



## RESEARCH ARTICLE

## OPEN ACCESS



## KCNQ10T1 promotes the proliferation and migration of psoriatic keratinocytes by regulating miR-183-3p/GAB1

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### KEYWORDS

GAB1;  
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proliferation;  
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### Abstract

**Background:** Differentially expressed long non-coding RNAs (lncRNA) have been reported to be involved in the proliferation and migration of keratinocyte. Potassium voltage-gated channel subfamily Q member 1 overlapping transcript 1 (KCNQ10T1) was implicated in the pathogenesis of various diseases, including cancer, sepsis, diabetic cardiomyopathy, and atherosclerosis. In this study, the influence of KCNQ10T1 on the proliferation and migration of psoriatic keratinocytes was explained.

**Methods:** Cultured human keratinocyte cell line (HaCaT) was incubated with tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ). Cell viability and migration were assessed by MTT assay and wound healing, respectively. Target miRNA of KCNQ10T1 was identified by luciferase activity and RNA immunoprecipitation (RIP) assays.

**Results:** KCNQ10T1 was up-regulated in TNF- $\alpha$ -treated HaCaT cell line, and knockdown of KCNQ10T1 reduced viability and suppressed the migration of TNF- $\alpha$ -treated HaCaT cell line. KCNQ10T1 was bound to microRNA-183-3p (miR-183-3p) and negatively regulated its expression. Over-expression of growth factor receptor binding 2-associated binding protein 1 (GAB1) counteracted with the suppressive effects of KCNQ10T1-induced silence on the viability and migration of TNF- $\alpha$ -treated HaCaT cells.

**Conclusion:** KCNQ10T1 silence suppressed the proliferation and migration of TNF- $\alpha$ -treated HaCaT cells through regulation of miR-183-3p/GAB1.

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## Introduction

Psoriasis, a papulosquamous, relapsing, and chronic dermatitis, affects about 1–3% of global population, with increasing incidences.<sup>1</sup> Although the pathogenesis and etiology of psoriasis are complicated, genetic, immune, environmental, and psychological factors are regarded as key regulators in its pathogenesis.<sup>2</sup> Inflammatory cell infiltration, neovascularization, keratinosis, and keratinocyte dysplasia are the pathological alterations of psoriasis.<sup>3</sup> Keratinocytes, predominant cell types of the epidermis, form barrier against environmental damages.<sup>4</sup> Abnormal migration and hyperproliferation of keratinocytes are implicated in the pathogenesis of chronic inflammatory skin diseases, such as psoriasis.<sup>5</sup> Therefore, suppression of psoriatic keratinocyte proliferation and migration ameliorated psoriatic lesional microenvironment and attenuated psoriasis.<sup>6</sup>

Long non-coding RNAs (lncRNAs) are differentially expressed in psoriatic skin compared to the healthy skin,<sup>7</sup> and lncRNAs are regarded as diagnostic biomarkers and therapeutic targets in psoriasis.<sup>8</sup> For example, lncRNA WAKMAR1 enhanced the migration of keratinocyte to regulate skin wound healing.<sup>9</sup> MEG3, long non-coding RNA, promoted cell apoptosis and repressed proliferation of activated cultured human keratinocyte cell line (HaCaT).<sup>10</sup> lncRNA potassium voltage-gated channel subfamily Q member 1 overlapping transcript 1 (KCNQ1OT1) has been reported to be involved in the pathogenesis of various diseases. KCNQ1OT1 ameliorated anesthesia-induced nerve injury,<sup>11</sup> and promoted osteogenic differentiation to attenuate osteolysis.<sup>12</sup> KCNQ1OT1 also regulated cancer cell proliferation, apoptosis, and metastasis.<sup>13–15</sup> Lipopolysaccharide-induced inflammatory response in mice was reduced by silence of KCNQ1OT1,<sup>16</sup> and the fracture healing was accelerated by KCNQ1OT1.<sup>17</sup> However, the role of KCNQ1OT1 in psoriasis remains unclear.

lncRNAs and microRNAs (miRNAs) are widely involved in competitive endogenous RNA (ceRNA) model, where lncRNAs act as sponges for miRNAs and play a role in disease.<sup>18</sup> MiR-26a-5p interacted with KCNQ1OT1 to mediate myocardial infarction.<sup>19</sup> KCNQ1OT1-microRNA-183-3p (miR-183-3p) axis was involved in proliferation and apoptosis of vascular smooth muscle cells.<sup>20</sup> Since miR-183-3p has been reported to repress the migration and proliferation of keratinocytes in psoriasis,<sup>21</sup> KCNQ1OT1 was hypothesized to participate in migration and proliferation of keratinocytes through regulation of miR-183-3p.

