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REVIEW

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Unraveling the interplay of CD8 + T cells and microRNA signaling in cancer: implications for immune dysfunction and therapeutic approaches

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Abstract

MicroRNAs (miRNAs) emerge as critical regulators of CD8 + T cell function within the complex tumor microenvironment (TME). This review explores the multifaceted interplay between miRNAs and CD8 + T cells across various cancers. We discuss how specific miRNAs influence CD8 + T cell activation, recruitment, infiltration, and effector function. Dysregulation of these miRNAs can contribute to CD8 + T cell exhaustion and immune evasion, hindering anti-tumor immunity. Conversely, manipulating miRNA expression holds promise for enhancing CD8 + T cell activity and improving cancer immunotherapy outcomes. We delve into the role of miRNAs in CD8 + T-cell function across different cancer types, including gliomas, gastric and colon cancer, oral squamous cell carcinoma, thyroid carcinoma, lymphomas, melanoma, breast cancer, renal cell carcinoma, ovarian cancer, uterine corpus endometrial cancer, bladder cancer, acute myeloid leukemia, chronic myelogenous leukemia, and osteosarcoma. Additionally, we explore how extracellular vesicles and cytokines modulate CD8 + T-cell function through complex interactions with miRNAs. Finally, we discuss the potential impact of radiotherapy and specific drugs on miRNA expression and CD8 + T-cell activity within the TME. This review highlights the immense potential of targeting miRNAs to manipulate CD8 + T-cell activity for the development of novel and improved cancer immunotherapies.

Highlights

- MiRNAs act as critical regulators of CD8+ T cell function within the tumor microenvironment (TME).
- Dysregulation of these miRNAs can lead to T cell exhaustion and immune evasion, compromising the body's ability to fight cancer.
- Manipulating miRNA expression offers a promising avenue for enhancing CD8+ T cell activity and improving cancer immunotherapy outcomes.
- Targeting miRNAs that regulate exhaustion markers, such as PD-1 and TIM-3, holds promise for reinvigorating exhausted CD8+ T cells and unleashing their anti-tumor potential.
- Developing effective delivery systems, such as nanoparticles or engineered T cells, for miRNA-based therapies within the TME is crucial for maximizing efficacy and minimizing off-target effects.

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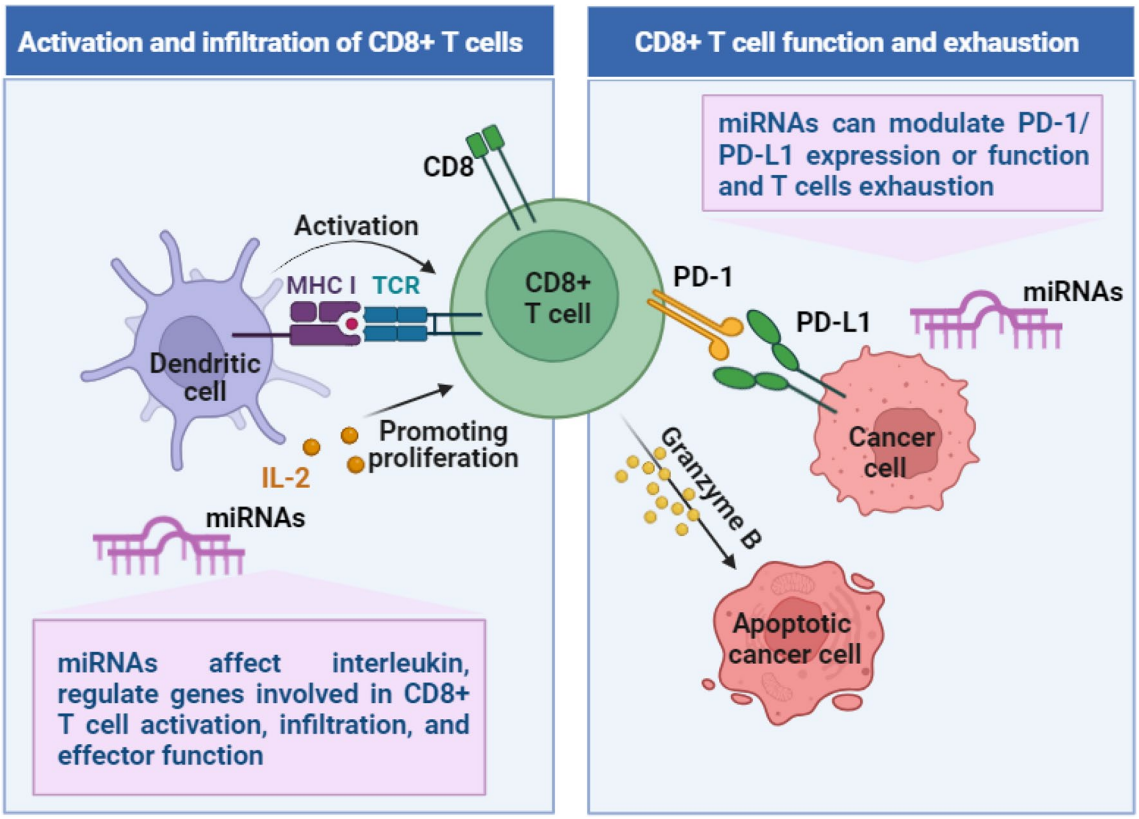
Keywords MicroRNAs (miRNAs), CD8 + T-cells, Tumor microenvironment (TME), Cancer, Extracellular vesicles, Cytokines, Radiotherapy, Drug therapy

Graphical Abstract



Introduction

CD8 + T-cells, which are cytotoxic T lymphocytes (CTLs), play a pivotal role in mounting an effective immune response against cancer and are strongly associated with positive clinical outcomes in various tumors, including breast, colorectal, ovarian, and pancreatic cancer. The cytotoxic function of CD8 + T-cells is attributed to their ability to produce the serine protease granzyme B, which induces apoptosis in target cells by disrupting cellular integrity. Furthermore, perforin pores facilitate the release of granzyme B from CD8 + T-cells, enabling its assault on target cells [1]. The effectiveness of cancer treatment using immune checkpoint inhibitors, including programmed cell death 1 ligand (PD-1) inhibitors, depends on the extent of CD8 + T-cell infiltration within tumors. CD8 + T-cells are fundamental to cancer immunotherapy, which aims to inhibit suppressive immune receptors and rejuvenate impaired T-cells. Dendritic cells play a significant role in activating, recruiting, and infiltrating CD8 + T lymphocytes within the tumor microenvironment (TME) by presenting tumor antigens through major histocompatibility class I (MHC-I) molecules [2]. The proliferation and preservation of activated CD8 + T-cells in an effector cytolytic state heavily depend on interleukin-2 (IL-2). Elevated levels of IL-2 can lead to the proliferation of CD4 + regulatory T (Treg) cells, which, when combined with other immunosuppressive cells, can transition of active CD8 + T-cells into a dysfunctional exhausted state. Maintaining a delicate equilibrium of IL-2 within the tumor microenvironment (TME) is vital for preserving the cytolytic function of anti-tumor CD8 + T-cells. However, the precise mechanisms that affect the activation, recruitment, and infiltration of these cells are not yet fully comprehended [3–5]. Recent advances in immuno-oncology have brought

about significant transformations in cancer treatment, enhancing effectiveness and offering personalized treatment alternatives. Nonetheless, the durability of positive responses may be limited, and side effects might necessitate the discontinuation of treatment, highlighting the ongoing need to continually improve treatment strategies. MiRNAs, known as microRNAs, are a group of endogenous non-coding RNA molecules that consist of 18–23 nucleotides. They can directly bind to the 3'-UTRs (3' untranslated regions) of target genes, leading to gene degradation or regulation of gene expression post-transcription. Extensive research has provided substantial evidence highlighting the significant association between miRNAs and various aspects of tumor biology, including tumor initiation, development, invasion, and metastasis [6–8]. Due to their ability to function without requiring exact base pairing, miRNAs can regulate a broad network of genes. They have also been observed to govern critical biological processes such as hematopoiesis, apoptosis, and cell proliferation. Consequently, the important role of miRNAs in tumor diagnosis and targeted therapy is garnering increasing attention [9, 10]. The use of miRNAs as therapeutic agents has gained considerable interest in cancer immunotherapy [11]. Additionally, miRNAs play a crucial role in regulating target mRNAs with complementary sequences. Through this mechanism, miRNAs can significantly influence specific biological pathways by simultaneously targeting multiple mRNAs within the same pathway. Consequently, miRNAs have the potential to exert substantial posttranscriptional control over cellular state, differentiation, and function. The expression of miRNAs undergoes dynamic regulation during the T-cell maturation, contributing to the developmental fitness of CD8 + T-cell precursors. However, current knowledge regarding the involvement of miRNAs in CD8 + T-cell differentiation primarily focuses on the differentiation of effector and memory subsets [12, 13].

In this regard, this review aims to comprehensively analyze the interplay between CD8 + T-cell dysfunction and miRNA-mediated regulatory mechanisms in cancer. It will explore how these interactions contribute to immune evasion and impact potential therapeutic strategies. The novelty of this work lies in its focus on the understudied area of miRNA involvement in CD8 + T-cell dysfunction within TME. By delving into the specific mechanisms by which miRNAs regulate CD8 + T-cell activation, recruitment, infiltration, and effector function, the review seeks to identify novel therapeutic targets that could improve the efficacy and durability of current cancer immunotherapies. This focus on the intricate interplay between CD8 + T-cells and miRNAs has the potential to pave the way for the development of more effective and personalized treatment approaches for various cancers.

MicroRNAs: regulating the fate of CD8 + T-cells in cancer immunity

The efficacy of CD8 + T-cell-mediated immune responses against tumors depends on establishing durable memory populations and preventing effector cell exhaustion. Although checkpoint blockade therapy has shown promise in reversing CD8 + T-cell exhaustion and improving anti-tumor outcomes, it falls short in generating effector cells with long-term memory potential. In vivo mouse models have demonstrated that let-7 miRNAs regulate the fate of CD8 + T-cells. Sustained expression of let-7 miRNAs promotes the formation of memory CD8 + T-cells and facilitates tumor clearance. The role of let-7 is associated with the preservation of metabolic homeostasis during T-cell activation, thereby maintaining the multipotency of effector cells rather than promoting their terminal differentiation. These findings shed light on the crucial role of let-7 miRNAs in determining CD8 + T-cell fate and provide insights into potential strategies for enhancing memory T-cell responses in cancer immunotherapy [14].

