Role of MiR-98 and Its Underlying Mechanisms in Systemic Lupus Erythematosus

Lin Xie and Jinhua Xu

ABSTRACT. Objective. T-lymphocyte apoptosis plays a critical role in the pathogenesis of systemic lupus erythematosus (SLE). However, the underlying regulatory mechanisms of apoptosis in SLE remain unclear. The aim of this study was to explore the role of miR-98 in SLE and its underlying mechanisms.

Methods. Western blotting and quantitative reverse transcription PCR (qRT-PCR) were used to analyze miR-98 and Fas expression. Luciferase reporter assays were performed to identify miR-98 targets. To modify miRNA levels, miR-98 mimics and inhibitor were transfected into cells. A lentiviral construct was used to overexpress the level of Fas in SLE CD4+ T cells. Gene and protein expression were determined by qRT-PCR and Western blotting. Apoptosis levels were evaluated by annexin V staining and flow cytometry.

Results. Compared to those of healthy donors, miR-98 was downregulated in SLE CD4+ T cells, whereas Fas mRNA and protein expression were upregulated. Upregulation of miR-98 by mimic transfection protected Jurkat cells against Fas-mediated apoptosis at both mRNA and protein levels, while miR-98 inhibitor induced the completely opposite effect. Luciferase reporter assays demonstrated that miR-98 directly targeted Fas mRNA. Further, miR-98 inhibitor induced apoptosis in primary healthy CD4+ T cells through the Fas-caspase axis, while upregulation of miR-98 in SLE CD4+ T cells led to the opposite effect.

Conclusion. The current study revealed that downregulation of miR-98 induces apoptosis by modulating the Fas-mediated apoptotic signaling pathway in SLE CD4+ T cells. These results suggest that miR-98 might serve as a potential target for SLE treatment. (J Rheumatol First Release June 15 2018; doi:10.3899/jrheum.171290)

Key Indexing Terms: miR-98, FAS, APOPTOSIS, CD4+ T CELLS, SYSTEMIC LUPUS ERYTHEMATOSUS
characteristic cytoplasmic and nuclear condensation, as well as DNA fragmentation. The FasL/Fas system has been well described in the establishment and maintenance of peripheral tolerance. Indeed, defects in either Fas or FasL in mice result in acceleration of SLE-like diseases. Increased FasL/Fas expression and caspase-3 activity together with subsequent increases in T-lymphocyte cell apoptosis (particularly in CD4+ T cells) are detected in human SLE. There is also evidence for modulation of the FasL/Fas system by secretion of soluble Fas in patients with SLE. Moreover, patients with juvenile-onset SLE exhibit upregulation of apoptosis-related protein Bcl-2 and Fas in total T-lymphocytes and CD4+ T cells. Based on these findings, CD4+ T cell apoptosis may be defective in SLE, and the FasL/Fas-mediated signaling pathway likely has a substantial influence on the process. Therefore, targeted inhibition of CD4+ T cell apoptosis is a key approach to treating SLE. However, the molecular components regulating Fas-mediated apoptosis in SLE CD4+ T cells remain poorly understood. MicroRNA (miRNA) are small noncoding RNA that regulate gene expression by acting on their target mRNA, resulting in translation inhibition or mRNA degradation. One of the first identified miRNA families, let-7/miR-98, has a great influence on cell proliferation, differentiation, apoptosis, and oncogenesis. In HeLa cells, miR-98 targets Fas and regulates Fas-mediated apoptosis in a dose-dependent manner. In addition, let-7/miR-98 expression is reduced in activation-induced cell death of CD4+ T cells, accompanied by increased Fas expression. By downregulating Fas/caspase-3 apoptotic signaling pathway, miR-98 regulates myocardial infarction–induced apoptosis. However, the functional role of miR-98 in CD4+ T cell apoptosis in patients with SLE has not been previously investigated.

In our study, we identified the expression patterns of miR-98 in CD4+ T cells from patients with SLE and explored the potential role and underlying mechanisms of miR-98 in regulating cell apoptosis and dysfunction in SLE. Our findings suggested that Fas might be one of several distinct targets of miR-98 that contribute to its ability to regulate cell survival and death by the regulation of apoptosis.

