respectively). Regarding lymphatic invasion, our obtained results have shown that the expression of miR-200a-3p, miR-200c-3p, miR-148a-3p, miR-191–5p, and miR-15b-5p are significantly increased in patients without lymphatic invasion than patients with lymphatic invasion (all P-values < 0.05). (Fig. 3). Regarding venous invasion, our results have demonstrated that the expression of miR-200c-3p and miR-148a-3p are significantly increased in patients without venous invasion than patients with venous invasion (both P-values < 0.05) (Fig. 4).

Furthermore, our results have indicated that miR-15b-5p, miR-148a-3p, miR-200c-3p, and miR-140–3p are significantly enriched for the PI3K/Akt signaling pathway (Fig. 5). Based on our results, miR-15b-5p, miR-200a-3p, and miR-148a-3p are significantly enriched for the category of microsatellite and chromosomal instability in colorectal cancer (Fig. 5). Besides, miR-15b-5p and miR-200a-3p are significantly enriched for the cell cycle (Fig. 5). Moreover, our results have shown that miR-138–5p, miR-200a-3p, and miR-140–3p are significantly enriched for the epithelial-mesenchymal transition (EMT) process in colorectal cancer (Fig. 5).

4. Discussion

Although there have been remarkable advances in treating colorectal cancer patients, this worrisome cancer is one of the leading causes of cancer-related morbidity and mortality [1]. A better understanding of tumor biology and the tumor microenvironment can pave the way for introducing novel therapeutic approaches for the affected patients.

Immune checkpoints are responsible for maintaining the immunosuppressive tumor microenvironment and preventing the stimulation of $CD8^+$ T-cells [45]. The PD-L1/PD-1 axis is one of the well-established inhibitory immune checkpoint axes. PD-1 can be expressed in T-cells and natural killer cells, ultimately suppressing anti-tumoral immune responses [46]. Accordingly, tumor-intrinsic PD-L1 can facilitate lymphatic metastasis, tumor growth, and de-differentiation of colorectal cancer cells [47]. Besides, tumor-intrinsic PD-L1 has been implicated in stimulating oncogenic pathways in colorectal cancer, leading to tumor development [6].

Targeting this axis via conventional monoclonal immune checkpoint inhibitors has been the center of efforts to stimulate anti-tumoral immune responses. However, conventional monoclonal immune checkpoint inhibitors have been predominantly effective for MSI-H and TMB-H colorectal cancer [48]. Therefore, multidisciplinary approaches might be needed to disrupt this inhibitory axis and inhibit tumor development in both MSI-H and MSS colorectal cancer. Recent findings have identified specific miRs as promising post-transcriptional regulators of PD-L1 in colorectal cancer, which can substantially inhibit both MSI-H and MSS colorectal cancer development and transform the immunosuppressive tumor microenvironment into a proinflammatory one. The following sections aim to discuss the therapeutic potentiality of the

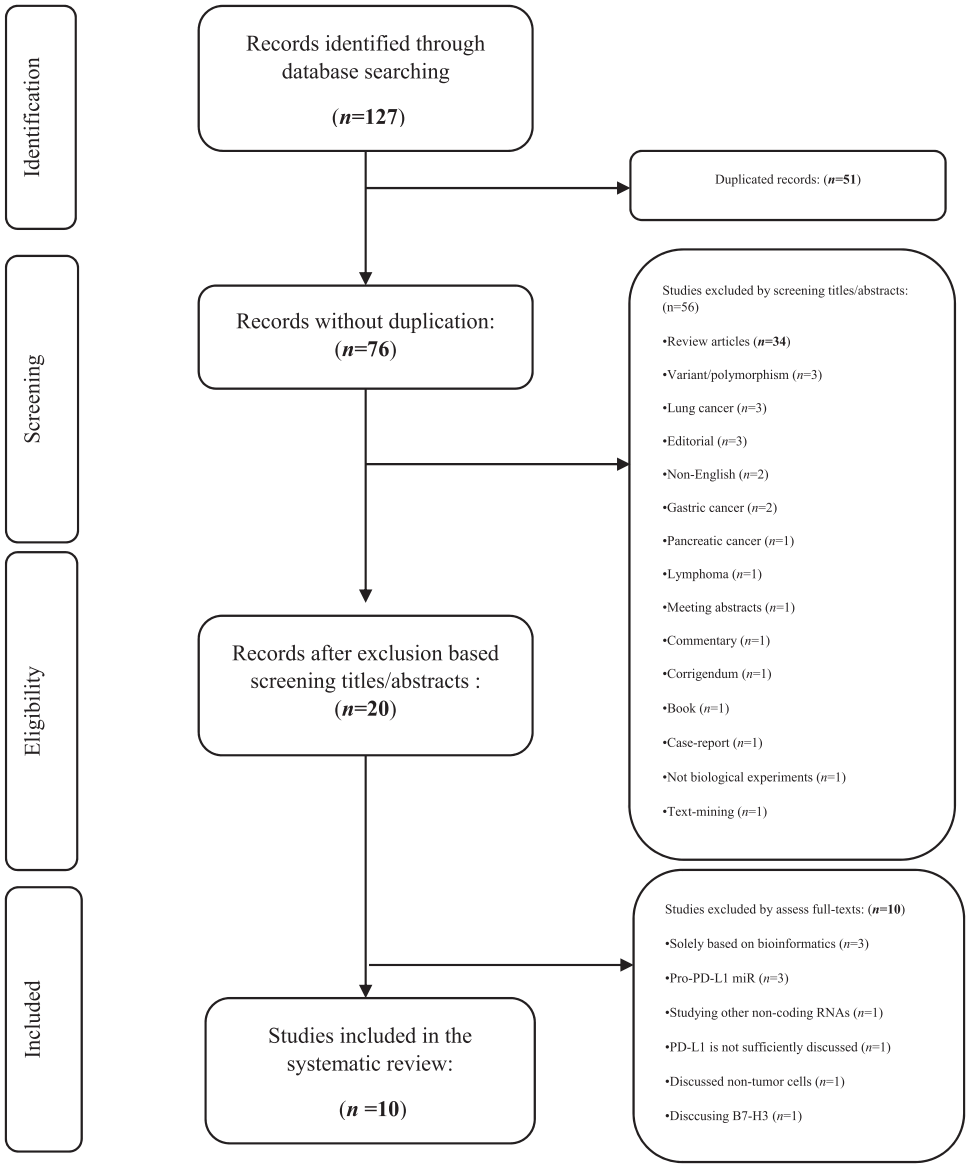

Fig. 1. The flow chart of study selection.

Table 2
The summary of the main findings of included clinical studies.

No.	The first author, year	Studied miR	Number of patients	Tumor stage 1 or 2 (TNM)	Tumor stage 3 or 4 (TNM)	Clinical association	HR, 95% CI, and P-value
1	Martinez-Ciarpaglini, 2018 [39]	miR-200a-3p	125	N/a	N/a	It can inhibit PD-L1 expression, and it is associated with suppressed EMT in the budding tumoral cells.	NS
2	Martinez-Ciarpaglini, 2018 [39]	miR-200c-3p	125	N/a	N/a	It can inhibit PD-L1 expression and suppress the EMT process.	0.12, [0.03–0.81], and P = 0.02
3	Chen, 2020 [23]	miR-93–5p	125	67	58	It can reverse the PD-L1-induced lymphatic metastasis, poor tumor differentiation, and high TNM stage. Besides, it can improve the survival of affected patients.	N/a
4	Jiang, 2019 [22]	miR-140–3p	31	N/a	N/a	It is downregulated in tumoral tissues compared to non-neoplastic tissues.	N/a
5	Ashizawa, 2019 [40]	miR-148a-3p	395	N/a	N/a	In 15% of colorectal cancers, it can inhibit the defective mismatch repair-induced PD-L1 overexpression.	N/a
6	Zhao, 2016 [20]	miR-138–5p	188	98	90	Its expression level is negatively associated with tumoral PD-L1 expression, TNM stage, Duke's stage level, and lymph node metastasis. Also, its upregulation is associated with the improved prognosis of affected patients.	N/a

Abbreviations: miR: microRNA, PD-L1: programmed death-ligand 1, and EMT: epithelial-mesenchymal transition.

Table 3
The summary of the main findings of included preclinical studies.

