


Review

MicroRNAs: immune modulators in cancer immunotherapy

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Summary

MicroRNA (miRNA) is a class of endogenous small non-coding RNA of 18–25 nucleotides and plays regulatory roles in both physiological and pathological processes. Emerging evidence support that miRNAs function as immune modulators in tumors. MiRNAs as tumor suppressors or oncogenes are also found to be able to modulate anti-tumor immunity or link the crosstalk between tumor cells and immune cells surrounding. Based on the specific regulating function, miRNAs can be used as predictive, prognostic biomarkers, and therapeutic targets in immunotherapy. Here, we review new findings about the role of miRNAs in modulating immune responses, as well as discuss mechanisms underlying their dysregulation, and their clinical potentials as indicators of tumor prognosis or to sensitize cancer immunotherapy.

Keywords: microRNAs, immunomodulation, cancer immunotherapy

Abbreviations: ACT: Adoptive cell therapy; CRC: Colorectal cancer; CTL: Cytotoxic (CD8+) T cell; DCs: Dendritic cells; EMT: Epithelial-mesenchymal transition; Foxp3: Forkhead box P3; gCSC: Glioma cancer stem cells; ICB: Immune checkpoint blockade; IgA: Immunoglobulin A; IKKs: I-kappaB kinases; miRNA: MicroRNA; ncRNAs: Non-coding transcripts; NSCLC: Non-small-cell lung cancer; PTX: Paclitaxel; RISC: RNA-induced silencing complex; RNAPolIII: RNA polymerase; Treg: Regulatory T; TEX: Tumor-derived exosomes; UTR: Untranslated region.

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Introduction

Cancer development and progression are accompanied by complex immune responses [1, 2]. As a new and promising treatment after traditional cancer therapies (surgery, radiotherapy, and chemotherapy), immunotherapy has gradually caught people's attention and recognition since 1945. It has been abundantly confirmed in murine tumor models as well as in humans and has become a pivotal treatment for various cancers. It depends on inducing an anti-tumor immune response by small molecule drugs or biological medicine to remove tumor and cure patients, which achieves non-invasive, safe, targeted specifically, and lower side effects. The objective of immunotherapy is to trigger and elevate specificity and longer memory of adaptive immune response, attaining tumor regression and therapeutic effects. Tumor immunotherapy commonly utilizes active and passive strategies. Active immunotherapy adopts anti-tumor vaccines to induce and enhance the specific immune response against tumor antigens. Instead, passive immunotherapy selects a more direct and rapid approach to rebuilt immune systems by delivering antibodies or lymphocytes with anti-tumor activity. Up to now, there are mainly three methods including adoptive cell therapy (ACT), tumor vaccines, immune checkpoint blockade (ICB) immunotherapy, and so on. All these therapies have led to important clinical advances and achieved great success.

MicroRNA (miRNA) is a class of endogenous small non-coding RNA of 18–25 nucleotides long. Early in 1993, Lee RC *et al.* first found that the small RNA encoded by *lin-4* gene in nematode [3]. Since then, multiple kinds of miRNAs and their corresponding targets have been screened and identified. Most of them are highly conserved across different species and have reported as important regulators both in physiological and pathological processes. More than 60% of human protein-coding genes are predicted to be under selective pressure to be regulated by miRNAs and involve in complex cellular processes, including development, proliferation, differentiation, apoptosis, and stress response [4, 5]. MiRNAs also play a central role in immune system, a vital defense system of body [6, 7]. Increasing evidence focusing on tumors explored miRNAs as key regulators in balancing immune response to control initiation and development of diseases, as well as new discovery of their new function mode and potential clinical significance in immunotherapy.

Biogenesis and action mode of miRNAs

MiRNA biogenesis and its function in cytoplasm

MiRNAs are encoded within intergenic regions or within the introns or exons of protein-coding genes of the genome. Generally, after transcription, cleavage, and

processing, mature miRNAs are transported from the nucleus to cytoplasm to be loaded into RNA induced silencing complex (RISC) [8, 9]. The cornerstone of the miRNA functioning is the formation of the RISC composing minimally of an AGO protein and a miRNA molecule. In which, miRNA base pairs with the 3' untranslated region (UTR) of mRNA, mediating target mRNA decay or detachment of ribosomes [10]. While, there are some miRNAs, like miR-10a, that can interact with the 5' untranslated region of miRNAs to enhance their translation [11] (Fig. 1A).

Transcriptional regulation by miRNAs in nucleus

Besides, miRNA in nucleus can also regulate their targets at the transcriptional level. It is through complementarity binding to the genic regions, especially the promoter, or to the non-coding transcripts (ncRNAs) derived from the promoter region [12–14]. These bindings may increase expression of protein-coding genes. For instance, human miR-373, as an activator of gene transcription induced both E-cadherin and cold-shock domain-containing protein 2 [15]. Possible mechanism underlying is via induction of binding and activity of RNA polymerase (RNAPolII) other chromatin modifiers like DNMTs, HDAC, and EZH2. Several components of RISC may be also involved in this process, especially AGO proteins [12, 13, 15–19] (Fig. 1A, a–b). It is interesting to note that a group of miRNAs, termed 'epi-miRNAs', has been reported to reciprocally modulate epigenetic regulators, suggesting the existence of a regulatory circuit between miRNAs and epigenetic modifiers [20, 21] (Fig. 1B). Liu suggested the epigenetic circuit of miR-126-DNMT1, in which, DNMT1, critical for gene-specific methylation, was highly expressed in esophageal cancer tissues and responsible for the hypermethylation of the promoter of miR-126 host gene and the subsequent silence of miR-126, whereas, overexpression of miR-126 feedback suppressed DNMT1 expression [20]. The 'epi-miRNAs' provides the evidence to support not only epigenetic modulations on miRNA expression but also epigenetic crosstalk between epigenetics and miRNAs.