MATERIALS AND METHODS

Subjects. A total of 48 patients with SLE, who were diagnosed based on the 1997 American College of Rheumatology classification criteria, were recruited from Huashan Hospital, Fudan University. Disease activity was assessed on the basis of the SLE Disease Activity Index (SLEDAI). Relevant clinical and laboratory information regarding the patients is summarized in Table 1. Thirty-nine age- and sex-matched healthy donors were recruited voluntarily. This study was approved by the Independent Ethics Committee of Huashan Hospital (No. 2017-101). Written informed consent was obtained from all subjects.

Cell isolation and culture. Peripheral blood mononuclear cells (PBMC) were isolated by density-gradient centrifugation, and CD4+ T cells were obtained by magnetic separation. Purified CD4+ T cells were cultured in OpTmizer CTS T-Cell Expansion SFM ( Gibco) supplemented with 1% L-glutamine and 1% penicillin/streptomycin. Jurkat cells (Chinese Academy of Sciences) were cultured in RPMI 1640 medium supplemented with 10% fetal bovine serum and 1% penicillin/streptomycin.

RNA extraction and quantitative reverse transcription PCR (qRT-PCR). Total RNA was extracted with TRIzol reagent (Invitrogen). Reverse transcription was performed to obtain cDNA for mRNA using PrimeScript RT Master Mix (Takara) and for miRNA using a First-strand cDNA synthesis kit (GeneCopoeia) as previously described. SYBR Premix Ex Taq II (Takara) and an All-in-one miRNA qRT-PCR Detection kit (GeneCopoeia) were used to carry out qPCR. GAPDH or U48 were used as internal controls. The following primers were used: Forward 5ʹ-TCT GGT TCT TAC GTC TGT TGC-3ʹ, reverse 5ʹ-CTG TGC AGT CCC TAG CTG TCC-3ʹ and GAPDH (forward 5ʹ-GGA GCG AGA TGC CTC CAA AAT-3ʹ, reverse 5ʹ-GGC TGT TGT CAT ACT TCT CAT GG-3ʹ). The primers for miR-98 and U48 were directly purchased from GeneCopoeia. All reactions were run in triplicate.

miRNA mimic, inhibitor, and cell transfections. Cells were transiently transfected with miR-98 mimics, miR-98 inhibitor, or mimic/inhibitor controls (GenePharma) using Lipofectamine RNAimax (Invitrogen), and were collected for further analysis 48 h later. The transfection efficiency, evaluated by flow-cytometric analysis relative to a carboxyfluorescein (FAM) dye-labeled miRNA mimic/inhibitor negative control, reached 70% to 80%.

Luciferase reporter assay. The 3’-untranslated region (3’-UTR) of Fas mRNA and its site-directed mutants were PCR-amplified and cloned into psiCHECK-2 vectors (Promega). Afterward, wild-type (WT) or mutated (MUT) luciferase plasmids and miR-98 mimics/negative controls were co-transfected into 293T cells. Luciferase activities were assessed using a Dual-Luciferase Reporter Assay System (Promega) in accordance with the manufacturer’s instructions.

Western blotting. A protein concentration assay kit was obtained from ThermoFisher. Proteins were separated on 12% sodium dodecyl sulfate-polyacrylamide gels and transferred to PVDF membranes (Millipore). The membranes were incubated with anti-Fas, anti-Cleaved Caspase-3, anti-Caspase-3, anti-Cleaved Caspase-8, anti-Caspase-8, anti-Cleaved Caspase-9, anti-Caspase-9, anti-Bax, anti-Bcl-2, and anti-GAPDH (Cell Signaling Technology) antibodies overnight at 4°C, followed by an incubation with corresponding horseradish peroxidase–conjugated secondary antibodies, according to previously published protocols. Detection was carried out using an enhanced chemiluminescence kit (Millipore). GAPDH was used as a loading control.

Lentiviral infection. Purified lentiviral particles containing Fas (LV-Fas) or GFP were used to carry out infection. Detection was carried out using flow-cytometric analysis relative to a carboxyfluorescein (FAM) dye-labeled miRNA mimic/inhibitor negative control, reached 70% to 80%.