In this study, the effects of KCNQ1OT1 on the proliferation and migration of tumor necrosis factor- $\alpha$  (TNF- $\alpha$ )-treated HaCaT cell line were investigated, with identification of the underlying mechanism.

## Materials and methods

### Cell culture and treatment

HaCaT (Chinese Academy of Sciences, Shanghai, China) cell line was maintained in Eagle's Minimum Essential medium (MEM; Lonza, Basel, Switzerland) with streptomycin-penicillin and 10% newborn calf serum (Lonza). Cells were seeded in a culture dish for 24 h, then incubated with

10-ng/mL TNF- $\alpha$  (Sigma Aldrich, St. Louis, MO, USA) for another 24 h for functional assays.

### Enzyme-linked-immunosorbent serologic assay (ELISA)

The culture medium of HaCaT was harvested, and the levels of TNF- $\alpha$ , IL-1 $\beta$ , and IL-6 were detected by commercial kits (Sigma Aldrich).

### Cell viability and wound healing

HaCaT cell line ( $1 \times 10^4$  cells/well) was incubated with TNF- $\alpha$ , and transfected with si-KCNQ1OT1 (#1 and #2) or the negative control (si-NC; 5'-CACGATAAGACAATGTATTT-3') (GenePharma, Suzhou, Jiangsu Province, China) by Lipofectamine 2000 (Sigma Aldrich). si-KCNQ1OT1 #1 and pcDNA-growth factor receptor binding 2-associated binding protein 1 (GAB1) (GenePharma) co-transfected into HaCaT cells. After 48 h, cells were seeded for another 24, 48, or 72 h, treated with 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) reagent (Sigma Aldrich) for 4 h, and incubated with 100- $\mu$ L dimethyl sulfoxide (DMSO). Absorbance at 490 nm was measured with microplate autoreader (Thermo Fisher, Waltham, MA, USA). For cell migration assay, HaCaT cells ( $1 \times 10^4$  cells/well) with indicated treatment and transfection were seeded and scratched. After 24 h, cells were photographed and the wound area was calculated.

### Dual luciferase reporter and RNA immunoprecipitation (RIP) assays

The potential binding target of KCNQ1OT1 was predicted by DIANA Tools prediction (<http://diana.imis.athena-innovation.gr/DianaTools/index.php>). Sequences of wildtype or mutant KCNQ1OT1 were subcloned into pmirGLO luciferase reporter vector (Promega, Madison, WI, USA), and named as KCNQ1OT1-wt or KCNQ1OT1-mut. HaCaT cells ( $3 \times 10^4$  cells/well) were seeded and co-transfected KCNQ1OT1-wt or KCNQ1OT1-mut with miR-183-3p mimics or the negative control (NC mimics; 5'-UCUACUCUUUCUAGGAGGUUGUGA-3'). After 48 h, the luciferase activities were determined by Lucifer Reporter Assay System (Promega). For RIP assay, HaCaT cells were transfected with pcDNA-KCNQ1OT1 (GenePharma) for 48 h, and lysed by Magna RIP Kit (EMD Millipore, Billerica, MA, USA). The lysates were incubated with protein G Sepharose beads coated with anti-IgG or anti-AGO2 antibodies (Abcam, Cambridge, MA, USA). The beads were harvested and RNAs were isolated for quantitative reverse transcription polymerase chain reaction (qRT-PCR) analysis.

### qRT-PCR

RNAs were isolated from HaCaT cells using Trizol (Invitrogen, Carlsbad, CA, USA), and reverse-transcribed into complementary DNAs (cDNA). The cDNAs were conducted with SYBR Green Master (Roche, Mannheim, Germany) for qRT-PCR analysis of KCNQ1OT1 and miR-183-3p. *GAPDH* or *U6* was used as an endogenous control. The used primer sequences are as follows: *GAPDH* (forward:

5'-ACCACAGTCCATGCCATCAC-3'; reverse: 5'-CCACCACCC TGTGCTGTA-3'), KCNQ10T1 (forward: 5'-GCACTCTGGGTCC TGTTC-3'; reverse: 5'-CACTTCCTGCCTCCTACAC-3'), miR-183-3p (forward: 5'-CGCGGTATGGCACTGGTAGA-3'; reverse: 5'-AGTGCAGGGTCCGAGGTATTC-3'), and U6 (forward: 5'-CTCGCTTCGGCAGCACA-3'; reverse: 5'-AACGCTTCACGAA TTTGCGT-3').

