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ORIGINAL RESEARCH

# LncRNA PVT1 Promotes the Progress of Hypertrophic Scar via Regulating the Proliferation and Migration of Myofibroblasts Through Targeting miR-29a-3p/STAT3

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**Purpose:** Hypertrophic scar (HS) is a common clinical disease during skin injury recovery. Although medicines have been listed for treatment, none are universally effective, and the details of the underlying molecular regulation are yet to be revealed. This research was aimed at exploring the clinical value of lncRNA PVT1 in HS formation and its potential mechanisms in human hyperplastic scar myofibroblasts (HSFs).

**Patients and Methods:** Fifty-seven HS patients were enrolled. RT-qPCR was conducted to examine the RNA levels of lncRNA PVT1, miR-29a-3p and STAT3. CCK-8, Transwell, and flow cytometry were used to analyze cell proliferation, migration, and apoptosis. The targeting relationship of PVT1/miR-29a-3p and miR-29a-3p/STAT3 was proved by the dual luciferase reporter.

**Results:** Relative expression of lncRNA PVT1 in human HS tissues was higher compared with normal tissues. LncRNA PVT1 silencing slowed proliferation and migration and accelerated apoptosis in human HSFs. miR-29a-3p was downregulated in human HS tissues, which was negatively correlated with PVT1 levels. LncRNA PVT1 was covalently bound to miR-29a-3p. miR-29a-3p played an important role in the proliferation, migration, and apoptosis of human HSFs. miR-29a-3p inhibitor rescued the negative influence of lncRNA PVT1 silencing on cells. STAT3 was covalently linked to miR-29a-3p.

**Conclusion:** LncRNA PVT1 was a potential biomarker for HS and regulated the biological behavior of human HSFs via miR-29a-3p/STAT3.

**Keywords:** lncRNA PVT1, hyperplastic scar, myofibroblasts, miR-29a-3p

## Introduction

Hyperplastic scar (HS) is caused by excessive repair of skin tissue after injury, including surgery, burns, and even mosquito bites and it usually develops within 3 months.[1] Clinically, HS can occur ranging from 30% to 90%, at any age and in any part of the skin.[2,3] Several clinical features of HS bring great somatopsychic disturbance to patients. HS presents as hypertrophic hyperemia and edema, along with bright or dark red color, higher than the skin surface and that increases patients' concerns about aesthetics. Besides, the poor flexibility of HS may lead to dysfunction, especially in joint mobility. Meanwhile, HS usually brings significant itching symptoms to patients in the long term. Although therapies for HS have been found, there is not yet a therapeutic strategy that is universally satisfactory clinically.[4,5] At the healed sites, the hyperplastic scar myofibroblasts (HSFs) of granulation tissue are crucial for wound healing and tissue repair.[6] Many elements are involved in the regulation of HSFs, acting individually or synergistically. Existing studies have found that HSFs are sensitive to proteins and cytokines, such as TGF-β, MMP, IL, FGF, and most are

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associated with fibrosis.[7–11] Therefore, the specific regulation of HSFs may provide a good prospect for clinical HS treatment.

The long non-coding RNA (lncRNA) is longer than 200 nucleotides and transcribed by Pol II. Although it cannot be translated into functional proteins, lncRNA has been identified as a regulator for gene expression by interactions with DNA, RNA, and proteins.[12] The regulatory role of lncRNA on gene expression is manifested in various fields including nerve, muscle, blood vessel, immunity and related pathologies.[13–16] It has also been proven that lncRNA plays important roles in regulating the survival and proliferation of cancer cells.[17] In recent years, emerging evidence has highlighted the undeniable role of lncRNA in skin-related diseases. The prognosis and immune microenvironment of patients with cutaneous melanoma have been reported to be associated with lncRNA[18] and LINC00893 has been identified as a suppressor of melanoma metastasis.[19] lncRNA BLACAT1 has been reported to promote the development of psoriasis via miR-149-5p.[20] A rosacea-related study also manifested the regulatory role of lncRNA NEAT1.[21] Subsequent evidence has emerged that lncRNAs are relevant to hyperplastic scar formation. Recently, for example, a study has shown that lncRNA MIR503HG accelerates scar progression by mediating the expression of Smad3.[22] In the same year, lncRNA PAPPA-AS1 is found to induce the development of HS.[23] Recently, studies focusing on tumor development have also shown that lncRNA PVT1 is closely related to cell proliferation, migration, and apoptosis.[24] Based on research in osteosarcoma cells, PVT1 controls cell proliferation and apoptosis.[25] Subsequent work has shown that knockdown PVT1 can suppress cell proliferation widely, whether in vitro or in vivo, and induces cell cycle arrest as well as apoptosis.[26] Given the common rapid growth characteristic between HS and tumor cells, we speculated that lncRNA PVT1 might have some correlation with HS. So far, the role of lncRNA PVT1 in scar formation has not been reported. In this research, we explored the expression level and the potential role of lncRNA PVT1 in the progress of hypertrophic scar.

