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Mini-Review

# Mir-155, a central modulator of T-cell responses

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**The activation of T cells is a tightly regulated process that has evolved to maximize protective immune responses to pathogens while minimizing damage to self-tissues. A delicate balance of cell-intrinsic, costimulatory, and transcriptional pathways as well as micro-environmental cues such as local cytokines controls the magnitude and nature of T-cell responses in vivo. The discovery of functional small noncoding RNAs called micro-RNAs (miRNAs) has introduced new mechanisms that contribute to the regulation of protein translation and cellular responses to stimuli. miRNAs are short (approximately 22 bp) RNA species, which bind to mRNAs and suppress translation. Due to their short length and imperfect base pairing requirements, each miRNA has the potential to regulate various pathways through the translational inhibition of multiple mRNAs. The human and mouse genomes each encode hundreds of miRNAs, and studying the function of miRNAs has led to the realization that they play important roles in diverse biological processes from development and cancer to immunity. This review focuses on the function of mir-155 in T cells and the impact of this miRNA on autoimmunity, tumor immunity, and pathogen-induced immunity.**

**Keywords:** CD8 T cells · Immune responses · Cellular activation · mir-155

## Introduction

Mir-155 was one of the first miRNAs discovered and has been identified as the functional element in the loci associated with lymphomas known as the B-cell integration cluster (*bic*) [1]. *Bic* is responsible for a subset of avian leukosis virus integration-induced lymphomas, but because *bic* does not encode a protein it was speculated that it functions through its RNA [2]. The discovery of miRNAs quickly led to the identification of mir-155 as the active element in *bic* [3, 4]. Previous studies have shown that mir-155 is sufficient to transform B cells, resulting in lymphoma in mice, thus indicating that mir-155 is involved in the cellular activation, proliferation, and survival of B cells [5]. Soon after this discovery, two independent groups published that germline deletion of mir-155 does not interfere with mouse development but has an impact on its immune function [6, 7]. The known involvement of mir-155 in lymphoma led both groups to examine B-cell responses, upon which they found that germinal center formation in response to vaccination is greatly impaired in mir-155-deficient mice.

When T-cell function was assessed in mir-155-deficient animals, it became clear that mir-155 serves various functions. Mir-155 levels are increased after stimulation of T-cells through TCR engagement [7–9]. Although the development of most T-cell subsets appeared normal in the absence of mir-155 in mice, $CD4^+$ T cells preferentially skewed to the Th2 lineage in vitro [6, 7]. A higher percentage of mir-155-deficient $CD4^+$ T cells produce IL-4 with fewer such T cells producing IFN-$\gamma$ under neutral stimulation conditions in vitro [6, 7]. This bias may be due to increased levels of the transcription factor c-Maf, which is important for the production of IL-4 [10], and which has been identified as a target of mir-155 [6]; however, further mechanistic studies are required. In human $CD4^+$ T cells, mir-155 targets the IFN-$\gamma$ receptor alpha subunit and regulates both skewing and proliferation of Th1 and Th2 subsets [11]. A role for mir-155 in regulatory T-cell (Treg)

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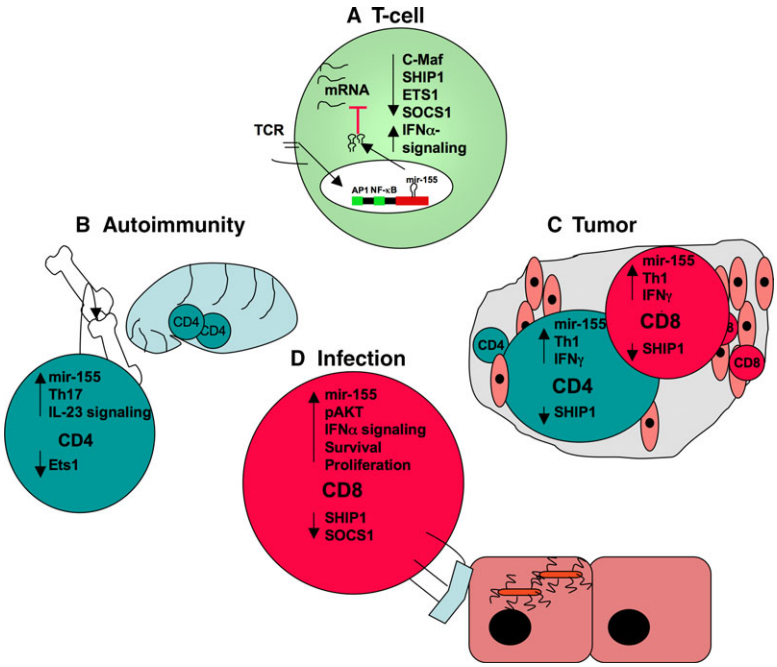