## Statistical analysis

All the results were expressed as mean  $\pm$  SEM. The statistical analysis was performed by one-way analysis of variance or student's *t*-test;  $P < 0.05$  was considered as statistically significant.

## Results

### KCNQ10T1 contributed to the proliferation of keratinocytes

HaCaT cell lines were incubated with TNF- $\alpha$  for instituting hyperproliferation in keratinocytes. KCNQ10T1 was up-regulated in TNF- $\alpha$ -induced HaCaT cells (Figure 1A). TNF- $\alpha$  treatment increased HaCaT cells viability (Figure 1B).

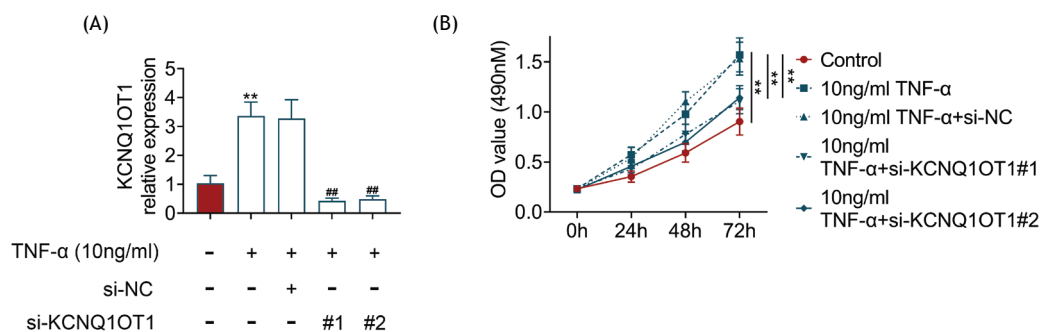
TNF- $\alpha$ -treated HaCaT cells were transfected with si-KCNQ10T1 #1 and #2 for the knockdown of KCNQ10T1 (Figure 1A). Knockdown of KCNQ10T1 reduced the TNF- $\alpha$ -induced HaCaT cells viability (Figure 1B), suggesting that KCNQ10T1 was involved in TNF- $\alpha$ -mediated HaCaT cells proliferation. Moreover, the levels of TNF- $\alpha$ , IL-1 $\beta$ , and IL-6 in HaCaT cells were increased post-TNF- $\alpha$  treatment (Supplemental Figure S1), and knockdown of KCNQ10T1 reduced TNF- $\alpha$ -induced levels of TNF- $\alpha$ , IL-1 $\beta$ , and IL-6 in HaCaT cells (Figure S1).

### KCNQ10T1 contributed to the migration of keratinocytes

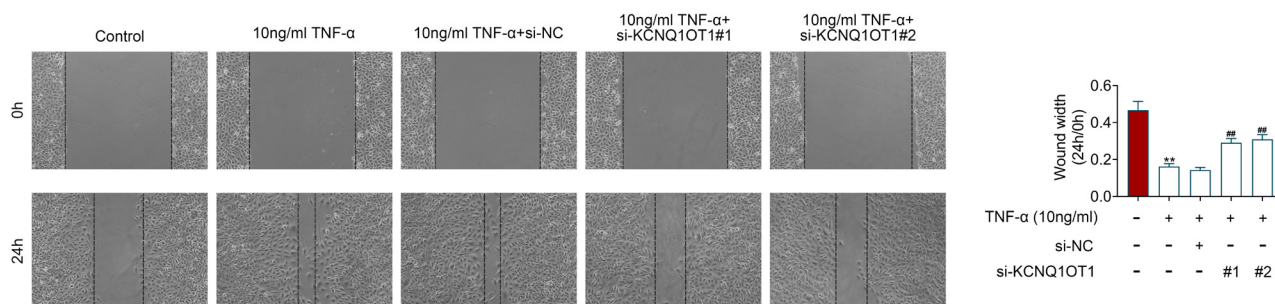
TNF- $\alpha$  treatment also induced the migration of HaCaT cells (Figure 2). However, knockdown of KCNQ10T1 suppressed TNF- $\alpha$ -induced HaCaT cells migration, suggesting the anti-migratory effect of KCNQ10T1-induced silence against TNF- $\alpha$ -induced hyperproliferation in keratinocytes.