No.	First author and year	Studied miR	Effect on PD-L1 expression	Cell line	Microsatellite state of studied cell lines
1	Jiang, 2019 [22]	miR-140–3p	It can decrease PD-L1 expression via inhibiting the PI3K/Akt pathway.	HCT116 and SW480	MSI, and MSS respectively
2	NABA, 2020 [41]	miR-140–3p	It can inhibit PD-L1 expression; its downregulation can increase PD-L1 expression in doxorubicin-treated tumoral cells.	HCT116	MSI
3	Zhang, 2017 [42]	miR-138–5p	It can inhibit PD-L1 expression.	HCT116	MSI
4	Chen, 2020 [23]	miR-93–5p	It can inhibit PD-L1 expression and downregulate MMP-1, MMP-2, and MMP-9 expression in colorectal cancer cells. Moreover, it can upregulate IL-2, TNF-α, and IFN-γ and suppress the expression of IL-1β, IL-10, and TGF-β in a co-culture system with T-cells.	HCT116 and SW620	MSI, and MSS respectively
5	Ashizawa, 2019 [40]	miR-148a-3p	It can bind to the 3-untranslated region of PD-L1 and inhibit the defective mismatch repair-induced PD-L1 expression.	HCT116 and SW837	MSI, and MSS respectively
6	Jin, 2020 [43]	miR-382–3p	It can inhibit PD-L1 expression.	Caco-2 and HCT116	MSS, and MSI respectively
7	Zhao, 2016 [20]	miR-138–5p	It can downregulate PD-L1 expression and inhibit tumor development in vivo.	HCT116 and SW620	MSI, and MSS respectively
8	Chen, 2018 [19]	miR-191–5p	In the RKO cells, its transfection is associated with decreased PD-L1 expression; however, its inhibitor transfection does not increase PD-L1 expression in LoVo cells.	RKO and LoVo	Both MSI
9	Liu, 2020 [44]	miR-15b-5p	It can substantially decrease the protein expression of PD-L1 in colorectal cancer. Infecting with a lentiviral and adeno-associated virus/ antisense miR-15b-5p has been associated with increased PD-L1 expression and depletion of $CD8^+$ T-cells in mice bearing colorectal cancer.	MC38, CT26, SW480, SW1116, SW620, and HT29	Murine colorectal cancer cell line, murine colorectal cancer cell line, MSS, MSS, MSS, and MSS, respectively.

Abbreviations: miR: microRNA, PI3K: phosphatidylinositol-3-kinase, AKT: protein kinase B, PD-L1: programmed death-ligand 1, MSI: microsatellite instable, MSS: microsatellite stable, and MMP: matrix metalloproteinase.

PD-L1-inhibiting miRs and their roles in the future therapy of colorectal cancer.

4.1. *miR-138–5p*

It has been reported that miR-138–5p can inhibit PD-L1 expression in HTC116 cells [42]. Consistent with this, Zhao et al. have reported that miR-138–5p can bind to the PD-L1 3′ untranslated region, suppress tumorigenesis, and prevent S-phase entry. Besides, they have found a strong negative association between PD-L1 expression and miR-138–5p in colorectal cancer tissues (OR=0.1712, 95% CI: 0.0911–0.3219 and P-value<0.0001). Furthermore, the increased expression of miR-138–5p has been associated with the improved prognosis of colorectal cancer patients [20]. Wang et al. have reported that miR-138–5p is substantially decreased in colorectal cancer tissues compared to normal tissues, and the replacement of miR-138–5p has been associated with decreased cell viability, stimulated apoptosis, reduced colony numbers in SW480 and HT29 cells [49]. In line with this, Xu et al. have shown that the expression of miR-138–5p is substantially decreased in colorectal tissues and the tissues from patients with lymphatic metastasis compared to normal tissues and the tissues from patients without lymphatic metastasis. Also, the inhibition of miR-138–5p has been associated with increased colony numbers, chemoresistance, and migration of colorectal cancer cells [50]. Recently, Wang et al. have shown that miR-138–5p can increase the cytotoxicity of oxaliplatin in oxaliplatin-resistant HT29 and SW480 cells [51]. Our in silico results have indicated that miR-138–5p is significantly enriched for the EMT process.

4.2. *miR-140–3p*

Chemoresistance is a daunting challenge in cancer treatment. Although the efflux of anti-neoplastic medications is a crucial step in developing chemoresistance, the immunosuppressive tumor microenvironment can also pave the way for the survival of tumor cells [52]. Doxorubicin can upregulate PD-L1 expression partially via miR-140–3p downregulation in HCT116 cells. Indeed, there is a negative correlation between PD-L1 expression and miR-140–3p in doxorubicin-treated HCT116 cells [41]. Consistent with this, Jiang et al. have shown that miR-140–3p can inhibit the PI3K/Akt pathway and establish a negative association with PD-L1 in colorectal cancer. Indeed, miR-140–3p can suppress tumor growth, inhibit tumor migration, downregulate Bcl-2 expression, and increase Bax expression [22]. Liu et al. have shown that the level of miR-140–3p is substantially decreased in colorectal patients with liver metastasis, and miR-140–3p can substantially decrease the proliferation of LoVo cells and diminish metastatic colorectal cancer cells in mice livers [53].

Compared to adjacent non-neoplastic tissues, miR-140–3p expression is substantially downregulated in colorectal cancer tissues [22]. Chen et al. have shown that miR-140–3p can decrease the cell viability