**Figure 1.** The effects of mir-155 on T cells in the context of autoimmunity, antitumor responses, and infection. (A) T-cell receptor engagement results in increased mir-155 levels in the T cell. The resulting translational repression of target mRNA molecules, several of which with identified T-cell function (listed), leads to increased functional activity of the T cell. (B) In the context of autoimmunity, mir-155 has an impact on skewing to the Th-17 lineage though the regulation of ETS1 expression and IL-23 signaling. (C) Antitumor T-cell responses require mir-155 to allow vigorous cellular expansion and IFN-γ production. (D) $CD8^+$ T cells require mir-155 to promote clonal expansion, survival, and memory generation as part of their antiviral and antibacterial responses.

biology has also been demonstrated, where the absolute number of Treg cells was found to be reduced in mir-155-deficient animals [12, 13]. By using a series of transplant experiments, it was shown that mir-155 is critical for Treg-cell survival in mice [12, 13]. Furthermore, it has been reported that SOCS1 is a target of mir-155 in Treg cells. Treg cells lacking mir-155 have hightened levels of SOCS1. This increased expression of SOCS1 then results in reduced STAT5 phosphorylation downstream of IL-2 receptor signaling [12]. These defects in mir-155-deficient T cells led researchers to study the impact of mir-155 on T-cell-associated functions in vivo in the context of autoimmunity, cancer, and the response to pathogens (Fig. 1A).

## Role of mir-155 in autoimmunity

High levels of mir-155 have been associated with several human autoimmune diseases including multiple sclerosis (MS) [14], rheumatoid arthritis (RA) [15], and atopic dermatitis [16]. The mouse model of MS, experimental autoimmune encephalomyelitis (EAE), depends in part upon $CD4^+$ T cells responding to IL-23 and skewing of these cells toward the $IL\text{-}17^+$ (Th17) lineage [17]. Several studies have now shown that mir-155-deficient animals have defects in skewing toward the Th17 lineage both in vivo and in vitro [18–21]. In addition, mice lacking mir-155 do not develop EAE [18–20] or collagen-induced arthritis [22]. This defect in IL-17 production is at least in part due to the inability of mir-155-deficient T cells to respond to IL-23, through the dysregulation of the transcription factor Ets1, which is a known suppressor of Th17 differentiation [20, 23, 24]. While several groups clearly demonstrated that mir-155-deficient T cells have impaired production of IL-17, the fact that IL-17 is not required for EAE induction [25] suggests a more complex role for IL-23 signaling in $CD4^+$ T cells (Fig. 1B).

## Role of mir-155 in tumor immunity

T cells play a major role in antitumor immune responses. In both melanoma and lymphoma transplantable tumor models, it has been demonstrated that tumors have a growth advantage in mice lacking mir-155 [26]. Tumor-bearing $mir\text{-}155^{-/-}$ mice have fewer tumor-infiltrating $CD4^+$ and $CD8^+$ T cells producing IFN-γ when compared to tumor-bearing wild-type (WT) mice. The requirement for mir-155 in antitumor $CD8^+$ T cells was also shown in a prophylactic vaccination model using adoptively transferred antigen (Ag)-specific $CD8^+$ T cells [9]. In this study, the adoptively transferred $mir\text{-}155^{-/-}$ $CD8^+$ T cells are not as efficient as WT T cells at mounting functional antitumor responses [9]. The reduced number of IFN-γ-producing cells lacking mir-155 is due to impaired T-cell function and not due to defective Ag-presenting capability or other environmental effects related to the absence of mir-155. It was also reported that SHIP1 is a functional target of mir-155 in $CD4^+$ T cells, as has been shown previously in myeloid cell types such as macrophages [27] and dendritic cells (DCs) [18]. SHIP1 suppresses Th1 responses [28] and reducing the levels of SHIP1 in $mir\text{-}155^{-/-}$ T cells restores IFN-γ production and antitumor responses [26] (Fig. 1C).

There are many unanswered questions regarding the role of mir-155 in antitumor T-cell responses. Since the tumor microenvironment does affect infiltrating T cells and induces an unresponsive state in some models, one wonders whether infiltrating lymphocytes in tumors have altered levels of mir-155. In addition, while there are clearly effects of mir-155 deficiency on IFN-γ

 

production by CD8$^+$ T cells [26], we know little about the functional ability of Ag-specific mir-155$^{-/-}$ CD8$^+$ T cells to engage and kill tumor targets.