Persistent antigens during chronic infections or cancer can cause exhaustion and reduced protective capacity in CD8 + T-cells, which are crucial for defending against pathogens and tumors. MicroRNAs (miRs) have been found to play a role in CD8 + T-cell responses, and among them, miR-29a has been identified as a critical regulator of T-cell exhaustion (TEX). By enforcing the expression of miR-29a, the responses of CD8 + T-cells can be improved, and exhaustion can be counteracted through the inhibition of exhaustion-driving pathways and the regulation of ribosomal biogenesis. This discovery highlights the significance of miR-29a as a key regulator of TEX and sheds light on its ability to redirect exhaustion toward a more advantageous state [12].

The miR-15a/16 gene cluster, present on both human and mouse chromosomes, plays a role in cancer progression and immune modulation. A recent study demonstrated that elevated levels of miR-16 suppressed the expression of NKG2D in CD8 + T-cells, resulting in an increased abundance of these cells in miR-15/16-/- mice. CD8 + NKG2D + T-cells obtained from miR-15/16-/- mice exhibited a stimulatory phenotype characterized by heightened interferon (IFN)-γ production and enhanced cytotoxicity. Additionally, the reduced levels of miR-16 in CD8 + T-cells of miR-15/16-/- mice indicated its involvement in inflammation regulation. These findings suggest that gene therapy strategies employing miR-16 overexpression might hold potential for treating patients with inflammatory conditions [15].

miR-155 enhances the anti-tumor capabilities of CD8 + T-cells by preventing them from undergoing senescence and exhaustion. This is achieved through the epigenetic suppression of factors that drive terminal differentiation. miR-155 indirectly boosts the activity of the Polycomb repressor complex 2 (PRC2) by promoting the expression of Phf19, a factor associated with PRC2. This is accomplished by reducing the levels of Ship1, an inhibitor of Akt. This regulatory pathway plays a role in regulating the differentiation of CD8 + T-cells, thereby opening up new possibilities for enhancing cancer immunotherapy by manipulating the epigenetic programming of CD8 + T-cell fate [16].

The involvement of miR-150 in the maturation of memory CD8 + T-cells is of significant importance. Inhibiting miR-150 was found to expedite the differentiation process of CD8 + T-cells into memory cells. This acceleration was accompanied by improved production of effector cytokines, enhanced recall response, and increased protection against infections. During the early activation phase, the levels of Forkhead box protein O1 (FoxO1) and T-cell factor 1 (TCF1) increased, and miR-150 directly targeted and suppressed FoxO1. These findings suggest that the suppression of FoxO1 by miR-150 plays a regulatory role in balancing the differentiation of CD8 + T-cells into effector and memory cells. This knowledge holds potential implications for vaccine development and the field of T-cell therapeutics [17]. miR-21 with recognized oncogenic properties, also plays a key role in regulating immune responses targeting tumors. The absence of miR-21 resulted in decreased cell proliferation, diminished cytokine production, and inhibited tumor growth. Additionally, the knockout of miR-21 activated CD4 + and CD8 + T-cells through the Phosphatase and TENsin homolog (PTEN) / phosphatidylinositol 3-kinase (Akt) pathway [18].

There is a molecular connection between epithelial-to-mesenchymal transition (EMT) and the immunosuppressive effects of CD8 + tumor-infiltrating lymphocytes (TILs), two critical factors in cancer advancement. MicroRNA-200 specifically targets programmed cell death 1 ligand 1 (PD-L1), a self-regulating agent that suppresses EMT and the spread of cancer. However, Zinc finger E-box binding homeobox 1 (ZEB1), an activator of EMT and a transcriptional repressor of miR-200, counteracts the repression of miR-200, resulting in immunosuppression of CD8 + T-cells and the promotion of metastasis [19].

The aberrant expression of Kinesin family member 2 C (KIF2C), a vital component in regulating mitosis, has been detected in different types of tumors, implicating its involvement in diverse tumor regulatory processes. Elevated levels of KIF2C have been linked to increased tumor cell motility, invasiveness, resistance to chemotherapy, and impaired DNA damage repair. Additionally, there is a notable association between KIF2C and microRNAs, as well as the infiltration of CD8 + T-cells within the tumor microenvironment. These findings highlight the potential of targeting KIF2C for the development of anti-cancer drugs and emphasize its significance in tumor biology and immune responses [8, 20]. The reviewed publications convincingly establish miRNAs as essential regulators of CD8 + T-cell responses in the tumor microenvironment. Emerging evidence suggests that manipulating miRNA expression could be a promising therapeutic strategy to enhance anti-tumor immunity. The studies discussed elucidate the molecular mechanisms underlying miRNA-mediated T-cell regulation, providing valuable insights into the potential of miRNA-based interventions.

While the studies discussed highlight the correlation between miRNA expression and T-cell phenotype, a deeper mechanistic understanding of how miRNAs exert their effects is often lacking. Future research should focus on elucidating the specific target genes and signaling pathways regulated by these miRNAs. Although miRNA-based therapeutics hold promise, challenges related to delivery, specificity, and potential off-target effects need to be addressed. Developing safe and effective miRNA-based interventions will require careful optimization and clinical evaluation.

Gastric cancer (GC)

The research study provides evidence supporting the downregulation of miR-128-3p in GC, which contributes to enhanced cell growth. The findings indicate an inverse correlation between miR-128-3p expression and the enrichment of tumor-infiltrating lymphocytes, with lower expression levels associated with poorer overall survival in GC patients. Nevertheless, in cases where the quantity of CD8 + T-cells was diminished, the increased expression of miR-128-3p exhibited a practical impact on the prognosis of GC. Additionally, the study identified IL-16 as a direct target of miR-128-3p, suggesting its potential as a therapeutic target for immunotherapy in GC [21]. Additionally, it was found that the tumor-suppressing function of miR-140 in GC was linked to higher levels of infiltrating cytotoxic CD8 + T-cells and decreased infiltration of myeloid-derived suppressive cells and regulatory T-cells [22].

miR-105-5p, acting as a transcription factor, directly targets a crucial cis-acting region within the 3′UTR of PD-L1. This targeting leads to downregulation of PD-L1 expression and subsequently facilitates the activation of CD8 + T-cells. This investigation is the first to highlight the involvement of miR-105-5p in cancer immune

surveillance. Notably, the overexpression of PD-L1 in AGS cells of GC hindered the activation of CD8 + T-cells. However, this inhibitory effect was partially reversed when miR-105-5p mimics were introduced via transfection [23].

Chronic gastric inflammation leads to an increase in the expression of miR-155, making patients more susceptible to the development of GC. MiR-155 is found at high levels in activated B and T-cells, as well as in monocytes and macrophages. MiR-155 decreases the expression of specific DNA mismatch repair (MMR) genes. In CD8 + T-cells lacking miR-155 that are present within tumor tissues, the use of antibodies against immune checkpoint proteins helps revive the expression of several miR-155 targets that were previously suppressed. This indicates that miR-155 may regulate similar pathways that contribute to enhancing the body's immune response against tumors [24, 25].

Lymph node metastasis (LNM) poses a significant challenge to the prognosis of gastric cancer, particularly in patients infected with Helicobacter pylori, as it is associated with increased lymphangiogenesis and immunosuppression within the lymph nodes. Recent research has identified miR-1246, which is highly expressed in plasma small extracellular vesicles (sEVs), as a promoter of lymphangiogenesis and remodeling in gastric cancer patients. This discovery suggests that miR-1246 could serve as a potential biomarker and therapeutic target for gastric cancer with lymph node metastasis (GC-LNM). Mechanistically, miR-1246 exerts its effects by suppressing Glycogen synthase kinase-3 beta (GSK3β) expression, thereby promoting the expression of β-Catenin and matrix metalloproteinase 7 (MMP7), while also inducing apoptosis of CD8 + T-cells [26, 27]. Table 1 highlights the diverse roles of specific miRNAs in GC, their effects on CD8 + T-cells, and their potential as therapeutic targets for immunotherapy and prognosis improvement in GC.

Colorectal cancer (CRC)

The researchers observed that the increased expression of Indoleamine 2,3-dioxygenase 1 (IDO1) significantly impacted the growth of xenograft tumors in BALB/c mice. Additionally, they uncovered the role of post-transcriptional regulation in IDO1 in colon cancer. The tumor-suppressive miRNA, miR-448, exerts a substantial inhibitory effect on the expression of IDO1 protein, thereby suppressing the apoptosis of CD8 + T-cells through the suppression of IDO1 enzyme activity. These findings provide a valuable theoretical foundation for the developing of novel immunotherapy strategies for the treatment of colon cancer [28, 29].

Tumor necrosis factor receptor type 2 (TNFR2) plays a crucial role in the activation, expansion, and stability of CD4 + forkhead box P3 (FoxP3) + Tregs, which contribute to immune evasion in tumors.

Tumor necrosis factor receptor 2 (TNFR2) is also expressed by effector CD8 + T-cells and is involved in their cytotoxic capabilities and apoptosis during the initial immune response. However, high expression of TNFR2 on cytotoxic CD8 + T-cells may diminish their effectiveness in combating tumors. The microRNA miR-125b-5p, which directly targets TNFR2, has the potential to counteract this effect. Treatment with Ago-125b-5p resulted in reduced TNFR2 expression on CD8 + T-cells in mice with colon tumors, thereby enhancing the effector function of CD8 + CTLs [30].