### KCNQ10T1 negatively regulated the expression of miR-183-3p

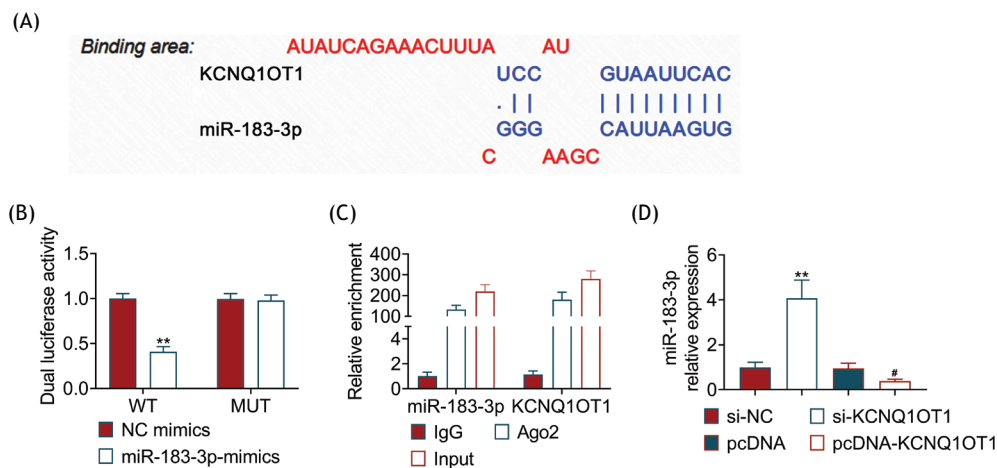
DIANA Tools prediction demonstrated that KCNQ10T1 contains potential binding sites of miR-183-3p (Figure 3A).



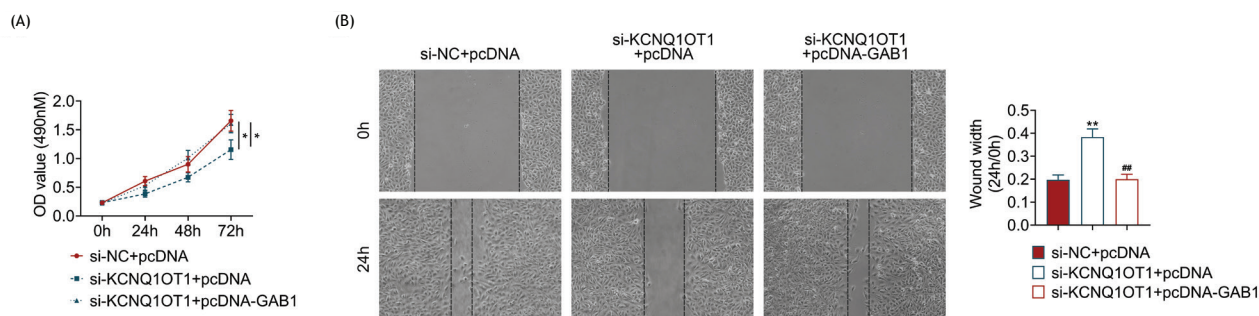
**Figure 1** KCNQ10T1 contributed to the proliferation of keratinocytes. (A) KCNQ10T1 was up-regulated in TNF- $\alpha$ -treated HaCaT cells, and transfection with si-KCNQ10T1 #1 and #2 reduced KCNQ10T1 expression in TNF- $\alpha$ -treated HaCaT cells. (B) Knockdown of KCNQ10T1 reduced the viability of TNF- $\alpha$ -induced HaCaT cells. \*\* $P < 0.01$  vs. control, ## $P < 0.01$  vs. 10 ng/mL TNF- $\alpha$ .



**Figure 2** KCNQ10T1 contributed to the migration of keratinocytes. Knockdown of KCNQ10T1 reduced the migration of TNF- $\alpha$ -treated HaCaT cells. \*\* $P < 0.01$  vs. control, ## $P < 0.01$  vs. 10 ng/mL TNF- $\alpha$ .