## Role of mir-155 in response to infectious agents

Ag-specific T-cell responses are critical for the clearance of, and protective memory to, many intracellular pathogens and viruses. Given that mir-155 levels are regulated after T-cell activation [6, 7], several groups have now tested whether mir-155 plays a role in T-cell responses to pathogens. The first report finding a requirement for mir-155 in T-cell responses to pathogens came from vaccination studies using *Salmonella typhimurium* [6]. The authors observed that mice lacking mir-155 are incapable of inducing a protective response to *S. typhimurium*, but the cell types that contribute to this defect were not identified in that study [6]. Mir-155$^{-/-}$ mice have also been found to have a reduced ability to clear *Helicobacter pylori* and subsequently do not develop severe gastric damage during infection due to impaired IFN-$\gamma$ production by T cells [29]. Several reports have recently shown that mir-155 regulates CD8$^+$ T-cell immunity to viral and intracellular bacteria [8, 9, 30, 31]. When mice lacking mir-155 were challenged with lymphocytic choriomeningitis virus (LCMV), influenza, or murine gammaherpes virus 68 (MHV-68), limited CD8$^+$ expansion as measured by tetramer staining was observed in all models. While the total number of Ag-specific CD8$^+$ T cells at the peak of the response is reduced in all three viral infections, the Ag-specific T cells are able to lyse targets and produce effector molecules such as IL-2, IL-4, IFN-α, TNF-α, and granzyme B [8, 9, 30, 31]. Despite the limited virus-specific CD8$^+$ T-cell response in mice lacking mir-155, these animals are nevertheless able to clear low-dose LCMV infection [9, 31]. This is not the case for both influenza and MHV-68 infections, where increased viral titers were observed in the lungs of infected mice at the time points measured [8, 30]. This disparity in viral clearance indicates that the reduced T-cell response that is induced in the absence of mir-155 has functional limitations dependent upon the nature of the pathogen, and that mir-155 is not required in all cases to clear infection.

The limited CD8$^+$ T-cell response during infection could result from many factors including reduced proliferation or impaired survival during expansion. After infection with *Listeria monocytogenes*, adoptively transferred Ag-specific CD8$^+$ T cells go through the same number of rounds of division as WT cells but fail to accumulate, suggesting a survival rather than proliferative defect [31]. However, it has been shown by sensitive methods that both proliferative (as measured by both Ki67$^+$ and BrdU uptake) and survival defects (as measured by Annexin V staining) can be observed in CD8$^+$ T cells from mice lacking mir-155 after LCMV infection [9]. Thus it appears that mir-155 impacts both the survival and the proliferation of CD8$^+$ T cells after activation, and that the magnitude of each parameter may depend on complex factors such as cytokine environment and Ag levels.

One hallmark of CD8$^+$ T-cell responses is the development of memory. Early differentiation of CD8$^+$ T cells into memory cells can be detected during the initial acute response to virus and bacteria. Cells responding to a pathogen can be divided into short-lived effectors (SLECs) and memory precursors (MPECs) based on the surface expression of CD127 (IL-7R) and KLRG1 [32]. The fate decision leading CD8$^+$ T cells down either of these lineages is thought to be due to the combined effects of cytokine exposure [33], TCR signal strength, and competition for Ag [34]. After clearing the initial infection, CD8$^+$ memory cells remain to protect the host from re-infection. These memory cells can be divided into two populations known as central memory ($T_{CM}$) and effector memory ($T_{EM}$) cells. These cells are defined based on anatomical location and the expression of CD62L, with $T_{CM}$ cells showing high expression of CD62L and $T_{EM}$ cells showing low CD62L expression [35].

The role of miRNAs in memory fate decisions has also been examined in CD8$^+$ T cells in both mice and humans. Distinct patterns of miRNA expression have been found to correspond to the activation state of CD8$^+$ T cells [36, 37]. CD8$^+$ T cells with a memory phenotype in healthy human peripheral blood express higher levels of mir-155 than naive cells, associating mir-155 with CD8$^+$ T-cell memory [38]. When murine CD8$^+$ T cells are cultured in vitro and skewed via cytokines to differentiate into effector and central memory subsets, $T_{CM}$ cells display lower levels of mir-155 when compared with $T_{EM}$ cells, which have high levels of mir-155 [30, 39]. The authors in both cases speculated that mir-155, among other miRNAs, is critical for the memory lineage fate decisions in CD8$^+$ T cells. Of note, these experiments maintained constant TCR stimulation while varying the addition of cytokines, and therefore the miRNA expression pattern observed is due to a single input (cytokines) into the lineage decision. The role of mir-155 in the development of CD8$^+$ memory lineages was also studied in the context of antiviral T-cell responses in vivo. The isolation of $T_{EM}$ cells and $T_{CM}$ cells from mice 60 days after infection with influenza virus confirmed the in vitro results, showing that mir-155 is maintained at a high level in $T_{EM}$ cells and downregulated in $T_{CM}$ cells [8], suggesting that mir-155 may indeed play a functional role in CD8$^+$ memory differentiation. When the expansion of CD8$^+$ T cells was measured early in infection with MHV-68, it was observed that T cells lacking mir-155 produce a higher ratio of MPECs to SLECs than WT cells [30]. Since the overall expansion of CD8$^+$ T cells in response to infection is lower, the total number of all memory cells produced is reduced when T cells did not express mir-155 (Fig. 1D).