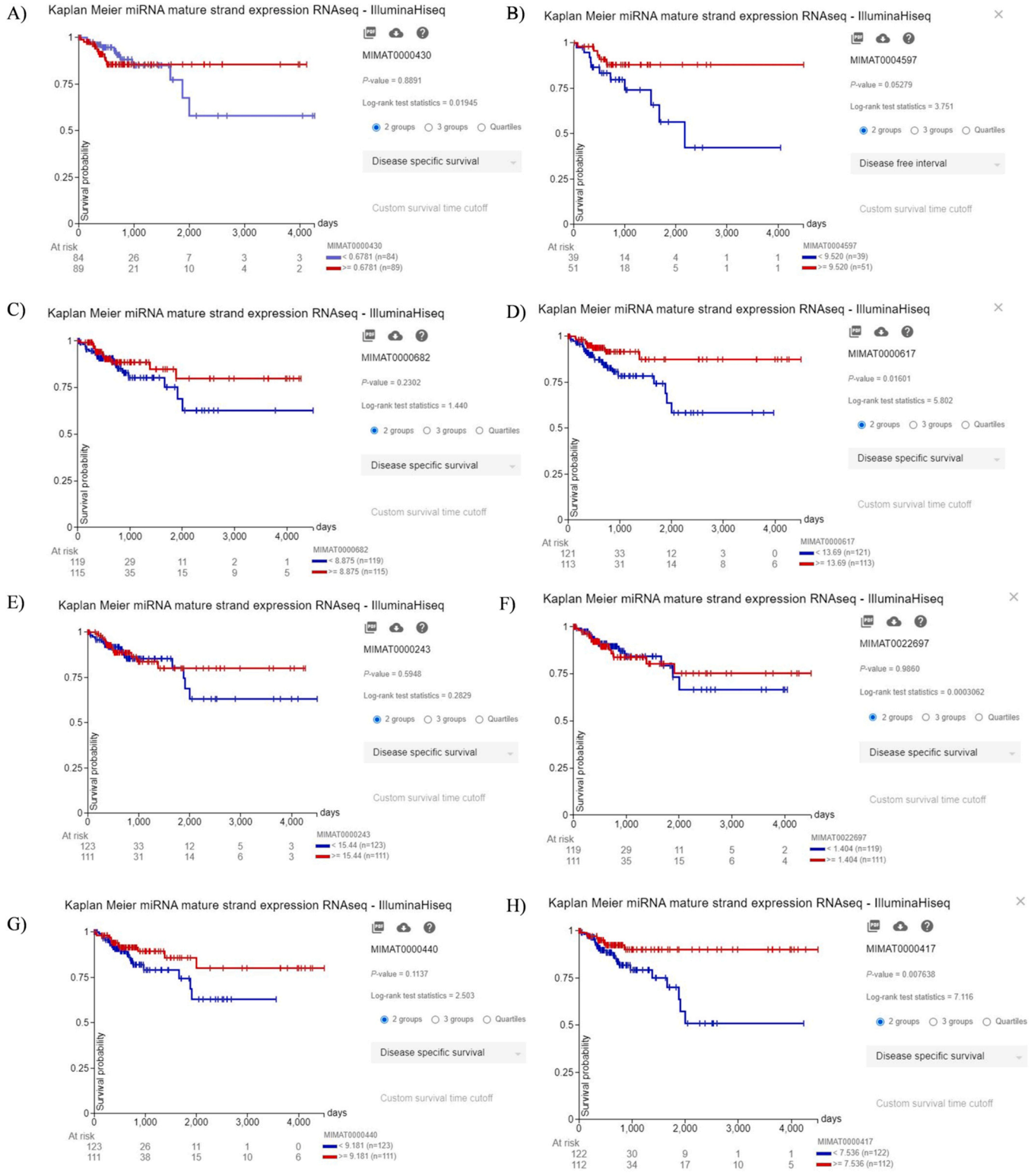

Fig. 2. The prognostic value of PD-L1-inhibiting miRs based on the analyzed data of the TCGA-COAD. A) Although the overexpression of miR-138–5p is associated with improved disease-specific survival, it is not statistically significant (P-value=0.8891). B) Although the overexpression of miR-138–5p is associated with improved disease-free interval, it is not statistically significant (P-value=0.05279). C) Although the overexpression of miR-200a-3p is associated with improved disease-specific survival, it is not statistically significant (P-value=0.2302). D) The overexpression of miR-200c-3p is significantly associated with improved disease-specific survival (P-value=0.01601). E) Although the overexpression of miR-148a-3p is associated with improved disease-specific survival, it is not statistically significant (P-value=0.2829). F) Although the overexpression of miR-382–5p is associated with improved disease-specific survival, it is not statistically significant (P-value=**0.9860**). G) Although the overexpression of miR-191–5p is associated with improved disease-specific survival, it is not statistically significant (P-value=0.1137). H) The overexpression of miR-15b-5p is significantly associated with improved disease-specific survival (P-value=0.007638).

Fig. 3. lymphatic invasion and PD-L1 inhibiting miRs A) There are no significant differences in the expression level of miR-138–5p between patients with lymphatic invasion and without lymphatic invasion (P-value=0.6555). B) There are no significant differences in the expression level of miR-140 between patients with lymphatic invasion and without lymphatic invasion (P = 0.5434). C) The expression level of miR-200a-3p is significantly increased in patients without lymphatic invasion than patients with lymphatic invasion (P-value=0.01549). D) The expression level of miR-200c-3p is significantly increased in patients without lymphatic invasion than patients with lymphatic invasion (P-value=0.00009402). E) The expression level of miR-148a-3p is significantly increased in patients without lymphatic invasion than patients with lymphatic invasion (P-value=0.00007872). F) There are no significant differences in the expression level of miR-382 between patients with lymphatic invasion and without lymphatic invasion (P-value=0.9224). G) The expression level of miR-191–5p is significantly increased in patients without lymphatic invasion than patients with lymphatic invasion (P-value=0.00002012). H) The expression level of miR-15b-5p is significantly increased in patients without lymphatic invasion than patients with lymphatic invasion (P-value= 0.003202).

of SW620 cells and inhibit the migration of colorectal cancer cells [54]. In line with this, Yang et al. have demonstrated that miR-140–3p can decrease the cell viability and colony numbers of colorectal cancer cells [55]. Recently, Liu et al. have reported that miR-140–3p inhibition can substantially increase cell viability and decrease the apoptosis and invasion of colorectal cancer cells. Also, miR-140–3p inhibition has been associated with increased expression of Zinc finger E-box binding protein 1 (ZEB1) and vimentin in colorectal cancer cells [53]. Our bioinformatic results have shown that miR-140–3p is significantly enriched for the PI3K/Akt signaling pathway.

4.3. *miR-200a-3p and miR-200c-3p*

It has been reported that there are inverse correlations between miR-200a-3p/miR-200c-3p and PD-L1 expression in tumor budding of colorectal cancer. In tumor budding, overexpressed miR-200c-3p is correlated with suppressed EMT and improved prognosis of colorectal patients (HR=0.12, 95% CI 0.03–0.81, P-value=0.02) [39]. In line with this, ZEB activation is associated with decreased expression of the miR-200 family and increased PD-L1 expression, which is partially responsible for suppressing the anti-tumoral immune responses of $CD8^+$ T-cells [56]. Yanlin et al. have reported that miR-200c-3p is substantially downregulated in colorectal cancer tissues compared to normal tissues, and miR-200c-3p can substantially suppress SNHG16, a

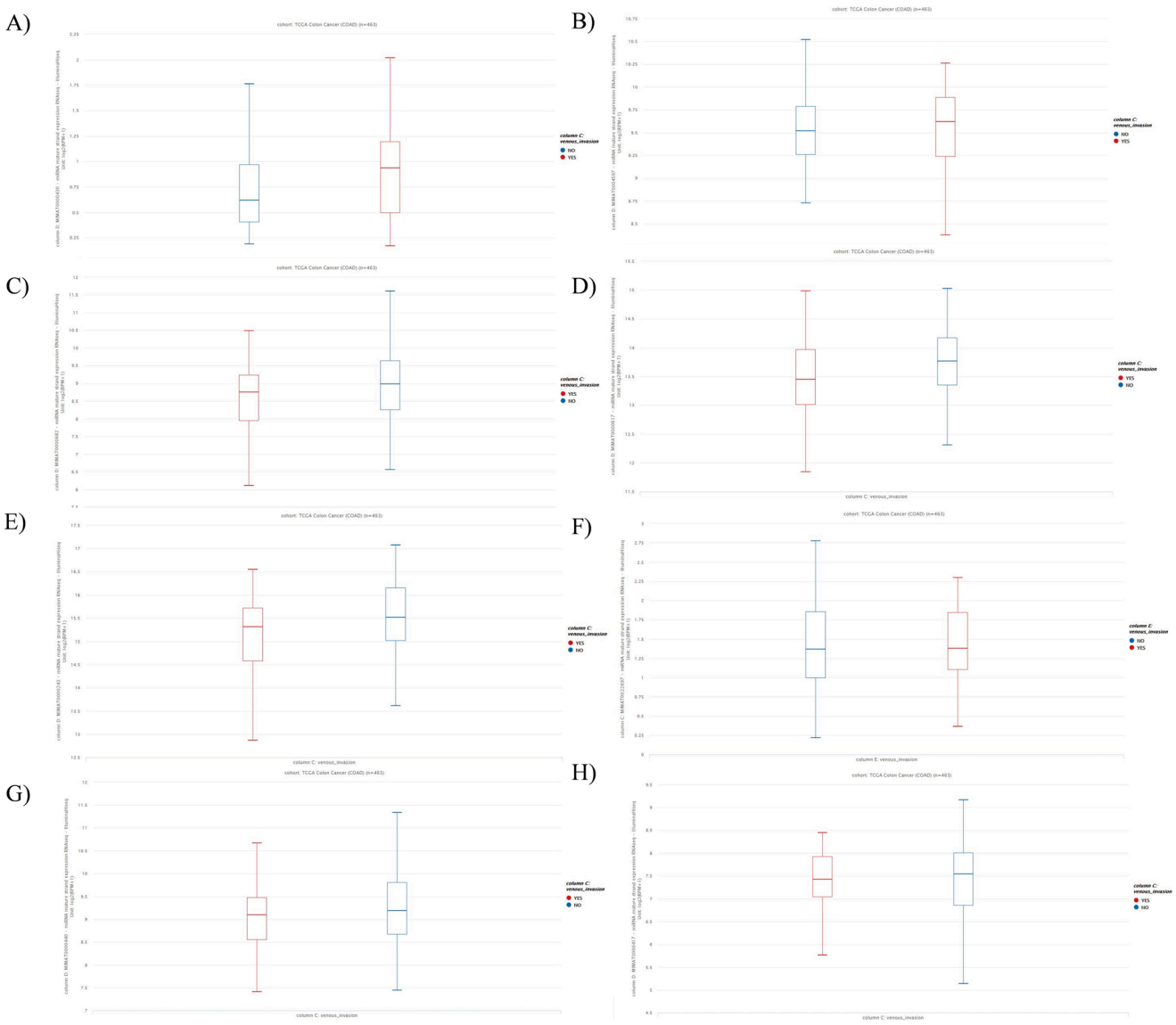

Fig. 4. Venous invasion and PD-L1 inhibiting miRs. A) There are no significant differences in the expression level of miR-138–5p between patients with venous invasion and without venous invasion (P-value=0.06783). B) There are no significant differences in the expression level of miR-140–3p between patients with venous invasion and without venous invasion (P-value=0.7851). C) There are no significant differences in the expression level of miR-200a-3p between patients with venous invasion and without venous invasion (P-value=0.07322). D) The expression level of miR-200c-3p is significantly increased in patients without venous invasion compared to patients with venous invasion (P-value=0.02177). E) The expression level of miR-148a-3p is significantly increased in patients without venous invasion compared to patients with venous invasion (P-value= 0.008039). F) There are no significant differences in the expression level of miR-382–3p between patients with venous invasion and without venous invasion (P-value= 0.7138). G) There are no significant differences in the expression level of miR-191–5p between patients with venous invasion and without venous invasion (P-value= 0.06333). H) There are no significant differences in the expression level of miR-15b-5p between patients with venous invasion and without venous invasion (P-value=0.3690).

pro-tumoral long-non-coding RNA, in colorectal cancer cells [57]. Pichler et al. have reported that miR-200a-3p restoration can increase the E-cadherin expression and decrease vimentin expression in colorectal cancer cells [58]. Recently, Di et al. have shown that miR-200a-3p restoration can decrease the clonogenicity, migration, and invasion of SW480 cells, which its antisense has dramatically reversed the mentioned effects [59]. Moreover, Jiang et al. have demonstrated that miR-200c-3p can also considerably decrease the migration of colorectal cancer cells [60]. Gao et al. have identified a strong negative association between lymph vascular invasion with the expression level of miR-200c-3p in colorectal cancer patients (OR=0.5439, 95% CI 0.3231–0.9155, P-value=0.0219). Besides, they have demonstrated that miR-200c-3p can increase apoptosis rate, decrease cell viability, upregulate p53 expression, and reduce the proliferation of colorectal cancer cells [61].