**Figure 3** KCNQ10T1 inhibited the expression of miR-183-3p. (A) The potential binding sites between KCNQ10T1 and miR-183-3p were predicted by DIANA Tools. (B) Transfection of miR-183-3p mimics reduced the luciferase activity of KCNQ10T1-wt, while it had no effect on KCNQ10T1-mut. (C) Enrichment of KCNQ10T1 and miR-183-3p in HaCaT cells after over-expression of KCNQ10T1. (D) Knockdown of KCNQ10T1 increased the expression of miR-183-3p in HaCaT cell, while over-expression of KCNQ10T1 decreased the expression of miR-183-3p. \* $P < 0.01$  vs. NC mimics or si-NC. # $P < 0.05$  vs. pcDNA.



**Figure 4** KCNQ10T1 contributed to the proliferation and migration of keratinocytes through regulation of miR-183-3p. (A) KCNQ10T1 silence-induced reduction in the viability of TNF- $\alpha$ -treated HaCaT cells was restored by the over-expression of GAB1. (B) Over-expression of GAB1 attenuated KCNQ10T1 silence-induced reduction in the migration of TNF- $\alpha$ -treated HaCaT cells. \* $P < 0.05$ , \*\* $P < 0.01$  vs. si-NC+pcDNA, ## $P < 0.01$  vs. si-KCNQ10T1+pcDNA.

Transfection with miR-183-3p mimics reduced the luciferase activity of KCNQ10T1-wt, while it had no significant effects on KCNQ10T1-mut (Figure 3B), demonstrating the binding relationship between KCNQ10T1 and miR-183-3p. Moreover, data from RIP assay depicted the enrichment of KCNQ10T1 and miR-183-3p in HaCaT cells after over-expression of KCNQ10T1 (Figure 3C), confirming that KCNQ10T1 was bound to miR-183-3p. KCNQ10T1 also negatively regulated the expression of miR-183-3p in HaCaT cell (Figure 3D), indicating that KCNQ10T1 might be a ceRNA of miR-183-3p in TNF- $\alpha$ -induced hyperproliferation in keratinocytes.

### KCNQ10T1 contributed to the proliferation and migration of keratinocytes through regulation of miR-183-3p-GAB1 axis

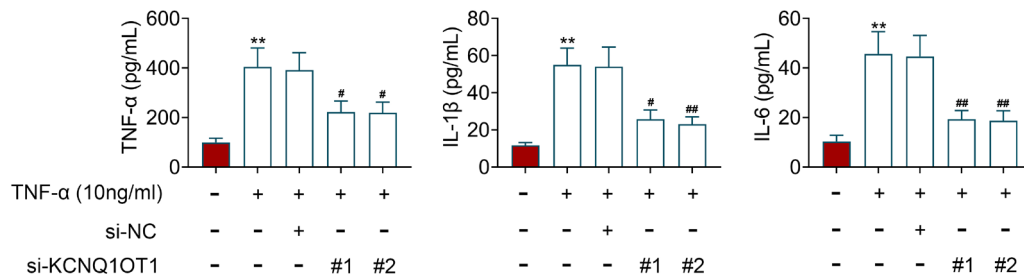
In order to investigate the role of KCNQ10T1/miR-183-3p/GAB1 in the progress of psoriasis, TNF- $\alpha$ -treated HaCaT

cell line was co-transfected with si-KCNQ10T1 #1 and pcDNA-GAB1. Silence of KCNQ10T1-induced reduction in the viability of TNF- $\alpha$ -treated HaCaT cell line was restored by the over-expression of GAB1 (Figure 4A). Over-expression of GAB1 also attenuated KCNQ10T1 silence-induced decrease in the migration of TNF- $\alpha$ -treated HaCaT cells (Figure 4B), revealing that KCNQ10T1 silence suppressed the proliferation and migration of keratinocytes through regulation of miR-183-3p-GAB1 axis.

### Discussion

Emerging evidence has shown that lncRNAs were dysregulated in patients with psoriasis, and lncRNAs function as ceRNAs to sponge miRNAs during the regulation of keratinocyte proliferation and disturbed differentiation.<sup>8</sup> Result of this study identified that a novel lncRNA, KCNQ10T1, was implicated in the pathogenesis of psoriasis.