Function of miRNAs in tumor-infiltrating immune cells and their crosstalk with tumor cells

Since the first discovery of miR-15a/16-1 cluster as the tumor-suppressor in chronic lymphocytic leukemia, tumor-related miRNAs have received unprecedented attention. More than 50% of human miRNAs have been reported to be located at sites of chromosomes that are always abnormal in cancer, such as gene deletion, rearrangements, amplification, or translocation

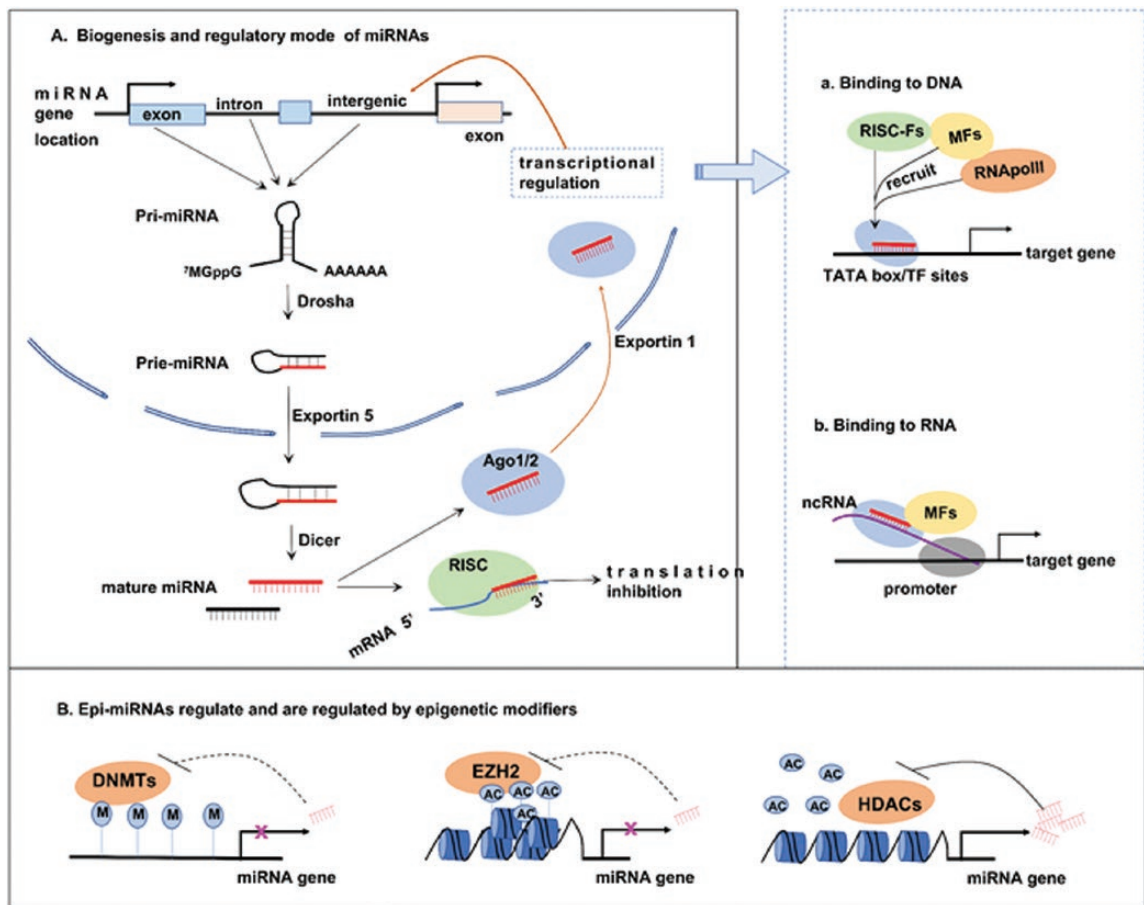


Figure 1 Biogenesis and action mode of miRNAs. (A) miRNA genes, located in the exons, introns, or intergenic regions of protein-coding genes can be transcribed into the primary miRNA (Pri-miRNA). The Pri-miRNA is processed by RNase III Droscha with its partner DGCR8 into the precursor miRNA (Pre-miRNA). Pre-miRNA is exported into cytoplasm by Exportin 5 and its cofactor RAN-GTP, and then processed by RNase III Dicer into the mature miRNA. In the cytoplasm, mature miRNAs are incorporated into the RNA-induced silencing complex (RISC) and bind to the 3' untranslated region (UTR) of its target mRNAs with complementarity, leading to their translational repression; sometimes, they bind to the 5'UTR of mRNAs to enhance their translation. Besides, several miRNAs can turn back to nucleus to regulate gene expression at the transcriptional level. (a–b) It is through complementarity binding to the genic regions, especially the TATA box and transcription factor (TF) binding sites within the promoter, or binding to the non-coding transcripts (ncRNAs) derived from the promoter region. Possible mechanism underlying is via induction of binding and activity of RNA polymerase (RNAPolIII) other chromatin modifiers (MFs) like DNMTs, HDAC, and EZH2. Several components of RISC may be also involved in this process, especially AGO proteins. (B) A group of miRNAs, termed 'epi-miRNAs', has been reported to reciprocally modulate epigenetic modifiers including DNA methyltransferases (DNMTs), Histone-lysine N-methyltransferase (EZH2), histone deacetylases (HDACs), which forms several regulatory circuits.