Table 1. Clinical and laboratory characteristics of patients with SLE in the study.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>SLE in Figure 1, n = 35</th>
<th>SLE in Figure 5, n = 13</th>
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<tbody>
<tr>
<td>Sex, male/female, n</td>
<td>4/31</td>
<td>1/12</td>
</tr>
<tr>
<td>Age, yrs, median (range)</td>
<td>33 (15–58)</td>
<td>30 (23–58)</td>
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<tr>
<td>SLEDAI score, median (range)</td>
<td>6 (0–16)</td>
<td>7 (0–13)</td>
</tr>
<tr>
<td>Anti-dsDNA, IU/ml, median (range)</td>
<td>201.7 (1–800)</td>
<td>116.9 (33.5–800)</td>
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<tr>
<td>C3, g/l, median (range)</td>
<td>0.63 (0.17–1.24)</td>
<td>0.78 (0.25–1.27)</td>
</tr>
<tr>
<td>C4, g/l, median (range)</td>
<td>0.10 (0.06–0.32)</td>
<td>0.13 (0.07–0.25)</td>
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<tr>
<td>Steroids, n</td>
<td>30/5</td>
<td>11/2</td>
</tr>
<tr>
<td>Secondary agents, n</td>
<td>25/10</td>
<td>9/4</td>
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*The medications that patients received when taking blood samples. Some patients received secondary antirheumatic agents, including methotrexate, azathioprine, cyclophosphamide, and chloroquine. SLE: systemic lupus erythematosus; SLEDAI: SLE Disease Activity Index.


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were purchased from GENECHEM. SLE CD4+ T cells were incubated with viral particles mixed with 8 μl/ml polybrene following centrifugation at 1000 g for 1 h. Twelve hours after infection, the cells were added to fresh complete medium and were collected for further analysis 72 h later. GFP was detected by fluorescence microscope after 72 h, and the ratio of GFP protein suggested whether cells were successfully infected. The overexpression efficiency of Fas was confirmed by qRT-PCR.

Apoptosis assay. Cell apoptosis was detected by flow cytometry analysis with an Annexin V Apoptosis Detection Kit FITC (eBioscience). Briefly, cells were washed once in PBS and resuspended in binding buffer at a concentration of 2 × 10^6 cells/ml. Cells (100 μl) were then incubated with FITC-annexin V (5 μl) for 15 min at room temperature and washed once in binding buffer, followed by resuspended in 200 μl of binding buffer with propidium iodide (5 μl). For SLE CD4+ T cells transfected with lentivirus expressing GFP spectrally overlapped between FITC-annexin V and GFP, allophycocyanin–annexin V in conjunction with 7-AAD was used to avoid the overlap. Data were acquired with a BD Accuri C6 or FACSCanto flow cytometer and analyzed using FlowJo software. Annexin V–positive apoptotic cells were quantified.

Statistical analysis. All data are expressed as the mean ± SEM. GraphPad Prism software was used for statistical analysis. Variables were comparatively analyzed using Student t test. Correlations were determined by Pearson correlation coefficient. For all statistical tests, a p value < 0.05 was considered statistically significant.

RESULTS

MiR-98 is downregulated in freshly isolated CD4+ T cells from patients with SLE. Because miR-98 has been found in several studies to influence apoptotic cell death, we performed qRT-PCR analysis to determine the expression of endogenous miR-98 in samples obtained from CD4+ T cells from 20 patients with SLE and 20 healthy donors. As shown in Figure 1A, miR-98 expression was much lower in SLE CD4+ T cells than in healthy control CD4+ T cells (p < 0.01), suggesting a specific association between decreased miRNA expression and the aberrant CD4+ T cell function in SLE. Next, we evaluated the correlations between miR-98 expression and clinical features. A significant negative correlation was observed between miR-98 levels and SLEDAI scores (r = −0.4305, p = 0.0373; Figure 1B). However, sex or age was not obviously associated with miR-98 expression (data not shown).