**Figure S1** TNF- $\alpha$  treatment increased the levels of TNF- $\alpha$ , IL-1 $\beta$ , and IL-6 in HaCaT cells, whereas knockdown of KCNQ10T1 reduced the levels of TNF- $\alpha$ , IL-1 $\beta$ , and IL-6 in TNF- $\alpha$ -treated HaCaT cells. \*\* $P < 0.01$  vs. control. # $P < 0.05$ , ## $P < 0.01$  vs. 10 ng/mL TNF- $\alpha$ .

Previous study has shown that TNF- $\alpha$  is implicated in the pathogenesis of psoriasis by increasing the proliferation and migration of keratinocytes.<sup>22</sup> Therefore, TNF- $\alpha$ -treated HaCaT cell line was widely used as a cell model of psoriatic keratinocytes.<sup>22</sup> Here, TNF- $\alpha$  treatment induced the up-regulation of KCNQ10T1 in HaCaT cells, suggesting that KCNQ10T1 might be involved in the development of psoriasis. However, the expression level of KCNQ10T1 in psoriatic lesional skin should be detected in the future research.

Hyperproliferation of keratinocytes mimics psoriasis lesional microenvironment through induction of infiltration of immunocytes and tancerthosis.<sup>23</sup> Migration of keratinocytes recapitulates the psoriasis lesional microenvironment and stimulates wound re-epithelialization during the development of psoriasis.<sup>23</sup> Suppression of migration and proliferation in keratinocytes facilitates the prevention of psoriasis.<sup>23</sup> Proliferation and migration of bladder cancer cells have been reported to be promoted by KCNQ10T1.<sup>24</sup> This study established that knockdown of KCNQ10T1 reduced cell viability and suppressed the migration of TNF- $\alpha$ -treated HaCaT cells, indicating the anti-proliferative and anti-migratory effects of KCNQ10T1-induced silence against psoriasis. Moreover, dysregulation of interplay between immune cells, keratinocytes, and skin-resident cells is a common pathogenesis of psoriasis.<sup>25</sup> Inflammatory cytokines secreted by immune cells promoted the proliferation and migration of keratinocytes,<sup>26</sup> and inhibition of inflammation is thus beneficial for psoriasis.<sup>26</sup> Considering that KCNQ10T1 contributed to lipopolysaccharide-induced inflammatory response in mice,<sup>16</sup> silence of KCNQ10T1 might exert anti-inflammatory effect against psoriasis.

MiR-183-3p was reported to suppress the proliferation and migration of keratinocytes,<sup>21</sup> and KCNQ10T1 could bind with miR-183-3p to regulate the proliferation and apoptosis of vascular smooth muscle cells.<sup>20</sup> Data from luciferase activity and RIP assays revealed the direct binding relationship between KCNQ10T1 and miR-183-3p. Moreover, KCNQ10T1 negatively regulated the expression of miR-183-3p in HaCaT cells, suggesting that KCNQ10T1 might regulate negatively miR-183-3p expression and thus contribute to the proliferation and migration of keratinocytes.

GAB1 was identified as a binding target of miR-183-3p, and was involved in the proliferation and migration of keratinocytes.<sup>21</sup> Previous study has shown that GAB1 is required for the differentiation and growth of epithelium,

and GAB1 regulates the migration of keratinocytes to participate in the development of psoriasis.<sup>27</sup> Results of this study revealed that over-expression of GAB1 counteracted with the suppressive effects of KCNQ10T1-induced silence on the proliferation and migration of TNF- $\alpha$ -treated HaCaT cells, thereby confirming that KCNQ10T1 contributed to psoriasis through regulation of miR-183-3p-GAB1 axis.

In summary, this was the first evidence demonstrating that KCNQ10T1 was up-regulated in TNF- $\alpha$ -treated HaCaT cells. Knockdown of KCNQ10T1 reduced cell viability and suppressed the migration of TNF- $\alpha$ -treated HaCaT cells through regulation of miR-183-3p-GAB1 axis. These results might provide a potential target for treating psoriasis. However, the effects of KCNQ10T1/miR-183-3p/GAB1 on the *in vivo* psoriatic model need further investigation.

## Competing interests

The authors state that there are no conflicts of interest to disclose.

## Contribution of authors

Ting Liu designed the study, and supervised the data collection; Xi Duan analyzed and interpreted the data; Jia He and Chuan Yang prepared the manuscript for publication and reviewed the draft. All authors read and approved the final manuscript.

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