during carcinogenesis [5]. Altered miRNA profiles have been reported in multiple cancers, and they can directly regulate tumor cell biology including cell proliferation, apoptosis, migration, as well as stemness. Function of miRNAs can be tumor-promoting or suppressive, which depends on their targets, and always involves synergy of several targets [22–24]. We reported miR-126 suppressed esophageal cancer cell proliferation and migration by interacting with ADAM9 mRNA 3'UTR [20]; while, both anti-apoptosis protein BLC2 and

cell-cycle-related protein PA28gamma were the targets of miR-7 in non-small-cell lung cancer (NSCLC) [25, 26]. More importantly, different from the previous knowledge that miRNA directly regulates tumor cell biology, our recent evidence revealed the role of tumor-related miRNAs in modulating anti-tumor immunity, and in linking crosstalk between tumor cells and immune cells surrounding, as well as discovered mechanisms underlying their dysregulation during tumorigenesis (Fig. 2A–C).

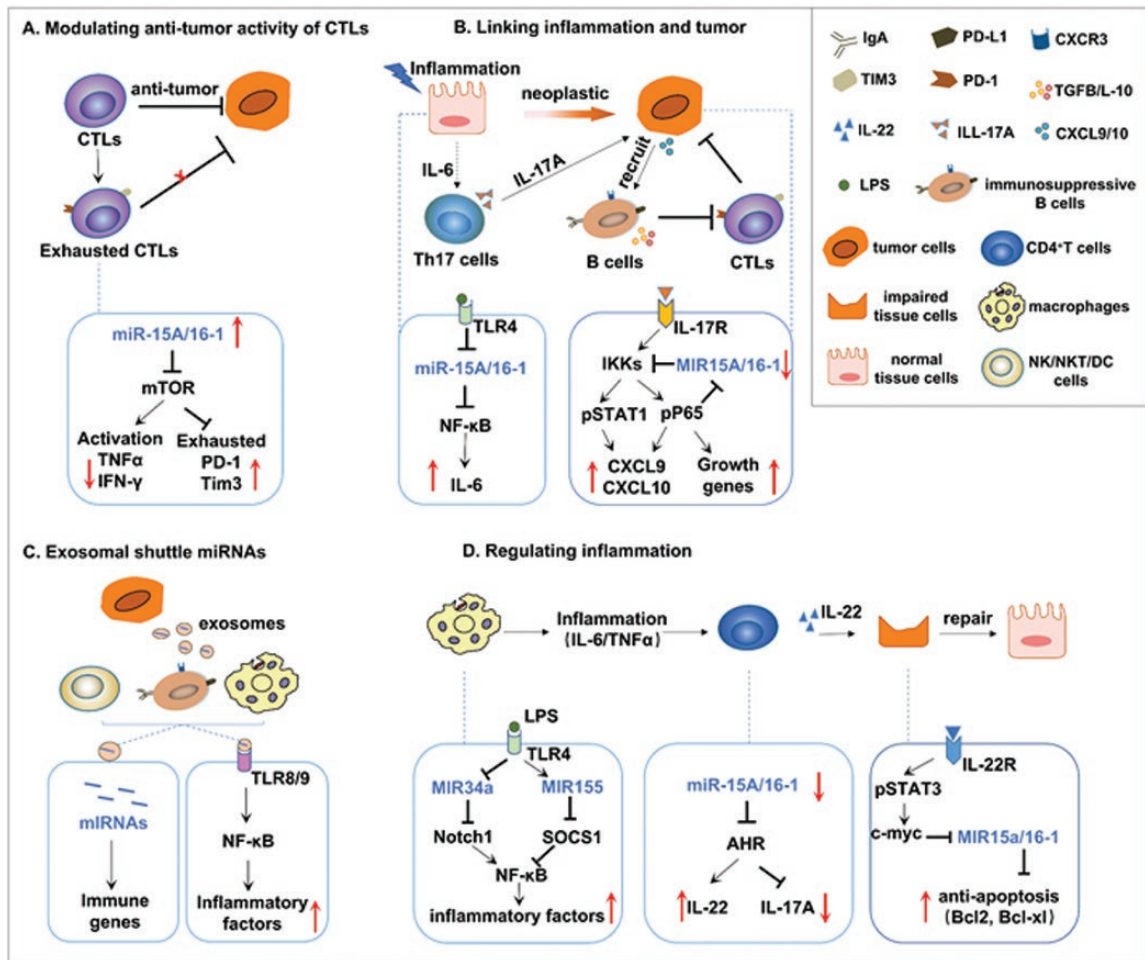


Figure 2 New findings in tumor reveal miRNAs as immune regulators. (A) MiR-15a/16-1 is increased in CD8⁺T cells of glioma tissues, which results in reduction of anti-tumor effect but induction of exhaustion of CD8⁺T cells. mTOR is the key target of miR-15a/16-1 in this process. (B) MiR-15a/16-1 cluster is downregulated in neoplastic epithelial cells, which cause infiltration of immunosuppressive B cells into neoplastic tissues, and subsequent inhibition of anti-tumor effect of CD8⁺T cells. In mechanism, miR-15a/16-1 could inhibit epithelial production of CXCL9 and CXCL10 by targeting I-kappaB kinases (IKKs)-NF-κB/STAT1 signaling. Decrease of miR-15a/16-1 in epithelial cells was triggered by IL-17A, and its decrease can upregulate IL-6 expression in an NF-κB-dependent manner to maintain Th17 cell differentiation. (C) Tumor-derived exosomes transport and delivery miRNAs into tumor infiltrating immune cells, possibly modulating their immunosuppressive function. Several exosomal shuttle miRNAs can act as ligands of Toll-like receptors (TLRs), triggering secretion of tumor-promoting and inflammatory mediators. (D) miRNA function in inflammatory response, and there is an opposite effect on LPS-induced macrophage response between miR-34a and miR-155. Aryl hydrocarbon receptor (AHR) is the direct target of miR-15a/16-1 in CD4⁺T cells. Decreasing miR-15a/16-1 in CD4⁺T cells can ameliorate inflammatory tissue injury in an IL-22-dependent manner. As a synergistic effect, decrease of miR-15a/16-1 level in damaged hepatocytes contributes to IL-22-mediated tissue repair by reducing cell apoptosis and promoting cell proliferation.

MiRNAs modulate anti-tumor activity of tumor-infiltrating immune cells

The role of tumor-related miRNAs in modulating anti-tumor immunity has gained more attention as immunotherapies entering clinic for tumor eradication. MiR-15a and miR-16-1 are previously reported to function by directly regulating tumor cell biology including cell proliferation, cell apoptosis, and cell cycle [27] (Fig. 2A).

