

RESEARCH ARTICLE

Open Access



Knockdown of lncRNA MIR31HG inhibits cell proliferation in human HaCaT keratinocytes

Jintao Gao^{1*}, Fangru Chen², Mingchun Hua³, Junfan Guo¹, Yuejuan Nong¹, Qinyan Tang¹, Fengxia Zhong¹ and Linxiu Qin¹

Abstract

Background: Psoriasis is a complex, chronic inflammatory skin disease with substantial negative effects on patient quality of life. Long non-coding RNAs (lncRNAs) are able to be involved in multitudes of cellular processes in diverse human diseases. This study aimed to investigate the potential involvement of lncRNA MIR31HG in HaCaT keratinocytes proliferation.

Results: The study showed that MIR31HG was significantly elevated in the lesional psoriatic skin compared with normal individuals' skin. Knockdown of MIR31HG inhibited HaCaT keratinocytes proliferation. Flow cytometry analysis showed that siRNA-mediated MIR31HG depletion induced cell cycle arrest in the G2/M phase. In addition, MIR31HG expression was found to be dependent on NF- κ B activation.

Conclusions: NF- κ B activation mediated MIR31HG upregulation plays an important role in the regulation of HaCaT keratinocytes proliferation. It could be a potential diagnostic biomarker and therapeutic target for psoriasis.

Keywords: Knockdown, lncRNA, MIR31HG, Proliferation, HaCaT keratinocytes

Background

Psoriasis is a complex, chronic inflammatory skin disease affecting 2–3% of the population worldwide [1]. Psoriasis is thought to be initiated by complex interactions between genetic and environmental factors [2]. Psoriasis lesions are characterized by epidermal hyperproliferation and aberrant differentiation of keratinocytes and infiltration of inflammatory cells into the dermis and epidermis, which manifests clinically in the thickening and scaling of skin lesions [3]. However, the underlying mechanisms remain largely elusive.

Long non-coding RNAs (lncRNAs) are defined as transcripts longer than 200 nucleotides, with no protein coding capacity [4]. Increasing evidences suggest that lncRNAs play essential roles in a wide range of biological processes [5]. Multiple lines of evidence link dysregulations of lncRNAs to diverse human diseases [6]. lncRNA PRINS (Psoriasis susceptibility-related RNA

Gene Induced by Stress) have been found to play important roles in the proliferation of keratinocytes and may contribute to psoriasis susceptibility [7–9]. lncRNA-MSX2P1 acts as a ceRNA (competitive endogenous RNA) directly binding to miR-6731-5p and regulating the expression of S100A7, thus affecting the development of psoriasis [10]. MIR31HG (also known as LOC554202), the host gene of intronic miRNA miR-31 is a 2166-nt lncRNA. MIR31HG has been reported to affect cell proliferation in various cancers [11–13]. However, the function of MIR31HG in psoriasis has not been investigated.

RNA-seq data revealed that MIR31HG is elevated in psoriasis lesions versus normal controls [14], suggesting MIR31HG may play a potential role in the pathogenesis of psoriasis. In the present study, we aimed to investigate the expression of MIR31HG in psoriasis lesions and normal skins and determine the effects of MIR31HG knockdown on the proliferation of human HaCaT keratinocytes.

*Correspondence: jintao_gao@glmc.edu.cn

¹ College of Biotechnology, Guilin Medical University, Guilin 541100, Guangxi, People's Republic of China

Full list of author information is available at the end of the article



Results

MIR31HG is upregulated in psoriasis lesions

qRT-PCR assay was used to determine the expression of MIR31HG in the lesional skin tissues from psoriasis patients and normal skin tissues from healthy individuals. The results showed that MIR31HG levels were significantly higher in lesional skin tissues compared with normal tissues (Fig. 1).

