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MiRNAs in cancer therapy: focusing on their bi-directional roles

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Abstract

MicroRNA (miRNA) dysregulation is causal in most, if not all, cancers. They silence the gene's expression by modulating messenger RNA (mRNA) through employing translational repression or degradation. MiRNA has the ability to target various genes, which involve various significant signaling pathway in cancer cells, to control cancer development and progression. As a result, manipulating miRNA expression levels for cancer therapy seems an attractive and novel therapeutic approach. However, certain miRNAs, which possess the bi-directional roles, could promote cancer cells growth, but also enhance T-cell immunity. Therefore, miRNA-based therapy could also kill T cells and other lymphocytes, ultimately resulting in promoting cancer growth, which makes miRNA-based cancer therapy process with caution. In this view, we will focus on these miRNAs with the bi-directional roles, and discuss their potential effects to cancer therapy. Ultimately, identified and dissected the miRNAs crossing both T-cell-mediated anti-tumor immunity and tumor cell growth will prove vital for the design of more effective and safer strategies for cancer therapy.

Keywords: microRNA, T-cell immunity, Cancer therapy, Bi-directional roles

Introduction

MicroRNAs (miRNAs, miRs) are short (approximately 22 nucleotides), non-coding regulatory RNAs and post-transcriptionally regulate gene's expression by binding to the 3′-untranslated region (UTR) of complementary target mRNA, causing either mRNA translation inhibition or mRNA instability [1, 2]. As crucial modulators, miRNAs participate in various biological processes such as development, differentiation, proliferation and survival, and distorted miRNAs expression and regulation has been implicated in many diverse pathologies especially in cancer [1, 3]. The vast majority of miRNAs are deregulated in most, if not all, cancers, for example, lung cancer, breast cancer and colorectal carcinoma and so on [4–7]. Based on their functional activities, many of these miRNAs are divided in two groups: oncogenic miRNAs (oncomiRs) or tumor-supp ressive miRNAs [8]. Generally, oncomiRs are overexpressed in neoplastic or cancerous lesions, leading to down-regulating their target mRNA with an anti-cancer role such as the miR-17-92 [9]. Tumor-suppressor miRNAs, by contrast, are under-expressed in cancers; an example of this is the miR-34 family in colorectal cancer, targeting e.g. FGFR1, INHBB and AXL [10]. When oncomiRs or tumor-suppressor miRNAs are inhibited or over-expressed, respectively, cancer cell phenotype (proliferation, metastasis, drug resistance and /or survival) may be markedly reduced. Mounting evidences have revealed that suppression of oncomiRs could inhibit cancer development and progression [11]. Thus, miRNAs have become one of the most attractive and promising targets for therapeutic intervention in cancer today.

However, miRs also play a significant role in innate and adaptive immune responses. Our immune system has evolved to kill altered-self cells with high specificity throughout the whole body, and T-cell-mediated immune responses controls cancer immunosurveillance and cancer elimination [12]. Several studies have demonstrated that various levels of T-cell immunity are regulated by specific miRNAs [13, 14]. These miRNAs participate in generic cell biological processes in T-cell's response to different signals, such as proliferation, differentiation and function. Interestingly, recent studies reveal that both T-cell activation and cancer development may share some miRNAs [15, 16]. Hence certain miRNAs have been shown to be oncogenic in most cancers, but also display the function of tumor elimination by regulating T-cell-mediated anti-tumor

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immune response [17, 18]. As a result, targeting miRNA strategy deployed to inhibit cancer cell growth often eliminates T cells and other lymphocytes. Reversely, the approaches aimed to activate T cells by delivering miRNAs inhibitors or mimics may ultimately turn out to promote cancer cell proliferation in practice. The fact that the bi-directional roles of miRNAs is not a surprise due to the large number of genes modulated by a particular miRNA [19, 20]. Therefore, focusing only tumor cell growth and ignoring their effects on T-cell proliferation and function when miRNAs as cancer therapeutics may represent an oversimplification that must be scrutinized in all cancer related miRNAs therapy studies with care. To date, this issue has been ignored, and few studies have directly tested its potential causes.

Cancer progression is not solely a function of the cancer cells themselves, but also of the cellular components and physical factors within the tumor microenvironment (TEM), leading to evading T-cell mediated immune surveillance and elimination [8]. In addition, miRNAs may have significantly influences on T-cell proliferation and function. Hence, it is necessary to consider the influence of miRNAs to both T cells and cancer cells themselves when testing miRNAs from a therapeutic standpoint. This view should take into account the bi-directional roles of miRNAs in both tumor cells and T cells in cancer therapy, not just the effects of the miRNAs that are specific to the cancer cells themselves. Here, we present several examples of when a miRNA exerts an oncogenic or tumor suppressive effect on the cancer cells themselves but an anti-cancer or pro-cancer effect by regulating T-cell-mediated anti-tumor immune response, or vice versa (summarized in Fig. 1).

