Decreased microRNA-155 Expression in Ocular Behcet’s Disease but Not in Vogt Koyanagi Harada Syndrome

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PURPOSE. MicroRNAs (miRNAs) have emerged as a class of gene expression regulators involved in immune regulation. In the present study, we investigated the role of miRNA in two uveitis entities: Behcet’s disease (BD) and Vogt Koyanagi Harada syndrome (VKH).

METHODS. The expression of five miRNAs was studied in PBMCs, DCs, and CD4⁺ T cells from BD patients with active and inactive uveitis, VKH patients with active uveitis, and healthy controls using real-time PCR. MiR-155 mimics and inhibitor were transfected to DCs to evaluate the effect on DC maturation and cytokine production by these cells and CD4⁺ T cells. Luciferase reporter assays and Western blotting were performed to identify the target gene of miR-155.

RESULTS. Only miR-155 expression was significantly decreased in PBMCs and DCs from BD patients with active uveitis and no differences were observed in the miRNA expression in cells from patients with VKH as compared with controls. Overexpression of miR-155 in DCs was shown to inhibit the production of IL-6 and IL-1β, and to promote the expression of IL-10 by these cells. MiR-155 transfected DCs significantly inhibited intracellular IL-17 expression in allogeneic CD4⁺ T cells; however, it did not influence the expression of cell surface markers CD80, CD40, CD83, CD86, and HLA-DR. Luciferase reporter assays revealed that TAB2 was a target gene of miR-155, which was confirmed by Western blotting.

CONCLUSIONS. The present results suggest that miR-155 expression is decreased in active BD but not in VKH patients. Downregulated miR-155 may be involved in BD pathogenesis by targeting TAB2. (Invest Ophthalmol Vis Sci. 2012;53:5665–5674) DOI:10.1167/iovs.12-9832

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**Materials and Methods**

**Clinical Specimens**

Twenty-three BD patients with active intraocular inflammation and active VKH syndrome patients who had not received any systemic corticosteroids or other immunosuppressive agents for at least 1 week before being referred to our hospital. BD patients without active intraocular inflammation were included if they had not received any systemic corticosteroids or other immunosuppressive drugs for at least 2 weeks before blood sampling. A total amount of 15 mL of blood was collected from each subject. PBMCs were isolated from heparinized blood samples by Ficoll-Hypaque density-gradient centrifugation. Peripheral CD4+ T cells were isolated from PBMCs by human CD4 microbeads (Miltenyi Biotec, Palo Alto, CA) according to the manufacturer's instructions. CD14+ positive monocytes were isolated using human CD14 microbeads (Miltenyi Biotec) according to the manufacturer's instructions. Isolated CD14+ cells (1.5 × 10^6 cells per well) were seeded in 24-well plates and cultured in RPMI 1640 medium supplemented with 10% fetal calf serum (Greeiner, Wemmel, Belgium), 100 U/mL penicillin, 100 μg/mL streptomycin, recombinant human granulocyte-macrophage colony-stimulating hormone (GM-CSF) 100 ng/mL (PeproTech, London, UK) and recombinant human IL-4 50 ng/mL (PeproTech) for 6 days to promote differentiation into immature DCs (iDCs). On day 3, half of the volume of the medium was replaced with fresh medium. On day 6 following culture, a pure population of DCs (imDCs). On day 3, half of the volume of the medium was replaced with fresh medium. On day 6 following culture, a pure population of DCs (imDCs) was identified by flow cytometry using a FC500 cytometer and more than 90% of purified CD1a+ cells were obtained. For DC maturation, 100 ng/mL LPS (100 ng/mL LPS was added to the cells at day 6 and cultured for 24 hours.

