Original article

MicroRNA-194 regulates keratinocyte proliferation and differentiation by targeting Grainyhead-like 2 in psoriasis

Xiaoyun Yu, Jingang An, Yunhui Hua, Zhai Li, Ning Yan, Weixin Fan, Chuan Su

Department of Pathogen Biology & Immunology, Jiangsu Key Laboratory of Pathogen Biology, Nanjing Medical University, Nanjing, Jiangsu 210029, China
Department of Dermatovenereology, The Second Hospital of Nanjing, Nanjing, Jiangsu 210003, China
Department of Dermatology, The Second Hospital of Xi’an Jiaotong University, Xi’an, Shaanxi 710004, China
Department of Dermatology, The First Affiliated Hospital of Nanjing Medical University, Nanjing, Jiangsu 210029, China

Abstract

MicroRNAs (miRNAs) are currently emerged as important regulators in psoriasis. Psoriasis is characterized by hyperproliferation and impaired differentiation of keratinocytes. miR-194 is a well-known regulator of cell proliferation and differentiation. However, the role of miR-194 in psoriasis pathogenesis remains unclear. In this study, we aimed to investigate the role of miR-194 in keratinocyte hyperproliferation and differentiation. We found that miR-194 was significantly downregulated in psoriatic lesional skin. Overexpression of miR-194 inhibited the proliferation and promoted the differentiation of primary human keratinocytes, whereas miR-194 suppression promoted the proliferation and inhibited their differentiation. Bioinformatic analysis predicted that the Grainyhead-like 2 (GRHL2) was a target gene of miR-194, which we further validated with a dual-luciferase reporter assay, real-time quantitative polymerase chain reaction (RT-qPCR), and Western blot analysis. The effect of miR-194 on cell proliferation and differentiation was significantly reversed by overexpression of GRHL2. Moreover, the expression of miR-194 and GRHL2 was inversely correlated in psoriatic lesional skin. Taken together, our results suggest that miR-194 inhibits the proliferation and promotes the differentiation of keratinocytes through targeting GRHL2. The downregulation of miR-194 expression may contribute to the pathogenesis of psoriasis and targeting miR-194 may represent a novel and potential therapeutic strategy for psoriasis.

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1. Introduction

Psoriasis is a severe autoimmune skin disease that affects approximately 3% of the world’s population [1,2]. Psoriasis lesions typically form by the hyperproliferation and impaired differentiation of keratinocytes, as well as infiltration of skin lesions by inflammatory cells [3]. Genetic and environmental factors are generally thought to be major causes of psoriasis [4]. Psoriasis is a lifelong disease that severely impairs the quality of life of patients [5], and yet therapeutic strategies are limited. Accordingly, understanding the molecular mechanism underlying the pathogenesis of psoriasis is fundamental for developing new treatments.

MicroRNAs (miRNAs) are a group of small, non-coding RNA molecules that have emerged as critical regulators of various pathological processes [6]. miRNAs regulate gene expression post-transcription by targeting the 3’-untranslated region (UTR) of its target gene [7,8]. This activity affords miRNAs the ability to regulate numerous cellular processes, including cell proliferation, apoptosis, and differentiation [9]. An increasing body of evidence has suggested that miRNAs also play an important role in the pathogenesis of psoriasis [10,11], and that various miRNAs are dysregulated in psoriasis skin lesions [12,13]. And of particular noteworthy, other studies have demonstrated that several miRNAs function to regulate the proliferation and differentiation of keratinocytes [14,15].
Currently, however, the exact role that miRNAs has in psoriasis remains largely unknown.

Grainyhead-like 2 (GRHL2) is an epithelial-specific, mammalian homolog of the *Drosophila* Grainyhead that plays an important role in regulating the differentiation, morphogenesis, and barrier function of the epithelium and the development of the epidermis [16–20]. A growing body of evidence has reported that GRHL2 is involved in the regulations of wound healing [21], epidermal integrity [22], and human airway epithelial functions [23]. GRHL2 is also a tumor-associated gene that regulates the proliferation of many cancer types [24–26]. Importantly, GRHL2 also regulates the proliferation of keratinocytes by modulation of human telomerase reverse transcriptase activity [27]. Furthermore, a study recently demonstrated that GRHL2 is highly expressed in psoriasis skin lesions and inhibits the differentiation of keratinocytes by transcriptional inhibition of the epidermal differentiation complex that contributes to the hyperproliferation of epithelial cells [28]. Targeting inhibition of GRHL2 inhibits the proliferation and promotes the differentiation of keratinocytes [29]. These studies suggest that GRHL2 plays an important role in the pathogenesis of psoriasis and may serve as a promising therapeutic target for psoriasis.