Increased expression of Fas and apoptosis in freshly isolated CD4+ T cells from patients with SLE. To determine whether the expression levels of Fas in SLE CD4+ T cells are comparable to those of miR-98, we carried out qRT-PCR and Western blot analysis using total RNA and proteins isolated from CD4+ T cells from patients with SLE and healthy donors. Fas mRNA (Figure 1C) and protein (Figure 1E) expression levels were higher in SLE CD4+ T cells than in...
healthy donors CD4+ T cells, which suggested the dependence of Fas expression on endogenous miR-98 expression in CD4+ T cells. A significant positive correlation was also observed between Fas mRNA levels and SLEDAI scores \((r = 0.4417, p = 0.0434; \text{Figure 1D})\). Because the major route for apoptosis induction in activated lymphocytes is through \(\text{Fas}^{16}\), we next examined the apoptosis levels in SLE. In line with previously published data\(^{11,31}\), the annexin V/PI double-staining assay showed that the percentage of freshly isolated CD4+ T cells that were apoptotic was significantly higher in patients with SLE than in healthy donors (Figure 1F).

**MiR-98 directly targets the 3'-UTR of Fas and downregulates Fas-mediated caspases.** To validate the effect of miR-98 on Fas regulation, we examined the effect of miR-98 by transfecting Jurkat cells with miR-98 mimics or miR-98 inhibitor (anti–miR-98). Both qRT-PCR and Western blot analysis showed that transfection with miR-98 mimics significantly reduced Fas expression at mRNA and protein levels, whereas transfection with miR-98 inhibitor, which blocked endogenous miR-98, boosted Fas expression (Figure 2A-2F), indicating that the expression of Fas is negatively regulated by miR-98.

To further elucidate the functional consequences of miR-98-mediated regulation of Fas, we investigated its role in regulating the expression of proteins involved in the Fas-mediated apoptotic pathway (cleaved caspase-3 and cleaved caspase-8) and the expression of intrinsic apoptosis molecules (cleaved caspase-9, Bax, and Bcl-2). As expected, the ratio of cleaved/total caspase-3 and cleaved/total caspase-8 expression was markedly downregulated by transfection of Jurkat cells with miR-98 mimics, whereas transfection with miR-98 inhibitor achieved the opposite effect. However, the ratio of cleaved/total caspase-9 and the expression of Bax and Bcl-2 remained almost unchanged (Figure 2B, 2C, 2E, and 2F).

To demonstrate a direct interaction between Fas and
miR-98, we performed a dual-luciferase reporter assay. With the aid of TargetScan\textsuperscript{32}, we predicted putative binding sites located in the 3′-UTR of Fas mRNA (Figure 3A). We co-transfected either control or miR-98 mimics with luciferase vectors bearing WT or MUT Fas 3′-UTR target sequences into 293T cells and measured luciferase activity. As expected, miR-98 mimics significantly decreased luciferase activity in the WT group but had no effect on the MUT counterpart (Figure 3B), suggesting that the inhibitory effect of miR-98 was mediated by binding to the predicted sites. Taken together, our results demonstrated that miR-98 directly targets the Fas 3′-UTR and suggested the potential involvement of miR-98 in the Fas-mediated apoptotic pathway.

**MiR-98 inhibitor induces Fas-mediated apoptosis in normal CD4+ T cells.** To further analyze the functional interaction between miR-98 and Fas in clinical samples, we assessed the effect of miR-98 inhibitor on isolated primary healthy CD4+ T cells. Figure 4A and 4B show that miR-98 inhibitor increased Fas expression at both mRNA and protein levels, along with increases in the expression of proteins involved in the Fas-mediated apoptotic pathway. Because the FasL/Fas pathway is the major inducer of T cell apoptosis, we attempted to investigate whether miR-98 could regulate Fas-mediated apoptosis by flow cytometry analysis. As shown in Figure 4D and 4E, inhibition of endogenous miR-98 increased the percentage of apoptotic cells in healthy CD4+ T cells, which resembled an “SLE-like” phenotype. In short, our results indicated that alterations in miR-98 could regulate Fas-mediated apoptosis in primary healthy CD4+ T cells.