Our bioinformatic results have indicated that the high expression of miR-200c-3p is significantly associated with improved disease-specific survival of affected patients (P-value=0.01601). Besides, our results have shown that the expression level of miR-200c-3p is substantially increased in patients without lymphatic/venous invasion than patients with lymphatic/venous invasion, and it is significantly enriched for the PI3K/Akt category. Also, the expression level of miR-200a-3p is significantly increased in patients without lymphatic invasion than patients with lymphatic invasion, and it is significantly enriched for the microsatellite and chromosomal instability in colorectal cancer, EMT, and cell cycle categories.

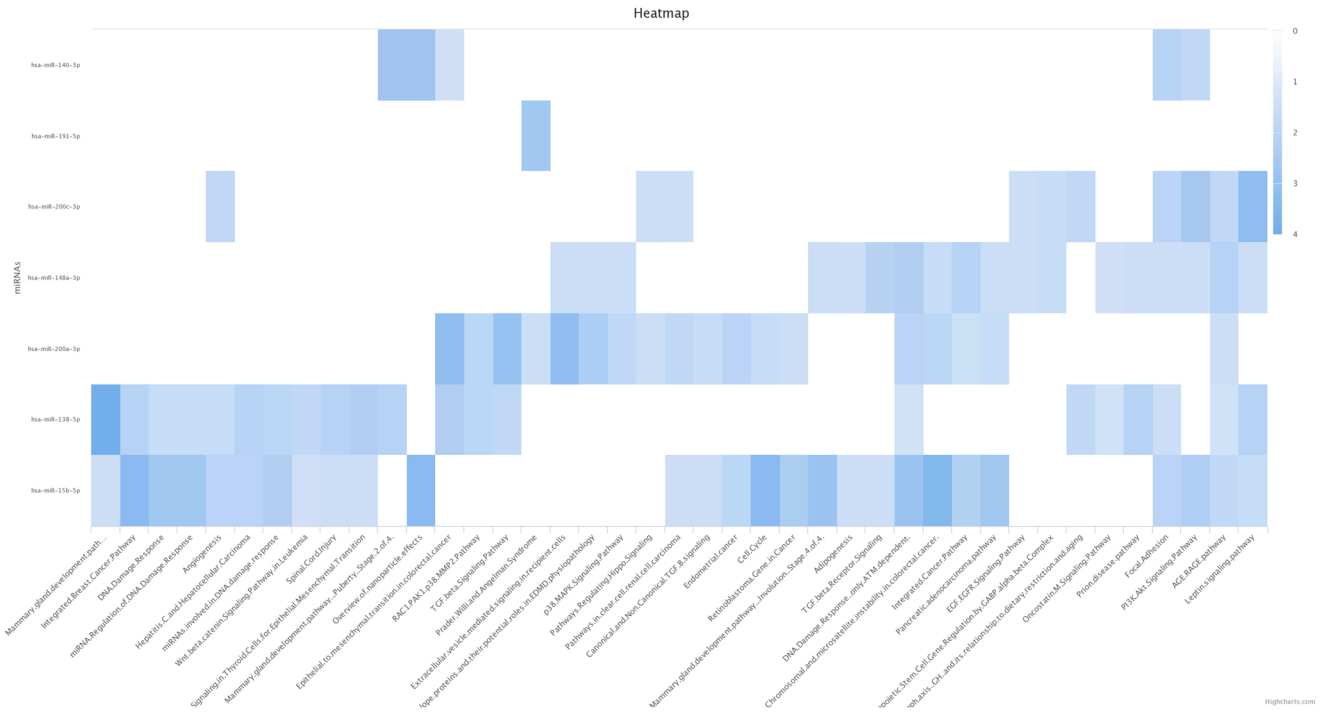

Fig. 5. Enriched WikiPathways of PD-L1-inhibiting miRs retrieved from our systematic review. The darker color indicates a more significant association. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

4.4. miR-93–5p

Chen et al. have reported that miR-93–5p can downregulate PD-L1 and inhibit the expression of matrix metallopeptidase (MMP)− 1, MMP-2, and MMP-9 in HCT116 and SW620 cells. Moreover, miR-93–5p has upregulated IL-2, TNF-α, and IFN-γ and downregulated IL-1β, IL-10, and TGF-β in a co-culture system with T-cells. Furthermore, miR-93–5p has been associated with decreased PD-L1-mediated lymphatic metastasis, improved tumor differentiation, and improved survival of affected patients [23]. Yang et al. have shown that miR-93–5p is substantially downregulated in colorectal cancer tissues. Besides, the XIST-mediated downregulation of miR-93–5p has been associated with hypoxia-inducible factor 1-α (HIF-1α) up-regulation, migration, and proliferation of colorectal cancer cells both in vivo and in-vitro [62]. Furthermore, miR-93–5p can inhibit the Wnt/β-catenin pathway in colorectal cancer and suppress tumor proliferation and migration [63, 64]. Also, Li et al. have shown that miR-93–5p can decrease the cell viability and invasion of colorectal cancer cells [65]. Recently, Liu et al. have shown that miR-93–5p can upregulate cleaved caspase-3, stimulate apoptosis, and decrease the cell viability of colorectal cancer cells [66].

4.5. miR-148a-3p

Ashizawa et al. have reported that miR-148a-3p can inhibit PD-L1 expression in colorectal cancer cells and suppress T-cell apoptosis. Besides inhibiting PD-L1 expression, its restoration has substantially decreased the colony numbers of colorectal cancer cells [40]. Peng et al. have reported that miR-148a-3p is substantially downregulated in colorectal cancer patients compared to healthy controls [67]. Shi et al. have also shown that miR-148a-3p expression is substantially decreased in colorectal tissues compared to normal tissues, and its high expression is associated with improved overall survival of colorectal cancer patients. They have reported that miR-148a-3p can decrease tumor migration, cell viability, invasion, and clonogenicity and stimulate apoptosis in colorectal cancer cells. Besides, miR-148a-3p has been associated with suppressed tumor growth in mice bearing cisplatin-resistant SW480 cells [68]. In line with these, Zhao et al. have demonstrated that miR-148a-3p restoration can remarkably decrease the proliferation and migration of SW480 and LoVo cells [69]. Our in silico results have shown that the expression level of miR-148a-3p is significantly increased in patients without venous/lymphatic invasion than patients with venous/lymphatic invasion, and it is enriched for the PI3K/Akt signaling pathway and microsatellite and chromosomal instability categories.

4.6. miR-382–3p

In HCT116 and Caco-2 cells, miR-382–3p can decrease the protein expression of PD-L1. Besides, miR-382–3p has been associated with decreased tumor proliferation and increased apoptosis in colorectal cancer cells [43]. In colorectal cancer, miR-382–3p is remarkably decreased in tumoral tissues, and its upregulation is associated with improved overall survival of affected patients. Ren et al. have reported that miR-382–3p can substantially decrease the proliferation and migration of HT29 cells [70].

4.7. miR-191–5p

Chen et al. have reported that miR-191–5p can inhibit PD-L1 expression in RKO cells; however, the delivery of miR-191–5p inhibitors into LoVo cells has not increased PD-L1 expression [19]. Qin et al. have indicated that miR-191–5p overexpression is correlated with poor overall survival and can suppress tissue inhibitor of MMP-3 in SW620 cells, paving the way for tumor migration [71]. Moreover, miR-191–5p has been implicated in cell growth and tumorigenicity in xenograft models of HCT116 cells [72]. Besides, Eizuka et al. have demonstrated that miR-191–5p is substantially upregulated in invasive colorectal cancer tissues compared to conventional adenomas [73].