miR-194 is a well-known tumor suppressor gene whose inactivation is implicated in cancers of the ovaries [30], lungs [31], and colorectum [32]. Studies have also demonstrated the importance of miR-194 in the differentiation of neurons [33], hepatocytes [34], osteoblasts [35], and epithelial [36] and mesenchymal stem cells [37]. However, the biological role of miR-194 in the pathogenesis of psoriasis, and particularly in regards to its influence on proliferation and differentiation of keratinocytes, remains unknown.

In this study, we aimed to investigate the biological role of miR-194 and the underlying molecular mechanism in regulating the pathogenesis of psoriasis. We found that miR-194 expression was significantly downregulated in psoriasis. Overexpression of miR-194 inhibited the proliferation and promoted the differentiation of keratinocytes. GRHL2 was identified as a direct target of miR-194 by which miR-194 regulated keratinocyte proliferation and differentiation. Moreover, an inverse correlation between miR-194 and GRHL2 was found in psoriatic skin. Taken together, our study demonstrates that miR-194 regulates keratinocyte proliferation and differentiation through targeting GRHL2 that may play an important role in the pathogenesis of psoriasis. Targeting GRHL2 by miR-194 may be a potential therapeutic option for psoriasis.

2. Materials and methods

2.1. Specimen collection

Fifteen patients with psoriasis and ten healthy subjects were enrolled in the present study. Psoriasis patients were recruited from the Department of Dermatovenereology, the Second Hospital of Nanjing (Nanjing, China). The psoriasis patients enrolled in this study had not received any local treatment for two weeks and had not used any systemically immunosuppressive medications for at least one month before study participation. Punch biopsies (4 mm) were collected from psoriasis patients at the lesional site. Punch biopsies collected from the nonirritated and noninflamed skin of healthy subjects were used as control. The specimens were immediately frozen in liquid nitrogen and stored at −80 °C for further use. The present study was reviewed and approved by Institutional Human Experiment and Ethic Committee of the Second Hospital of Nanjing and was performed in accordance with the Declaration of Helsinki. The written informed consents were obtained from all participants.

2.2. Cell cultures

Primary human keratinocytes were isolated from healthy skin as previously described [38]. Isolated cells were grown in keratinocyte serum-free medium supplemented with keratinocyte growth supplement (Invitrogen, Carlsbad, CA, USA) and 1/100 streptomycin-penicillin mix (Sigma, St. Louis, MO, USA). Human 293T embryonic kidney cells were purchased from the American Type Culture Collection (Manassas, VA, USA) and maintained in Dulbecco’s modified Eagle’s medium (Invitrogen) containing 10% fetal bovine serum (Invitrogen) and 1/100 streptomycin-penicillin mix (Sigma). All cells were cultured at 37 °C in a humidified atmosphere containing 5% CO₂.

2.3. Real-time quantitative polymerase chain reaction (RT-qPCR)

Total RNA was extracted with Trizol reagent (Invitrogen) in accordance with the manufacturer’s instructions. For the detection of mRNA expression of GRHL2, CK1 and CK10, RNA was reverse transcribed into cDNA with a Moloney murine leukemia virus reverse transcriptase (Takara, Dalian, China). GAPDH was used as the control for normalization. For detection of miR-194 expression, RNA was reverse transcribed into cDNA using the TaqMan microRNA reverse transcription kit (Applied Biosystems, Carlsbad, CA, USA). U6 was used as the control for normalization. Gene-specific amplification was performed with SYBR green master mix kit (Bio-Rad, Hercules, CA, USA) and specific primers using an Applied Biosystems AB7500 Real-Time PCR system (Applied Biosystems). The PCR cycling conditions were 35 cycles of 10 s at 94 °C, 35 s at 55 °C, and 30 s at 72 °C. The primer sequences were as follows: GRHL2: 5’-GAGAGCTCCTTTACACACAGAG-