Bi-directional roles of miRNAs in cancer cells and T cells

MiRNA-21

As the most prominent example of a miRNA that could as either an oncomiR in cancer cell themselves or a tumor suppressor via regulating T cells proliferation and activation, we consider miR-21. As one of the first identified oncomiRs, miR-21 has been shown to be the most generally over-expressed miRNA in the vast majority of solid and hematological malignancies [21]. Extensive studies have implicated the integral role of miR-21 in tumor pathogenesis and during all other stages of carcinogenesis, as follows: i) down-regulation of miR-21 in glioblastoma cells could induce caspases activation and promote apoptosis, which shows that miR-21 can serve as an anti-apoptotic factor [22]. ii) In response to mouse skin carcinogenesis protocol, absence of miR-21 in mice showed a marked decrease in papilloma formation, and overexpression of miR-21 in vivo leads to a pre-B malignant lymphoid-like phenotype and promotes Kras-mediated lung tumorigenesis [23–25]. iii) Metastasis is a key factor of cancer-related death, knock down of miR-21 in B16 cells result in decreasing extravasation and distal metastasis, and the survival rate of the mice tail-vein injected with *miR-21*$^{-/-}$ B16 cells was markedly enhanced, suggesting that miR-21 acts as an pro-metastatic factor [26]. iv): Drug resistance is a major clinical obstacle to the successful treatment of cancer. Prior studies have shown that over-expression of miR-21 leads to chemoresistance in several cancer types, such as breast and ovarian cancer [7, 27]. v): knock down of miR-21 in hepatocellular carcinoma cells could reduce tumor cell proliferation, migration, and cell cycle [28]. The oncogenic activity of miR-21 may be reconciled by taking into account the fact that each miRNA has the capacity of targeting tens to hundreds of different genes. In the case of miR-21, targets include mRNA encoding anti-apoptotic factors (BCL-2, TIMP3, FASL, BMPR2, PDCD4 and PTEN), Pro-proliferative factors (PTEN, SPRY1/2, TGFBR2 and HNRPK), invasion and metastasis promoters (PPARA, TPM1, TIMP3 and MARCKS), and pro-angiogenesis factors (TIMP3 and RECK) [29]. Therefore, several studies have been showed that miR-21 may act as a novel therapeutic target for human cancer, and inhibiting miR-21 in cancer cells has achieved some success.

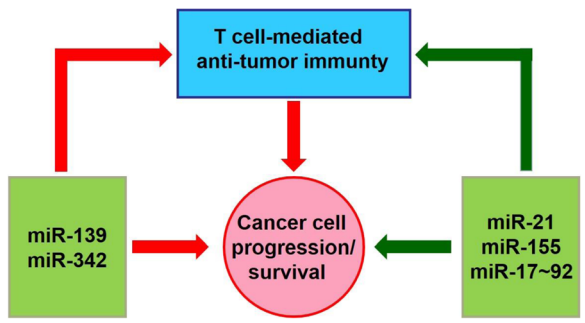

Fig. 1 Examples of miRNAs that have the bi-directional roles in cancer therapy. miRNAs inhibition or overexpression may promote cancer cells growth, but also enhance T-cell immunity. Green arrows, positive regulation; red arrows, negative regulation

However, miR-21 also plays a major role in regulating T-cell immunity. MiR-21 expression is induced during T cell proliferation and function [30]. MiR-21 inhibits apoptosis in activated T cells in part via targeting tumor suppressor gene *Tipe2*, and also regulates T lymphocyte activation by increasing IL-2, Rab34 and Tri1 expression [31, 32]. Further supporting the function of miR-21 in T cells activation is that miRNA-21 depletion impaired T-cell-mediated immune response to stimulations [33]. In addition, an analogous role for miR-21 was found for tumor-associated T cells. *MiR-21*$^{-/-}$ mice could accelerated the grafted tumor growth via slowing both $CD4^+$ and $CD8^+$ cells proliferation as well as reducing their cytokine production. Although deletion of miR-21 in cancer cells could significantly retard cancer growth [34], systematic injection of anti-miR-21 oligonucleotides

did not show marked inhibition of the anti-cancer ability in the tumor-bearing animals, possible because miR-21 inhibition in cancer cells was compensated by the reduction of the activity of the T cell-mediated anti-cancer immune response by the anti-miR-21 strategy [15]. Together, these studies clearly demonstrated that the importance of considering miR-21's role in tumor-infiltrating T cells when designing miR-21-based therapeutics.