Given the fact that the Chen et al. have not investigated the effect of miR-191–5p on the cell viability/apoptosis/chemosensitivity/autophagy/migration/invasion and they only have demonstrated the inhibitory effect of miR-191–5p on PD-L1 and Qin et al. and Zhang et al.

have shown that miR-191–5p can facilitate tumor development and the migration of colorectal cancer cells, this PD-L1-inhibiting miR cannot be a suitable therapeutic agent for treating colorectal cancer. Our bioinformatic results have shown that the expression level of miR-191–5p is significantly increased in patients without lymphatic invasion than patients with lymphatic invasion.

4.8. miR-15b-5p

Recently, Lui et al. have shown that the infection with a lentivirus/adeno-associated virus/antisense miR-15b-5p can substantially stimulate colorectal cancer development. They have shown that the miR-15b-5p can considerably increase the sensitivity of the colorectal cancer cells to T-cell-mediated tumor death. Besides, the co-administration of this complex with anti-PD-1 antibodies has remarkably increased the proportion of $CD8^{+}$ IFN-γ^{+} T-cells in tumor-infiltrating T-cell and improved the survival of affected mice over the tumor-bearing mice that only received anti-PD-1 antibodies [44]. Besides, miR-15–5p has increased the chemosensitivity of colorectal cancer to 5-fluorouracil both in vitro and in vivo [74]. Moreover, miR-15–5p has substantially increased the expression of pro-apoptotic genes in xenograft colorectal cancer treated with radiotherapy and dendritic cells [75]. Zhao et al. have demonstrated that miR-15–5p can substantially enhance the chemosensitivity of colorectal cancer cells to fluorouracil, and the combined therapy with

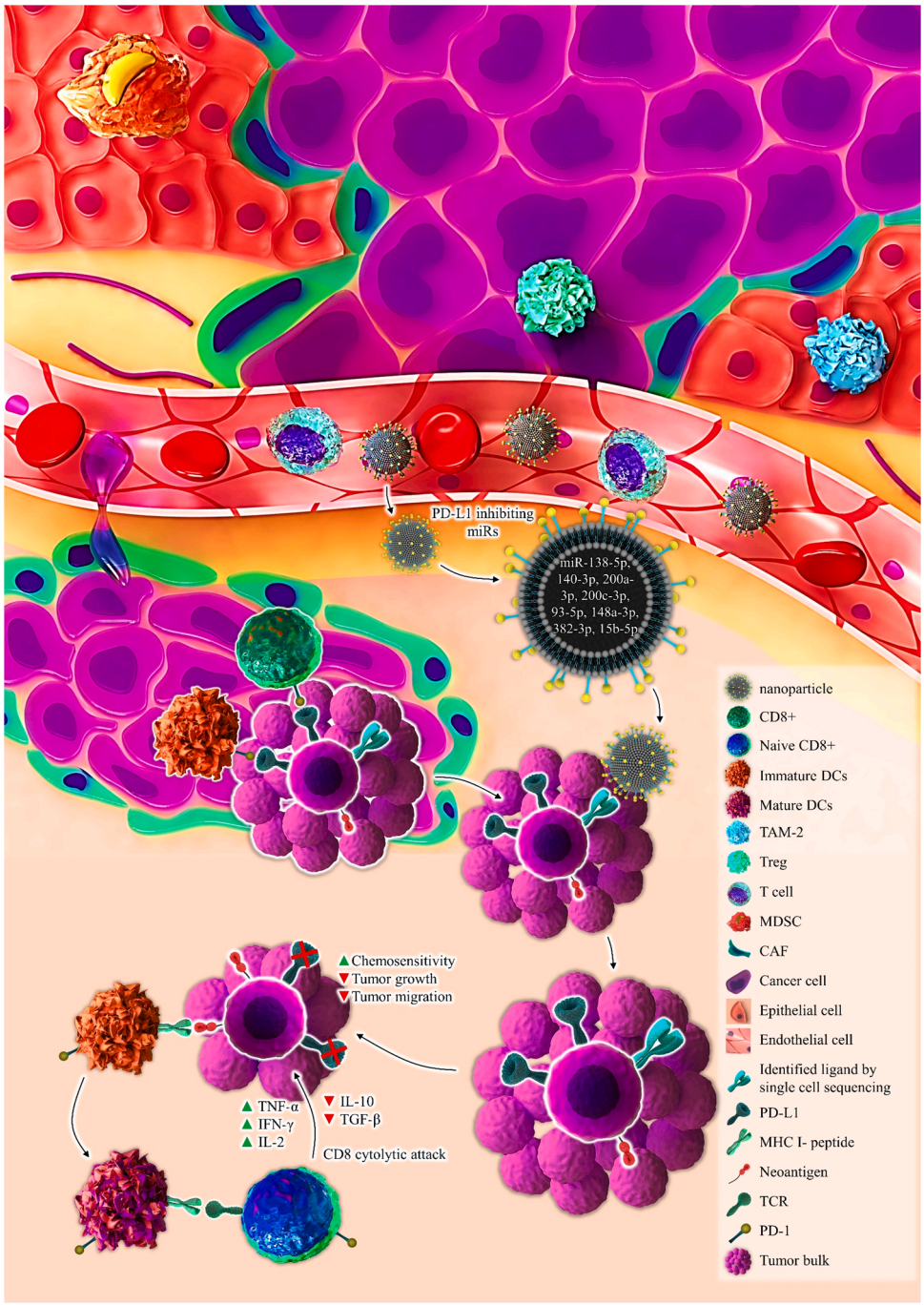

Fig. 6. The tumor microenvironment of colorectal cancer and nanoparticles loaded with PD-L1-inhibiting miRs. The delivery of PD-L1-inhibiting miRs can inhibit tumor growth, reduce tumor migration, and enhance the chemosensitivity of tumoral cells. Besides, these miRs can promote the anti-tumoral immune responses via downregulating tumoral PD-L1 expression in colorectal cancer cells.

miR-15–5p and fluorouracil can substantially decrease tumor volume compared to monotherapy with fluorouracil in mice bearing colorectal cancers. Besides, miR-15–5p has remarkably increased the apoptosis rate in SW620 and HCT116 cells [74]. Besides inhibiting PD-L1, treatment with miR-15b-5p antisense has been associated with increased tumor development in mice bearing colorectal cancer [44]. Recently, Huang et al. have indicated that miR-15–5p can decrease the proliferation of HCT116 and LoVo [76].

Our bioinformatic results have demonstrated that the increased expression of miR-15b-5p is significantly associated with improved disease-specific survival (P-value=0.007638), and it is enriched for the microsatellite and chromosomal instability in colorectal cancer, PI3K/Akt signaling pathway, and cell cycle categories. Furthermore, the expression level of miR-15b-5p is remarkably increased in patients without lymphatic invasion than patients with lymphatic invasion.

Collectively, the delivery of miR-140–3p, miR-382–3p, miR-148a-3p, miR-93–5p, miR-200a-3p, miR-200c-3p, miR-138–5p, and miR-15b-5p can substantially inhibit colorectal cancer development and transform immunosuppressive tumor microenvironment into a proinflammatory one (Fig. 6). In light of the encouraging results, these miR, as multi-target tumor-suppressive agents, can be considered as a promising therapeutic approach for treating colorectal cancer; nevertheless, there is a need for further studies before their translation into the clinic.

4.9. Future direction in treating colorectal cancer: from bench to bedside

The current scoping review has highlighted the currently available evidence on the therapeutic potentiality of PD-L1-inhibiting miRs for treating colorectal cancer. However, effective, safe, and specific miR delivery is still challenging for translating miR-based gene therapy into the clinic. Therefore, the following sections aim to briefly discuss the recent advances in miR-delivery and how single-cell sequencing-guided biocompatible miR-delivery can improve the efficacy, safety, and specificity of miR delivery.

4.9.1. The therapeutic side of miRs: an introduction to the carriers

Although most clinical studies regarding miR-based gene therapy are in phase I or II, this approach has shown promising results to modulate the expression of oncoproteins in preclinical studies [77]. Growing preclinical studies use carriers to deliver siRNAs and miRs to tumoral cells [78]. Although viral carriers have been one of the primary introduced carriers for gene therapy, serious concerns regarding their safety have been raised. Besides limitations in their sizes, virus-based gene delivery has been associated with immune-related adverse events and unwanted inflammation development. Therefore, nonviral carriers, e.g., lipid-based, polymer-based, and inorganic vectors, have been proposed [79]. Ideal vehicles should protect the cargo against the RNases in the serum, precisely deliver the cargo to the target cells, facilitate cargo uptake, and not induce toxicity in the body. The following sections discuss the advantages and disadvantages of nonviral carriers and provide a blueprint for delivering the aforementioned miR-targeting PD-L1 in colorectal cancer.