In CRC, miR-148a-3p has emerged as a probable regulator of calnexin (CANX) and exhibits tumor-promoting properties by targeting the CANX/MHC-I axis. Interestingly, higher expression of CANX in tumors has been

Table 1 The different miRNAs and their roles in gastric cancer including their effects on CD8 + T-cells and potential therapeutic implications

miRNA	Role in gastric cancer	Effect on CD8 + T-cells	Therapeutic potential	Refs.
miR-128-3p	Downregulated	Inverse correlation with tumor-infiltrating lymphocytes; Practical impact on GC prognosis in decreased CD8 + T-cell quantity	Potential therapeutic target for immunotherapy in GC; Direct targets IL-16	[21]
miR-140	Upregulated	Higher levels of infiltrating cytotoxic CD8 + T-cells; Decreased infiltration of myeloid-derived suppressive cells and regulatory T-cells	Tumor-suppressing function	[22]
miR-105-5p	Downregulated	Facilitates activation of CD8 + T-cells	Directly targets PD-L1; Regulator of cancer immune surveillance	[23]
miR-155	Upregulated	Antibodies against immune checkpoint proteins help revive the expression of miR-155 targets in CD8 + T-cells within tumor tissues	Potential regulator of pathways enhancing the immune response against tumors	[24]
miR-1246	Upregulated	Induces apoptosis of CD8 + T-cells; Suppresses GSK3β expression; promotes β-Catenin and MMP7 expression	Potential biomarker and therapeutic target for GC-LNM; Promoter of lymph angiogenesis and remodeling in GC-LNM	[25]

associated with improved overall survival in colorectal cancer patients. Moreover, inhibition of miR-148a-3p leads to the restoration of surface levels of MHC-I and enhances the efficacy of CD8 + T-cell-mediated immune responses. These findings suggest that targeting the miR-148a-3p/CANX/MHC-I pathway holds promise as a rationale for immunotherapy approaches in CRC patients [31]. Elevated levels of circRNF216 have been shown to suppress metastasis and function as a competitive endogenous RNA by sequestering miR-576-5p, thereby relieving its repression on the target gene ZC3H12C. By upregulating ZC3H12C, there is an enhancement in the infiltration of CD8 + T-cells, leading to the ultimate inhibition of CRC progression. These findings highlight circRNF216 as a promising therapeutic target and diagnostic marker for CRC, indicating its potential in developing novel therapeutic strategies and improving the early detection of CRC [32]. Furthermore, in CRC, the levels of HCG18 and PD-L1 were increased, whereas miR-20b-5p was decreased. HCG18, therefore played a role in advancing tumor growth, causing resistance to cetuximab treatment, and suppressing the activity of CD8 + T-cells through the miR-20b-5p/PD-L1 pathway [33].

Researchers have been investigating ways to disrupt the activation of tumor-associated macrophages (TAMs) or reprogram them into tumor-suppressive types due to their critical role in tumor growth and spread. They discovered that the administration of miR-1246 mimics in nude mice increased the proportion of TAMs in vivo, disrupting the infiltration and functionality of CD8 + T-cells in CRC. The results also revealed that exosomal miR-1246 interacts with the exosomal sorting protein hnRNPA2B1, and exogenous miR-1246 influences TAM polarization at a post-transcriptional level [34].

Additionally, increased expression of miR-491 in CD8 + T-cells has been observed in mice with CRC leading to inhibition of cell proliferation, the promotion of apoptosis, and a decrease in interferon-γ production within CD8 + T-cells. MiR-491 targets specific molecules such as cyclin-dependent kinase 4, T-cell factor 1, and B-cell lymphoma 2-like 1 within CD8 + T-cells. Furthermore, tumor-derived TGF-β induces the expression of miR-491 in CD8 + T-cells. Collectively, these findings indicate that miR-491 functions as a negative regulator of T lymphocytes within TME [35].

Through analysis of the bioinformatics database, it has been observed that KCNQ1OT1 has an impact on CD8 + T-cells. A newly discovered immune evasion mechanism involves the tumor-promoting effects of long non-coding RNA (lncRNA) KCNQ1OT1. This mechanism operates through the autocrine effect of exosomes derived from tumor cells. These exosomes mediate the miR-30a-5p/USP22 pathway, which regulates the ubiquitination of PD-L1. As a result, the CD8 + T-cell response is inhibited, promoting the development of CRC [36].

In summary, the interplay between miRNAs and CD8 + T-cells in colon cancer is complex, involving both tumor-suppressive and tumor-promoting factors. Figure 1 illustrates how different miRNAs can influence CD8 + T-cell activity. On one side, miRNAs like miR-448, miR-125b-5p, miR-148a-3p (indirectly), circRNF216, and miR-20b-5p (upregulated) can enhance CD8 + T-cell function by targeting IDO1, TNFR2, MHC-I antigen presentation, ZC3H12C expression, and PD-L1, respectively. Conversely, miR-1246, miR-491, and KCNQ1OT1 can suppress CD8 + T-cell activity by promoting TAM polarization, inhibiting proliferation and function, and stabilizing PD-L1 expression, respectively. Understanding these diverse miRNA regulations within the tumor microenvironment holds promise for identifying novel therapeutic targets to improve CD8 + T-cell-mediated anti-tumor immunity in colon cancer.

Pancreatic cancer

Pancreatic cancer, a malignancy affecting the digestive tract, has shown varying associations with miR-194-5p expression. In some cases, high levels of miR-194-5p have been linked to the disease. A recent study observed that elevated miR-194-5p expression in patients with pancreatic cancer correlated with improved survival rates. Conversely, increased expression of PD-L1 was associated with poorer survival outcomes. The ectopic upregulation of miR-194-5p in pancreatic cancer cells resulted in significant inhibition of cell migration, invasion, and proliferation, as demonstrated in experimental studies. Moreover, in a mouse model, miR-194-5p exhibited the potential to impede the progression of pancreatic cancer by promoting the infiltration of CD8 + T-cells and inducing the production of IFN-γ [37].

Hepatocellular carcinoma (HCC)

The immune evasion in HCC primarily stems from the impaired functionality of CD8 + T-cells, however; T-cell-mediated antitumor immune response is the basis of liver cancer immunotherapy. In a comprehensive analysis conducted by Yan et al., focused was on RNAs associated with activated memory CD4 + T-cells and CD8 + T-cells in liver cancer. The findings revealed that the upregulation of certain T-cell-related genes, such as CD5L, Eomesodermin (EOMES), and CST7, was associated with a promising prognosis in liver cancer patients. Notably, the expression of these genes was controlled by specific microRNAs and lncRNAs. Specifically, has-miR-23b-3p and lncRNA AC104820.2 were found to control the activation of memory CD4 + T-cell-related genes, while

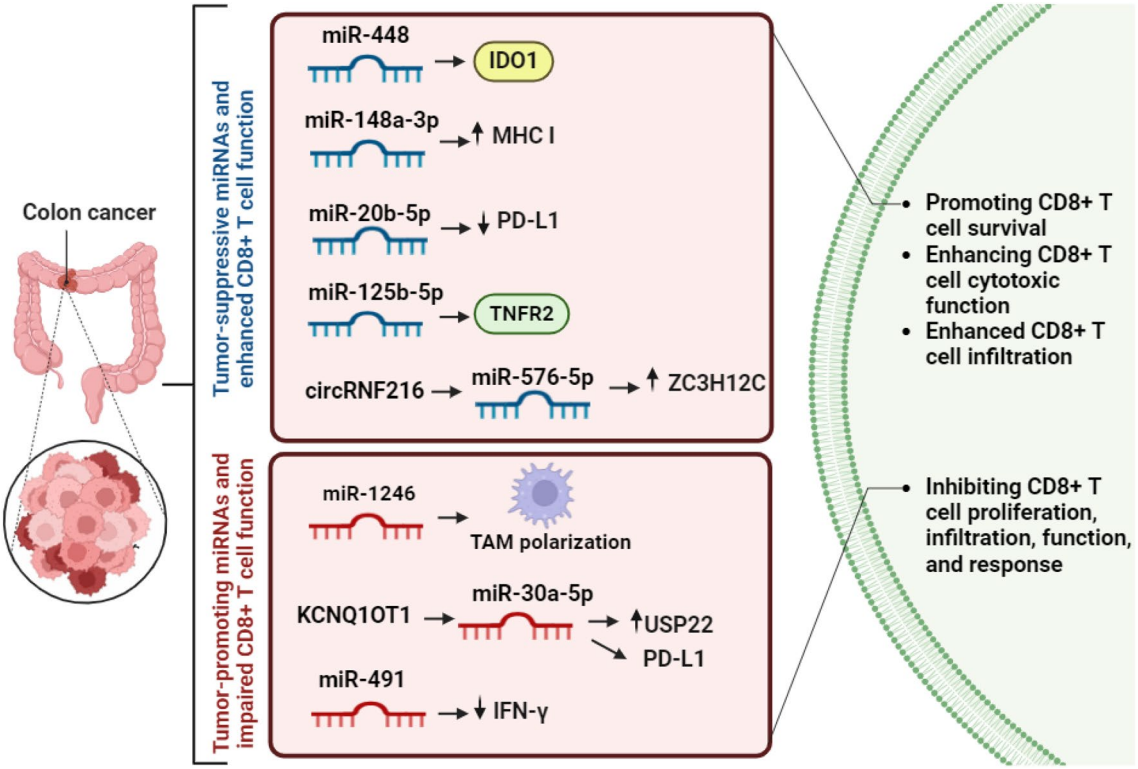


Fig. 1 The multifaceted roles of miRNAs in regulating CD8 + T-cell function within colon cancer's TME. Different miRNAs exhibit either tumor-suppressive or tumor-promoting effects by targeting specific genes or pathways crucial for CD8 + T-cell activity

has-miR-23a-3p and lncRNA AC000476.1 were implicated in the regulation of CD8 + T-cell-related genes [38].

ZMIZ1 has been identified as an oncogene involved in HCC, and a circular RNA called circZMIZ1 (hsa_circ_0018964) originates from the ZMIZ1 gene. In HCC, circZMIZ1 was found to upregulate both circZMIZ1 and KCNJ2, while downregulating miR-15a-5p. Furthermore, HCC patients exhibited an increased proportion of KCNJ2/CD8 + T-cells. The suppression of circZMIZ1 resulted in the inhibition of apoptosis in CD8 + T-cells and an increase in cytotoxicity. In an in vivo study using orthotopic HCC mice models, it was observed that the expression of circZMIZ1 and KCNJ2 was elevated, accompanied by an increased proportion of KCNJ2/CD8 + T-cells and a decrease in the expression of miR-15a-5p. These findings suggest that circZMIZ1 plays a role in dampening the anti-tumor activity of CD8 + T-cells in HCC by regulating the miR-15a-5p/KCNJ2 axis [39].

The researchers identified an upregulation of long non-coding RNA nuclear-enriched autosomal transcript 1 (NEAT1) and T-cell immunoglobulin and mucin domain-3 (TIM-3) in peripheral blood mononuclear cells (PBMCs) obtained from patients with HCC. They discovered that inhibiting NEAT1 led to a reduction in CD8 + T-cell apoptosis and an enhancement of cytolytic activity against HCC cells. This effect was mediated through the miR-155/Tim-3 pathway. These findings suggest that targeting NEAT1 could potentially improve the efficacy of immunotherapy by modulating the miR-155/Tim-3 pathway [40].