Knockdown of MIR31HG inhibits HaCaT keratinocytes proliferation

In order to determine the possible effects of aberrant MIR31HG expression on keratinocyte proliferation, we applied siRNA targeting MIR31HG to suppress its expression in HaCaT keratinocytes. qRT-PCR assay showed that MIR31HG expression was significantly suppressed by specific siRNA (Fig. 2a). The growth curves detected by CCK8 showed that MIR31HG knockdown dramatically decreased HaCaT keratinocytes growth from 48 h post-transfection (Fig. 2b). Consistent with the results of CCK8 assays, EdU incorporation was significantly reduced following siRNA transfection (Fig. 2c). Keratin 6 (KRT6) and keratin 16 (KRT16) are considered to be the hallmarks of psoriatic keratinocytes hyperproliferation [15–17]. qRT-PCR assay showed that MIR31HG knockdown resulted in significant reduction of the

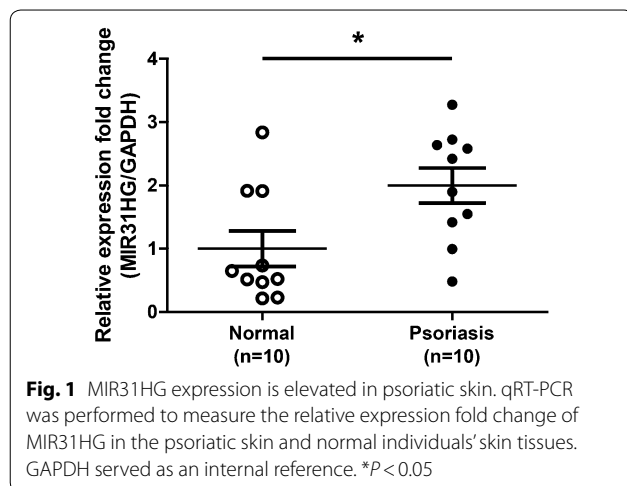
expression of KRT6 and KRT16 (Fig. 2d). These results indicated that MIR31HG knockdown can inhibit HaCaT keratinocytes proliferation. In order to explore the potential reasons for cell growth suppression after MIR31HG knockdown, the cell cycle was analyzed by flow cytometry. MIR31HG silencing significantly decreased the percentage of S phase cells and increased the percentage of G2/M phase cells, indicating that MIR31HG knockdown can inhibit HaCaT keratinocytes proliferation by the induction of G2/M arrest (Fig. 2e).

NF- κ B activation is required for the upregulation of MIR31HG

miR-31 is located within the intron of MIR31HG. NF- κ B activation is essential for miR-31 expression [18]. In order to investigate whether the expression of MIR31HG is dependent on NF- κ B activation, we stimulated HaCaT keratinocytes with IL-17A, IL-22, TNF- α and IL-1 α . In psoriasis, pro-inflammatory cytokines including IL-17A, IL-22, TNF- α and IL-1 α may contribute to the pathophysiology of the disease [2, 19]. IL-17A, IL-22, TNF- α and IL-1 α have been reported to be able to activate NF- κ B signaling [20, 21]. We found that all of the tested inflammatory cytokines were able to stimulate MIR31HG expression (Fig. 3b). In addition, specific siRNA targeting p65 was applied to suppress its expression. qRT-PCR assay showed that p65 expression was significantly suppressed by specific siRNA (Fig. 3a). p65 knockdown resulted in significant reduction of the expression of MIR31HG in HaCaT keratinocytes stimulated with different kinds of cytokines (IL-17A, IL-22, TNF- α or IL-1 α) (Fig. 3b). Consistent with the results of sip65, disruption of NF- κ B pathway by BAY11-7082 (BAY, NF- κ B inhibitor) abolished cytokines-induced MIR31HG expression (Fig. 3b). These data indicated that MIR31HG expression is dependent on NF- κ B activation.