MiRNA-155

Another typical example of this phenomenon is provided by miR-155. Similar to miR-21, miR-155 is commonly over-expressed in a large number of solid and hematological malignancies, and has been involved in the development of leukemia, colon and prostate cancer [35–38]. Over-expression of miR-155 in B cells in mice could induce a preleukemic pre-B cell proliferation and ultimately lead to a frank B cell malignancy [39]. Some of targets (TP53INP, SOCS1, CEBPB and APC) of miR-155 control apoptosis, proliferation, cell cycle progression, invasion, migration and stemness [40]. In addition, miR-155 overexpression is also involved in genome instability and drug resistance, for example, miR-155 overexpression could increase mutation and enhance genomic instability by targeting MLH1 and MSH2/6 via affecting multiple DNA repair pathways [41], as well as down-regulation of miR-155 successfully resensitizes tumors to multiple chemotherapeutic agents in an orthotropic lung cancer model [42]. Meanwhile, silence of miR-155 was also successfully used in miR-155 overexpressed lymphomas treatment [43].

However, there is an interesting overlap that miR-155 is considered as an oncomiR, but also plays important roles in anti-cancer immune response [44]. MiR-155 is associated with Th1/Th2 differentiation. Up-regulation of miR-155 in naive $CD4^+$ T cells leads to polarized differentiation preferentially into Th1 cells by targeting the IFN-γ receptor alpha chain (IFNGR1). Reversely, $CD4^+$ T cells lacking miR-155 were more prone to polarize towards Th2 cells, as well as decrease IFN-γ and IL-2 secretion upon antigenic stimuli [45–47]. In addition, miR-155 also targets CTLA-4 (cytotoxic T-lymphocyte antigen-4), a negative regulator of T-cell activation, suggesting that a second, independent pathway via miR-155 enhancing T cell activation [48]. Also, absence of miR-155 could weaken T cell trafficking and antiviral $CD8^+$ T cell responses [49–52]. These studies implies that deletion of miR-155 in tumor-associated T cells might inhibit anti-cancer immune response and promote rather than retard tumor growth. This notion is supported by the fact that *miR-155*$^{-/-}$ $CD8^+$ T cells were ineffective at inhibiting tumor growth [17]. Based on the effects on T-cell immunity and cancer cells themselves, the use of anti-miR-155 as a cancer therapeutic approach should proceed with caution.

miR-17-92

Other example of miRNAs that may have the bi-directional roles of miRNAs in cancer cells and T cells are miR-17-92. MiR-17-92 have been identified to be up-regulated in various cancers, such as breast cancer, colon cancer and gastric cancer, enhances proliferation, inhibit apoptosis, and confer pro-metastasis function in cancers, thereby promoting cancer-progression [9, 53–55]. However, several studies have demonstrated that the miR-17-92 cluster promoted polarization towards a type 1 phenotype, for example, miR-19b and miR-17 were crucial in enhancing Th1 responses and inhibiting differentiation into inducible Tregs (regulatory T cells) by down-regulating their target genes, such as PTEN (miR-19b), TGFβRII and CREB1 (both miR-17) [56–58]. In addition, miR-17-92 is also up-regulated in $CD8^+$ T cells, could promote IFN-γ secretion, and enhance cytotoxicity in response to stimulation. Also, miR-17-92 increases the frequency of $CD8^+$ memory T-cells produce IFN-γ, as well as resists TGF-β-mediated suppression [59, 60]. In a word, these results emphasize the great complexity of the miRNA's function in tumor therapy.

Other miRNAs

Other miRNAs such as miR-139 and miR-342, have also similar roles in both cancer cells and T cells. Both miRNAs could target several oncogenes and are classified as tumor suppressor in various cancers [61–63]. However, miR-139 and miR-342 inhibition could boost T cell cytotoxicity by down-regulating perforin and EOMES expression [64]. Thus, testing a miRNA's effect on both T-cell immunity and cancer cells themselves may be of the utmost importance when development a miRNA-based therapeutic agents for cancer.