# Materials and Methods

## Study Objects

This study continuously enrolled 57 hS patients gave informed consent with hyperplastic scars from Peking University Third Hospital and was conducted with permission of the Ethics Committee. This study was performed in line with the principles of the Declaration of Helsinki. The scar tissues in the affected area met the Patient and Observer Scar Assessment Scale (POSAS) evaluation criteria. Any sample inconsistent with histopathological diagnostic criteria was excluded. The HS and nearby tissues within 3 centimeters were taken into account. Significantly, these patients had neither radiation or chemotherapy nor other immune, skin, or tumor diseases. Furthermore, the scar should be characterized as protruding from adjacent normal skin, not exceeding the original wound, and hard in texture. All samples were collected and stored at −80 °C in a refrigerator. Basic sample information of clinical HS patients is shown in Table 1. Generally, their ages ranged from 29 to 51, including 21 males and 36 females. Their lesions were widespread in the head/neck, limbs and trunk, derived from piercing, trauma, surgery, and the lesion size varied from 0.3 $cm^2$ to 2.0 $cm^2$.

## qRT-PCR

Total RNA was isolated following PBS wash. Samples were added into Trizol for RNA extraction. The cDNA synthesis kit was used for reverse transcription and the product was used for qRT-PCR assay, with internal control β-actin. $2^{-\Delta\Delta Ct}$ methods were used to evaluate the relative expression level. Primers of lncRNA PVT1 (F: 5'-GGGGAATAACGCTGGTGGAA-3', R: 5'-CCCATGGACATCCAAGCTGT-3), miR-29a-3p (F: 5'-CGCGTAGCACCATCTGAAAT-3', R: 5'-AGTGCAGG GTCCGAGGTATT-3'), β-actin (F: 5'-CCTCTCCCAAGTCCACACAG-3', R: 5'-GGGCACGAAGGCTCATCATT-3') and STAT3 (F: 5'-ATCACGCCTTCTACAGACTGC-3', R: 5'-CATCCTGGAGATTCTCTACCACT-3') were synthesized for qPCR.

## Cell Proliferation Assay

Human HSFs cells were seeded into 96-well plates, with $1 \times 10^3$ cells per well and cultured for 12 hours. After treatment, additional incubation for 0, 24, 48 and 72 hours, respectively, was needed. One hour before incubation ended, CCK-8 reagents were added. An enzyme immunoassay analyzer was used to detect the optical density value at 450 nm.

**Table 1** Basic Data Statistics of Patients with Hypertrophic Scar

| Items | Mean ± Standard Deviation) or N (%) |
|---|---|
| Age, years | 40.11±10.88 |
| Gender, n (%) | |
| Male | 21 (36.84) |
| Female | 36 (63.16) |
| Site of lesions n (%) | |
| Head/neck | 11 (19.30) |
| Limbs | 20 (35.09) |
| Trunk | 26 (45.61) |
| Predisposing factor n (%) | |
| Piercing | 38 (66.67) |
| Trauma | 11 (19.30) |
| Surgery | 8 (14.03) |
| Lesions size ($cm^2$) n (%) | |
| 0.3–0.8 | 29 (50.88) |
| 0.9–1.4 | 20 (35.08) |
| 1.5–2.0 | 8 (14.04) |

## Transwell Migration Assay

The migration of human HSFs was assessed by a transwell experiment. Eight micrometer-aperture chambers were applied to the migration assay, and cells were placed into the supernatant chambers with enough DMEM medium. The subjacent chambers were also filled with sufficient culture fluid. Twenty-four hours later, the number of migrating cells was counted after fixation, staining in virtue of a microscope.

## Flow Cytometry for Apoptosis Test

The Annexin V-FITC/PI Double Staining Cell Apoptosis Assay Kit was used to detect apoptotic cells, 48 h later after transfection, cells were collected into a tube for centrifugation and then suspended in binding buffer. Annexin V-FITC and PI were added to cell suspension for staining. After incubation at room temperature, a flow cytometer was used to assess cell apoptosis.

## Dual-Luciferase Reporter Assay

The wild-type 3'UTR of PVT1 ((WT-PVT1), mutant PVT1 (MUT-PVT1), wild-type STAT3 (WT- STAT3) and mutant STAT3 (MUT-STAT3) were cloned into the pmirGL3 vector, severally. The human HSFs were seeded in 96-well plates, then co-transfected with the reporter vectors and miR-29a-3p mimic, mimic NC, miR-29a-3p inhibitor or inhibitor NC, respectively. The Dual-Luciferase Reporter Assay System was employed in order to detect the activation performed of luciferase in human HSFs.