G-3’ (forward) and 5’-GGCACTAAGGCTACTGTTT-3’ (reverse); CK1: 5’-AAGGGATGTCAGCAGAC-3’ (forward) and 5’-GGCACTAAGGCTACTGTTTT-3’ (reverse); CK10: 5’-GACAACGTACAAGGCTAAAAG-3’ (forward) and 5’-CCACACCTGGTTGAC-3’ (reverse); GAPDH: 5’-GCCAAACATGGGACAAATTC-3’ (forward) and 5’-GCCAAACATGGGACAAATTC-3’ (reverse); miR-194: 5’-GCAGGCAGTATCGAACCAC-3’ (forward) and 5’-GCCAAACATGGGACAAATTC-3’ (reverse); and U6: 5’-GTCACGACAGGGTCTTCCAG-3’ (forward) and 5’-GCCTTCAGAATTGCTGCCTC-3’ (reverse). The relative gene expression was analyzed by the 2^-ΔΔCt method.

2.4. In situ hybridization

Frozen skin biopsy specimens were fixed with 10% neutral formalin and embedded in paraffin, and 10-μm-thick sections were prepared. Sections were hybridized with digoxigenin-labeled human mature miR-194 probes (Exiqon, Vedbaek, Denmark). Slides were washed at 51 °C and then incubated with alkaline phosphatase-conjugated digoxigenin antibody for 1 h at room temperature. Sections were visualized by using BM purple AP substrate (Roche Applied Science, Indianapolis, IN, USA) according to the manufacturer’s instructions. The stained sections were observed and photographed with a microscope (Olympus, Tokyo, Japan).

2.5. Cell transfection

The miR-194 mimics, miR-194 inhibitor, and negative control miRNAs (miR-NC) were purchased from GenePharma (Shanghai, China). Briefly, 50 nM miRNA oligonucleotides were transfected into cells using Lipofectamine 2000 reagent (Invitrogen) in accordance with the manufacturer’s instructions. For the rescue assay, a full-length open reading frame of GRHL2 was inserted into a...
pcDNA3.0 vector (Invitrogen) and transfected into cells using Lipofectamine 2000 reagent (Invitrogen).

2.6. Cell proliferation assays

Cell proliferation was determined by 3-(4,5-dimethyl-thiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) and bromodeoxyuridine (BrdU) assays. For MTT assay, cells were plated into 96-well plates and cultured for 24 h. Cells were then transfected with miR-194 mimics, miR-194 inhibitor or miR-NC over 48 h. Next, the medium was refreshed, to which 20 μL/well MTT solution (5 mg/mL; Sigma) was added. After a 4-h incubation, the medium was removed and the formazan crystal was dissolved in dimethyl sulfoxide (200 μL/well; Sigma). Finally, the absorbance at 490 nm was measured with a microplate spectrophotometer (Bio-Tek Instruments, Winooski, VT, USA).

The BrdU assay was a BrdU cell proliferation assay kit (Cell Signaling Technology, Danvers, MA, USA) completed in accordance with the manufacturer’s instructions. Briefly, cells were seeded into a 96-well plate. After treatment with either a miR-194 mimics, miR-194 inhibitor or miR-NC for 48 h, 10 μL of BrdU solution was added to each well and incubated for 1.5 h. Next, the medium was discarded and cells were incubated first with 150 μL denaturing solution for 30 min and then with an anti-BrdU/ peroxidase conjugate for 1 h at room temperature. Finally, the substrate was added and incubated for 30 min at room temperature and the absorbance at 450 nm was measured with a microplate spectrophotometer (Bio-Tek Instruments). Each cell proliferation assay was performed in triplicate.

2.7. Western blot analysis

Total protein was extracted using RIPA lysis buffer and the protein concentration determined with a BCA kit (Beyotime, Haimen, China). A total of 25 μg/lane was separated by sodium dodecyl sulfate-polyacrylamide gel electrophoresis and then transferred to a polyvinylidene difluoride membrane (Amersham, Little Chalfont, UK) by a semi-dry blotting apparatus (Bio-Rad). The membrane was then blocked with 2.5% skimmed milk for 1 h at 37 °C and blotted with primary anti-GRHL2, anti-CK1, anti-CK10, and anti-GAPDH were antibodies overnight at 4 °C. After a 1-h incubation with a horseradish peroxidase-labeled secondary antibody (Biosis, Beijing, Chian; 1:2000), protein bands were detected with an enhanced chemiluminescence kit (Amersham). Finally, the relative protein expression was quantitated within Image-Pro Plus 6.0 software. All primary antibodies were purchased from Abcam Trading (Shanghai) Company Ltd (Shanghai, China).