The effect on cancer therapy of their bi-directional roles

As a novel therapeutic option, regulatory miRNAs to retard cancer development and progression even eliminate cancer are attracting more and more attention [65]. However, their bi-directional roles may be an obstacle for miRNA-based therapies to clinical treatment. Restoring miRNA function using a synthetic miRNA (for tumor suppressor miRNAs) or suppressing the activity of a miRNA by anti-miRNA oligonucleotides (for oncogenic miRNAs) could inhibit cancer cells proliferation, metastases and so on, but they could also affect the anti-tumor function of immune cells especially T cells, in tumor microenvironment. Hence delivering miRNA mimics or anti-miRNAs into cancer tissues may not exert their anti-tumor effect, possible because miRNAs suppression or over-expression in tumor cells to retard tumor growth is neutralized by the inhibition of the function of the T cell-medicated anti-tumor immunity by the targeting miRNAs strategy, for example, anti-miR-21 approach [15]. To overcome the

barrier, efforts should be made to develop novel and specifically targeted systems to tumor cells to avoid the influence of miRNAs to T cell-medicated anti-tumor immunity [66].

In addition, manipulating miRNAs for T cells to improve the anti-tumor activity of adoptively transferred tumor-reactive T cells should be a more promising approach for miRNA-based cancer therapies. It has been proved to be effective that T cells could be isolated, treated with miRNAs mimics or anti-miRNAs oligonucleotides and then reintroduced into tumor-bearing animals [67]. MiRNAs could improve adoptive T cell immunotherapy from the following aspects: (1) boosting TCR sensitivity, some miRNAs could regulates TCR signaling by targeting key inhibitory phosphatases (DUSP10 or PTPN2) to promote T cell activation such as miR-21 and miR-155 [14]; (2) enhancing T cell fitness, overexpressing miR-17~92 in anti-EGFRvIII CAR-modified T cells could enhance their anti-tumor activity [68]; (3) augmenting effector functions, miR-139 and miR-342 inhibition could promote T cell effector functions [64].

Conclusions

Adoptive cell transfer (ACT)-based immunotherapy, especially microRNA-based redirected tumor-reactive T cells, has shown promise as a potentially curative means for patients with advanced cancer. Although some miRNAs (miR-21 and miR-155 and so on) have dual roles in tumor progression, they are also key regulators of T cell activation, proliferation and effector functions, which are all important factors involving the therapeutic outcome of ACT-based immunotherapy. Meanwhile, miRNA-based therapy offers some advantages over other gene engineering strategies and protein-target-based immune modulation, for example, miRNAs could target multiple molecules simultaneously, and manipulating a single miRNA could rebuild T cell behavior and bypass the need for complex transcriptional reprogram. Lastly, due to their small size, miRNA mimics and inhibitors could be easily integrated into existing multicistronic TCR and CAR platforms. Therefore, a further understanding of the role that miRNAs play in T cell fate and behavior is driving us closer to the prospect of safe and effective miRNA-based redirected T cell therapies.

In addition, the complexity of cancer development and progression make development a cancer therapeutic approach need to think about the effects to both cancer cells and tumor-associated T cells, especially miRNA-modulating therapies. Targeting miRNAs could simultaneously effect on many genes expression and even certain key signaling pathways, which participate in both T-cell proliferation and cancer development, such as NF-κB and Akt pathways. Hence, this phenomenon is really possible that miRNA-based therapy ultimately results in promoting cancer growth. Depending on the balance between modulation of miRNAs in cancer cells and the effects of the miRNAs on T-cell-mediated anti-cancer immunity, the miRNAs may produce an overall net anti-cancer or net pro-cancer effects. Preclinical trials show lots of miRNAs with significantly potential in cancer therapy, but these data are mainly from miRNAs-modulated tumor cells using in vitro and immunocompromised xenograft models, and eliminate the effects of miRNAs to T-cell-mediated anti-cancer immune response. To then end, we strongly recommend the use of immunocompetent mouse models in preclinical trials of potential miRNA therapeutics to give consideration to our body immune system and cancer cells themselves. Therefore, identified and dissected the miRNAs crossing both T-cell immunity and cancer cell growth is of the utmost importance, as there is currently plenty of excitement in the administration of exogenous miRNAs mimics and miRNAs inhibitors for controlling cancer growth. Such studies may be necessary and urgent in driving miRNA-based therapeutics from preclinical trials to clinical practice.

Abbreviations

ACT: Adoptive cell transfer; CTL: $CD8^+$ cytotoxic T lymphocytes.; CTLA-4: Cytotoxic T-lymphocyte antigen-4; MiRNA or miR: microRNA; mRNA: Messenger RNA; OncomiRs: Oncogenic miRNAs; TEM: Tumor microenvironment; Tregs: Regulatory T cells; UTR: Untranslated region

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Availability of data and materials

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Authors' contributions

W. H., J. Z. and L. D. conceived this seminar. W. H., J. X. and Z. H. wrote the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

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Consent for publication

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Competing interests

The authors declare that they have no competing interests.

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