**DC-CD4+ T Coculture**

The imDCs were transfected with controls (negative control mimics or inhibitors with irrelevant sequence), miR-155 mimics (double-stranded RNA [dsRNA] oligonucleotides), and miR-155 inhibitors (single-stranded chemically modified oligonucleotides) at a final concentration of 100 nM. After 48 hours, DCs were stimulated with 100 ng/mL LPS for 24 hours and then washed and cocultured with CD4+ T cells obtained from healthy controls. The mixed lymphocyte reaction was set up by culturing the purified CD4+ T cells from different tested groups (1 × 10^6 cells/0.2 mL of RPMI 1640 complete medium per well in triplicate) with allogeneic monocyte-derived DCs obtained 24 hours after maturation. Coculture was performed at a DC:T ratio of 1:4 in 96-well plates for 7 days, and the CD4+ T cells were collected for intracellular IL-17 assay by flow cytometry.

**RNA Preparation and Real-Time Quantitative PCR Analysis**

Total RNA, containing miRNA, was extracted with TRIzol (Invitrogen, Carlsbad, CA) following the manufacturer's instructions. RNA concentrations were determined with a Nano instrument (NanoDrop Technologies, Wilmington, DE). For miRNA analysis, miRNA TaqMan assays for the five miRNAs and U6 small nuclear RNA (Applied Biosystems, Foster City, CA) as internal control were used according to the manufacturer's instructions. The sequence of the primers used was not provided by the manufacturer and is covered by a patent. The relative expression level of miRNAs was normalized to that of the internal control U6 by using the 2^(-ΔΔCt) cycle threshold method.

**Transfection of Human Monocyte-Derived DCs with miRNA Mimics and Inhibitors**

We used miR-155 mimics (dsRNA oligonucleotides) and miR-155 inhibitors (single-stranded chemically modified oligonucleotides) from GenePharma (Shanghai, China) for the overexpression and inhibition of miR-155 activity in human monocyte-derived DCs (mo-DCs), respectively. Negative control mimics or inhibitors (GenePharma) were used as matched controls. For transfection of mo-DCs, 1.5 × 10^6 cells were seeded in 24-well plates and cultured in RPMI 1640 medium. To overexpress or silence miR-155, imDCs were transfected with miR-155 mimics or inhibitors at a final concentration of 100 nM using Lipofectamine 2000 (Invitrogen) at day 4 and cultured for 48 hours.

**Cell Cytotoxicity Assay**

To investigate the effects of transfection on the viability of DCs, the Cell Counting Kit-8 (CCK8, Sigma) assay was used, which is based on the conversion of water-soluble tetrazolium salt, WST8 [2-(2-methoxy-4-nitrophenyl)-3-(4-nitrophenyl)-5-(2,4-disulphophenyl)-2H-tetrazolium, monosodium salt] to a water-soluble formazan dye upon reduction in the presence of an electron carrier by dehydrogenases. In brief, isolated CD14+ cells (1 × 10^6 cells per well) were seeded in 96-well plates and cultured in 100 ng/mL GM-CSF and 50 ng/mL IL-4 to promote differentiation into iDCs. The miR-155 mimics or inhibitors were transfected into cells at different final concentrations (0, 20, 50, 100, 200 nM) on day 4 and cultured for 48 hours. To detect cytotoxicity, 10 μL of CCK8 was added to each well. The optical density was read at 450 nm using a microplate reader (Molecular Devices, Sunnyvale, CA). Cells cultured without transfection were used as the control. All groups were tested five times.

**ELISA for IL-6, IL-10, IFN-γ, and IL-1β**

Serum levels of IL-1β and IL-17 were measured with a human DuoSet ELISA development kit (R&D Systems, Minneapolis, MN) according to the manufacturer's protocols. IL-6, IL-10, IFN-γ and IL-1β levels in the supernatants were also detected using the same method.

**Flow Cytometry**

To evaluate the transfection rate of miR-155 mimics or inhibitors in mo-DCs, cells were gently washed after transfection for 48 hours and directly detected by flow cytometry. For cell surface marker analysis, DCs were incubated for 30 minutes at 4°C with fluorescein-conjugated and isotype-matched antibodies in the labeling solution. To detect intracellular expression of IL-17 in CD4+ T cells cocultured with mo-DCs pretreated with mimics or inhibitors, cells were recovered and stimulated with 100 ng/mL phorbol 12-myristate 13-acetate (PMA) and 1 μg/mL ionomycin (Sigma) for 5 hours. During the final 4 hours, 10 μg/mL Brefeldin A (Sigma) was added to the cultured CD4+ T cells. The stimulated cells were washed, fixed, permeabilized, and subsequently stained with anti-CD3, anti-CD8, and anti-IL-17 antibodies or appropriate isotypes (eBioscience, San Diego, CA). Flow cytometry was conducted on FACS Aria (BD Bioscience, San Diego, CA) and the data were analyzed with FACS Diva Software (BD Bioscience).
Western Blotting for TAB2 Protein