2.8. Dual-luciferase reporter assay

Bioinformatic analysis of miR-194 was performed by using network databases including microRNA.org-Targets and Expression (http://www.microrna.org/) and TargetScan (http://www.targetscan.org). The 3′-UTR of GRHL2, including the miR-194 binding sites, and the mutant 3′-UTR of the GRHL2 seed region of the predicted miR-194 binding site were cloned into a pmirGLO dual-luciferase vector (Promega, Madison, WI, USA). For the dual-luciferase reporter assay, 293T cells were plated into 24-well plates and co-transfected with the pmirGLO vector and miR-194 mimics. After a 48-h incubation, cells were harvested and lysed. The relative luciferase activity was detected by the Dual-Luciferase Reporter Assay System (Promega) operated in accordance to the manufacturer’s instructions.

2.9. Statistical analyses

Data are expressed as the mean ± standard deviation. Statistical analyses were performed using SPSS version 11.5 software (SPSS Inc., Chicago, IL, USA). Differences were assessed by one-way analysis of variance and P-values adjusted with Bonferroni’s post hoc test.
Fig. 2. miR-194 inhibited the proliferation of keratinocytes. (A) RT-qPCR analysis of miR-194 expression in keratinocytes transfected with miR-194 mimics, miR-194 inhibitors or miR-NC for 48 h (n=3). Cell proliferation was detected by MTT (B) and BrdU (C) assays at 48 h after transfection (n=3). *P<0.05 and **P<0.01 vs. miR-NC.

Fig. 3. miR-194 promotes the differentiation of keratinocytes. The keratinocytes were transfected with miR-194 mimics, miR-194 inhibitors or miR-NC for 72 h. The mRNA expression of CK1 (A) and CK10 (B) was detected by RT-qPCR analysis (n=3). The protein expression of CK1 (C) and CK10 (D) was detected by Western blotting (n=3). The relative protein expression was quantitated by Image-Pro Plus 6.0 software. *P<0.05 vs. miR-NC.
test. Correlation analyses were made with Spearman’s correlation analysis test. A P-value less than 0.05 was considered statistically significant.

3. Results

3.1. miR-194 is downregulated in psoriasis

To investigate the contribution of miR-194 to psoriasis, we first examined the expression of miR-194 in lesional and non-lesional skin from psoriasis patients by RT-qPCR analysis. The results showed that the miR-194 expression was significantly less in psoriasis lesional skin as compared with psoriasis non-lesional skin and healthy skin samples (Fig. 1A). In situ hybridization assay showed that miR-194 was mainly expressed in the basal layers of the epidermis and was highly expressed in healthy skin and psoriasis non-lesional skin (Fig. 1B), indicating a keratinocyte-specific expression of miR-194. However, the expression level was decreased in psoriasis lesional skin (Fig. 1B). Furthermore, we isolated the epidermis from the dermis and then determined its miR-194 expression. We found that miR-194 expression was also markedly reduced in epidermis from psoriasis lesional skin as compared with that from healthy skin and non-lesional skin of psoriasis patients (Fig. 1B). These results suggest that miR-194 is decreased in psoriasis.

3.2. miR-194 suppresses the proliferation of keratinocytes

To investigate the potential biological role of miR-194 in psoriasis, we analyzed the effect of miR-194 on the proliferation of keratinocytes. We performed gain-of-function and loss-of-function experiments by transfection of keratinocytes with either a miR-194 mimic or miR-194 inhibitor, respectively. The expression of miR-194 was subsequently confirmed by RT-qPCR (Fig. 2A). We then examined the effect of miR-194 overexpression or suppression on the proliferation of keratinocytes by MTT and BrdU assays. The results showed that the overexpression of miR-194 significantly inhibited the proliferation of keratinocytes (Fig. 2B and C). In contrast, suppression of miR-194 markedly increased proliferation of transfected keratinocytes (Fig. 2B and C). Our data imply that miR-194 may affect the proliferation of keratinocytes.