To investigate the impact of exosomal circCCAR1 on resistance to anti-PD1 therapy in HCC, researchers developed a mouse model (huNSG mice) that incorporated human immune system components. The findings demonstrated elevated levels of circCCAR1 in both tumor tissues and exosomes, leading to the accelerated growth and metastasis of HCC in laboratory experiments as well as in living organisms. HCC cells secreted circCCAR1 in a manner dependent on heterogeneous nuclear ribonucleoprotein A2/B1 (hnRNPA2B1). CD8 + T-cells internalized exosomal circCCAR1, resulting in their dysfunction by stabilizing PD-1 protein. Consequently, circCCAR1 played a role in promoting resistance to anti-PD1 immunotherapy. *In summary*, the circCCAR1/miR-127-5p/WTAP feedback loop plays a significant role in promoting the growth and metastasis of HCC. This loop also contributes to immunosuppression by facilitating CD8 + T-cell dysfunction in HCC [41].

The overexpression of miR-429 in HepG2 cells has been shown to have inhibitory effects on cell proliferation, invasion, and clonogenicity. Additionally, it promotes apoptosis and induces infiltration of both CD4 + and CD8 + T-cells. Furthermore, miR-429 plays a role in preventing an immunosuppressive microenvironment in HCC by targeting and suppressing PD-L1 expression. In a subcutaneous xenograft tumor model in mice, the overexpression of miR-429 demonstrates reduced tumorigenesis, increased levels of CD4 + and CD8 + T-cells, decreased Tregs, and diminished apoptosis and depletion of CD8 + T-cells [42].

Kupffer cells (KCs) are vital in safeguarding against HCC by communicating with other immune cells. In a study involving FVB/NJ mice, researchers induced HCC and increased the expression of microRNA-206 in KCs. The findings revealed that the injection of AKT/Ras resulted in the M2 polarization of KCs, causing a decrease in cytotoxic T-cells, which promoted the development of HCC. MicroRNA-206 targeted Klf4, enhancing the production of M1 markers, which facilitated the M1 polarization of macrophages and enabled the recruitment of CTLs to the liver through CCR2. Disrupting the interaction between microRNA-206 and Klf4 in KCs and depleting CD8 + T-cells compromised the ability of miR-206 to prevent HCC [43].

A novel nanoformulation called galactose-targeted lipid calcium phosphate (Gal-LCP) has been developed by researchers. This innovative approach enables the efficient and specific delivery of miR-122, yielding promising results in the prevention of liver metastasis and the prolongation of survival in various models of colorectal cancer liver metastasis. The delivery of miR-122 using Gal-LCP has demonstrated the downregulation of key genes involved in inflammation pathways. Moreover, it has shown the ability to enhance the CD8 + /CD4 + T-cell ratio and reduce the infiltration of immunosuppressive cells within the liver. These effects contribute to creating a more favorable environment for an effective antitumor immune response [44] (Table 2).

Rectal adenocarcinoma

By analyzing two miRNA datasets sourced from Gene Expression Omnibus (GEO) and The Cancer Genome Atlas (TCGA), the investigators observed a strong association between miR-21-5p and miR-455-5p with unfavorable prognosis and elevated expression levels in rectal adenocarcinoma. These miRNAs were found to be enriched in key signaling pathways including TGF- β, Wnt, MAPK, and PI3K-AKT. Their heightened expression was linked to a reduction in CD4 + and CD8 + T-cell populations [45].

Lung cancer

The upregulation of has-circRNA-002178 has been consistently observed in both lung adenocarcinoma (LUAD) cancer cells and tissues. circRNA-002178 plays a significant role in modulating the expression of PD-L1 by acting as a miR-34 sponge in cancer cells, contributing to the induction of T-cell exhaustion. Additionally, it has been found that circRNA-002178 can be transferred to CD8 + T-cells through exosomes, leading to the induction of PD-1 expression. These findings emphasize the multifaceted role of circRNA-002178 in LUAD, including its impact on tumor immune evasion mechanisms, its potential as a diagnostic biomarker, and its involvement in modulating T-cell responses [46].

In the context of lung cancer, the expression of XIST is elevated in tumor tissues, whereas miR-34a-5p exhibits decreased expression. The upregulation of XIST is associated with an increase in PDL1 expression, leading to significant effects on cell proliferation, apoptosis, metastasis, and aggression. Furthermore, XIST directly targets miR-34a-5p, resulting in the inhibition of cytokine secretion and the advancement of immunosuppressive molecules. The intricate interplay between XIST, miR-34a-5p,

Table 2 Regulation of CD8 + T-cell function by miRNAs and lncRNAs in HCC

miRNA/lncRNA	Target gene/pathway	Effect on CD8 + T-cells	References
has-miR-23b-3p, lncRNA AC104820.2	T-cell-related genes (CD5L, EOMES, CST7)	Upregulation	[32]
has-miR-23a-3p, lncRNA AC000476.1	CD8 + T-cell-related genes	Upregulation	[32]
circZMIZ1	miR-15a-5p/KCNJ2 axis	Suppresses apoptosis and increases cytotoxicity	[33]
NEAT1	miR-155/Tim-3 pathway	Reduces apoptosis, enhances cytolytic activity	[34]
CircCCAR1	miR-127-5p/WTAP	Promotes dysfunction by stabilizing PD-1	[35]
miR-429	PD-L1	Promotes infiltration, prevents immunosuppressive microenvironment	[36]
miR-206	Klf4/M1 polarization	Recruits CTLs, inhibits cell development	[37]

and PDL1 plays a crucial role in determining the malignancy of lung cancer cells and influencing the immune function of CD8 + T-cells. These findings underscore the significance of the XIST/miR-34a-5p/PDL1 axis in lung cancer and its impact on tumor progression and immune responses of CD8 + T-cells [47]. Elevated levels of miR-6794-5p result in a reduction in the proportion of activated CD8 + T-cells and an increase in M2 macrophages, indicating a shift towards an immunosuppressive and tumorigenic state. These findings emphasize the critical involvement of miR-6794-5p in promoting the polarization of macrophages towards the M2 phenotype, while concurrently suppressing the functional capabilities of CD8 + T-cells. Consequently, the dysregulation of miR-6794-5p contributes significantly to the progression and metastasis of lung tumors [48].

In lung cancer, miR-760 exhibits low expression while IDO2 demonstrates high expression levels. By mimicking miR-760, cell growth, invasiveness, and migration are suppressed, and the protein levels of IDO1 are downregulated. Additionally, miR-760 inhibits the apoptosis of CD8 + T-cells by modulating the function of the IDO1 enzyme. These findings highlight that miR-760 plays a role in suppressing CD8 + T-cell responses in lung cancer through the regulation of IDO1. This research provides a foundation for the development of innovative vaccination therapies for lung cancer [49]. Besides, miRNA-15b is upregulated in CD8 + memory T-cells compared to effector T-cells. The introduction of miRNA-15b mimics into CD8 + T-cells through transfection showed promising results in preventing T-cell apoptosis. This effect was achieved by the miR-15b mimics inhibiting the translation of death effector domain-containing DNA binding protein (DEDD). Ectopic miRNA-15b could inhibit the activation of CD8 + T-cells and promote the expression of CD44 through unknown pathways [50].

The suppression of miR-301a has been shown to promote the expansion of CD8 + T-cells and increase the production of IFN-γ within TME, resulting in enhanced antitumor immune responses in lung cancer. Additionally, miR-301a deletion has been found to reduce tumor metastasis by upregulating the expression of Runx3 and facilitating the recruitment of CD8 + T-cells. Conversely, inhibition of miR-301a inhibits cell migration. These findings highlight the significance of miR-301a as a potential target for therapeutic interventions aimed at bolstering CD8 + T-cell-mediated antitumor immunity and suppressing tumor metastasis [51].

Furthermore, Let-7 b as a potential strategy for lung cancer prevention demonstrates its ability to suppress the expression of PD-L1 and PD-1 within the tumor microenvironment. This suggests that let-7b may contribute to the promotion of antitumor immune responses. Additionally, the treatment leads to a reduction in PD-1 expression in CD8 + T-cells and PD-L1 expression in lung tumor cells [52].

The complement system plays a crucial role in tumor immune evasion and CD8 + T-cell activation. Researchers have identified that epidermal growth factor receptor (EGFR)/Wnt signaling triggers the induction of β-catenin-mediated expression, which subsequently acts as a sponge for miR-216b and miR-150. These two microRNAs target CD55 and CD59, respectively, resulting in the suppression of the complement system and a reduction in cytokine secretion. This intricate interplay between EGFR/Wnt signaling, β-catenin-mediated expression, miR-216b, miR-150, and their respective target genes highlights the significance of these molecular mechanisms in regulating immune responses within TME. To activate the complement system and CD8 + T-cells, researchers have found that CD55/CD59-neutralizing antibody treatment or manipulation of the β-catenin-mediated expression promoter can be effective. These interventions have been instrumental in inhibiting tumor growth. Furthermore, the combination of anti-CD55/CD59 and anti-PD-1 antibody treatments has demonstrated a synergistic effect in inhibiting tumor progression. Interestingly, in human lung cancer specimens, the levels of CD55/CD59 exhibit an inverse correlation with the infiltration of M1 macrophages and CD8 + T-cells [53].

Accordingly, Fig. 2 illustrates the complex interplay between miRNAs, their targets, and their influence on CD8 + T-cell function in lung cancer. This highlights the potential for therapeutic strategies that target these regulatory molecules to modulate CD8 + T-cell responses in lung cancer.

CD8 + T-cells exhibit dysfunction in non-small cell lung cancer (NSCLC). A study has found that the expression levels of circUSP7 are higher in human NSCLC tissues compared to non-tumor tissues. This observation suggests a correlation between unfavorable clinical prognosis and the dysfunction of CD8 + T-cells in NSCLC patients. NSCLC cells primarily release CircUSP7 through exosomes, which hinders the secretion of IFN-γ, TNF-α, Granzyme-B, and Perforin by CD8 + T-cells. Additionally, CircUSP7 enhances the expression of Src homology region 2 (SH2)-containing protein tyrosine phosphatase 2 (SHP2) by acting as a sponge for miR-934. The presence of CircUSP7 in NSCLC patients could potentially contribute to resistance against anti-PD1 immunotherapy [54].