**MiR-98 mimics ameliorate Fas-mediated apoptosis in CD4+ T cells from patients with SLE.** Because the endogenous miR-98 level in SLE CD4+ T cells was lower than that in healthy CD4+ T cells (Figure 1A), we next examined the functional role of miR-98 mimics in SLE CD4+ T cells. As expected, the expression of Fas and Fas-mediated apoptotic proteins (cleaved/total caspase-3 and cleaved/total caspase-8) was markedly downregulated by miR-98 mimic transfection, whereas cleaved/total caspase-9, Bax, and Bcl-2 expression was almost unchanged (Figure 5A, 5B, and 5C). In addition, flow cytometry was used to validate the protective role of miR-98 in Fas-mediated apoptosis in SLE CD4+ T cells. As shown in Figure 5D, miR-98 mimic treatment decreased the apoptosis percentage. To further investigate whether the effects of miR-98 were mediated through Fas, we transfected control vector or Fas expression vector into SLE CD4+ T cells using a lentiviral transfection system, which overexpressed miR-98 and analyzed the effects of Fas overexpression (LV-Fas) on cell apoptosis. Dramatically, the results indicated that Fas reversed the function of miR-98 overexpression, which suppressed apoptosis in SLE CD4+ T cells (Figure 5E). These results indicated that miR-98 overexpression could partially ameliorate Fas-mediated cell apoptosis in patients with SLE and could be used for SLE treatment.

**DISCUSSION**

T cell apoptosis is well documented in SLE and regarded as a predominant factor leading to the release of autoantigens that may cause autoimmunity\textsuperscript{8,33}. Elucidating the underlying molecular mechanisms and identifying effective therapeutic targets are critical for inhibiting apoptosis and relieving the associated cell dysfunction in SLE. MiR-98 was examined in our study because of its potential role in the CD4+ T cell-mediated immune response and its close association with apoptosis, according to previous studies\textsuperscript{26,27,28}. However, little information is available regarding miR-98 in the regulation of apoptosis in SLE CD4+ T cells.

Mounting evidence suggests the involvement of aberrant expression of miRNA in the pathogenesis of SLE\textsuperscript{34}. In our present study, the expression of miR-98 in freshly isolated peripheral SLE CD4+ T cells was remarkably lower than that in the CD4+ T cells of healthy donors. Decreased miR-98 expression was negatively correlated with clinical disease activity, indicating that miR-98 may serve as a new disease target.
biomarker. These results are in line with previous studies, which showed that miR-98 is significantly downregulated in the CD4+ T cells from SLE patients with skin lesions and also chronic renal pathology, and in the PBMC from patients with active SLE. Despite the clear influence of female sex on the risk of autoimmunity and SLE disease activity, the underlying mechanisms remain poorly understood. So far, a few miRNA have been reported to be sex-differentially expressed or responsive to sex hormones, and might contribute to the etiopathogenesis of SLE. Among these is miR-98, which is localized to chromosome X. MiR-98 is proved to be downregulated after estrogen treatment, and to be associated with sex differences in rheumatoid arthritis and SLE. In addition, miR-98 is lower in PBMC from healthy women than in those from men. The activation of interferon (IFN)-α signaling is enhanced by 17β-estradiol by downregulating miR-98 expression, which provides an alternative perspective for understanding the mechanism underlying the sex difference in SLE. Thus, we sought to identify whether miR-98 contributes to the disproportionate prevalence of SLE in women. However, in our study, miR-98 expression in CD4+ T cells was weakly correlated with sex (p = 0.8875, data not shown). In addition to the different lymphocyte subsets studied, we attribute this to the small sample size (female: n = 37, male: n = 3), because women of childbearing age develop SLE about 9 times more often than men do. Moreover, in our study we also observed a high IFN signature in SLE CD4+ T cells; of note, miR-98 correlated positively with OASL mRNA expression (r = 0.7347, p = 0.0006), but not with expression of the other 4 IFN-inducible genes (MX1, OAS1, ISG15, and LY6E; data not shown). The exact role of OASL in SLE in a larger sample size deserves to be studied in more depth. Further, miR-98 negatively regulates interleukin (IL)-10 production in macrophages after lipopolysaccharide (LPS) stimulation, and increased serum IL-10 in patients with SLE produces much higher levels of IL-10 than do those from healthy controls, and increased serum IL-10 in patients with SLE promotes apoptosis of T cell subsets through the caspase-8 pathway initiated by Fas signaling. These findings all suggest that miR-98 is indeed involved in the pathogenesis of SLE.

Cell apoptosis mainly occurs through 2 pathways. The extrinsic pathway is triggered by the binding of FasL to Fas, leading to caspase-8 and caspase-3 activation, which initiates multiple pro-apoptotic processes. The intrinsic pathway, which also involves mitochondria, is triggered by the release of cytochrome c, which binds to caspase-9 and triggers the downstream apoptotic cascade.