3.3. miR-194 promotes the differentiation of keratinocytes

To further investigate the biological role of miR-194 in psoriasis, we further examined the effect of miR-194 on the differentiation of keratinocytes by detecting the expression of keratinocyte differentiation markers (cytokeratin 1 (CK1) and cytokeratin 10 (CK10)) by RT-qPCR analysis showed that the mRNA expression of CK1 and CK10 was significantly upregulated by miR-194 overexpression (Fig. 3A and B). Furthermore, the protein expression of CK1 and CK10 was also markedly upregulated by miR-194 overexpression (Fig. 3C and D). Conversely, suppression of miR-194 inhibited the expression of CK1 and CK10 (Fig. 3A–D). These results, therefore, suggest that miR-194 promotes the differentiation of keratinocytes.
3.4. miR-194 targets the 3′-UTR of GRHL2 and regulates expression of GRHL2

To understand the molecular basis underlying miR-194’s influence on the proliferation and differentiation of keratinocytes, we used bioinformatics analysis to predict the mRNA targets of miR-194 wherein we identified GRHL2, an important regulator of keratinocyte differentiation [28], as a putative target of miR-194 (Fig. 4A). To confirm whether GRHL2 is a functional target of miR-194, we subsequently performed a dual-luciferase reporter assay. The 3′-UTR of GRHL2 containing the complementary sequences to the miR-194 seed sequences was cloned into a reporter vector. Co-transfection of wild-type (WT) GRHL2 3′-UTR construct and miR-194 mimics into 293T cells resulted in a significant reduction in luciferase activity (Fig. 4B). However, the miR-194 mimics showed no notable effect on the luciferase activity of the mutant (MT) GRHL2 3′-UTR constructs (Fig. 4B). Moreover, overexpression of miR-194 significantly decreased the expression of GRHL2 at both the mRNA (Fig. 5A) and protein (Fig. 5B) levels in keratinocytes. However, suppression of miR-194 markedly increased the expression of GRHL2 mRNA and protein (Fig. 5A and B). Taken together, these results suggest that GRHL2 is a direct target of miR-194 in keratinocytes.

3.5. Overexpression of GRHL2 abrogates the effect of miR-194 overexpression

To verify whether miR-194 functions by GRHL2 in keratinocytes, we then performed a rescue experiment. For this, we co-transfected keratinocytes with both miR-194 mimics and GRHL2-expressing vectors without the 3′-UTR. The results showed that GRHL2-expressing vector transfection markedly restored the suppressed GRHL2 expression induced by the overexpression of miR-194 (Fig. 6A and B). The inhibitory effect of miR-194 overexpression on the proliferation of keratinocytes was markedly reversed by restoration of GRHL2 (Fig. 6C and D). Furthermore, the effect of miR-194 overexpression on the differentiation of keratinocytes was also significantly abrogated by the overexpression of GRHL2 (Fig. 7A–D). Taken together, these results suggest that GRHL2 is a direct target of the miR-194 in keratinocytes.

3.6. miR-194 expression inversely correlates with GRHL2 expression in psoriasis skin lesions

To further verify the association between miR-194 and GRHL2 in psoriasis, we performed correlation analysis between the expressions of miR-194 and GRHL2 in psoriasis skin lesions. We found that GRHL2 mRNA expression was significantly greater in psoriasis lesional skin than that in psoriasis non-lesional skin and healthy skin (Fig. 8A). We then correlated the expression of GRHL2 mRNA with that of miR-194 in the same psoriasis lesional skin. Our results showed that miR-194 expression was inversely – and significantly – correlated with the expression of GRHL2 in psoriasis lesional skin (Fig. 8B). The data suggests that the downregulation of miR-194 expression might contribute to the upregulation of GRHL2 observed in psoriasis, and may even still contribute to its pathogenesis.

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4. Discussion

We have investigated the biological contribution of miR-194 to the pathogenesis of psoriasis. Herein we found that miR-914 was significantly downregulated in psoriatic lesional skin and epidermis. The functional experiments demonstrated that miR-194 inhibited the proliferation and promoted the differentiation of keratinocytes, possibly through targeting and inhibiting GRHL2. Collectively, our results demonstrate for the first time the critical contribution of miR-194 in regulating the proliferation and differentiation of keratinocytes.