Head and neck squamous cell carcinoma (HNSCC)

The researchers investigated the impact of LINC01123, B7-H3, and miR-214-3p on tumor progression,

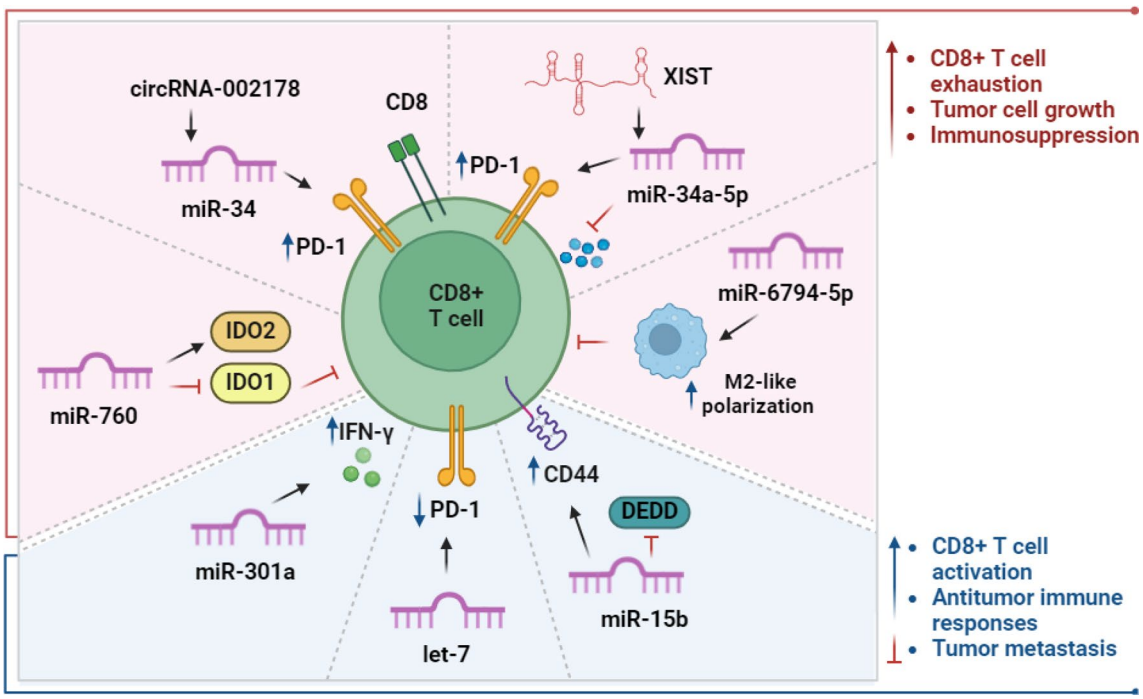


Fig. 2 Role of mRNAs in regulating CD8 + T-cell responses in lung cancer

CD8 + T-cell-mediated immune response, and the tumorigenicity of HNSCC. Specifically, they examined how LINC01123 competes with miR-214-3p for binding and targets B7-H3. The findings indicated that both LINC01123 and B7-H3 exhibited high expression levels in HNSCC and were linked to unfavorable prognoses. Alterations in the expression levels of these genes, whether through overexpression or downregulation, hindered the functionality of CD8 + T-cells, thereby promoting the progression of HNSCC [55].

Glioma

Qiu et al. explored the impact of miR-155 in enhancing the anti-glioma capabilities and uncovering the underlying mechanism involved. They created a mouse model with a knockout of miR-155 and another model with glioma, enabling a comparison of glioma progression and the accumulation of CD8 + T-cells. They also performed transfections of miR-155 mimics and inhibitors into T-cells and subsequently analyzed their proliferative and invasive activities. The findings revealed that the absence of microRNA-155 in CD8 + T-cells hindered their anti-tumor capabilities by reducing their ability to proliferate and invade. Additionally, it was discovered that FoxO3a acted as a suppressor of Akt and Stat5 signaling, exerting a regulatory influence on these pathways [56]. Besides, miR-15a and miR-16 inhibit tumor growth and prolong glioma survival in mice which is associated with the accumulation of tumor-infiltrating CD8 + T-cells. CD8 + T-cells that infiltrate tumors and lack miR-15a/16 exhibited reduced levels of PD-1, Tim-3, and LAG-3 expression, while demonstrating enhanced secretion of IFN-γ, IL-2, and TNF-α. miR-15a/16-/- CD8 + T-cells displayed higher active phenotypes, more cytokines, and faster expansion than WT CD8 + T-cells. The findings suggest that miR-15a/16 deficiency can inhibit glioma progression by targeting the mammalian target of rapamycin (mTOR) indicating potential immunotherapy through targeting miR-15a/16 in tumor-infiltrating immune cells [57].

Oral squamous cell carcinoma (OSCC)

A study investigated the expression of CRNDE in tumor-infiltrating CD8 + T-cells from patients with OSCC and observed that CRNDE levels were elevated and negatively associated with IFN-γ production. CRNDE can induce CD8 + T-cell exhaustion by acting as a miR-545-5p sponge, which increases TIM-3. TIM-3 is an important immune checkpoint that suppresses cancer immunity. Conversely, the absence of CRNDE leads to increased miR-545-5p levels and a decrease in TIM-3 expression. This activation of CD8 + T-cells and inhibition of TIM-3 promotes the anti-tumor effect within the cells [58].

The expression levels of circKRT1 and PDL1 were found to be significantly elevated in oral squamous cell carcinoma (OSCC). Knocking down circKRT1 resulted

in the repression of OSCC cell growth, migration, invasion, and the apoptosis of CD8 + T-cells. Conversely, it enhanced CD8 + T-cell cytotoxicity increased and the percentage of these cells. The inhibitory effects of circKRT1 on OSCC progression and immune evasion were found to be associated with the inhibition of PDL1 expression. CircKRT1 acted as a sponge for miR-495-3p and targeted PDL1, thereby regulating OSCC progression and immune evasion through the miR-495-3p/PDL1 axis [59].

Thyroid carcinoma

The expression levels of Urothelial cancer associated 1 (UCA1) and PD-L1 were elevated in tissues and cells of anaplastic thyroid carcinoma (ATC). Inhibiting the expression of these genes enhanced the ability of cytotoxic CD8 + T-cells to kill ATC cells. UCA1 also negatively regulates the expression of miR-148a, which targeted PD-L1 and caused its downregulation. Moreover, UCA1 impeded the cytotoxic effects of CD8 + T-cells and reduced cytokine secretion by acting through PD-L1 and miR-148a. Lastly, silencing UCA1 or PD-L1 in ATC cells restored the suppression of the cytotoxic effects [60].

Lymphoma

The expression of miR-340-5p is positively associated with the presence of CD8 + TILs in patients with diffuse large B-cell lymphoma (DLBCL). Overexpression of miR-340-5p leads to the restoration of CD8 + T-cell function. Additionally, the investigation revealed that miR-340-5p directly affects the biological activity of DLBCL cells, independent of CD8 + T-cell involvement [61].

Another study examined the involvement of lncRNA MALAT1 in controlling tumor development and immune evasion capabilities in DLBCL. The findings indicated that MALAT1, PD-L1, and CD8 + were increased in DLBCL tissues, whereas miR-195 was decreased. It was discovered that MALAT1 acted as a sponge for miR-195, thus regulating the expression of PD-L1. Treatment with short hairpin RNA targeting MALAT1 (ShMALAT1) resulted in elevated levels of miR-195 and reduced levels of PD-L1. This treatment effectively hindered cell proliferation, migration, and immune evasion capabilities. Additionally, it promoted the proliferation of CD8 + T-cells while inhibiting their apoptosis. Knocking down MALAT1 suppressed EMT-like processes through the Ras/ERK signaling pathway [62].

Upregulation of miR-155 is linked to reduced levels of peripheral blood CD8 + T-cells and the suppression of T-cell receptor signaling. The upregulation of miR-155 induces Fas-mediated apoptosis in CD8 + T-cells, a process that can be targeted by anti-PD-1 and anti-PD-L1 antibodies. Furthermore, miR-155 upregulation was found to increase the expression of PD-L1 in lymphoma cells, leading to the recruitment of CD8 + T-cells and the inhibition of their functionality by dephosphorylating AKT and ERK. Inhibition of PD-L1 was observed to slow tumor growth in the context of miR-155 upregulation, suggesting the efficacy of PD-L1 blockade in treating B-cell lymphoma with heightened miR-155 levels [63].

Melanoma

The efficacy of PD-1 immunotherapy in the treatment of melanoma is often hindered by its low response rate and the development of treatment resistance. A crucial factor in this process is the induction of tumor cell ferroptosis, which is triggered by IFN-γ derived from tumor-infiltrating CD8 + T-cells. Through a comprehensive study involving RNA sequencing and biochemical assays, it has been discovered that the upregulation of miR-21-3p plays a significant role in facilitating IFN-γ-mediated ferroptosis. By enhancing lipid peroxidation and increasing the sensitivity of cells to ferroptosis, miR-21-3p achieves this effect by targeting thioredoxin reductase 1 (TXNRD1) and promoting the generation of lipid reactive oxygen species. Notably, the overexpression of miR-21-3p in tumors synergizes with anti-PD-1 antibody treatment, leading to the promotion of tumor cell ferroptosis. These findings shed light on the potential of targeting miR-21-3p as a strategy to enhance the effectiveness of anti-PD-1 immunotherapy through the induction of tumor cell ferroptosis [64].

Elevated levels of miR-155 in CD8 + T-cells that infiltrate tumors may indicate the effectiveness of local antigen-specific CD8 + T-cell responses. Increased miR-155 expression correlates with a greater number of cytokine-producing cells. Furthermore, treatment with anti-PD-1 antibodies resulted in higher miR-155 expression and enhanced tumor control mediated by specific CD8 + T-cells. Similarly, the overexpression of miR-155 promoted the prolonged persistence of exhausted CD8 + T-cells in models of chronic viral infection [65].

The impacts of KCNQ1OT1 on melanoma tissues, cells, and CD8 + T-cells were examined by the researchers. They observed an increase in the expression of KCNQ1OT1 in melanoma tissues, which was associated with an unfavorable prognosis. By reducing the levels of KCNQ1OT1, the researchers were able to suppress the proliferation, migration, and invasion of melanoma cells. KCNQ1OT1 played a role in controlling the advancement of melanoma by functioning as a sponge for miR-34a. Through its interaction with miR-34a, KCNQ1OT1 also influenced the regulation of the Signal transducer and activator of transcription 3 (STAT3), which in turn impacted the transcriptional regulation of PD-L1.