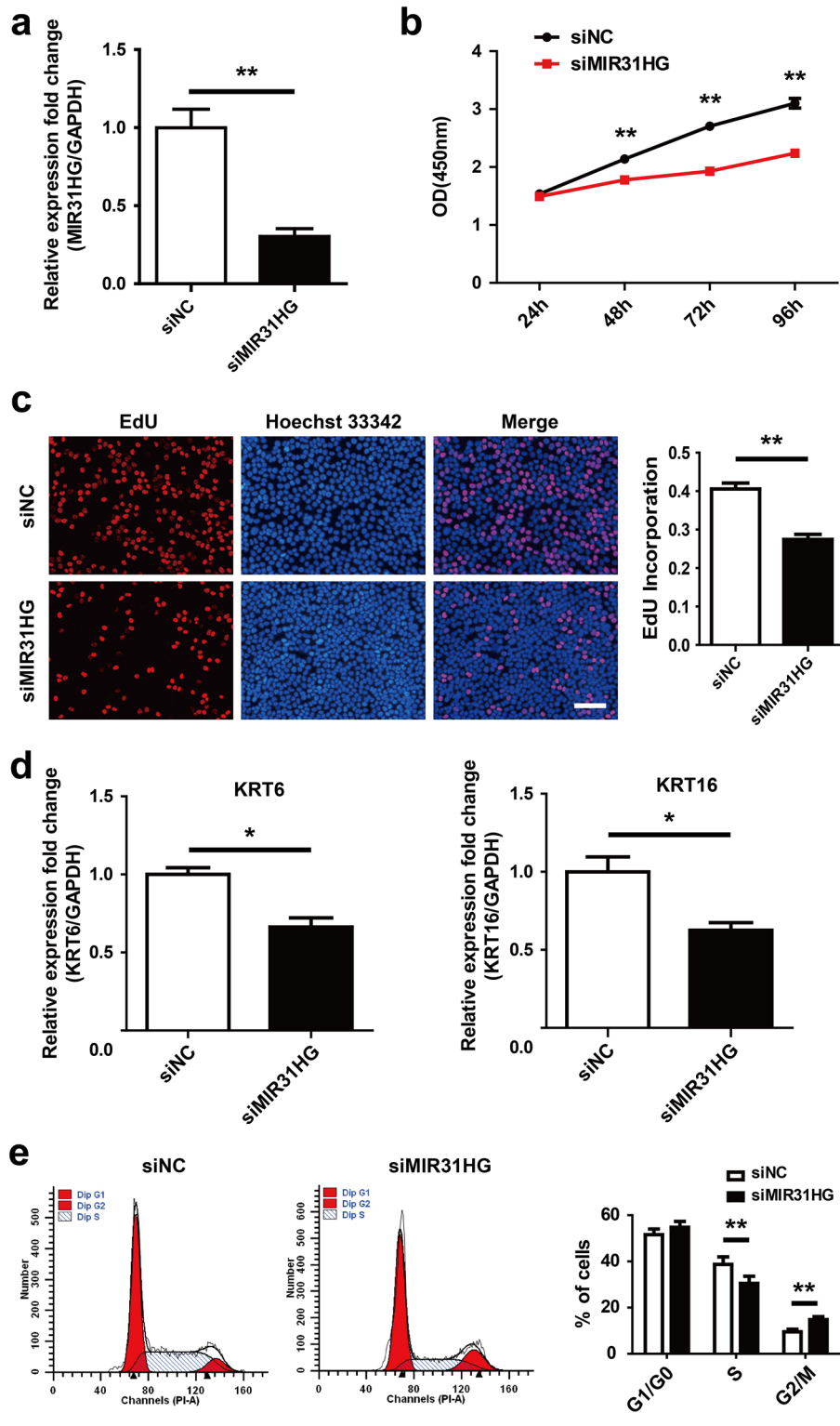
Discussion

Psoriasis is a chronic, immune-mediated skin disease characterized by keratinocyte hyperproliferation and immune cell infiltration [1]. Although a lot of details are known regarding its pathogenesis, much remains to be elucidated and understood. LncRNAs are a new class of regulatory RNAs being involved in multitudes of cellular



(See figure on next page.)

Fig. 2 MIR31HG knockdown inhibits HaCaT keratinocytes proliferation. **a** HaCaT keratinocytes were transfected with 50 nM scramble siRNA (siNC) or MIR31HG siRNA (siMIR31HG) for 48 h. qRT-PCR was performed to measure the expression of MIR31HG. Transcript levels were normalized to GAPDH expression. ** $P < 0.01$. **b** CCK-8 assays were carried out to record the growth curves of HaCaT keratinocytes transfected with 50 nM siNC or siMIR31HG. ** $P < 0.01$. **c** EdU incorporation assays were used to detect the proliferation rate of HaCaT keratinocytes transfected with 50 nM siNC or siMIR31HG for 48 h. EdU incorporation rate was analyzed using Image-pro Plus 6.0 software. Scale bars, 100 μ m. ** $P < 0.01$. **d** KRT6 and KRT16 expression was measured by qRT-PCR in HaCaT keratinocytes transfected with 50 nM siNC or siMIR31HG for 48 h. * $P < 0.05$. **e** The cell cycle distribution of HaCaT keratinocytes at 48 h post-transfection with 50 nM siNC or siMIR31HG was analyzed by flow cytometry. ** $P < 0.01$