## PPI Network Construction

The protein–protein interaction (PPI) network was constructed based on the STRING database (https://www.string-db.org/) and the Cytoscape software. Data about PPI pairs obtained from the STRING database was imported into Cytoscape

for visualization. The parameter of PPI score was 0.4. The closeness connection between nodes was observed and the node degree was counted.

## Statistical Analysis

Student's t-tests or one-way ANOVA analysis in GraphPad Prism 7 was applied for data analysis. The correlation was assessed by means of Pearson correlation analysis. Results were shown as mean ± SD. $P$ <0.05 meant a significant difference.

# Results

## Relative Expression of lncRNA PVT1 in Human HS Tissues

To investigate the role of lncRNA PVT1 in the HS generation process, fifty-seven paired samples were collected for RNA extraction and RT-PCR through conventional experimental procedures. As shown in Figure 1A, the relative

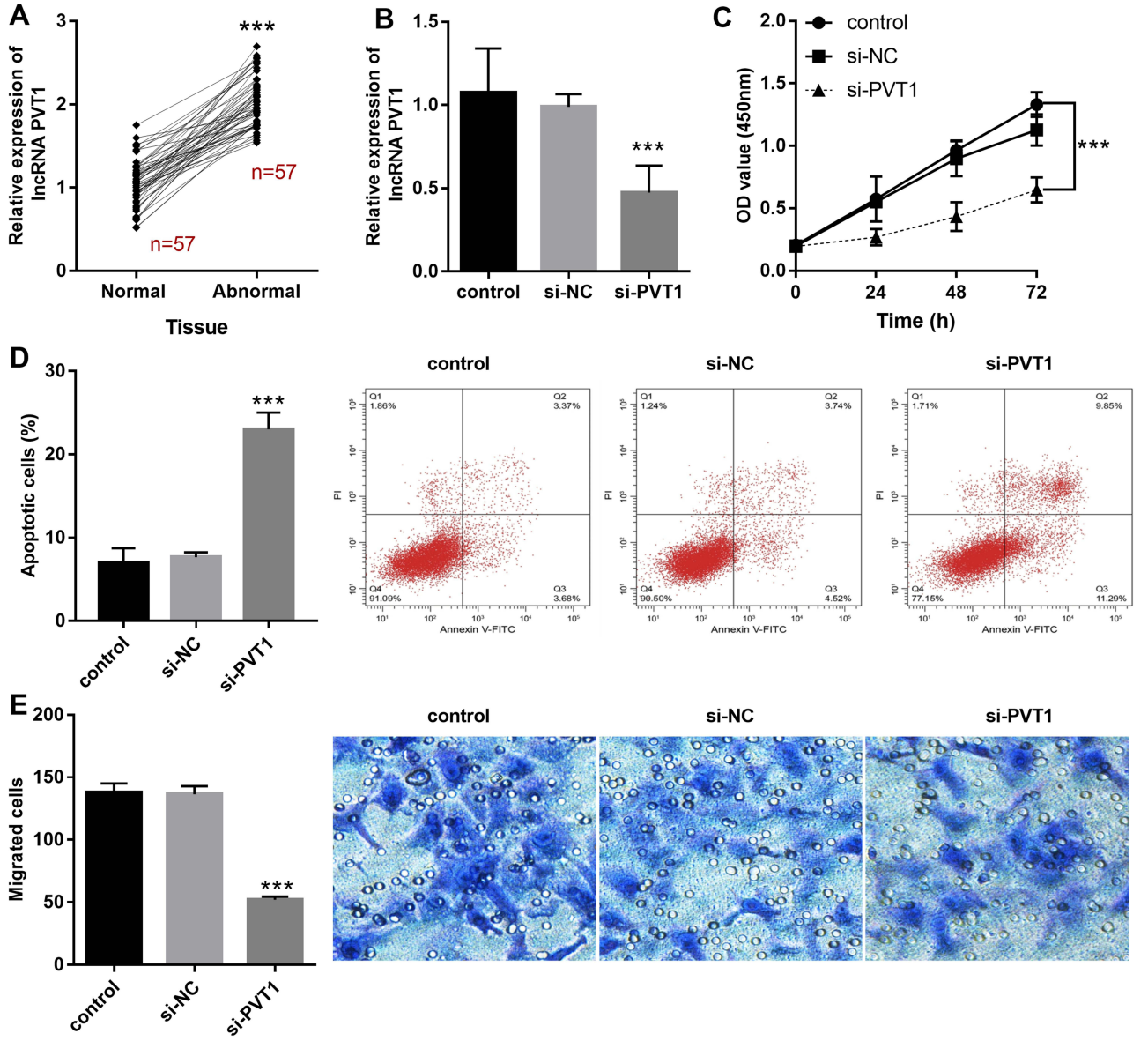


**Figure 1** Expression of lncRNA PVT1 in HS tissues and its effect on human HSFs. (**A**) Relative expression of LncRNA PVT1 in HS tissues (n = 57), compared with nearby normal groups (n = 57). (**B**) Expression of lncRNA PVT1 was silenced by si-PVT1 transfection into human HSFs and measured by Q-PCR. (**C**) Cell proliferation was detected via the CCK-8 experiment. (**D**) The number of apoptotic cells was calculated by flow cytometry. In the flow cytometric analysis of human HSFs, early and apoptotic cells were in the lower and upper right quadrants, respectively. The histogram depicted the overall cell apoptosis status. (**E**) The transwell assay was employed for evaluating the migration of human HSFs. Three repetitions were required for each experiment and each sample was bio-replicated 3 times. (**A**–**E**): Student's *t*-test. *** means $P$ <0.001 compared to the control group.

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expression of PVT1 in HS tissues was significantly higher than that in its adjacent normal tissues ($P < 0.001$). It suggested that the up-regulated expression of lncRNA PVT1 might be closely related to HS formation.