Silencing KCNQ1OT1 resulted in decrease in PD-L1 levels and simultaneously boosted the cytotoxicity and proliferation of CD8 + T-cells. These findings indicate that KCNQ1OT1, which is overexpressed in melanoma cells, influences immune evasion by affecting the miR-34a/STAT3 axis [66].

Breast cancer

MicroRNAs play a crucial role in the regulation of immune checkpoint proteins, and in CD8 + T-cells that overexpress PD-1, these miRNAs may undergo downregulation. Specifically, miR-149-3p, which acts as a mimic of these checkpoint receptors, was found to decrease apoptosis, alleviate T-cell exhaustion features, and suppress the expression of mRNAs encoding PD-1, BTLA, TIM-3, and Foxp. Nevertheless, miR-149-3p not only resulted in the downregulation of exhaustion markers and immune checkpoint proteins but also induced upregulation of T-cell proliferation and the secretion of effector cytokines. Importantly, the administration of miR-149-3p also enhanced the ability of CD8 + T-cells to effectively eliminate targeted mouse breast tumor cells [67]. Elevated levels of miR-21 were observed in both breast cancer tissues and cells, which were associated with increased expression of PD-L1. Treatment with anti-PD-L1 antibody reduced tumor weight and volume, and decreased the number of CD3 + CD8 + positive cells [68].

Promising treatment options for triple-negative breast cancer (TNBC) patients involve immune checkpoint inhibitors that specifically target PD-1 or its ligand PD-L1. Despite the potential of these therapies, only a small number of patients experience a complete or partial response to anti-PD-1 treatment. The dysfunction of CD8 + T-cells plays a significant role in allowing TNBC to evade the immune system. The expression of cirmiR-20a-5p, a circular RNA (cirmiRNA) released by TNBC cells, is increased in both plasma and culture supernatant. This upregulation of cirmiR-20a-5p is associated with a poorer prognosis in TNBC. CirmiR-20a-5p specifically targets the nuclear protein ataxia-telangiectasia (NPAT) leading to a reduction in NPAT expression within CD8 + T-cells. Inhibition or targeting of cirmiR-20a-5p could represent a promising and innovative approach to overcoming TNBC resistance to anti-PD-1 immunotherapy [69]. Furthermore, circ-0000512, which is found to be upregulated in patients with TNBC, plays a significant role in cell proliferation and migration. Knockdown of circ-0000512 resulted in reduced proliferation and migration of TNBC cells. Conversely, overexpression of circ-0000512 led to enhanced ubiquitination of PD-L1 protein in TNBC cells by inhibiting CMTM6. Additionally, the impression of circ-0000512 promoted the expression of CMTM6 by acting as a sponge for miR-622. Silencing circ-0000512 increased the ratio of CD8 + T-cells and enhanced their ability to induce lethality in TNBC cells [70].

Renal cell carcinoma (RCC)

A research investigation focused on the impaired functioning of T-cells in individuals with RCC discovered that CD8 + T-cells obtained from RCC patients exhibited lower levels of gene products associated with preventing cell death and promoting cell growth compared to healthy donors. This was attributed to the malfunctioning suppressor activity of miR-29b and miR-198 in CD8 + T-cells specific to RCC. Additionally, the research revealed that targeted blocking of miR-29b or miR-198 in PBMCs obtained from individuals with RCC led to an increase in the levels of JAK3 and MCL-1 proteins, resulting in a notable enhancement of cell survival under laboratory conditions. These findings indicate that the disruption of miR-29b and miR-198 in CD8 + T-cells of RCC patients is connected to impaired immune function, suggesting the potential development of therapeutics targeting these microRNAs to rectify T-cell abnormalities within living organisms [71].

Ovarian cancer (OC)

Yin et al. explored the influence of extracellular vesicles (EVs) originating from M2-polarized TAMs on the proliferation of ovarian cancer cells and the apoptosis of CD8 + T-cells. Their findings indicate that M2-TAMs facilitate OC cell proliferation and induce CD8 + T-cell apoptosis through the secretion of EVs. Notably, the results reveal high expression levels of NEAT1, a gene differentially expressed in OC tissues, in both M2-derived EVs and OC cells co-cultured with M2-derived EVs. The upregulation of NEAT1 leads to increased expression of ZEB1 and PD-L1, thus confirming the tumor-promoting effects of NEAT1 delivered by M2-derived EVs on OC cell proliferation, CD8 + T-cell apoptosis, and overall tumor growth [72]. The efficacy of immunotherapies in treating high-grade serous ovarian cancer (HGSC) is hindered by the presence of an immunosuppressive tumor microenvironment and insufficient infiltration of CD8 + T-cells into the tumor. However, a recent study has pinpointed miR-146a as a critical factor governing the infiltration of CD8 + T-cells in HGSC tumors. The expression of miR-146a within tumors is associated with favorable anti-cancer immune characteristics in HGSC. Introducing miR-146a into murine models of HGSC leads to a reduction in tumor growth. This microRNA directly targets IL-1 receptor-associated kinase 1 and tumor necrosis factor receptor-associated factor 6 adaptor molecules [73].

Uterine corpus endometrial cancer (UCEC)

miR-765, the most significantly downregulated microRNA in UCEC, exhibits a negative relationship with Proteolipid protein 2 (PLP2) in UCEC lesions. Estrogen plays a pivotal role in the downregulation of miR-765, thereby promoting the development of UCEC through estrogen receptor (ER) β signaling. However, the selective ER degrader Fulvestrant effectively mitigates the estrogen-mediated regulation of miR-765/PLP2 expression and UCEC progression, acting in both ERβ-dependent and -independent manners. Furthermore, exosomes derived from CD45RO-CD8 + T-cells release a higher amount of miR-765 compared to CD45RO + CD8 + T-cells. These findings shed light on the intricate regulatory mechanisms involving miR-765, estrogen signaling, and UCEC development, highlighting the potential therapeutic implications of targeting this miRNA in UCEC treatment [74].

Bladder cancer

Exosomes derived from circTRPS1 were found to have a regulatory effect on the intracellular balance of reactive oxygen species and the induction of CD8 + T-cell exhaustion in bladder cancer. These findings provide evidence supporting the tumor-promoting function of circTRPS1 through the circTRPS1/miR-141-3p/GLS1 pathway. By acting as a miR-141-3p sponge, exosome-derived circTRPS1 promotes the activation of GLS1. Consequently, the heightened expression of GLS1 not only amplifies the proliferation and invasiveness of bladder cancer cells but also impedes the anti-tumor immune response within the bladder cancer microenvironment [75].

A different circular RNA called circRNA_0013936, which originates from bladder cancer can augment the immunosuppressive function of polymorphonuclear myeloid-derived suppressor cells (PMN-MDSCs) by controlling the levels of fatty acid transporter protein 2 (FATP2) and receptor-interacting protein kinase 3 (RIPK3) expression. The circRNA_0013936 derived from bladder cancer exosomes was found to increase the expression of FATP2 by sequestering miR-320a through the circRNA_0013936/miR-320a/JAK2 pathway. Simultaneously, it reduced the expression of RIPK3 by sequestering miR-301b-3p through the circRNA_0013936/miR-301b-3p/CREB1 pathway. Ultimately, this led to the production of immunosuppressive molecules, resulting in significant impairment of CD8 + T-cell function and diminished secretion of IFN-γ by CD8 + T-cells. These findings have the potential to unveil novel therapeutic targets for the clinical management of bladder cancer in humans [76].

Acute myeloid leukemia (AML)

The overexpression of miR-103a-2-5p as a tumor suppressor effectively reduces the expression of LILRB3, leading to the inhibition of AML cell growth and the induction of apoptosis. Furthermore, miR-103a-2-5p exerts its effects by suppressing the Nrf2/HO-1 axis, resulting in elevated levels of intracellular reactive oxygen species (ROS) that contribute to AML cell apoptosis. Additionally, miR-103a-2-5p shows potential in enhancing the response of CD8 + T-cells by inhibiting LILRB3 expression. These findings highlight the therapeutic potential of miR-103a-2-5p in AML treatment and its ability to modulate both tumor cell behavior and the immune response [77].

In the context of AML with nucleophosmin (NPM1) mutations, the long-term outcomes remain unsatisfactory. A recent study sheds light on the immune dysfunction observed in CD8 + T-cells when co-cultured with leukemic cells from patients with NPM1-mutated AML. It was discovered that leukemic cells release miR-19a-3p into the tumor microenvironment using sEVs. This release is regulated by the NPM1-mutated protein/CCCTC-binding factor/poly (A)-binding protein cytoplasmic 1 signaling axis. The internalization of miR-19a-3p by CD8 + T-cells subsequently suppresses the expression of SLC6A8, a transporter responsible for creatine uptake [78].

T-cell dysfunction is a prevalent problem among individuals with leukemia, greatly affecting treatment outcomes and prognosis. In this study, it was discovered that peripheral blood CD3 + T-cells from patients with chronic myelogenous leukemia exhibited decreased expression of NFAT2 and pri-miR-17. The activation, differentiation, and cytokine expression of CD8 + naive T-cells derived from human umbilical cord blood were found to be dependent on miR-20a-5p, which is regulated by NFAT2. These findings highlight the significance of NFAT2 and miR-20a in the regulation of functional CD8 + T-cells and suggest that they could serve as potential targets for enhancing T-cell function in leukemia immunotherapy [79].

Osteosarcoma

Liu et al. investigated the impact of miR-200a on cell death and growth of CD8 + T-cells, revealing that miR-200a prompted apoptosis and hindered the proliferation of CD8 + T-cells. Moreover, when miR-200a was overexpressed in osteosarcoma cells, it also hindered the ability of CD8 + T-cells to secrete substances. Similarly, the immune system suppression caused by miR-200a was strongly associated with the increased expression of PD-L1. This was evident from the fact that administering anti-PD-L1 antibodies partially reversed the

immunosuppressive effects of osteosarcoma cells on CD8 + T-cells [80].