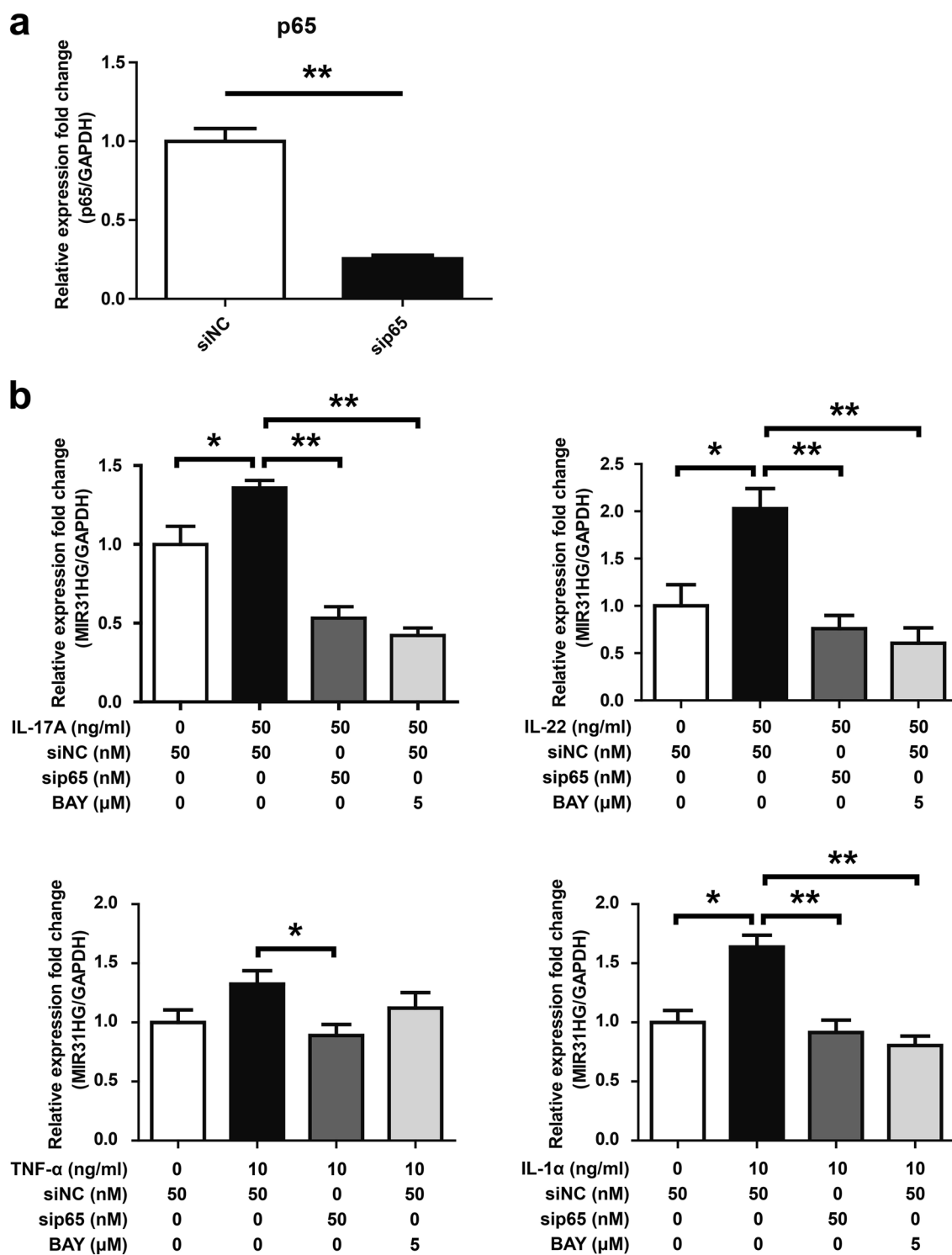


Fig. 3 MIR31HG expression is dependent on NF-κB signaling. **a** The relative expression fold change of p65 mRNA was measured by qRT-PCR in HaCaT keratinocytes transfected with 50 nM siNC or sip65 for 48 h. GAPDH served as an internal reference. ****** $P < 0.01$. **b** HaCaT keratinocytes transfected with sip65 or pretreated with BAY11-7082 (BAY) for 1 h were stimulated with different kinds of cytokines (IL-17A, IL-22, TNF-α or IL-1α) for 24 h. The relative expression fold change of MIR31HG transcript was measured by qRT-PCR. GAPDH served as an internal reference. ***** $P < 0.05$, ****** $P < 0.01$

processes [5]. Recently, transcriptome approaches identified distinct lncRNA expression profile in psoriatic lesions [14, 22], suggesting lncRNAs may play potential roles in the pathogenesis of psoriasis.