Our recent work reveals the novel role of tumor-related miR-15a/16-1 cluster in modulating CD8⁺T cell (CTL)-mediated anti-tumor activity and thereby controlling tumor development [28]. MiR-15a/16-1 was increased in CTLs in mice bearing GL261-derived glioma. The miR-15a/16-1-deficient CTLs in glioma showed higher active phenotypes, more cytokines secretion and faster expansion. They had lower expression of exhausted

markers including PD-1, Tim-3, and LAG-3, but stronger secretion of anti-tumor factors including IFN- γ and TNF- α , indicating more sensitive to immune checkpoint blockade therapy as well as owning more active immune responses. In mechanism, mTOR was identified as the target of miR-15a/16.

Other research has also revealed several miRNAs and their function in tumor-infiltrating T cells. MiR-23a and miR-130/301 display inhibiting effects on CTL immune responses [29, 30]; while, miR-17/92, miR-21, miR-124, and miR-155 can promote the maturation of CTL cells into effector or memory cell subsets [31–36]. For instance, miR-21 could activate CTL cells via the PTEN/Akt pathway in response to stimulations; while upregulating miR-23a reduced CTL expression of anti-tumor effector molecules, including granzyme B and IFN- γ by targeting BLIMP-1 [29]. Additionally, Dudda *et al.* showed that Mir155(-/-) CD8(+) T cells were ineffective at controlling tumor growth, whereas miRNA-155 overexpression enhanced the antitumor response [37]. Moreover, miRNA roles have been also elucidated in regulatory T (Treg) cell biology, with particular attention to miR-124, miR-142-3p, miR-146a, and miR-155, several of which may be regulated by forkhead box P3 (Foxp3) [31, 38–41]. Some of them are involved in balancing effective and regulatory function of tumor-infiltrating T cells to maintain the anti-tumor immune homeostasis, which would provide a new insight in cancer immunotherapy.

Tumor-triggered remodeling of immune microenvironment regulated by miRNAs

Since 2011, inflammation is considered as a hallmark of cancer. Several miRNAs, such as miR-126, miR-21, miR-34, miR-155, miR-146, miR-15, miR-16, and so on have been identified as regulators of inflammatory processes and inflammation-associated diseases [42, 43]. One miRNA plays a role in diverse inflammation-associated diseases [44, 45], and an inflammatory disease is regulated by a pattern of miRNAs [46, 47]. Numerous miRNAs exert function in the regulation of pro-inflammatory and anti-inflammatory pathways, particularly, TLR, NF- κ B, and TGF- β pathways [1, 43, 48]. Some other miRNAs participate in activation of both innate and adaptive immune cells including macrophages, neutrophils, T cells, B cells, and so on [42, 49]. Our recent work identifies new role of miRNAs in modulating innate and adaptive immune response as well as provides new insight in exploring inflammatory injury repair (Fig. 2D).