Exploiting CD8 + T-cell-microRNA crosstalk through EVs and cytokines

In the TME of CRC, there is a high presence of TAMs, which have been linked to unfavorable outcomes. While CRC cells exhibit low levels of PD-L1, TAMs, display abundant expression of this protein. The secretion of sEVs by CRC cells triggers a phenomenon known as M2-like polarization, leading to increased PD-L1 expression. Consequently, there is an increase in the macrophages abundance and a decrease in the activity of T-cells. These effects are mediated by miR-21-5p and miR-200a, which are derived from CRC. These microRNAs contribute to the suppression of CD8 + T-cell activity and promote the growth of tumors. A potential novel approach for the treatment of CRC involves inhibiting the secretion of sEV containing these miRNAs and targeting PD-L1 in TAMs [81].

Recent research by Jung et al. has introduced a novel approach involving the generation of IL-2-tethered small extracellular vesicles (IL-2-sEVs) from engineered Jurkat T-cells. These sEVs exhibit anti-cancer effects that can be further enhanced. Jurkat T-cells express IL-2 on their plasma membranes and IL-2-sEVs were found to enhance the anti-cancer capabilities of CD8 + T-cells without affecting regulatory T-cells. Additionally, IL-2-sEVs downregulated PD-L1 expression in melanoma cells. The effects were mediated by various microRNAs, such as miR-181a-3p, which were upregulated in response to IL-2 stimulation and are resident within IL-2-sEVs. Importantly, the combination of IL-2-sEVs with existing anti-cancer drugs demonstrated a remarkable improvement in anti-cancer efficacy in vivo, achieved through the down-regulation of PD-L1 expression [82]. In a recent study, it was discovered that EVs originating from CD4 + T-cells can enhance the antitumor response of CD8 + T-cells. This enhancement occurs through increased proliferation and activity of CD8 + T-cells while having no impact on regulatory T-cells. Notably, EVs derived from IL-2-stimulated CD4 + T-cells exhibit an even stronger effect in promoting an antitumor response. These EVs, in conjunction with IL-2, serve as crucial communicators between CD4 + and CD8 + T-cells. The findings of this study offer potential avenues for cancer immunotherapy by stimulating a CD8 + T-cell-mediated antitumor response [83] (Fig. 3).

IL-8, an important cytokine involved in paracrine signaling, has been identified as a promoter of migration and invasion in GC cells. A newly discovered circular RNA, circ_0073453, functions as a miR-146a-5p

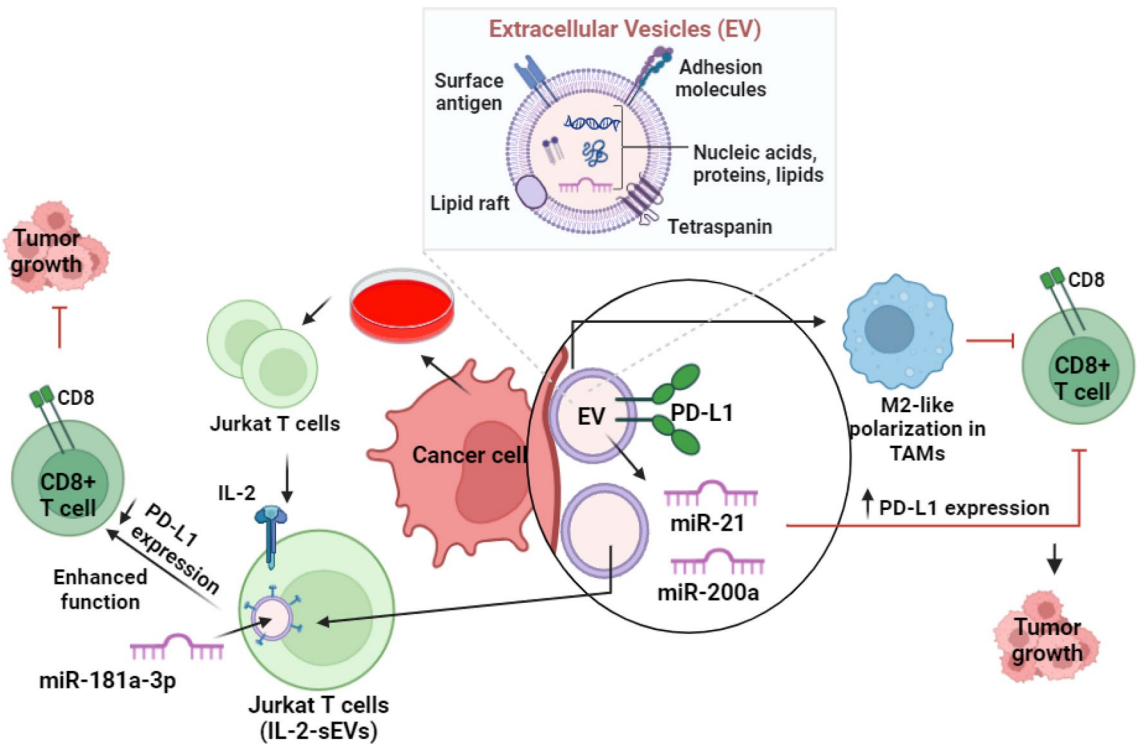


Fig. 3 Exploiting CD8 + T-cell-microRNA Crosstalk through EVs in tumor microenvironment. On the left side, the engineered EVs and interleukin have a stimulatory effect on CD8 + T-cells, whereas, on the right side, the suppressive effects of tumor-derived EVs on CD8 + T-cells are illustrated

sponge, leading to increased expression and secretion of IL-8, thereby facilitating metastasis of gastric cancer cells. Circ_0073453 plays a role in modulating IL-8 secretion, which in turn enhances PD-L1 expression in gastric cancer cells, enabling resistance against cytotoxic CD8 + T-cell-mediated killing [84].

miR-92a derived from gliomas stimulates the production of IL-6 and IL-10 in natural killer T (NKT) cells, which can inhibit the activity of cytotoxic CD8 + T-cells. The presence of miR-92a is crucial for promoting the expression of IL-6 and IL-10 in NKT cells within gliomas. Consequently, the NKT-cells expressing IL-6 and IL-10 exhibit a significant reduction in the expression of molecules that combat tumor growth compared to control NKT-cells. These IL-6 and IL-10-producing NKT-cells demonstrate diminished susceptibility to apoptosis when exposed to glioma cells, thereby exerting immunosuppressive effects on the functioning of CD8 + T-cells [85]. In contrast, stimulation of miR-193b in cases of laryngeal cancer results in the inhibition of CD8 + T-cell functions due to the induced production of IL-10 [86, 87].

In nasopharyngeal cancer (NPC), B cells that have been activated by miR-21 hinder the functioning of cytotoxic CD8 + T-cells. Additionally, miR-21 present in NPC, stimulates the growth of IL-10-producing B cells, which are capable of suppressing the activities of CD8 + T-cells [88].

MiR-155 plays a crucial role in facilitating the immune responses of CD8 + T-cells against cancer. When miRNA-155 is overexpressed, it enhances the body's ability to mount an effective antitumor response. Conversely, a deficiency in miRNA-155 leads to an accumulation of suppressors of cytokine signaling-1 (SOCS-1), disrupting cytokine signaling through STAT5, resulting in faulty immune responses [89].

Unraveling the mechanistic link between radiotherapy and enhanced CD8 + T-cell response in tumor rejection

The abscopal effect, characterized by the rejection of tumors outside the radiation field, plays a crucial role in the effectiveness of radiotherapy. A mouse model was employed to investigate this phenomenon, utilizing a range of techniques including RNA sequencing, immunofluorescence, and flow cytometry. The findings demonstrated that radiotherapy significantly impeded the progression of tumors and lung metastasis while improving the tumor microenvironment. The underlying mechanism involved the release of tumor-derived exosomes containing circPIK3R3, which were absorbed by macrophages. These exosomes facilitated the secretion of I-IFN and M1 polarization through the miR-872-3p/IRF7 axis, thereby activating the JAK/STAT signaling pathway in CD8 + T-cells [90]. The combination of radiotherapy and anti-PD1 treatment demonstrated a substantial improvement in tumor metastasis within the TME and enhanced the observed abscopal effect in cancer, leading to increased infiltration of CD8 + T-cells into the tumor [90]. In experiments conducted on mice with introduced, miR-21, treatment with radiotherapy or an anti-PD-L1 antibody resulted in reduced tumor weight and volume. Additionally, these treatments led to a decrease in the number of CD3 + CD8 + positive cells, lowered levels of IL-2 and IFN-γ in the serum, and decreased expression of PD-L1 [68]. Scientists have discovered that increased levels of miR-195 and miR-16 are associated with improved biochemical recurrence-free survival in individuals with prostate cancer. However, these miRNAs exhibit an opposite correlation with the expression of PD-L1, PD-1, CD80, and Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4). Reinstating the expression of miR-195 and miR-16 enhances the effectiveness of radiotherapy by activating T-cells within the tumor microenvironment. This activation promotes the growth of functional cytotoxic CD8 + T-cells while inhibiting the activity of myeloid-derived suppressor cells and regulatory T-cells [91]. Scientists have created a novel vaccine called meAAV (adenovirus-associated virus) neoAg, which is designed to counteract the immune checkpoint inhibitory mechanisms present in the host, specifically PD-1/PD-L1 inhibition in dendritic cells (DCs). This vaccine has been modified with fragments that inhibit Toll-like receptor 9 (TLR9), a receptor involved in immune responses, as well as a PD-1 trap and PD-L1 miRNA. These modifications enhance the longevity of meAAV in the body and stimulate the activation of T-cell responses that target neoantigens (neoAgs) in murine models of CRC and breast cancer with intact immune systems. This vaccine, when used in conjunction with radiotherapy, not only enhances the capacity for presenting antigens but also sustains the specific cytotoxic T lymphocyte responses against neoAgs. This combined approach resulted in the complete eradication of CRC and a significant delay in tumor growth in breast cancer-bearing mice [92, 93].

Impairing CD8 + T-cells to promote cancer growth

Diuron, also known as DCMU (3-(3,4-dichlorophenyl)−1,1-dimethylurea), is an herbicide that can have detrimental effects on the immune cells of humans, specifically CD8 + T-cells. Through an investigation involving functional studies and analysis of miRNA and RNA sequencing data, it was observed that diuron influences the expression of miRNAs. This modulation of miRNA expression subsequently results in a decrease in the secretion of cytokines and granzyme B by the CD8 + T-cells. MiRNAs such as hsa-miR-3135b and hsa-miR-21-5p play a role in controlling these

secretions, leading to a decrease in the cytotoxic activity of CD8 + T-cells against cancer cells. This implies that DCMU diminishes the capabilities of T-cells, thereby creating a favorable environment for the expansion of cancer [94].