4.9.1.1. PEI. Since 1995 PEI has been extensively utilized as the backbone for gene delivery due to its high transfection efficacy. Indeed, the polycation nature of PEI can condense the desired gene. Besides, its low pKa value can pave the way for lysing the vesicles after endocytosis, leading to gene liberation [80–82]. Vahidian et al. have demonstrated that PEI can effectively deliver siRNAs into tumoral cells [83]. Consistent with this, Ibrahim et al. have demonstrated that the systematic and local delivery of miR-33a and miR-145 using low molecular weight PEI can substantially decrease the tumor size and induce apoptosis in mice model of colorectal cancer [84]. Recently, Kunz et al. have also shown that the delivery of anti-oncogenic miRs via PEI-based nanoparticles can substantially inhibit tumor growth in vivo [85].

Despite the satisfactory efficacy of PEI in gene delivery, it can induce apoptosis and adverse events via interacting with apoptosis-related proteins, like heat-shock proteins [82]. In this regard, recent advances have partially decreased their excessive toxicity. For instance, decreasing the weight of PEIs has reduced the excessive positive charge of the early PEIs and improved their degradation [84]. Another approach for reducing the excessive positive charge of PEI is pegylation. Pegylation of PEI can reduce toxicity and increase the stability of the complex. Wu et al. have shown that this complex can effectively deliver EZH2-shRNA and efficiently inhibit EZH2 without inducing high toxicity [86].

To increase the specificity of PEI-based nanoparticles, the conjugation of peptides and antibodies specific to tumoral cells has been proposed. Ewe et al. have demonstrated that grafting anti-HER1 antibody to PEG/PEI has shown promising results regarding the uptake, stability, and toxicity both in vitro and in vivo [87]. In line with this, Mokhtarzadeh et al. have shown that conjugation of PNC 27 and PNC 28, whose ligands can be overexpressed in tumoral cells, into PEI can exclusively deliver the desired gene into tumoral cells [88]. However, the non-biodegradability nature of PEI has raised serious questions about their translations into clinic practice [80].

4.9.1.2. Super carbonate apatite as an inorganic vehicle. The main advantages of this approach are the low toxicity, low cost, and easy production of inorganic vehicles [81]. Since highlighting all the advances in inorganic vehicle developments is out of the scope of the current study, the recent studies on the super carbonate apatite, as an inorganic-based carrier studied in colorectal cancer, are briefly discussed below.

The intravenous administration of miR-4711–5p via super carbonate apatite has substantially reduced tumor size in animal models of colorectal cancer. The systematic administration of this complex has not been associated with substantial weight body loss in mice [89]. The same vehicle has been used to deliver miR-4689; the intravenous delivery of miR-4689/super carbonate apatite complex has been relatively tolerable in mice models of colorectal cancer. However, it has led to a considerable rise in the BUN level [90]. Oh et al. have designed an inorganic vector coated with a ligand specific to target tumoral cells. Their results have indicated that the conjugation of folic acid with their vector can enhance the specificity of vehicle uptake without changing the vector structure [91]. Therefore, the conjugation of antibodies/peptides to these carriers might be associated with increased specificity of carriers.

4.9.1.3. Liposomes. Liposomes can offer high flexibility in gene and drug delivery [92,93]. Since the cell surface of cancer cells is substantially negative-charged, the cationic liposomes have shown relatively high specificity in the cancer context. In line with this, the systematic delivery of miR-215 in neutral liposome/miR-215 complex has been associated with the accumulation of miR-215 in various organs of animal models of colorectal cancer without substantially decreasing tumor size [94]. However, positively charged liposomes can also lead to liver and spleen accumulation, ultimately resulting in reticuloendothelial clearance [95]. Moreover, the cationic head of this kind of liposome can interact with neutrophils and induce subsequent toxicity [96]. Indeed, the early generation of liposomes has failed to induce long-lasting therapeutic effects due to their fast clearance by the reticuloendothelial system. Pegylation is an appropriate answer for preventing its clearance. Moreover, pegylation can reduce the cytotoxicity of catatonic liposomes; thus, it can prevent fusion with the negatively charged plasmatic membrane of normal cells [96]. Nevertheless, recent findings have raised questions about its safety due to its deposition in the lung and liver following repetitive injection of pegylated vehicles [97].

Besides the fast clearance of liposomes from the bloodstream, their limitations in the sustained release could be considered another

disadvantage. In this regard, pH-sensitive liposomes have been introduced. The low pH of the tumor microenvironment compared to the physiological pH is the basis of the development of pH-sensitive liposomes. For this purpose, dioleoylphosphatidylethanolamine (DOPE) is one of the extensively used extensions to liposomes. Lee et al. have shown that the administration of DC-Chol/DOPE/PEG liposomes has been associated with a high concentration of siRNA release in the tumor microenvironment [98]. Seraj et al. have also indicated that the DC-Chol/DOPE/PEG liposomes containing siRNAs can lead to the long-term inhibition of target genes in tumoral cells without resulting in immune-related adverse events and off-target effects [99].

Ionizable liposomes are neutral in the blood circulation, but in the acidic tumor microenvironment, they become cationic, leading to the effective delivery of their cargos. Liu et al. have shown that siRNA delivery into the hypoxic tumor microenvironment via ionizable liposomes can be successfully achieved in animal models [100]. However, a recent phase I clinical trial has halted due to the adverse immune-related events in liver cancer patients after treatment with miR-34a/ionizable liposome complex (MRX34) [101]. Nevertheless, another clinical trial has shown that MRX34 has an acceptable safety level and can elicit anti-tumoral activity in a subset of patients with refractory solid cancer [102]. In a phase I clinical trial, the delivery of Bcl-2-DNAi via ionizable liposomes has been well-tolerable in patients with solid cancers [103].

Another relatively novel approach is the conjugation of the liposome with ligands that can specifically bind to tumoral cells with overexpressed receptors, e.g., EGFR and CD44. Shigehiro et al. have demonstrated that the conjugation of liposomes with trastuzumab, as an antibody against EGFR, can considerably increase the specificity and efficacy of liposomes to deliver paclitaxel in mice models of colorectal cancer [104]. The same concept has been successfully investigated in breast cancer and glioblastoma cells in liposomes conjugated with hyaluronan [105,106]. Recently, Yao et al. have developed a liposomal-based nanoparticle for treating colon tumors, loaded with chemotherapeutic agent and oligonucleotide and fabricated with antibodies specific for death receptor 5. They have shown that this complex can specifically and effectively inhibit tumor development in mice models [107]. Therefore, the conjugation with ligands specific to the cancer cells can be a promising approach for delivering cargo to target cancer cells.

4.9.2. Biocompatible vehicles: time to overcome the safety barrier?

Although the positive charge of nanoparticles is essential for condensing the genetic cargo, the positive charge can facilitate inflammation and its clearance from the blood. On the other hand, these non-biocompatible carriers can accumulate in the liver and spleen and lead to toxicity. Indeed, biocompatible materials can address these shortcomings of these carriers and offer a well-tolerable and safe vehicle for gene delivery. Combining biocompatible structures with the above-mentioned carriers can increase their safety [108,109].

4.9.2.1. Polyester-based biocompatible carriers. Polyesters, developed from polymerizing polyhydric alcohol with adding apolybasic acid, are one of the biocompatible carriers that their safety and low immunogenicity have gained particular attention in gene therapy. However, their hydrophobe nature requires conjugation with the above-mentioned carriers for effective delivery [108]. Herein, we briefly introduce recent advances in applying three polyester-based carriers, i.e., PLA, PCL, PLGA, for targeted therapy in cancers.

Although PEI has shown remarkable efficacy in gene delivery, its toxicity has been challenging for its clinical translation. Recent findings have indicated that the combination of PLA with PEI can substantially reduce its toxicity and confer excellent delivery capacity. Ding et al. have shown that the PEI-PLA complex can effectively deliver siRNA to HCT116 cells. Indeed, the efficacy of PEI-PLA in delivering siRNA has been comparable to the commercial Lipo2000. Besides its high efficacy, the PEI-PLA has induced less cytotoxicity than PEI nanoparticles [110]. The combination of PLA with pegylation has also been promising in cancer gene therapy. Liu et al. have demonstrated that the PLA-PEG complex can effectively deliver siRNA to tumoral cells, and its systematic administration in xenograft mice is not associated with toxicity and the activation of the innate immune system [111]. The combination of PLA with pegylation in cationic lipid-containing siRNA has been associated with substantial internalization and endosomal escape, which ultimately led to remarkable inhibition of target gene expression. Besides successful preservation of siRNA structure in this complex, the systematic administration of this complex has been associated with considerable inhibition of tumor development in mice bearing tumors [112]. Recently, Luo et al. have demonstrated that HA fabrication can increase the specificity of the methoxy-PEG-PLA-HA-based complex to deliver its cargo to CD44-positive tumoral cells. Besides, this complex has not substantially accumulated in the liver of animal models [113].