Human mo-DCs (1.5 × 10⁶) were seeded into 24-well plates and transfected with mimics and inhibitors. Forty-eight hours after transfection, cells were lysed with the cell lysis buffer containing 50 mM Tris-HCl (pH 7.4), 150 mM NaCl, 1% Triton X-100, 1% sodium deoxycholate, 0.1% SDS, 2 mM EDTA, and 100 μM phenylmethanesulfonyl fluoride. Protein concentrations of the extracts were measured with a protein assay (Bio-Rad, Richmond, CA). Equal amounts of the extracts were loaded and subjected to 10% SDS-PAGE, transferred onto polyvinylidene difluoride membrane and incubated before blotting with the indicated antibodies and bands were detected with Luminol/Enhancer Solution (Pierce, Rockford, IL). TAB2 and glyceraldehyde-3-phosphate dehydrogenase (GAPDH) antibodies were obtained from Cell Signaling Technology (Beverly, MA). Relative expression levels were quantified using Quantity One software, version 4.52 (Bio-Rad).

3′-UTR Luciferase Reporter Assays

Wild-type and mutated 3′-UTR sequences of TAB2 were cloned into the pMIR-REPORT Luciferase miRNA Expression Reporter Vector (Ambion, Austin, TX) according to the standard protocol. HEK293T cells, obtained from American Type Culture Collection (Manassas, VA), were maintained in Dulbecco’s modified Eagle’s medium and cultured to 70% confluence in 24-well plates. After 20 hours, the firefly luciferase reporter gene construct (200 ng per well) and pRL-CMV Renilla luciferase construct (4 ng per well) were cotransfected with Lipofectamine 2000 (Invitrogen), together with either negative control or the miR-155 mimics. Luciferase activities were measured 24 hours after transfection using the DualLuciferase Reporter Assay System (Promega, Madison, WI).

miRNA Expression in BD and VKH

Statistical Analysis

Student’s t-test and one-way ANOVA were applied using SPSS 17.0 software (SPSS Inc., Chicago, IL). Data are shown as mean ± SD. P values less than 0.05 were considered significant.

RESULTS

Significantly Decreased Expression of miR-155 Is Observed in BD Patients with Active Uveitis, but Not in VKH Patients with Active Uveitis

Five known immunologically relevant miRNAs (miR-155, miR-146a, miR-326, miR-181a, miR-17) were screened in PBMCs, DCs, and CD4⁺ T cells from BD patients with active uveitis, VKH patients with active uveitis, and healthy controls (Fig. 1). The results showed that only the miRNA-155 expression was significantly decreased in PBMCs and DCs, but not CD4⁺ T cells from BD patients with active intraocular inflammation as compared with those without active disease or healthy controls. A further experiment with a larger group of controls and BD patients with active and inactive uveitis confirmed these results. There was no detectable difference in the miRNA expression in the PBMCs between VKH patients with active uveitis and healthy controls. We also investigated whether there was a relationship between the expression of miRNA-155 and serum levels of relevant cytokines in patients. The serum levels of IL-1β and IL-17, however, remained below the detection level in sera from both patients and healthy controls.
miR-155 Inhibits the Production of IL-6 and IL-1β, and Promotes the Production of IL-10 by imDCs, but Has No Effect on DC Maturation