Targeting microRNAs in CD8 + T-cells: a novel cancer therapy

The proteasome inhibitor bortezomib can modify the expression of miRNAs in CD8 + T-cells, with a notable impact on miR-155, a crucial cellular miRNA involved in T-cell function. This finding indicates that bortezomib induces the downregulation of negative regulatory proteins, such as Suppressor of cytokine signaling 1 (SOCS1), and inositol polyphosphate-5-phosphatase (SHIP), through a miR-155-dependent mechanism. Treating activated CD8 + T-cells with bortezomib results in a significant decrease in the expression of PD-1 and the SHIP1 + phenotype. Consequently, PD-1-mediated T-cell exhaustion is suppressed. Combining bortezomib with other immunotherapies has the potential to enhance therapeutic outcomes by addressing T-cell exhaustion within the tumor microenvironment [95].

Research has shown that metformin has anticancer properties by regulating T-cell activities. In patients with lung cancer who received metformin treatment, there was an increase in the frequencies of memory stem and central memory T-cells. Metformin helped produce memory CD8 + T-cells and improved their ability to resist apoptosis. CD8 + T-cells treated with metformin exhibited elevated levels of Eomes, which is the gene targeted by miR-107. This indicates that miR-107 plays a role in the differentiation of memory T-cells by controlling the expression of Eomes. These findings suggest that metformin has the potential to reprogram the differentiation of CD8 + T-cells, thereby offering potential benefits for cancer treatment [96] (Fig. 4).

Conclusion

In conclusion, miRNAs play a pivotal role in orchestrating CD8 + T-cell function within the TME. This review highlights the multifaceted roles of miRNAs in regulating CD8 + T-cell activation, recruitment, infiltration, and effector function. Understanding the intricate network of miRNA-mediated regulation offers a unique opportunity to manipulate the anti-tumor immune response. By targeting specific miRNAs that promote CD8 + T-cell

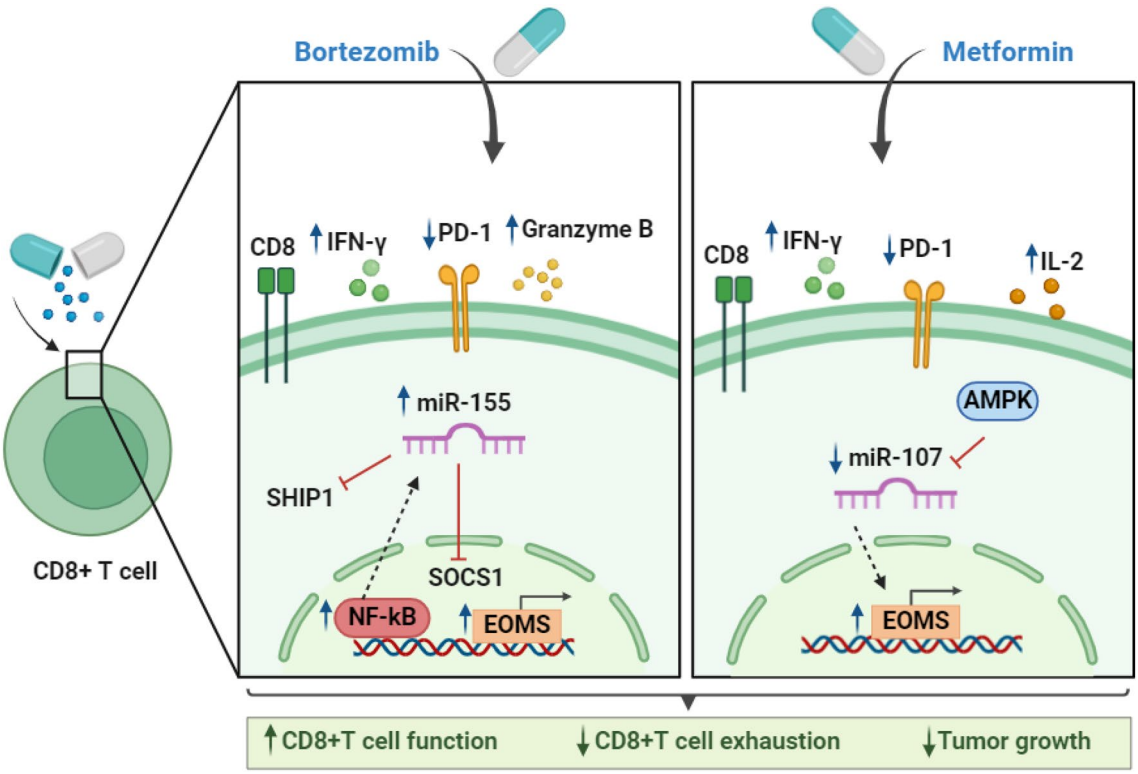


Fig. 4 Regulating microRNAs in CD8 + T-cells for enhanced cancer therapy. bortezomib treatment of activated CD8 + T-cells upregulates miR-155, leading to the downregulation of SOCS1 and SHIP1 proteins. This, in turn, suppresses PD-1 expression. Besides, metformin treatment reduces miR-107 expression in CD8 + T-cells

activation, infiltration, and effector function, we can potentially overcome T-cell exhaustion and immune evasion, leading to more effective cancer immunotherapies.

In this regard, by deciphering the specific miRNAs that enhance CD8 + T-cell activity in different cancer types, we can identify potential therapeutic targets. Upregulating tumor-suppressive miRNAs like miR-149-3p (breast cancer) or miR-448 (colon cancer) could enhance CD8 + T-cell infiltration and function. Conversely, silencing immunosuppressive miRNAs like miR-21 (multiple cancers) or miR-155 (lymphoma) could reinvigorate exhausted T-cells and unleash their anti-tumor potential. Additionally, exhausted CD8 + T-cells present a significant hurdle in immunotherapy. Targeting miRNAs that regulate key exhaustion markers, such as PD-1 and TIM-3, could be a promising strategy. For instance, miRNAs like miR-340-5p (lymphoma) have been shown to enhance CD8 + T-cell function by downregulating PD-1 expression.

Moreover, developing effective delivery systems to specifically target miRNAs within the TME is crucial for therapeutic success. Utilizing nanoparticles, viral vectors, or engineered T-cells to deliver miRNA mimics or inhibitors could maximize efficacy while minimizing off-target effects. Further research is needed to explore the complex interactions between miRNAs, the TME, and other immune cell populations. Additionally, conducting clinical trials to evaluate the safety and efficacy of miRNA-based therapies in cancer patients is essential for translating these promising findings into tangible clinical benefits. Unraveling the miRNA regulatory network within the TME holds the key to unlocking the full potential of CD8 + T-cells for robust and durable antitumor immunity. By harnessing the power of miRNA manipulation, we can move closer to a future where cancer immunotherapies are more precise, potent, and ultimately, curative.

Abbreviations

CTLs	Cytotoxic T lymphocytes
PD-1	Programmed cell death 1 ligand
IL-2	Interleukin-2
Treg	Regulatory T
TME	Tumor microenvironment
3′-UTRs	3′ Untranslated regions
TEX	T-cell exhaustion
PRC2	Polycomb repressor complex 2
Foxo1	Forkhead box protein O1
TCF1	T-cell factor 1
PTEN	Phosphatase and TENsin homolog
Akt	Phosphatidylinositol 3-kinase
EMT	Epithelial-to-mesenchymal transition
TIL	Tumor-infiltrating lymphocytes
PDL-1	Programmed cell death 1 ligand 1
ZEB1	Zinc finger E-box binding homeobox 1
KIF2C	Kinesin family member 2 C
GC	Gastric cancer
MMR	DNA mismatch repair
LNM	Lymph node metastasis
sEVs	Small extracellular vesicles
MMP7	Matrix metalloproteinase 7
GSK3β	Glycogen synthase kinase-3 beta
IDO1	Indoleamine 2,3-dioxygenase 1
TNFR2	Tumor necrosis factor receptor type 2
FoxP3	Forkhead box P3
TNFR2	Tumor necrosis factor receptor 2
CRC	Colorectal cancer
CANX	Calnexin
MHC-I	Major histocompatibility class I
TAMs	Tumor-associated macrophages
LncRNA	Long non-coding RNA
EOMES	Eomesodermin
HCC	Hepatocellular carcinoma
NEAT1	Nuclear-enriched autosomal transcript 1
TIM-3	T-cell immunoglobulin and mucin domain-3
PBMCs	Peripheral blood mononuclear cells
hnRNPA2B1	Heterogeneous nuclear ribonucleoprotein A2/B1
KCs	Kupffer cells
Gal-LCP	Galactose-targeted lipid calcium phosphate
TCGA	The Cancer Genome Atlas
GEO	Gene Expression Omnibus
LUAD	Lung adenocarcinoma
DEDD	Death effector domain-containing DNA binding protein
IFN	Interferon
EGFR	Epidermal growth factor receptor
NSCLC	Non-small cell lung cancer
SHP2	Src homology region 2 (SH2)-containing protein tyrosine phosphatase 2
HNSCC	Head and neck squamous cell carcinoma
mTOR	Mammalian target of rapamycin
OSCC	Oral squamous cell carcinoma
ATC	Anaplastic thyroid carcinoma
UCA1	Urothelial cancer associated 1
DLBCL	Diffuse large B-cell lymphoma
ShMALAT1	Short hairpin RNA targeting MALAT1
TXNRD1	Targeting thioredoxin reductase 1
STAT3	Signal transducer and activator of transcription 3
TNBC	Triple-negative breast cancer
RCC	Renal cell carcinoma
OC	Ovarian cancer
EVs	Extracellular vesicles
UCEC	Uterine corpus endometrial cancer
PLP2	Proteolipid protein 2
PMN-MDSCs	Polymorphonuclear myeloid-derived suppressor cells
FATP2	Fatty acid transporter protein 2
RIPK3	Receptor-interacting protein kinase 3
AML	Acute myeloid leukemia
ROS	Oxygen species
NPM1	Nucleophosmin
NKT	Natural killer T
NPC	Nasopharyngeal cancer
SOCS-1	Suppressors of cytokine signaling-1
CTLA-4	Cytotoxic T-lymphocyte associated protein 4
AAV	Adenovirus-associated virus
DC	Dendritic cells
TLR9	Toll-like receptor 9
NeoAgs	Neoantigens
SOCS1	Suppressor of cytokine signaling 1
SHIP	Inositol polyphosphate-5-phosphatase

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