We proved evidence supporting inflammation-triggered dysregulation of miRNAs. Take miR-15a/16-1

as an example, we identified miR-15a/16-1 as a linker between colitis and colorectal cancer [50]. MiR-15a/16-1 in epithelia cells was downregulated during tumorigenesis and reconstructed the immunosuppressive microenvironment to facilitate tumor progress. More importantly, we found that IL-17 was increased in this process and responsible for the dysregulation of miR-15a and 16-1, which was NF- κ B signaling dependent (Fig. 2B). Similarly, Omrane *et al.* showed that in the immune microenvironment of colorectal tumor, microRNAs including miR-21, miR-146a, and miR-155 belong to the Th17 pathway [51]. Moreover, we reviewed other studies and found that miR-142-5p and miR-130a-3p were regulated by IL-4 and IL-13 in macrophages in chronic inflammation, microRNA-146a was interleukin 1 β responsive in THP-1 cells, and miR-23a could be upregulated by TGF- β in tumors [52–54]. These data suggest that inflammatory mediators are also important factors in triggering miRNAs disorders.

MiRNAs in tumor cells can alter percentage or function of immune cells surrounding to construct the comfortable 'soil' for the growth of the tumor itself. Our reports in colorectal cancer (CRC) illustrated that downregulation of miR-15a/16-1 cluster in neoplastic epithelial cells reconstructed the immunosuppressive microenvironment to facilitate tumorigenesis [50] (Fig. 2B). A decrease of miR-15a/16-1 in epithelia cells caused more tumor-infiltrating B cells. B cells are known as antibody producers and play in humoral immunity, we found a higher immunoglobulin A (IgA) positive in CRC-infiltrating B cells. The IgA⁺B cells highly expressed suppressive factors like IL-10, TGF- β , and PD-L1 and facilitated tumor progress by repressing the proliferation and activation of CD8⁺T cells. Moreover, IgA⁺B cells expressed more CXCR3, which were likely to be recruited by miR-15a/16-deficient tumor cells. In mechanism, I- κ B kinases (IKKs), especially IKKE and IKKB was identified as the targets of miR-15a/16, and overexpressing miR-15a/16-1 in epithelial cells suppressed CXCL9 and CXCL10 secretion by downregulating IKKs expression and the subsequent activation of STAT1 and NF- κ B signaling. Increasing miR-15a/16-1 restrained infiltration of these immunosuppressive B cells into colorectal cancer (CRC), resulting in repression of CRC. The negative correlation between levels of miR-15a/16 and numbers of IgA⁺B cells was found in human CRC tissues; high levels of miR-15a/16 and low numbers of IgA⁺B cells might be indicators for longer survival times of CRC patients. Based on these findings, the use of miRNA mimics to modulate immunosuppressive B cell accumulation is a potential new therapeutic strategy for combatting colorectal cancer.

Similar to this study, other miRNAs were also reported to function in remodeling immune cells in tumor microenvironment. For instance, deregulation of miR-34a in portal vein tumor thrombosis remodeled the tumor microenvironment through manipulation of Tregs [55]; in which, the Treg recruitment chemokine CCL-22 was a target of miR-34a. Upregulating miR-124 in glioma cancer stem cells (gCSC) reversed gCSC-mediated immunosuppression of T-cell proliferation and induction of Foxp3⁺Treg [31]. Additionally, miR-126/126* pair was reported to be able to modulate the composition of the microenvironment of primary tumors in order to contrast breast cancer metastasis by regulating CCL2 expression of cancer cells in an SDF-1 α -dependent manner [56].

In addition to affecting the recruitment of immune cells, miRNAs in tumors can alter the immune cells surrounding by targeting checkpoints, of which, PD-L1 is the outstanding target. The relationships among miRNAs, PD-L1, and tumor-infiltrating lymphocytes have been investigated. In acute myeloid leukemia, tumor suppressor MiR-34a targeted PD-L1 and functioned as a potential immunotherapeutic target [57]. Overexpression of miR-142-5p could also inhibit PD-L1 expression on tumor cells, which resulted in the increase of IFN- γ and TNF- α secreting CD8⁺ T lymphocytes [58]. Moreover, by targeting PD-L1, the suppressive role of miR-140 was associated with the increased infiltrating of cytotoxic CD8⁺ T cells and the decreased infiltrates of myeloid-derived suppressive cells and regulatory T cells [59]. Other microRNAs including miR-574, miR-570, miR-513, miR-197, miR-34a, and miR-200 have also been proven to negatively regulate PD-L1, as a novel role of pro-survival signaling in cancer [60].

Exosomal shuttle miRNAs involve in crosstalk between tumor cells and immune cells

MiRNAs in the tumor can also be transferred from tumor cells to the surrounding immune cells, thus changing the immune response, in which, exosomes are the important carrier and transporter. Exosomes are 30–100 nm in diameter, with a classic ‘cup’ or ‘dish’ morphology, contain proteins and genetic messages like mRNAs, DNA fragments, and microRNAs [61]. These exosomal shuttle miRNAs can be shuttled from a donor cell to recipient cells to affect their activation and function [62]. Our recent ongoing research in colorectal cancer showed miRNA profiles in tumor-derived exosomes (TEX) were distinguished with that from normal epithelia cells. The up-regulated miRNAs like miR-135b, miR-146a, and miR-150 were enriched in tumor infiltrating B cells,

possibly modulating their immunosuppressive function (Fig. 2C). Tumor-immune crosstalk can be mediated by soluble factors (contact-independent) and ligand-receptor pairs (contact-dependent).