As IL-6, IL-1β, IFN-γ, and IL-10 have been found to play an important role in immune regulation, a further in vitro study was designed to examine whether the miR-155 had an effect on the production of these cytokines. As shown in Figure 2, the different concentrations of mimics or inhibitors did not influence the viability of DCs and in vitro infection of mimics led to stable exogenous gene expression with approximately 70% efficiency in purified DCs, as indicated by the carboxy-fluorescein (FAM) reporter fluorescence. The miR-155 mimics and inhibitors were successfully transfected to imDCs, as shown by their overexpression and a decreased expression of miR-155 respectively. DCs overexpressing miR-155 were shown to significantly inhibit the production of IL-6 and IL-1β and promoted the expression of IL-10 as compared with those transfected with an irrelevant sequence control. DCs with a decreased expression of miR-155 were able to produce higher amounts of IL-6 and IL-1β but a lower level of IL-10 as compared with controls (Fig. 3). There was no detectable IFN-γ production either in DCs overexpressing miR-155 or in those with a decreased expression of miR-155. Another experiment was performed to examine whether miR-155 could influence the maturation of DCs. The results showed that neither the transfection of miR-155 mimics nor the transfection of miR-155 inhibitor had an effect on the expression of the tested surface markers including CD80, CD40, CD83, CD86, and HLA-DR (Fig. 4).

miR-155 is Negatively Associated with Intracellular IL-17 Expression of CD4+ T Cells in a T Cell/DC Coculture System

To investigate the intrinsic effect of DCs on the production of IL-17 by CD4+ T cells, an important proinflammatory cytokine, imDCs were transfected with miR-155 mimics or inhibitor and
were then cocultured with allogeneic CD4⁺ T cells. The results showed that imDCs containing miR-155 mimics significantly inhibited intracellular IL-17 expression by CD4⁺ T cells as compared with those containing an irrelevant sequence control. Coculture of immature DCs transfected with miR-155 inhibitor resulted in a higher expression of IL-17 by CD4⁺ T cells as compared with cocultures with DCs transfected with an irrelevant sequence control (Fig. 5).

**miR-155 Significantly Inhibits the Expression of Functional mRNA Target**

To gain insight into the molecular mechanism of miR-155, we used bioinformatics tools to identify its potential target. From TargetScan and miRBase, we discovered miR-155 base pairs with sequences in the 3' UTR of TAB2 (Fig. 6A). TAB2 plays a...
role in the TLR/IL-1 signal transduction cascade and was selected as a candidate in this study.\textsuperscript{25} We then tested whether miR-155 could directly repress the identified mRNA targets through 3\textsuperscript{\prime}-UTR interactions. Our results showed that overexpression of miR-155 significantly inhibited luciferase activity of a reporter containing the wild-type TAB2 3\textsuperscript{\prime}-UTR but not that of a reporter with a mutated 3\textsuperscript{\prime}-UTR, which indicated that miR-155 specifically targets via the predicted binding sites (Fig. 6B).

A further experiment was also performed to introduce miR-155 mimics and inhibitor into mo-DCs followed by the analysis of TAB2 expression using Western blotting. The results showed that miR-155 suppressed the expression of TAB2 at the protein level (Figs. 6C, 6D). In view of the decreased expression of miR-155 in active BD patients compared with the healthy controls and the direct inhibitory effect of miR-155 on target TAB2, we further investigated the TAB2 protein expression in DCs from BD patients with active uveitis. The result showed that the expression of TAB2 protein was increased in DCs from BD patients with active uveitis compared with healthy controls (Figs. 6E, 6F).