PCL is another biocompatible carrier that can maintain the controlled release of the cargo. Indeed, its sufficient endocytosis and low toxicity might be its major superiority over others [114]. Feldmann et al. have shown that the PEI-PCL-PEG-based biocompatible carriers can effectively deliver siRNA to tumoral cells, which is comparable to Lipofectamine [115]. Akbari et al. have demonstrated that PCL-PEG can effectively deliver loaded cargo to tumoral cells [116]. The conjugation of antibodies to the PCL-PEG-based nanoparticles has also been promising in preclinical studies. Hu et al. have shown that the trastuzumab-PCL-PEG-based nanoparticles can effectively deliver miRs and chemotherapeutic agents to tumoral cells both in vitro and in vivo [117]. The Fa-PCL-PEG-PEI-based nanoparticles have also been associated with high efficacy in delivering siRNA into tumoral cells and prolonged stability in the bloodstream of animal models [118,119]. Therefore, the combination of the PCL with conventional polymers can overcome their toxicity without substantially affecting their high efficacy in delivery.

PLGA, synthesized from glycolic acid and lactic acid, is another biocompatible and biodegradable vehicle evaluated in a phase II clinical trial (NCT01676259). Saraf et al. have shown that PLGA- ES100, as a pH-sensitive material, can effectively deliver the loaded cargo to the tumor microenvironment of colon cancer [120]. Wang et al. have reported that the delivery of miR-542–3p/doxorubicin via HA/PEI/PLGA complex can specifically induce apoptosis in $CD44^{+}$ tumoral cells [121]. Li et al. have demonstrated that the HA/PEI/PLGA complex can also show affinity to tumoral cells, and the pretreatment of tumoral cells with HA can substantially decrease this affinity. This indicates that the presence of HA as the ligand on the surface of the nanoparticle and its receptor on the surface of target cells plays a pivotal role in increasing the response rate and specificity of this approach [122]. Consistent with these, Liang et al. have shown that PLGA/PEI-cet/HA nanoparticles can effectively facilitate cellular uptake in colorectal cancer cells both in vitro and in vivo [123]. Recently, Phung et al. have developed a PLGA-PEG-Fa-based nanoparticle for delivering miR-200c and doxorubicin, which has been associated with decreased expression of PD-L1 expression on the murine colorectal cancer cells, the increased infiltration of $CD8^{+}$ T-cells, and dendritic cells maturation. The conjugation of Fa has been associated with a remarkable increase accumulation of nanoparticles in the tumor microenvironment. Although there has been a considerable accumulation of these nanoparticles in the liver, no cytotoxicity to major organs and substantial weight loss have been noted in treated mice bearing tumors [124]. Zheng et al. have also demonstrated that Fa-PLGA/PLA-PEG can successfully deliver miRs in mice bearing colorectal cancer, without resulting in noticeable organ damages, like hepatocytes death [125]. Therefore, the conjugation of biocompatible polyester-based polymers, e.g., PLGA, into the conventional nanoparticles might be a promising approach for delivering PD-L1-inhibiting miRs for treating colorectal cancer.

4.9.2.2. Polysaccharide-based biocompatible carriers. Polysaccharides, synthesized by the monosaccharides joined with glycoside linkage, are biocompatible vehicles that can be undergone multiple chemical modifications. Despite their fast clearance and endosomal escape that can be addressed via modifications, their safety, and biocompatibility, and their low cost have paved the way for the application of their conjugated forms for cancer therapy [108]. Thus, their conjugation with PEI and PEG-based nanoparticles might be an appealing approach for gene delivery. Besides HA, the following aimed to introduce two biocompatible and biodegradable nanoparticles, i.e., chitosan, and dextran, as promising nanoparticles for gene delivery.

Chitosan, synthesized from D-glucosamine and N-acetyl-D-glucosamine, has a positively charged global structure. Furthermore, it can open tight intracellular junctions and improve gene uptake [126]. Therefore, it can be an appealing strategy for gene delivery. Besides, pegylation can improve caveolae-dependent and clathrin-independent endocytosis, protect the complex against the hydrolases, and prevent the fast clearance of polysaccharide-based nanoparticles [127]. Salimifard et al. have shown that chitosan-PEG-HA-PLA can effectively deliver loaded-siRNAs into tumoral cells in animal models bearing colorectal cancers and improve the survival of affected mice [128]. Sun et al. have demonstrated that PEG-chitosan can confer higher stability, effectively deliver siRNAs, and inhibit tumor growth both in vivo and in vitro [129]. The fabrication of chitosan into PEI has also been promising in preclinical studies. Zhao et al. have reported that PEI-chitosan is approximately 1000 effective than chitosan nanoparticles to induce gene expression in tumoral cells. Besides, PEI-chitosan nanoparticles have substantially elicited lesser toxicity than PEI-based nanoparticles [130]. Jere et al. have indicated that chitosan-PEI can effectively deliver siRNA into tumoral cells and silence target mRNA [129]. Besides, Zhao et al. have indicated that conjugation of HA in chitosan oligosaccha ride-PEI, via interaction of CD44 on the target cells, can increase the specificity of nanoparticles and reduce their toxicity [131]. In line with this, Helmi et al. have shown that the fabrication of anti-HER2 antibodies into PEG-chitosan nanoparticles can selectively deliver cargo to target tumoral cells compared to normal cells [132].

Dextran is a biocompatible microbial-derived branched glucan that has gained particular attention in gene delivery because of its low toxicity. Gong et al. have developed PEI/dextran/iron oxide-based nanoparticles that can be directed to the tumor microenvironment via applying a magnetic field. Indeed, magnet-guided complex deriving has reduced nanoparticles accumulation in the spleen and decreased their clearance [133]. Recently, Wang et al. have developed dextran/lipid-ba sed nanoparticles to deliver a chemotherapeutic agent and siRNA to tumoral cells. Their in vivo results have shown that this nanopar ticle-based siRNA/drug delivery can remarkably decrease tumor gro wth compared to the free drug [134]. Besides, the pH-sensitivity nature of this complex can also increase the specificity of the delivery. It has been shown that pH-sensitive dextran-PEI can effectively deliver cargo in the acidotic tumor microenvironment [135]. Tseng et al. have developed cet-PEG-dextran-cetuximab-superparamagnetic iron oxide-based nanoparticles that have enabled the MRI-mediated imaging of tumoral tissues and induced apoptosis in tumoral cells [136]. Indeed, this concept might be applied to the early diagnosis and treatment of cancers.

4.9.3. Future perspectives in gene delivery: single-cell sequencing-guided biocompatible-based delivery

Overall, the advances in biocompatible nanoparticles and their integration in traditional vehicles, like PEI, can provide ample opportunities to reduce the toxicity of the traditional carriers without substantially altering their delivering efficacy. To increase the specificity of the nanoparticles, the conjugation of peptides/antibodies specific to the tumoral cells might be needed. The recent advances in single-cell sequencing of tumoral cells can reveal the specifically upregulated neoantigens that can be used to fabricate specific antibodies/peptides into nanoparticles [137–140]. Indeed, single-cell sequencing approaches have provided novel insights into the genetic properties of tumoral cells. These approaches can study cells at the single-cell level and identify neoantigens. The ideal neoantigen for gene/drug delivery should be ideally overexpressed in tumor cells, and normal cells do not express them [141]. Nevertheless, the vast intratumoral heterogeneity can be a daunting challenge for developing specific ligands for tumoral cells.

However, machine learning approaches can facilitate the identification of these specific and individualized neoantigens. Joshi et al. have developed a machine learning-based technology that can precisely and in a more cost-effective manner identify the tumoral cells from non-cancerous cells and map the tumoral heterogeneity at the single-cell level [142]. Besides identifying the related ligands, single-cell sequencing technologies can aid in evaluating the fate of the nanoparticles in animal models before their clinical translation. In this regard, Wang et al. have investigated the efficiency of their developed nanoparticles to accumulate in the tumor microenvironment and studied whether the complexes are mainly uptaken by the tumoral cells or the immune cells residing in the tumor microenvironment [143]. Moreover, single-cell technologies can allow us to select which nanoparticles can preferentially reject tumors regardless of their grafted antibodies. Recently, Yang et al. have identified a carrier via utilizing mass cytometry by time-of-flight that has potently stimulated anti-tumoral immune responses and rejected tumor in vivo [144].