As support, Zhou *et al.* found that exposure of dendritic cells (DCs) to pancreatic cancer derived exosomes caused downregulation of TLR4-induced production of cytokines necessary for the maturation and function of DCs, for which, miR-203 secreted into exosomes was responsible [63]. Moreover, other TEX miRNAs, including miR-212-3p, miR-451, miR-214, miR-92a, miR-210, and miR-23a have been also reported to regulate tolerance of DCs, T cell differentiation and NK-/NKT cell-mediated cytotoxicity [64]. Other new evidence shows that miRNA transported by TEX can act as TLR's ligands. For instance, oncogene miR-21 and miR-29a secreted into exosomes by NSCLC cell or neuroblastoma could bind to Toll-like receptors TLR7 and TLR8, triggering the secretion of pro-metastatic inflammatory cytokines [65]. Moreover, taking miR-210, miR-23a, and miR-451 as examples, release of TEX-miRNAs might be triggered by the hypoxic or glucose-deficient tumor microenvironment [66–68].

Clinical potential of miRNAs in modulating cancer immunotherapy

Potential in predicting cancer survival and sensitizing chemotherapy

MiRNAs have shown exciting potential application in predicting survival and cancer therapy. We found that tumor-suppressive miR-126 was of lower level in esophageal cancer tissues, which was correlated with short survival time of patients, implying their potential function as a prognosis indicator [20]. Notably, research from Jian Zhou *et al.* with independent validation in a large cohort of 934 participants identified a microRNA panel (miR-122, miR-192, miR-21, miR-223, miR-26a, miR-27a, and miR-801) that provided a high diagnostic accuracy of HCC [69].

MiRNAs in tumors, such as miR-221/222, miR-328, miR-326, and miR-34a have been reported to alter chemosensitivity of cancer cells [70]. We found miR-7 was upregulated in paclitaxel (PTX)-treated NSCLC cells and identified increasing miRNA-7 sensitizes NSCLC cells to PTX therapy by targeting EGFR [71]. Similarly, Exosomes containing miR-122 combined with sorafenib treatment and significantly reduced HepG2 tumors [72]. These results provide evidence supporting for altering endogenous level of miRNAs may be a potential therapeutic strategy for adjuvant chemotherapy of cancer, and exosomes may be used as a carrier.

Potential in modulating cancer immunotherapy

In recent years, the research of microRNA connected with immunotherapy is heated and achieved remarkable results. The discovery and clinical application of PD-1 and CTLA-4 successfully caught people's attention to ICB immunotherapy and opened a new era of immunotherapy (Fig. 3). So far, the inhibitory immune signals found on the surface of T cells include CTLA-4, PD-1, LAG-3, TIM-3, VISTA, BTLA, and so on. Although ICB has led to important clinical advances and achieved great success because of the durable responses and enhancement of survival rates in skin cancer, lung cancer, kidney cancer, and so on, many clinical studies indicated that there are still a large number of patients showing no response and resistant to the treatment. Therefore, it is necessary to find efficient predictive biomarkers for better patient selection, and prognostic biomarkers to measure the outcomes.

Mir-33a with tumor-suppressive ability directly interacts with 3'UTR in mRNA of PD-1 and PD-L1 leading to decreasing the expression of the two genes. Boldrini *et al.* identified that patients suffering lung cancer would have a favorable outcome with a low level of PD-1 and high expression of miR-33a indicating that the potential of miR-33a is a good prognostic biomarker [73]. In contrast with miR-33a, miR-20b, miR-21, and miR-130b are oncogenic and overexpressed in colorectal cancer cells (CRC). Overexpressed miR-20b, miR-21, and miR-130b inhibit the expression of PTEN, a PI3K/AKT

signaling pathway suppressor, which in turn upregulates PD-L1 achieving tumorigenesis [74]. Therefore, the three microRNAs seem to indirectly regulate PD-L1. Among them, miR-21 relying on the character of circulating in blood is more favored by people, and can be seen as a potential noninvasive predictive biomarker in tumor immunotherapy [75].

Moreover, miRNA can be the therapeutic target to enhance the efficiency in ICB immunotherapy dependent on their interaction with immune checkpoints. There are seven tumor suppressor microRNAs targeting PD-L1 including miR-34a, miR-200, miR-570, miR-513, miR-138-5p, miR-424-5p, and miR-197 which can be the immune checkpoint inhibitors. They all suppress expression of PD-L1, suggesting that delivering these microRNAs or their mimics can enhance immune response for tumor to reach the therapeutic aim [76–80]. In addition, miRNA has functions to impede tumor immune escape, but also prevent metastasis. miR-200 is known as a repressor of EMT (epithelial-mesenchymal transition through, a critical driver for metastasis) by negatively regulating ZEB1 and ZEB2 (E-cadherin Transcriptional Repressors), as well as can directly modify PD-L1 expression in tumor cells [81]. For mesothelioma patients, low levels of miR-200 have been identified to related to high PD-L1 levels and poor prognosis, suggesting the potency for prediction [82, 83]. And the same situation appears in NSCLC and indicates that early-stage NSCLC patients with the expression of miR200/PD-L1 axis may be beneficial