## LncRNA PVT1 Silencing Slowed Proliferation and Migration and Accelerated Apoptosis in Human HSFs

To identify the role lncRNA PVT1 played during HS formation, a knockdown lncRNA PVT1 assay was first conducted in human HSFs using si-PVT1 and the effective transfection was validated by RT-PCR (Figure 1B). The CCK-8 assay demonstrated that the viability was substantially reduced after lncRNA PVT1 knockdown (Figure 1C). The apoptotic cells were significantly increased based on loss function of lncRNA PVT1 (Figure 1D). The assessment of the cell migration capacity revealed that the downregulation of lncRNA expression effectively hindered the migratory behavior of cells (Figure 1E). The evidence suggested that lncRNA PVT1 played a significant role during the progress of HS formation.

## LncRNA PVT1 Covalently Bound with miR-29a-3p

As is known, lncRNA regulates the process of gene expression. The ENCORI database was utilized to expect the underlying miRNA binding to lncRNA PVT1. Luciferase reporting experiments were used to further validate the predicted results and ensure their authenticity. By online Prediction, miR-29a-3p was considered to be a candidate binding covalently (Figure 2A). Following transfection with miR-29a-3p mimics, luciferase activity was distinctly weakened, while inhibition of miR-29a-3p can enhance luciferase activity for WT-PVT1 (Figure 2B). In contrast, enhancement or inhibition of miR-29a-3p had no effect on MUT-PVT1 (Figure 2C). Hence, lncRNA PVT1 targets miR-29a-3p directly in human HSFs. Clinically, the expression level of miR-29a-3p was reduced in HS tissues compared with the normal group (Figure 2D). The correlation analysis indicated that they were negatively correlated in HS tissues ($r = -0.7234$, Figure 2E).

## Role of miR-29a-3p in Proliferation, Migration and Apoptosis of Human HSFs

To further explore the role of miR-29a-3p, cell transfection experiments were carried out to increase or decrease the miR-29a-3p level in human HSFs. The efficiency was measured by qRT-PCR (Figure 3A). Enhanced expression of miR-29a-