In this study, we observed that the expression of MIR31HG is elevated in the lesional skin compared with normal individuals' skin (Fig. 1). MIR31HG has been found dysregulated in human cancers and can regulate the cell proliferation positively or negatively [11, 23]. To better understand the potential roles of MIR31HG during psoriasis, we transfected with MIR31HG-specific siRNA and analyzed the effect on HaCaT keratinocytes proliferation. By MIR31HG-specific siRNA transfection, MIR31HG expression decreased 70% (Fig. 2a), and this MIR31HG silencing resulted in inhibition of HaCaT keratinocytes growth (Fig. 2b). EdU, a nucleoside analog of thymidine, is readily incorporated into cellular DNA during DNA replication. EdU assay showed that the percentage of incorporated cells is reduced following MIR31HG knockdown (Fig. 2c). KRT6/KRT16 keratin pair is induced in hyperproliferative psoriatic keratinocytes, but not found in normal keratinocytes [24]. KRT6 and KRT16 are considered to be hyperproliferation-associated keratins and to be the hallmarks of psoriasis [15–17]. MIR31HG-deficient cells exhibited reduced levels of KRT6 and KRT16 (Fig. 2d). Moreover, flow cytometry analysis showed that siRNA-mediated MIR31HG depletion induced cell cycle arrest in the G2/M phase (Fig. 2e).

Dysregulated crosstalk between dysfunctional keratinocytes and abnormal immune cells may drive keratinocyte hyperproliferation and aberrant differentiation in psoriasis. Keratinocytes are responsive to key dendritic cell-derived and T-cell-derived cytokines including interferons, TNF, IL-17, and the IL-20 family of cytokines, and in turn produce proinflammatory cytokines to sustain or even shape the psoriatic inflammatory process [1]. NF- κ B signaling may well act as a link in this crosstalk [3]. miR-31 is located within the intron of MIR31HG, and its induction requires NF- κ B activation [18]. In order to investigate whether MIR31HG expression requires NF- κ B activation, we stimulated HaCaT keratinocytes with IL-17A, IL-22, TNF- α and IL-1 α . These cytokines have been reported to be able to activate NF- κ B signaling [20, 21]. Our results showed that IL-17A, IL-22, TNF- α and IL-1 α were able to elevate MIR31HG expression (Fig. 3b). In addition, siRNA-mediated knockdown of p65 resulted in significant reduction of cytokines-induced MIR31HG expression (Fig. 3b). The similar results were observed in HaCaT keratinocytes treated with BAY11-7082 (BAY, NF- κ B inhibitor) (Fig. 3b). These data indicated that MIR31HG expression is dependent on NF- κ B activation. Our data highlight the critical role of NF- κ B signaling pathway in psoriatic

keratinocyte hyperproliferation. These data suggest that MIR31HG may be an attractive target for therapeutic intervention of psoriasis in the future.

Conclusions

In conclusion, knockdown of MIR31HG inhibits the proliferation of HaCaT keratinocytes resulted from induction of cell cycle arrest. MIR31HG expression is dependent on NF- κ B activation. Our findings provide evidence that MIR31HG plays an important role in regulation of keratinocytes hyperproliferation in psoriasis and may be an attractive therapeutic target. However, further studies are required to clarify the mechanism for MIR31HG knockdown inducing cell cycle arrest in HaCaT keratinocytes.

Methods

Cell culture and exposure to IL-17A, IL-22, TNF- α or IL-1 α

HaCaT keratinocytes were obtained from Kunming Cell Bank, Kunming Institute of Zoology, Chinese Academy of Science (Kunming, China), cultured in Dulbecco's modified Eagle's medium (DMEM) containing 10% Fetal Bovine Serum (FBS) and maintained at 37 °C with 5% CO₂.

IL-17A, IL-22, TNF- α and IL-1 α were purchased from PeproTech (Rocky Hill, NJ, USA). Cells were cultured to 80% confluence and incubated with IL-17A (50 ng/ml), IL-22 (50 ng/ml), TNF- α (10 ng/ml) or IL-1 α (10 ng/ml) for 24 h.