**Figure 5.** Effect of DC transfection with miR-155 mimics and miR-155 inhibitor on IL-17 expression of CD4\textsuperscript{\textaplus} T cells. Transfected DCs were cocultured with CD4\textsuperscript{\textaplus} T cells, whereafter CD4\textsuperscript{\textaplus} T cells were recovered, stimulated with PMA/ionomycin for 5 hours, and subjected to FACS analysis (1 \times 10\textsuperscript{4} cells). (A) Representative dot plots from five independent experiments. Numbers indicate percentages of positive cells in that quadrant. (B) Quantitative analysis of IL-17–expressing CD4\textsuperscript{\textaplus} T cells. Data are shown as mean \pm SD (n = 5 per group). Ctrl, ctrl mimics; miR-155, miR-155 mimics; Ctrl\textsubscript{i}, ctrl inhibitor; miR-155\textsubscript{i}, miR-155 inhibitor. *P < 0.05.
miR-155 targets human TAB2. (A) Predicted interaction between the miR-155 seed region and its target sites match on 3'-UTR of human TAB2 mRNA, determined from TargetScan (http://www.targetscan.org). (B) HEK293T cells were cotransfected with 200 ng wild-type or mutated TAB2 3'-UTR firefly luciferase reporter plasmids, 4 ng pRL-CMV Renilla luciferase reporter plasmids, together with either negative control or the has-miR-155 mimics. Luciferase activities were measured 24 hours after transfection using the Dual-Luciferase Reporter Assay System. Data are the mean ± SD (n = 6) of one representative experiment. Similar results were obtained in at least three independent experiments. (C) Human mo-DCs (1.5 × 10^6) were transfected with control mimics and miR-155 mimics or control inhibitor and miR-155 inhibitor at a final concentration of 100 nM as
indicated. After 48 hours, TAB2 protein was detected by Western blotting. GAPDH served as a loading control. The immunoreactive bands shown are from a representative experiment. Similar results were obtained from four independent experiments. (D) The band intensities were quantified and statistical analysis was performed. NC, negative control; Ba, BD patients with active uveitis. *P < 0.05; **P < 0.01.

In view of the decreased expression of miR-155 in active BD patients, we further investigated whether this downregulated miR-155 correlated with serum levels of certain relevant cytokines; however, we did not find any association of miR-155 and the production of relevant cytokines because the serum level of IL-1β and IL-17 remained below the detection limit of the assay we used. Because earlier reports showed that the serum IL-6 level was also undetectable in BD patients and healthy controls,34 we did not compare the relationship of downregulated miR-155 and the expression of this cytokine. A further study was designed to explore whether miR-155 could influence in vitro cytokine production and the maturation of DCs, a population critical for the induction of immune response and immune tolerance.55,56 The results showed that overexpression of miR-155 significantly inhibited the LPS-induced production of pro-inflammatory cytokines including IL-6 and IL-1β, but increased the expression of anti-inflammatory cytokines such as IL-10. However, it did not influence the maturation of DCs. These results were, by and large, in agreement with those reported earlier.31 In the latter study, the expression level of major histocompatibility complex II and costimulatory molecules, important indexes of DC maturation, of bone marrow–derived DCs in miR-155-deficient mice was normal, whereas the stimulatory ability of these DCs for T-cell proliferation was significantly impaired. These results suggest that miR-155 could exert its role in BD pathogenesis possibly through modulating relevant cytokines produced by DCs rather than by regulating their functional status. As DCs exert their function mainly through modulating T cells,37 we further investigated the effect of DCs with up- or downregulated miR-155 expression on IL-17 production by allogeneic CD4+ T cells. Interestingly, we found that overexpression of miR-155 could significantly inhibit intracellular IL-17 production by CD4+ T cells, whereas downregulated miR-155 expression promoted intracellular IL-17 production by CD4+ T cells. Collectively, these results suggest that a decreased miR-155 expression may lead to the production of certain proinflammatory cytokines and downregulated expression of IL-10, an important anti-inflammatory cytokine, thereby contributing to BD development.

To further explore the mechanisms involved in the cytokine regulation of miR-155, further experiments were performed to identify the target gene for miR-155. Among the potential direct mRNA targets of miR-155, a number of targets have been identified in murine or in human systems, such as TAB2, c-Maf, PU.1, SHIP1, AGTR1, and MMP3.25,31,32,38–40 In this study, we focused on TAB2 as a target gene of miR-155 in view of its role in the modulation of IL-1β and IL-6, two important cytokines involved in autoimmune and inflammatory disease pathogenesis. As a multifunctional signaling molecule, TAB2 is a part of a molecular complex containing the TNF receptor-associated factor 6 (TRAF6) and has been shown to facilitate IL-1–dependent TRAF6 ubiquitination.41 It promotes activation of the inflammatory response on TLR4 or IL-1 receptor triggering and activation of the TLR/IL-1 signaling pathway.42,43 Our studies used both Luciferase reporter assays and Western blotting experiments to identify TAB2 as a target of miR-155 in BD. These findings are in agreement with an earlier report.25