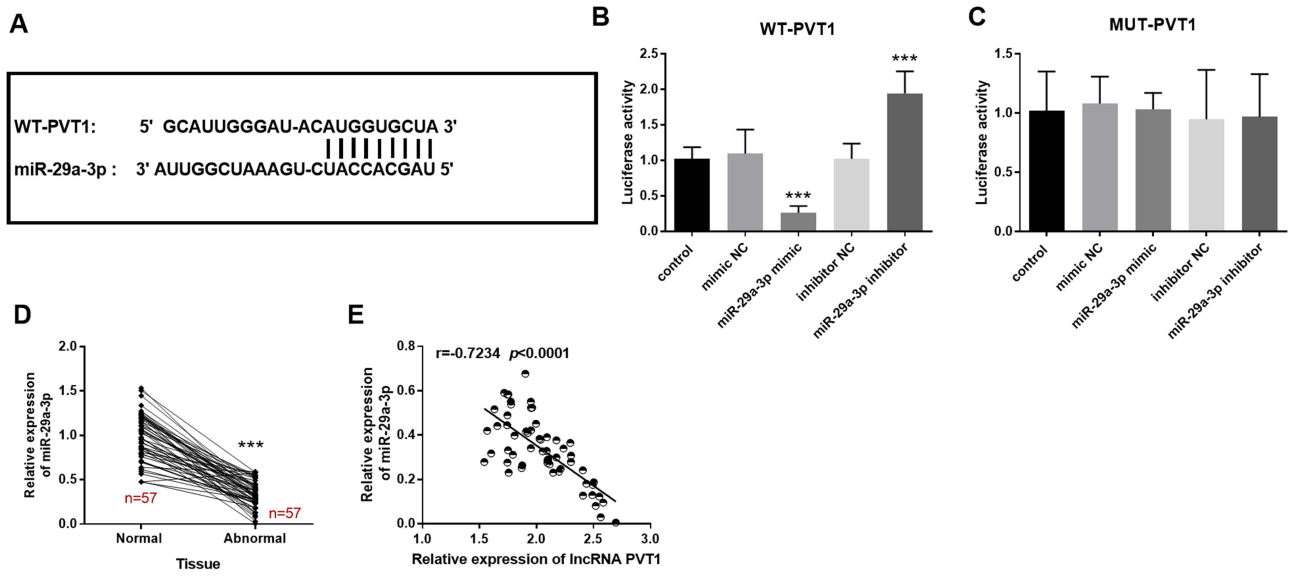


**Figure 2** LncRNA PVT1 covalently bound to miR-29a-3p. miR-29a-3p regulated the expression of wild type PVT1 (WT-PVT1) instead of mutant PVT1 (MUT-PVT1) by Luciferase report. (**A**) The covalent binding sites between lncRNA PVT1 and miR-29a-3p. (**B** and **C**) Luciferase reporter experiments were used to analyze the interaction between lncRNA PVT1 and miR-29a-3p in human HSFs. (**D**) The expression level of miR-29a-3p was measured by qRT-PCR in HS tissues (n = 57) against controls (n = 57). (**E**) The correlation between LncRNA PVT1 and miR-29a-3p via Pearson correlation analysis. Three repetitions were required for each experiment and each sample was bio-replicated 3 times. (**B** and **C**): One-way analysis of variance. (**D**) Student's *t*-test. *** means $P < 0.001$ compared to control.


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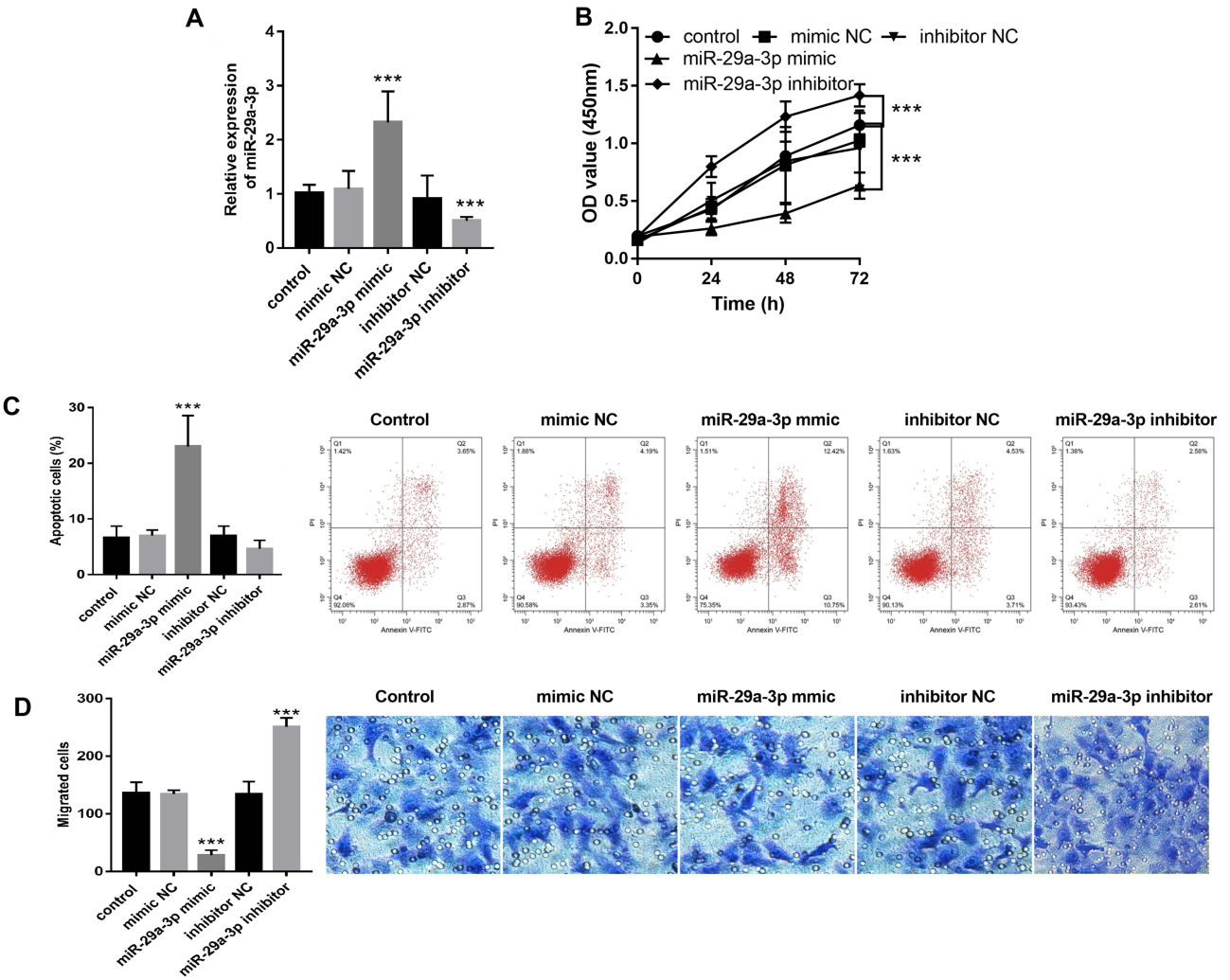