Human tissue samples

Punch biopsies (4 mm) were taken from lesional skin areas of 10 patients with psoriasis who received no medical treatment within recent 4 weeks (7 male and 3 female, average age 53.3 years). Normal skin specimens were taken from healthy individuals undergoing plastic surgery. All samples were collected immediately, snap frozen in liquid nitrogen and stored at -80 °C until RNA extraction. Before participation in this study, all individuals provided informed consent. The study was approved by the Ethics Committee of Affiliated Hospital of Guilin Medical University.

Quantitative RT-PCR assays (qRT-PCR)

Total RNA was isolated from HaCaT keratinocytes and skin biopsies using TRIzol™ reagent (Invitrogen). cDNA was synthesized using RevertAid First Strand cDNA Synthesis Kit (ThermoFisher). Quantitative PCR was carried out with SYBR Green qPCR Master Mix (Biomake, Houston, USA) as described previously [25] in CFX96 Touch™ Real-Time PCR Detection System (Bio-Rad). The reaction procedure was 95 °C for 5 min, followed by 40 cycles at 95 °C for 5 s, 60 °C for 10 s and 72 °C for 10 s.

GAPDH served as an internal reference. The relative gene expression was analyzed by the $2^{-\Delta\Delta C_t}$ method. Primers sequences were used as follows:

KRT6, 5'-GGGTTTCAGTGCCAACTCAG-3' (forward) and

5'-CCAGGCCATACAGACTGCGG-3' (reverse);

KTR16, 5'-TTCCCCAGCTGCATATAAAGGT-3' (forward) and

5'-GCAGTTGGCTGAAAGAAGGAAA-3' (reverse);

MIR31HG, 5'-TCCCAGTTTCAGACCACC-3' (forward) and

5'-CCAGGCTATGTCTTTCCTCTAT-3' (reverse);

p65, 5'-GCGAGAGGAGCACAGATACC-3' (forward) and

5'-AGGGGTTGTTGTTGGTCTGG-3' (reverse);

GAPDH, 5'-CACATGGCCTCCAAGGAGTAA-3' (forward) and

5'-TGAGGGTCTCTCTTTCCTCTTGT-3' (reverse).

siRNAs and transfection

The small interfering RNAs (siRNAs) were designed and obtained from Guangzhou RiboBio Co., Ltd (Guangdong, China) and transfected with riboFECT™ CP Transfection Kit (RiboBio) according to the manufacturer's protocol. Briefly, HaCaT keratinocytes were cultured to 30–50% confluence and then transfected with 50 nM scramble siRNA (siNC) or specific siRNA for 24–96 h.

The sequences of siRNAs were 5'-TCACTCTACACTCTTGATTTT-3' (siMIR31HG) and 5'-GGATTGAGGAGAAACGTAATT-3' (sip65).

CCK8 assay

Cell viability was measured using Cell Counting Kit-8 (CCK8) (Dojindo Molecular Technologies, Inc., Kumamoto, Japan). HaCaT keratinocytes were seeded into 96-well plates, cultured to 30–50% confluence and then transfected with siRNAs for 24, 48, 72 and 96 h. CCK-8 solution was added and incubated for 2 h at 37 °C. Absorbance at 450 nm was measured using Multiskan Spectrum (ThermoFisher).

EdU assay

EdU (5-ethynyl-2'-deoxyuridine) incorporation assay was performed using iClick™ EdU Andy Fluor™ 488 Imaging Kit (GeneCopoeia, Guangzhou, China) according to the manufacturer's protocol. Briefly, HaCaT keratinocytes were seeded into 24-well plates, cultured to 30–50% confluence and then transfected with siRNAs for 48 h and then incubated with 50 μM EdU for 2 h at 37 °C. Cells were fixed with 4% paraformaldehyde for 15 min, permeabilized with 0.5% Triton X-100 for 20 min, then stained with iClick EdU solution and Hoechst 33342 in dark. Images were captured using Nikon Eclipse Ti-U

microscope. EdU incorporation rate was analyzed using Image-pro Plus 6.0 software.

Flow cytometry analysis of cell cycle

HaCaT keratinocytes were seeded into 6-well plates, cultured to 30–50% confluence and then transfected with siRNAs for 48 h. Cells were harvested, washed with cold phosphate-buffered saline (PBS) and fixed in 70% ethanol at 4 °C overnight. RNA was removed by using RNase A at 37 °C for 30 min. Finally, Cells were stained with propidium iodide (PI) for 30 min at room temperature and analyzed on FACS Aria III flow cytometer (BD Biosciences).