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**Figure 4.** MiR-98 inhibitor induces Fas-mediated apoptosis in normal CD4+ T cells. A. Analysis by qRT-PCR of Fas mRNA expression in CD4+ T cells from healthy donors (n = 3) 48 h after transfection with miR-98 inhibitor. B. Western blot analysis of Fas and apoptosis-related protein expression in CD4+ T cells from healthy donors (n = 3) 48 h after transfection with miR-98 inhibitor. C. Histograms show the fold changes in Fas, Bax, and Bcl-2 protein expression and the ratio of cleaved/total caspase-3, 8, and 9 protein expression after transfection with miR-98 inhibitor. D. Apoptosis levels were measured using annexin V/PI staining and flow cytometry in CD4+ T cells from healthy donors (n = 4) 48 h after transfection with miR-98 inhibitor. E. Percentage of annexin V–positive apoptotic cells. Data shown are representative of 3 or more independent experiments (mean ± SEM). *p < 0.05. **p < 0.01. miR-98: microRNA98; qRT-PCR: quantitative reverse transcription PCR.
which involves the activation of pro-apoptotic Bcl-2 family members, is characterized by the release of cytochrome C from the mitochondria, resulting in the activation of downstream caspase-9 and caspase-3. We simultaneously examined whether these 2 pathways were involved in miR-98–mediated T cell protection.

First, we analyzed the expression of death receptor member Fas in clinical samples and found that the expression of Fas was dramatically upregulated in SLE CD4+ T cells, in agreement with previous studies. MiR-98 significantly reversed the expression of Fas mRNA and protein. Moreover, Western blotting showed that the ratio of cleaved/total caspase-8 and cleaved/total caspase-3 in Jurkat and SLE CD4+ T cells was markedly downregulated by miR-98 mimics. Apoptosis levels were measured using FITC-Annexin V/PI staining and flow cytometry in CD4+ T cells from patients with SLE (n = 6) 48 h after transfection with miR-98 mimics. Graph indicates the percentage of annexin V–positive apoptotic cells. E. SLE CD4+ T cells (n = 3) were infected with LV-Fas or LV-vector for 72 h and then transfected with miR-98 mimics for 48 h, followed by APC-Annexin V/7-AAD staining and flow cytometry. Graph indicates the percentage of annexin V–positive apoptotic cells. Data shown are representative of 3 or more independent experiments (mean ± SEM). *p < 0.05.

Another apoptosis signaling pathway is mediated by the Bcl-2 protein family, which includes pro-apoptotic members (Bax, Bak, and Bim) and anti-apoptotic members (Bcl-2, Bcl-xl, and Mcl-1). Our results showed that the expression of Bcl-2 and Bax was neither affected by miR-98 mimic transfection nor by miR-98 inhibitor. Therefore, we speculated that miR-98 has limited effects on the intrinsic pathway of CD4+ T cell apoptosis in SLE.

Even as miR-98 has emerged as one of the regulators of apoptosis in CD4+ T cells, the mechanism of the decreased expression of miR-98 in SLE is not clear. It was reported that miR-98 was downregulated after estrogen or high glucose treatment or following LPS stimulation, but was upregulated in a hypoxia-inducible factor-1α–dependent manner.
or by glucocorticoid. In addition to the above potential environmental (exogenous) factors, it would also be of interest to investigate the genetic (endogenous) factors, such as methylation status of the miR-98 gene in SLE and transcription factors that bind to the promoter region of miR-98, which could clarify the mechanism of the defective expression of miR-98 and the subsequent loss of immune tolerance in patients with SLE.

Our findings revealed that miR-98 is important in the pathogenesis of SLE. MiR-98 downregulation contributes to the dysregulation of apoptosis in SLE, partially through direct interaction with the Fas 3′-UTR, resulting in aberrant T cell responses. Increased expression of miR-98 may benefit the maintenance of T-lymphocyte homeostasis under physiological conditions, and miR-98 oligonucleotides might be helpful for relieving Fas-mediated apoptosis in SLE. Thus, modulation of miR-98 is a novel therapeutic strategy for this disease. Further research investigating the possible causes of the downregulation of miR-98 in SLE is required. Moreover, additional investigation on transgenic animal models (such as treating SLE mice with miR-98 agomi) would help us to identify the in vivo function of miR-98.

REFERENCES