**Figure 3** Influence of miR-29a-3p on HSFs' function. (**A**) Relative expression of miR-29a-3p was assessed by Q-PCR to ensure successful cell transfection. (**B**) CCK-8 experiment was used to detect cell proliferation. (**C**) Flow cytometry was performed to show cell apoptosis. In the flow cytometric analysis of human HSFs, early and apoptotic cells were in the lower and upper right quadrant, respectively. The histogram depicted the overall cell apoptosis status. (**D**) Cell migration was shown via a transwell assay. Three repetitions were required for each experiment and each sample was bio-replicated 3 times. (**A**–**D**): Student's *t*-test. *** $P < 0.001$, compared with the control group.

3p by corresponding mimics significantly inhibited cell activity and migration and reinforced cell apoptosis. On the contrary, miR-29a-3p inhibitor was obviously beneficial to elevating the proliferation (Figure 3B) and migration (Figure 3D) ability of cells and inhibiting cell apoptosis (Figure 3C). This evidence declared that the contributions of miR-29a-3p to HSFs' function, might be indispensable for lncRNA PVT1 regulation.

## miR-29a-3p Inhibitor Rescued the Negative Influence of lncRNA PVT1 Silencing on Cells

Function-loss and salvage experiments were performed by co-transfection to verify whether lncRNA PVT1 regulated the formation of HS through miR-29a-3p. Si-PVT1, as well as miR-29a-3p inhibitor, were transfected into human HSFs, and we subsequently analyzed the expression level of miR-29a-3p between different groups (Figure 4A). Experimental results demonstrated that remarkably reduced cell activity and enhanced apoptosis caused by PVT1 silencing were rescued visibly by miR-29a-3p inhibitor (Figure 4B and C). Furthermore, the reduced cell migration was reversed by the miR-29a-3p inhibitor successfully (Figure 4D). Therefore, miR-29a-3p was the target of lncRNA PVT1 during the process of HS generation.