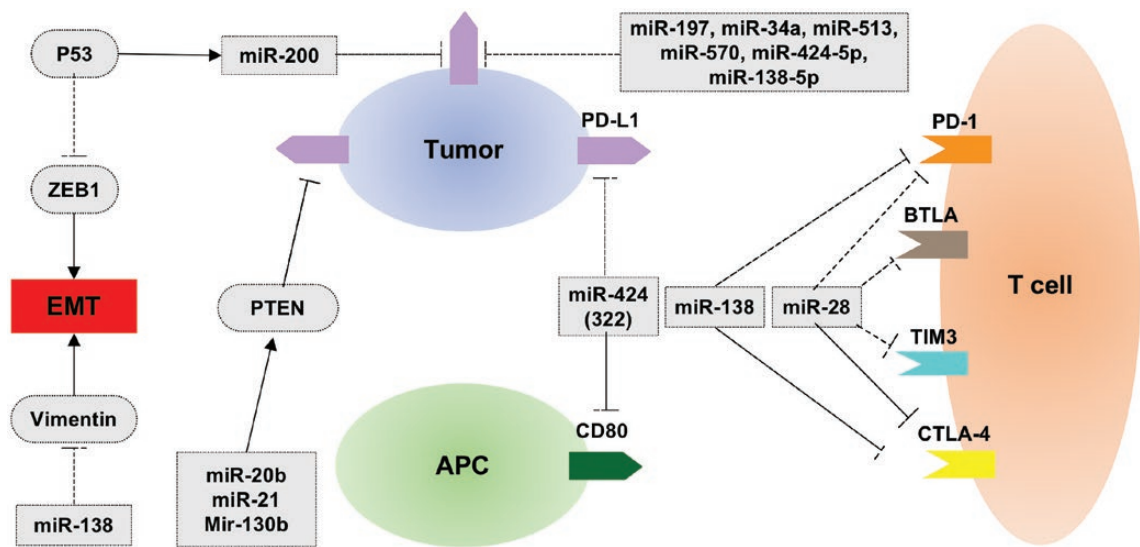


Figure 3 The application of miRNAs in immune checkpoint blockade immunotherapy. The immune checkpoints on the surface of T cells and their ligands expressed on tumor cells or APCs are all modulated by miRNAs. The illustration shows the relationship between these miRNAs and their targets. T type dotted line indicates suppression; black solid arrows indicate upregulation.

Table 1 The clinical values of MicroRNA include predictive, prognostic, and therapy in immunotherapy

| Application | MiRNAs | Cancer type | Effect of MiRNAs | References |
|------------------|--------------------|---|--|--|
| Predictive value | miR-18b | Hepatitis C virus-related | Serum miRNA-27a and miRNA-18b are correlated with metastasis and outcome. | [89] |
| | miR-27a | Hepatocellular carcinoma | | |
| | miR-21 | Hepatocellular carcinoma | MiR-21 enhances resistance to IFN- α and 5-FU therapy. | [90] |
| | miR-26a | Cholangiocarcinoma | Serum miR-26a is related with metastasis of CCA. | [91] |
| | miR-122 | Hepatocellular carcinoma | Low level of MiR-122 predicts a weak immune response to IFN therapy. | [92] |
| | miR-125b | Rectal adenocarcinoma | High level of tissue and serum miR-125b suggests poor efficiency of treatment in Locally Advanced Rectal Cancer. | [93] |
| | miR-216a | Glioblastoma | High level of miR-216 predicts longer survival after DC vaccination immunotherapy. | [94] |
| | miR-216b | | | |
| | miR-3753p | Ovarian clear cell carcinoma | Serum miR-3753p, miR-193a-5p, and miR-1228-5p indicate immune response after GPC3 vaccine therapy. | [95] |
| | miR-193a-5p | | | |
| | miR-1228-5p | | | |
| | miR-6826 | Metastatic colorectal cancer | Plasma miR-6826 and miR-6875 are negative biomarkers to evaluate vaccine treatment. | [96] |
| | miR-6875 | | | |
| | Prognostic value | MiR-15a/16 | Colorectal cancer | Reduction of MiR-15a/16 relates poor prognosis |
| miR-17-5p | | Metastatic melanoma | MiR-17-5p upregulates PD-L1, causing resistant to BRAFi or MEKi. | [97] |
| miR-26 | | Hepatocellular carcinoma | High miR-126 expression relates to longer overall survival. | [98] |
| miR-33a | | Lung adenocarcinoma | MiR-33a via PD-1/PD-L1 regulation becomes a positive prognostic marker in lung cancer. | [73] |
| miR-129 | | Bladder Cancer | High expression of miR-129 is related to poor outcome. | [99] |
| miR-138-5p | | Colorectal cancer | Low level miR-138-5p is related with short survival. | [100] |
| miR-142-5p | | Pancreatic cancer | Overexpression of miR-142-5p promotes anti-cancer immune response through inhibiting PD-1/PD-L1 pathway. | [58] |
| miR-148a-3p | | Breast cancer | Low level of miR-148/152 family suggests poor outcome and survival. | [101] |
| miR-148b-3p | | | | |
| miR-152-3p | | | | |
| miR-323 | | Glioblastoma multiforme | High expression of miR-326/miR-130a predict good outcome; low expression of miR-323/miR-329/miR-155/miR-210 predict long survival. | [102] |
| miR-326 | | | | |
| miR-329 | | | | |
| miR-1-130a | | | | |
| miR-155 | | | | |
| miR-210 | | | | |
| miR-218-5p | Gallbladder cancer | Low expression of miR-218-5p related to poor outcome. | [103] | |
| miR-200 | Mesothelioma | Low levels of miR-200 related to high PD-L1 levels and poor prognosis, suggesting the potency for prediction. | [83] | |