## Potential targets that are altered by mir-155

Every miRNA is predicted to interact with, and potentially modulate the level of, translation of hundreds of mRNAs. Thus, mir-155 most likely functions via the modulation of protein networks in T cells. Several mir-155 targets have been identified that have a clear impact on CD8$^+$ T cells. Regulatory proteins in the PI3K/AKT pathway have been identified as targets of mir-155 [27, 40]. One

 

study observed reduced AKT phosphorylation after TCR engagement in mir-155$^{-/-}$ CD8$^+$ T cells, coinciding with an in vivo survival defect of those cells after infection with *L. monocytogenes* [31]. The phosphatase SHIP1 has previously been shown to be a target of mir-155 in myeloid cells [18, 27, 41] and CD4$^+$ T cells [26]. Increased levels of SHIP1 protein have been observed in mir-155-deficient CD8$^+$ T cells [26]. However, in another report, SHIP1 was not upregulated in mir-155$^{-/-}$CD8$^+$ T cells [8] indicating that further studies defining the role of SHIP1 as a target of mir-155 in CD8$^+$ T cells would be informative.

SOCS1 has also been shown to be a functional target of mir-155 in Treg cells [12]. An increase in SOCS1 levels in CD8$^+$ T cells lacking mir-155 could also contribute to the observed phenotype of impaired proliferation and survival by limiting signaling through cytokines such as IL-2. The levels of SOCS1 protein as well as mRNA transcripts are higher in CD8$^+$ T cells lacking mir-155 compared to their WT counterparts [9]. Reduced levels of STAT5 phosphorylation after exposure to IL-7 or IL-15 in the case of naive T cells, and IL-2 or IL-15 in effector cells was observed in mir-155$^{-/-}$ cells compared with WT cells [9]. However, another study did not observe defects in STAT5 phosphorylation after exposure to various doses of IL-2 [31]. This discrepancy may be due to differences in kinetics of measurement or culture conditions as the timing of receptor-proximal events such as phosphorylation of STATs is difficult to accurately determine in vitro.

Expression profiling of mRNA from activated WT or mir-155$^{-/-}$ CD8$^+$ T cells revealed that many signaling components associated with the interferon response are increased in mir-155−/− CD8$^+$ T cells after activation relative to WT T cells [8]. Interestingly, Ag-specific CD8$^+$ T cells lacking mir-155 have been shown to have increased phosphorylation of STAT1 in response to Type I interferon signaling [8]. The functional impact of increased type 1 interferon signaling on mir-155 knockout CD8$^+$ T cells was confirmed by studies knocking down either IRF7 or STAT1, which resulted in a partial rescue of cellular expansion in response to viral challenge in vivo [8]. In summary, it is likely that mir-155 has an impact on multiple target proteins, such as SOCS1 and pathways including IFN and PI3K/AKT, which contribute to the proliferation and survival of CD8$^+$ T cells during pathogenic infections.

## Conclusions and perspectives

Since the first genetically modified mice lacking mir-155 were created, it has become clear that this miRNA has powerful affect on T-cell function. High levels of expression of mir-155 are associated with inflammation and autoimmunity. Both the regulation of cytokine production in CD4$^+$ T cells and the survival and proliferation of CD8$^+$ T cells are controlled in part by the levels of mir-155 within these cells. It would be beneficial to develop approaches to reliably manipulate miRNA levels in patients to effect desired outcomes, whether it is to reduce mir-155 in the case of autoimmunity or to increase its levels after vaccination. There are clearly plausible future clinical applications for treatments modulating mir-155 levels.

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*Abbreviations:* **Ag**: antigen · **AKT**: protein kinase b · **bic**: B-cell integration cluster · **CD62L**: L-selectin · **CD127/IL-7R**: interleukin-7 receptor · **DC**: dendrtic cell · **IRF7**: interferon regulatory factor 7 · **KLRG1**: killer cell lectin-like receptor subfamily G member 1 · **LCMV**: lymphochoriomeningitis virus · **MHV-68**: murine gammaherpes virus-68 · **MPECs**: memory precursors · **miRNA**: microRNA · **MS**: multiple sclerosis · **RA**: rheumatoid arthritis · **SHIP1**: inositol 5-phosphatase 1 · **SLECs**: short-lived effector cells · **TCM**: central memory cells · **TEM**: effector memory cells

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