Therefore, the integration of the obtained data from the single-cell sequencing of tumoral cells into the biodegradable/biocompatible-based nanoparticles for delivering miR-140–3p, miR-382–3p, miR-148a-3p, miR-93–5p, miR-200a-3p, miR-200c-3p, miR-138–5p, and miR-15b-5p can increase the specificity of the miR delivery, decrease the toxicity of traditional nanoparticles, transform the immunosuppressive tumor microenvironment into the proinflammatory one, suppress tumor development, reduce tumor migration, and enhance chemosensitivity of tumoral cells to chemotherapeutic agents (Fig. 6). In other words, single-cell sequencing-guided biocompatible-based delivery of miR-140–3p, miR-382–3p, miR-148a-3p, miR-93–5p, miR-200a-3p, miR-200c-3p, miR-138–5p, and miR-15b-5p might answer the daunting challenges that clinicians are facing in treating colorectal cancer patients. However, further studies are needed before the translation of this approach into the clinics.

5. Some considerations regarding miR-based therapy for treating colorectal cancer

Despite the promising results regarding the therapeutic potentiality of PD-L1-inhibiting miRs for treating colorectal cancer, all PD-L1-inhibiting miRs do not always suppress tumor development. Indeed, miRs are multi-target natures, and investigating the effect of a miR on one oncoprotein might not provide adequate insights into the overall effect in treating tumoral cells. Therefore, relying solely on bioinformatic results to identify PD-L1-inhibiting miRs, as therapeutic miRs, can be misleading. In this regard, Chen et al. have reported that miR-191–5p can inhibit PD-L1 expression in RKO cells [19]; however, Qin et al. have shown that miR-191–5p can facilitate tumor migration in colorectal cancer cells [71]. Besides, it has been shown that miR-191–5p can increase the tumorigenesis of colorectal cancer in mice bearing HCT116 cells [72]. In this scoping review, we have provided evidence for the overall effect of PD-L1-inhibiting miRs on colorectal cancer cells. Our observed results have indicated that all currently and experimentally identified PD-L1-inhibiting miRs except miR-191–5p, i.e., miR-140–3p, miR-382–3p, miR-148a-3p, miR-93–5p, miR-200a-3p, miR-200c-3p, miR-138–5p, and miR-15b-5p, can substantially inhibit the development of colorectal cancer.

The other issue of miR-based gene therapy is its safe, effective, and specific delivery. It is well-established that the overall effect of miRs is tissue-dependent. For instance, miR-191–5p can promote tumor

development in colorectal cancer [72]; however, miR-191–5p can substantially stimulate apoptosis and suppress migration in renal cell carcinoma [145]. It has been shown that miR-15b-5p can remarkably inhibit tumor development in colorectal cancer [44]. Nevertheless, Wu et al. have demonstrated that miR-15b-5p can increase the proliferation and the colony numbers in breast cancer [146]. Shen et al. have shown that miR-93–5p inhibition can decrease the migration and invasion of gastric cancer cells, and miR-93–5p mimics can increase the migration and invasion of gastric cancer cells. Besides, increased expression of miR-93–5p has been substantially associated with decreased overall survival and disease-free survival of patients with gastric cancers [147]. However, as discussed above, miR-93–5p can decrease cell viability, stimulate apoptosis, and suppress the invasion of colorectal cancer cells [65,66]. For addressing this issue, there is a need to develop safe, effective, and specific carriers to precisely deliver the identified tumor-suppressive PD-L1-inhibiting miRs to colorectal cancer. In the current study, we have discussed the current options for safe, effective, and specific miR delivery and proposed a novel strategy to maximize the specificity and safety of miR delivery.

The other issue with this approach is that somatic mutations might substantially change the binding capacity of PD-L1-inhibiting miRs to their target mRNAs. For instance, Wang et al. have shown that a somatic mutation in PD-L1 can substantially decrease the affinity of a PD-L1-inhibiting miR in gastric cancer. Of interest, the presence of that mutation has been strongly associated with PD-L1 overexpression in gastric cancer (OR=14.4, 95% CI 6.36–32.5 and $P = 1.44 \times 10^{-10}$) [148]. Therefore, the administration of PD-L1-inhibiting miRs should be personalized based on the genetic properties of each patient.

Overall, the proposed approach can potentially change the landscape of colorectal cancer therapy; however, some questions remain to be answered. First, is the combined therapy of these miRs replacement with conventional treatments superior over these miRs replacement? Second, concerning the application of high technology for finding related ligands, the cost-effectiveness of this approach should be evaluated. Third, how can somatic mutations affect this approach? Can combined replacement of PD-L1-inhibiting miRs be a proper answer to potential somatic mutations? Fourth, how the conventional anticancer therapies can impact the miR properties of the exposed colorectal cancer tissues? Finally, does race have a role in determining the efficacy of this proposed approach? These kinds of undiscussed questions should be carefully investigated before considering its translation into the clinics.

The current scoping review has several strengths. First, this scoping review has shed light on the therapeutic potentiality and clinical significance of PD-L1-inhibiting miRs and reviewed the current literature to elucidate their overall effect on colorectal cancer. Second, this scoping review has had an extension, i.e., discussing the potentiality of biocompatible/biodegradable nanoparticles and single-cell sequencing technologies to facilitate the translation of preclinical findings. However, our study has several limitations, as well. First, we have only included the studies published in English. Second, the protocol of the current study was not publicly registered.

6. Conclusion

The current scoping review has demonstrated that miR-191–5p, miR-382–3p, miR-148a-3p, miR-93–5p, miR-200a-3p, miR-200c-3p, miR-138–5p, miR-140–3p, and miR-15b-5p can inhibit tumoral PD-L1 expression in colorectal cancer. Besides inhibiting tumoral PD-L1, miR-140–3p, miR-382–3p, miR-148a-3p, miR-93–5p, miR-200a-3p, miR-200c-3p, miR-138–5p, and miR-15b-5p can transform the immunosuppressive tumor microenvironment into the proinflammatory tumor microenvironment, enhance the chemosensitivity of tumor cells, arrest cell-cycle, inhibit oncogenic signaling pathways, reduce tumor migration, and stimulate tumoral cell apoptosis in colorectal cancer cells. We have found that the increased expression of miR-200c-3p in tumor budding and the elevated expression of miR-138–5p have been associated with improved prognosis of colorectal cancer patients. Based on our bioinformatic findings, high expression levels of miR-200c-3p and miR-15b-5p are associated with improved disease-specific survival of affected patients. Besides, the expression of miR-200a-3p, miR-200c-3p, miR-148a-3p, miR-191–5p, and miR-15b-5p is remarkably increased in patients without lymphatic invasion than patients with lymphatic invasion. Furthermore, the expression levels of miR-200c-3p and miR-148a-3p are substantially increased in patients without venous invasion than patients with venous invasion. Overall, the delivery of miR-140–3p, miR-382–3p, miR-148a-3p, miR-93–5p, miR-200a-3p, miR-200c-3p, miR-138–5p, and miR-15b-5p via single-cell sequencing-guided biocompatible/biodegradable nanoparticles can increase the specificity of miR delivery, transform the immunosuppressive tumor microenvironment into the proinflammatory one, reduce the toxicity of traditional nanoparticles, inhibit tumor development, decrease tumor migration, and enhance the chemosensitivity of tumoral cells regardless of their microsatellite state. Nevertheless, further investigations are needed to answer the above-mentioned questions before its translation into clinics.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CRediT authorship contribution statement

Mahdi Abdoli Shadbad: Conceptualization, Methodology, Software, Formal analysis, Investigation, Writing – original draft. **Zahra Asadzadeh:** Investigation. **Afshin Derakhshani**: Formal analysis. **Negar Hosseinkhani**: Writing – original draft. **Ahad Mokhtarzadeh**: Writing – review & editing. **Amir Baghbanzadeh**: Visualization. **Khalil Hajiasgharzadeh**: Writing – review & editing. **Oronzo Brunetti**: Software, Writing – review & editing. **Antonella Argentiero**: Software, Visualization. **Vito Racanelli**: Writing – review & editing. **Nicola Silvestris**: Supervision, Writing – review & editing. **Behzad Baradaran**: Supervision, Writing – review & editing.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

Acknowledgments

We appreciate the researchers of the Immunology Research Center, Tabriz University of Medical Sciences, Tabriz, Iran.

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