Table 1 Continued

| Application | MiRNAs | Cancer type | Effect of MiRNAs | References |
|-------------------|----------------------|--|--|------------|
| Therapeutic value | miR-23a | Melanoma | MiR-23a delivers a miRNA-targeting method to increase CTL cytotoxicity and keeps immune response. | [29] |
| | miR-29b | Colorectal cancer | MiR-29b inhibits CRC growth and metastasis. | [104] |
| | miR-34a | Lung cancer | MRX34, an engineering agent consisting of miR34a mimics and liposomal nanoparticle, inhibits PD-L1 expression. | [105] |
| | miR-93 | Lymphocytic Leukemia | MiR-93 and miR-106b mimics decrease CXCL12 and PD-L1 expression. | [106] |
| | miR-106b | | | |
| | miR-124 | Glioma | MiR-124 promotes efficiency of adoptive T cell transfer | [31] |
| | miR-138-5p | Colorectal cancer | MiR-138-5p mimics enhances therapeutic efficiency. | [100] |
| | miR-146a | Hepatocellular carcinoma | MiR-146a inhibits sensitivity against IFN- α cytotoxic effects. | [107] |
| | miR-148a | Melanoma | miR-148 inhibitors as adjuvants induce CTL response. | [108] |
| | miR-155 | Lymphoma | MiR-155 induces lymphangiogenesis by targeting NKTL cells. | [109] |
| | miR-182 | Hepatocellular carcinoma | MiR-182 expression activates NK cells. | [110] |
| Let-7 | Colorectal carcinoma | let-7a decrease immunocompetence by T cells. | [111] | |

from utilizing miR-200 mimics to block PD-L1 [77, 83]. Moreover, miR-200 has the ability to impede tumor immune escape via activating P53 by targeting zinc-finger E-box-binding homeobox 1. miR-138 also has the function in preventing metastasis by lowering vimentin expression, and can inhibit the expression of PD-1 and CTLA-4 on the surface of effector and regulatory T cells [84]. Wei *et al.* administered miR-138 to murine gliomas and observed tumor shrinking, the phenomenon continued even after stopping delivering miR-138, indicating the therapeutic effect of miR-138 [85]. In ovarian cancer, miR-424(322) expression is not only inverse association with PD-L1 and CD80, but also highly related to chemoresistance. miR-424 overexpression attenuated CD80/CTLA-4 signaling pathway via inhibiting CD80 levels on antigen presenting cells, especially dendritic cells (DCs), thereby reversing the sensitivity of epithelial ovarian carcinoma and promoting T cell immune response and anti-cancer effect [77, 86]. MiR-28 is an Intriguing tumor-suppressive miRNA which was found in exhausted PD-1⁺ T cells and caused concern because of the 30% reducing expression in melanomas. After research, miR-28 shows ability to restore the function of T cells to secrete cytokines IL-2 and TNF- α by blockage PD-1, CTLA-4, TIM3, and BTLA, demonstrating the potency to be the cancer therapeutic target [87]. The clinical values of other miRNA are shown in Table 1.

Conclusion

Given that both miRNAs and immune system function in a variety of physiological and pathological processes, considering this point, it is not surprising that miRNAs function as cancer immune modulators. Altered profiles of miRNAs have been reported in multiple cancers, and identified as tumor suppressor or oncogenic depending on their targets. More importantly, tumor-miRNAs affect tumorigenesis not only directly by regulating tumor cell biology including cell proliferation apoptosis and cell cycle, but also by modulating anti-tumor immunity, and linking the crosstalk between tumor cells and immune cell. Moreover, accumulating evidence has also explained the mechanisms underlying dysregulation of tumor-related miRNAs, in which, we found that persistent inflammatory stimulation is the key inducer, and epigenetic modulations including DNA methylation, histone acylation, and even posttranslational modifications are involved. Together, they form a complex epigenetic network in tumor. Due to their significant function, some of miRNAs have been highlighted as indicators of tumor prognosis, or as potential modulators in cancer immunotherapy. MRX34, the first replacement therapy based

on miRNA, is a liposomal-nanoparticle-based miR-34a mimic that has entered into Phase I clinical trial for liver cancer treatment and displayed some bright and promising responses, however, finally withdrawal the drug from the trial due to general toxicity. Therefore, another important aim of miRNA therapy is to develop a safe and powerful delivery vector system [77, 88].

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Author contributions

Y.X.: Data curation, formal analysis, methodology, visualization, writing original draft, writing review, and editing. Z.W.: methodology, resources, software, writing review, and editing. Z.L., J.X., Z.X., and M.J.: methodology, software, and visualization. R.L. and Y.C.: Conceptualization, funding acquisition, project administration, supervision, writing and reviewing, and editing.

Conflict of interest

The authors have declared that no conflict of interest exists.

Data availability

No new data were generated or analyzed in support of this research.

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