Statistical analysis

Data were presented as means ± standard errors of three independent experiments. Statistical significance was determined by Student's t test. A *P* values < 0.05 was considered statistical significant.

Abbreviations

lncRNAs: long non-coding RNAs; MIR31HG: miR-31 host gene; KRT6: keratin 6; KRT16: keratin 16; siRNA: small interfering RNA; qRT-PCR: quantitative real-time PCR; CCK8: Cell Counting Kit-8; EdU: 5-ethynyl-2'-deoxyuridine; PI: propidium iodide.

Authors' contributions

JtG designed the study and drafted the manuscript. FC and MH contributed materials and helped to review the manuscript. JfG, YN, QT, FZ, LQ coordinated to perform the experiments and analyze the data. All authors read and approved the final manuscript.

Author details

¹ College of Biotechnology, Guilin Medical University, Guilin 541100, Guangxi, People's Republic of China. ² Department of Dermatology, Affiliated Hospital of Guilin Medical University, Guilin 541001, Guangxi, People's Republic of China. ³ Department of Plastic Surgery, Affiliated Hospital of Guilin Medical University, Guilin 541001, Guangxi, People's Republic of China.

Acknowledgements

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Availability of data and materials

All data generated or analysed during this study are included in this published article.

Consent for publication

Not applicable.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Affiliated Hospital of Guilin Medical University, and the written informed consent was also obtained from each participant in advance.

Funding

This study was supported by Natural Science Foundation of Guangxi Zhuang Autonomous Region (Grant No: 2016GXNSFBA380146) and Project of Improving the Basic Ability of Young and Middle-aged Teachers of Guangxi Zhuang Autonomous Region (Grant No: KY2016YB329).

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Received: 12 June 2018 Accepted: 29 August 2018