A growing body of studies has demonstrated that miRNAs play an important role in the pathogenesis of psoriasis [10,11]. Furthermore, an increased expression of miR-203 in psoriatic skin
results in a decrease or suppressor of cytokine signaling 3 coupled to the activation of the signal transducer and activator of transcription-3 (STAT3) that contributes to the development of psoriasis [39]. miR-146a meanwhile is one of the most highly expressed miRNAs in psoriatic skin lesions, whose expression is positively correlated with interleukin (IL)-17 – an important cytokine in the pathogenesis of psoriasis – through its inhibition of the IL-1 receptor-associated kinase 1 [40]. Elevated miR-21 in psoriatic skin leads to activation of the IL-6/STAT3 pathway in murine models of psoriasis [41]. Meigen et al. reported that miR-21 is upregulated in psoriasis, inhibiting the apoptosis of T cells in psoriatic skin lesions [42]. Increased expression of miR-221 and miR-222 contributes to psoriasis by promoting the proliferation of epidermal cells through targeting matrix metalloproteases [43]. Similarly, miR-31 promotes the proliferation of keratinocytes by targeting of protein phosphatase 6 [44]. The downregulation of miR-125b in psoriasis results in an increased proliferation, and decreased differentiation, of keratinocytes by targeting the fibroblast growth factor receptor 2 [14], miR-424a and miR-99 also play an important role in the development of psoriasis by inhibiting the proliferation, whilst promoting the differentiation, of keratinocytes [45,46]. miR-184, miR-210, miR-138, miR-424 and miR-217 have also been reported to play important roles in the pathogenesis of psoriasis [29,47–49]. The present study found that miR-194 is a novel miRNA that is involved in regulating the pathogenesis of psoriasis. We demonstrated that miR-194 regulated the proliferation and differentiation of keratinocytes through targeting GRHL2 mRNA. Our study suggests that miR-194 may be used as a potential molecular target for therapeutic strategies.

The miR-194 plays an important role in many pathological and physiological processes [35,50,51], miR-194 has been suggested as a tumor suppressor that inhibits cell proliferation through targeting various target genes in numerous cancers [30–32,52–54]. To date, the role of miR-194 in psoriasis has not been studied. Here, we reported an important role of miR-194 in the non-malignant, hyperproliferative disease, psoriasis. We demonstrated that miR-194 could inhibit the proliferation of keratinocytes and that the decreased expression of miR-194 in psoriatic lesional epidermis may contribute to the hyperproliferation of keratinocytes in psoriasis.

Previous studies have also highlighted the important role miR-194 has in regulating cellular differentiation. miR-194, for example, was able to regulate the differentiation of intestinal epithelial cells by targeting the hepatocyte nuclear factor-1 alpha [36,55]. Furthermore, Xu et al. reported that miR-194 modulated chondrogenic differentiation of adipose-derived stem cells by targeting SOX5 mRNA [37]. Interestingly, miR-194 also regulates the differentiation of osteoblasts by inhibiting the signal transducer and activator of transcription 1 [35]. And, miR-194 is implicated in regulating the differentiation of neurons [33] and hepatocytes [34]. Herein, for the first time, we report the role of miR-194 in regulating the differentiation of keratinocytes. We also showed that miR-194 promotes the differentiation of keratinocytes, thereby implying a potential therapeutic target for psoriasis treatments.

In this study, we have verified that GRHL2 was a direct target of miR-194. We showed that miR-194 could directly target the 3' -UTR of GRHL2 and thereby inhibit GRHL2 expression. GRHL2 plays an important role in regulating the differentiation, morphogenesis, and barrier function of the epithelium, as well as orchestrating epidermal development [16–20]. GRHL2 is reported to promote the proliferation of keratinocytes by regulating the activity of the human telomerase reverse transcriptase [27]. Importantly, GRHL2 protein expression is strongly induced in the thickened epithelial layer of the psoriatic tissues and GRHL2 inhibits the differentiation keratinocyte by suppressing genes clustered at the epidermal differentiation complex [28]. A more recent study demonstrates that GRHL2 is abundantly expressed in psoriasis skin lesions and suppression of GRHL2 by miR-217 inhibits the proliferation and promotes the differentiation of keratinocytes [29]. In this study, we have demonstrated that GRHL2 miRNA expression is highly expressed in psoriasis skin lesions and inversely correlates with miR-194 expression. We showed that miR-194 inhibits the proliferation and promotes differentiation of keratinocytes by targeting GRHL2. The decreased expression of miR-194 in psoriasis skin lesions may induce the high expression of GRHL2 that contributes to the development and progression of psoriasis. Our findings support the notion that targeting GRHL2 by specific miRNAs may be a potential therapeutic strategy for psoriasis treatments.

In conclusion, our study suggests that miR-194 inhibits the proliferation and promotes the differentiation of keratinocytes by targeting GRHL2, providing a novel insight into understanding the pathogenesis of psoriasis. miR-194 may represent a novel and potential therapeutic target for psoriasis treatments.

Conflict of interests

The authors declare no conflict of interest.

References


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