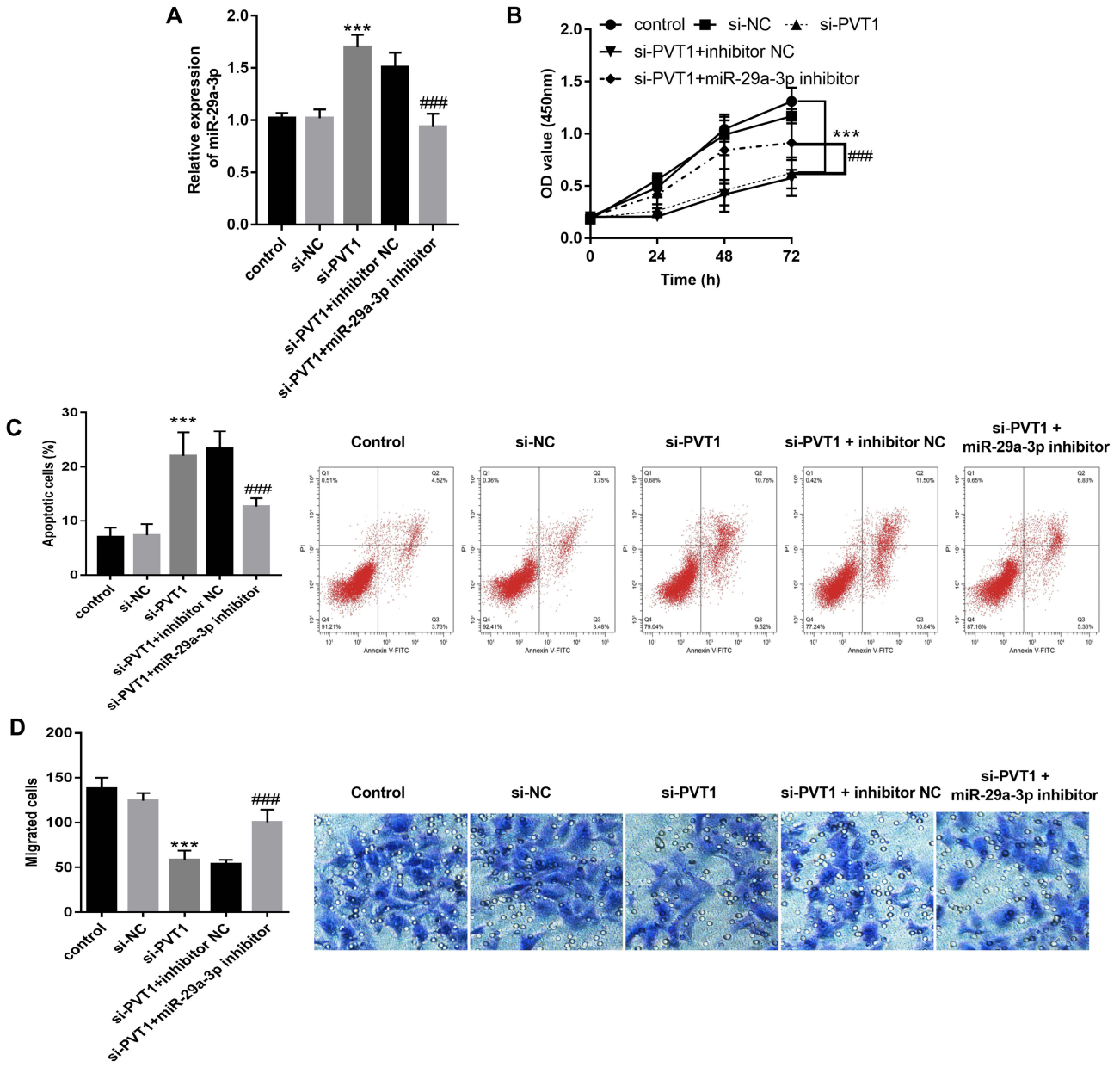


**Figure 4** The miR-29a-3p inhibitor rescued the negative influence of si-PVT1 on human HSFs. (**A**) Expression level of miR-29a-3p was used to ensure effective transfection between different groups. (**B**) CCK-8 kit was used to detect cell proliferation. (**C**) Apoptotic cells were calculated by means of flow cytometry. In the flow cytometric analysis of human HSFs, early and apoptotic cells were in the lower and upper right quadrant, respectively. The histogram depicted the overall cell apoptosis status. (**D**) Transwell assay was employed to indicate cell migration. Three repetitions were required for each experiment and each sample was bio-replicated 3 times. (**A**–**D**): Student's *t*-test. *** $P$ <0.001 against the control group. ### $P$ <0.001 against si-PVT1 group.

## STAT3 Was Covalently Linked to miR-29a-3p

To elucidate the regulatory mechanisms of miR-29a-3p, we investigated its potential downstream targets using the ECORI, miRDB, miRmap, miRwalk, and TargetScan databases. A total of 259 genes were predicted to interact with miR-29a-3p (Figure 5A). Subsequent PPI analysis highlighted promising candidate targets downstream of miR-29a-3p with high node degree (Figure 5B). Dual-luciferase assays confirmed that miR-29a-3p targets STAT3, with predicted binding sites shown in Figure 5C. In human HSFs, luciferase activity in the WT-STAT3 group was significantly modulated by miR-29a-3p overexpression or knockdown instead of the MUT-STAT3. Additionally, the luciferase activity was identified to be inversely correlated with miR-29a-3p expression levels, suggesting that miR-29a-3p regulates STAT3 expression. Subsequent co-transfection experiments were designed to investigate the regulatory effects of PVT1 and