Published online: 04 September 2018

References

- Nestle FO, Kaplan DH, Barker J. Psoriasis. *N Engl J Med*. 2009;361(5):496–509.
- Greb JE, Goldminz AM, Elder JT, Lebwohl MG, Gladman DD, Wu JJ, Mehta NN, Finlay AY, Gottlieb AB. Psoriasis. *Nat Rev Dis Primers*. 2016;2:16082.
- Lowes MA, Bowcock AM, Krueger JG. Pathogenesis and therapy of psoriasis. *Nature*. 2007;445(7130):866–73.
- Novikova IV, Hennelly SP, Tung CS, Sanbonmatsu KY. Rise of the RNA machines: exploring the structure of long non-coding RNAs. *J Mol Biol*. 2013;425(19):3731–46.
- Mercer TR, Dinger ME, Mattick JS. Long non-coding RNAs: insights into functions. *Nat Rev Genet*. 2009;10(3):155–9.
- Wapinski O, Chang HY. Long noncoding RNAs and human disease. *Trends Cell Biol*. 2011;21(6):354–61.
- Sonkoly E, Bata-Csörgő Z, Pivarcsi A, Polyanka H, Kenderessy-Szabo A, Molnar G, Szentpali K, Bari L, Megyeri K, Mandi Y. Identification and characterization of a novel, psoriasis susceptibility-related noncoding RNA gene, PRINS. *J Biol Chem*. 2005;280(25):24159–67.
- Szegedi K, Sonkoly E, Nagy N, Németh IB, Bata-Csörgő Z, Kemény L, Dobozy A, Széll M. The anti-apoptotic protein G1P3 is overexpressed in psoriasis and regulated by the non-coding RNA, PRINS. *Exp Dermatol*. 2010;19(3):269–78.
- Szegedi K, Göblös A, Bacsa S, Antal M, Németh IB, Bata-Csörgő Z, Kemény L, Dobozy A, Széll M. Expression and functional studies on the noncoding RNA, PRINS. *Int J Mol Sci*. 2012;14(1):205–25.
- Qiao M, Li R, Zhao X, Yan J, Sun Q. Up-regulated lncRNA-MSX2P1 promotes the growth of IL-22-stimulated keratinocytes by inhibiting miR-6731-5p and activating S100A7. *Exp Cell Res*. 2018;363(2):243–54.
- Yang H, Liu P, Zhang J, Peng X, Lu Z, Yu S, Meng Y, Tong WM, Chen J. Long noncoding RNA MIR31HG exhibits oncogenic property in pancreatic ductal adenocarcinoma and is negatively regulated by miR-193b. *Oncogene*. 2016;35(28):3647–57.
- Shih J-W, Chiang W-F, Wu A-T, Wu M-H, Wang L-Y, Yu Y-L, Hung Y-W, Wang W-C, Chu C-Y, Hung C-L. Long noncoding RNA lncHIFCAR/MIR31HG is a HIF-1 α co-activator driving oral cancer progression. *Nat Commun*. 2017;8:15874.
- Ma X, Qi S, Duan Z, Liao H, Yang B, Wang W, Tan J, Li Q, Xia X. Long non-coding RNA LOC554202 modulates chordoma cell proliferation and invasion by recruiting EZH2 and regulating miR-31 expression. *Cell Prolif*. 2017;50(6):e12388.
- Tsoi LC, Iyer MK, Stuart PE, Swindell WR, Gudjonsson JE, Tejasvi T, Sarkar MK, Li B, Ding J, Voorhees JJ. Analysis of long non-coding RNAs highlights tissue-specific expression patterns and epigenetic profiles in normal and psoriatic skin. *Genome Biol*. 2015;16(24):10.1186.
- Thewes M, Stadler R, Korge B, Mischke D. Normal psoriatic epidermis expression of hyperproliferation-associated keratins. *Arch Dermatol Res*. 1991;283(7):465–71.
- Leigh IM, Navsaria H, Purkis PE, McKay IA, Bowden PE, Riddle PN. Keratins (K16 and K17) as markers of keratinocyte hyperproliferation in psoriasis in vivo and in vitro. *Br J Dermatol*. 1995;133(4):501–11.
- Korge B, Stadler R, Mischke D. Effect of retinoids on hyperproliferation-associated keratins K6 and K16 in cultured human keratinocytes: a quantitative analysis. *J Invest Dermatol*. 1990;95(4):450–5.
- Yan S, Xu Z, Lou F, Zhang L, Ke F, Bai J, Liu Z, Liu J, Wang H, Zhu H, et al. NF- κ B-induced microRNA-31 promotes epidermal hyperplasia by repressing protein phosphatase 6 in psoriasis. *Nat Commun*. 2015;6:7652.
- Guilloteau K, Paris I, Pedretti N, Boniface K, Juchaux F, Huguier V, Guillet G, Bernard F-X, Lecron J-C, Morel F. Skin inflammation induced by the synergistic action of IL-17A, IL-22, oncostatin M, IL-1 α , and TNF- α recapitulates some features of psoriasis. *J Immunol*. 2010;184(9):5263–70.
- De Simone V, Franze E, Ronchetti G, Colantoni A, Fantini M, Di Fusco D, Sica G, Sileri P, MacDonald T, Pallone F. Th17-type cytokines, IL-6 and TNF- α synergistically activate STAT3 and NF- κ B to promote colorectal cancer cell growth. *Oncogene*. 2015;34(27):3493.
- Bonizzi G, Karin M. The two NF- κ B activation pathways and their role in innate and adaptive immunity. *Trends Immunol*. 2004;25(6):280–8.
- Gupta R, Ahn R, Lai K, Mullins E, Debbaneh M, Dimon M, Arron S, Liao W. Landscape of long noncoding RNAs in psoriatic and healthy skin. *J Invest Dermatol*. 2016;136(3):603–9.
- Ding J, Lu B, Wang J, Wang J, Shi Y, Lian Y, Zhu Y, Wang J, Fan Y, Wang Z, et al. Long non-coding RNA LOC554202 induces apoptosis in colorectal cancer cells via the caspase cleavage cascades. *J Exp Clin Cancer Res*. 2015;34:100.
- Korver JE, van Duijnhoven MW, Pasch MC, van Erp PE, van de Kerkhof PC. Assessment of epidermal subpopulations and proliferation in healthy skin, symptomless and lesional skin of spreading psoriasis. *Br J Dermatol*. 2006;155(4):688–94.
- Wang L, Huang D, Huang C, Yin Y, Vali K, Zhang M, Tang Y. Enhanced human somatic cell reprogramming efficiency by fusion of the MYC transactivation domain and OCT4. *Stem Cell Res*. 2017;25:88–97.

Ready to submit your research? Choose BMC and benefit from:

- fast, convenient online submission
- thorough peer review by experienced researchers in your field
- rapid publication on acceptance
- support for research data, including large and complex data types
- gold Open Access which fosters wider collaboration and increased citations
- maximum visibility for your research: over 100M website views per year

At BMC, research is always in progress.

Learn more biomedcentral.com/submissions