**DISCUSSION**

Since the discovery of miRNAs, tremendous effort has been devoted to determining their biologic functions and a potential link between miRNAs and various diseases in humans. In the present study, we investigated a possible involvement of miRNAs in the pathogenesis of two uveitis entities, namely BD and VKH. The results showed a significantly decreased expression of miR-155 in PBMCs and mo-DCs of BD patients with active uveitis but not in VKH patients with active uveitis. The miR-155 transfected DCs were shown to inhibit the production of IL-6 and IL-1β in association with an upregulated IL-10 expression. They were also able to significantly inhibit intracellular IL-17 expression of allogeneic CD4+ T cells. Luciferase reporter assays and Western blotting identified TAB2 as the target gene of miR-155. Moreover, we found an increased expression of TAB2 in DCs from BD patients with active uveitis as compared with healthy controls. These results collectively suggest that downregulated miR-155 expression may be involved in the pathogenesis of BD.

The miRNAs are believed to be involved in the physiological or pathological processes in vivo by targeting multiple functionally related proteins or a key protein target.26–27 A number of miRNAs have been shown to play a critical role in the immune system or inflammatory response by regulating the differentiation of various immune cell subsets.28–30 In the present study, five known immunologically relevant miRNAs based on miRBase and relevant reports were selected as candidates and their expression was investigated in BD patients, VKH patients, and controls. We found a significantly downregulated expression of miR-155 in the PBMCs and DCs of BD patients with active uveitis. Interestingly, we found that a decreased expression of miR-155 was observed only in active BD patients but not in active VKH patients. This result suggests that downregulated expression of miR-155 may be a unique event in BD patients with active uveitis and that different mechanisms are involved in BD as compared with VKH disease. Our result is generally consistent with earlier reports by Rodriguez et al.31 They have shown that miR-155 knockout mice suffer from an exaggerated autoimmune response in the lungs with marked leukocyte invasion.31 However, our result is somewhat different from that reported in the RA and in the experimental autoimmune encephalomyelitis (EAE) model.18,32 In RA patients, an increased miR-155 expression was observed in synovial fibroblasts compared with those from osteoarthritis patients.32 In an EAE model, CD4+ T cells were shown to have a higher expression of miR-155 and silencing of miR-155 was shown to ameliorate disease activity.19 The reasons as to the controversies are not understood but could be due to the origins of the tested cells or the differences in the disease models employed. Recently, Ishida et al.53 reported an upregulated expression of miR-142-5p and miR-21 and a downregulated expression of miR-182 in association with an increased IL-17 expression in experimental autoimmune uveoretinitis. It would be interesting to investigate the expression of these miRNAs and their role in BD and VKH disease in future studies.
Furthermore, in order to investigate whether the observed decrease in miR-155 expression to active BD patients could directly correlate TAB2 expression, we measured TAB2 protein expression in DCs from active BD patients and found an increased expression of TAB2 in BD patients with active uveitis compared with healthy controls. Based on our results and previous studies, it is likely that a downregulated miR-155 expression leads to a dysregulation in the control of the TLR/IL-1 signaling transduction pathway through at least partially targeting TAB2.

It is worthwhile to point out that there are some limitations in our study. Our result showed a decreased expression of miR-155 in DCs in BD patients with active uveitis as compared with VKH patients with active uveitis. It is not clear whether the decreased miR-155 expression is also present in other uveitis entities, such as idiopathic acute or chronic anterior uveitis, ocular sarcoidosis, and retinal vasculitis. Furthermore, our study focused on only one target gene, TAB2. It is not clear whether the effect of miR-155 observed in this study is mediated solely by TAB2 or by a combination of a number of target genes.

In conclusion, our study revealed that miR-155 expression was downregulated in active BD patients. MiR-155 was able to negatively regulate the production of proinflammatory cytokines by DCs via TLR/IL-1 signaling cascade by targeting TAB2. The downregulated miR-155 expression could be involved in the pathogenesis of BD due to a loss of control concerning the production of proinflammatory cytokines by DCs and CD4⁺ T cells.

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References