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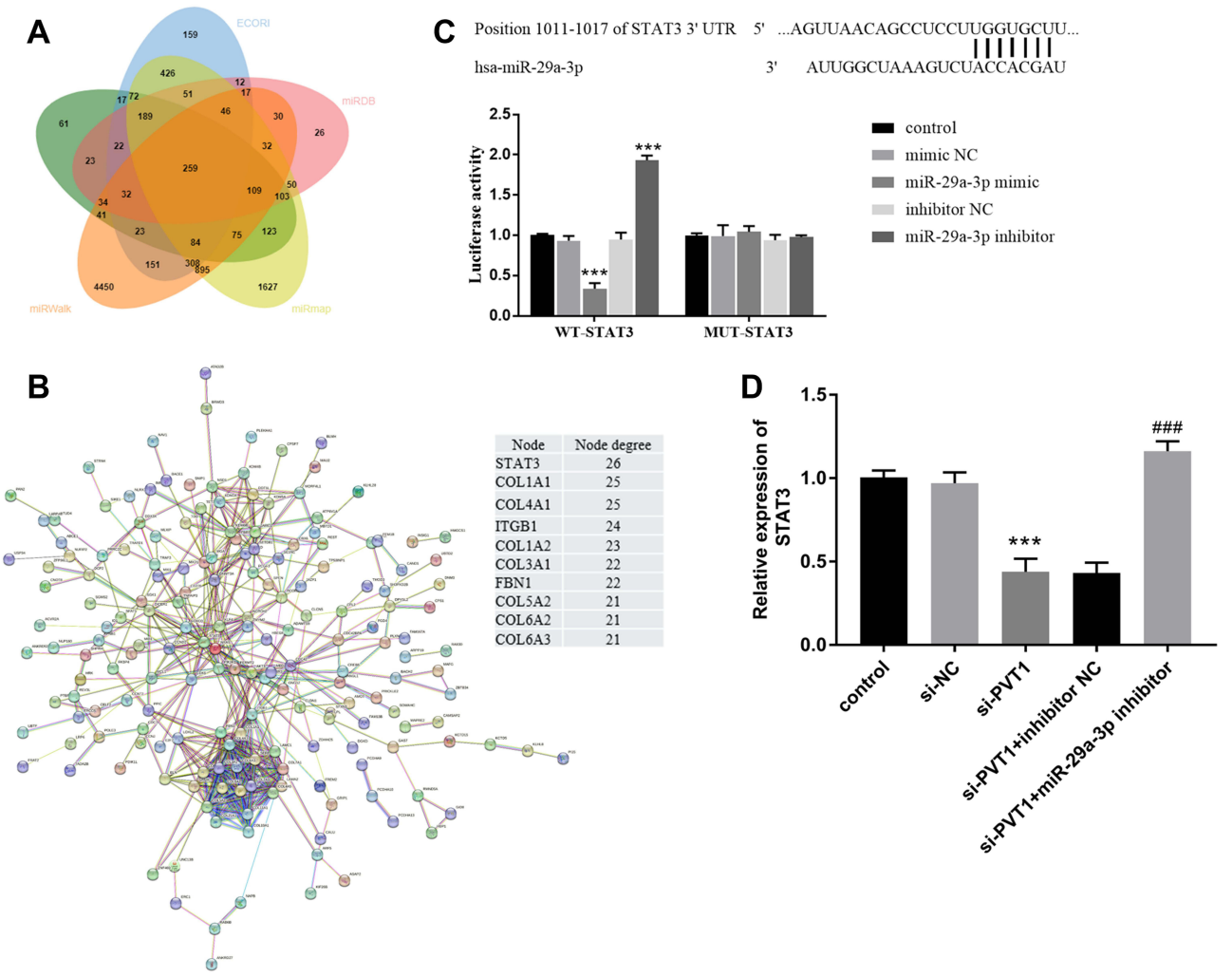


**Figure 5** The miR-29a-3p interacted with STAT3 in human HSFs. (**A**) The target genes predicted to interact with miR-29a-3p. (**B**) PPI network analysis. (**C**) Confirmation of the target relationship between miR-29a-3p and STAT3 by the dual-luciferase assays. (**D**) The regulating effect of PVT1 and miR-29a-3p on STAT3 expression. *** *P* <0.001 against the control group. ### *P* <0.001 against si-PVT1 group.

miR-29a-3p on STAT3 expression, as shown in Figure 5D. Cell transfection experiments showed that silencing PVT1 led to decreased expression of STAT3, which was significantly rescued by subsequent co-transfection with miR-29a-3p inhibitor.

## Discussion

Clinical HS is a particularly common disease of over-recovery after skin injury. Although treatments are available, there is no universal cure at present. In the long term, it is essential to explore a precisely targeted therapy to improve clinical treatment. At present, long non-coding RNAs have been found to possess a powerful ability to regulate gene expression. Our study demonstrated that lncRNA PVT1 enhanced myofibroblast proliferation, migration, and restrained their apoptosis to regulate the progression of HS via miR-29a-3p/STAT3 pathway.

HS is attributed to excessive proliferation and migration of myofibroblast, accompanied by fibrosis, inflammation and accumulation of extracellular matrix during wound recovery.[27,28] Existing therapies like laser, surgery, traditional herbal medicine have limited effects and cannot satisfy medical demand.[29,30] In addition, the mechanism of HS formation remains unclear. In this context, research on molecular therapy for HS has been developed. LncRNAs have been confirmed to have the ability to regulate HSFs cell function and further participate in the progression of diseases.[31–33] Results in this study showed that lncRNA PVT1 was obviously upregulated in HS tissues compared to control and

knockdown lncRNA PVT1 with small interfering RNA in human HSFs led to a phenotype with prominently decreased proliferation and migration and enhanced cell apoptosis. It is consistent with present reports that lncRNA PVT1 is well connected with the occurrence, proliferation, and apoptosis in different cancers.[34] Until now, research suggests that LncRNA PVT1 is closely related to cell fibrosis. In diabetic nephropathy, results state that PVT1 restrains fibrosis in a mouse model through manipulating miR-325-3p/Snail1.[35] In silica-induced pulmonary fibrosis, lncRNA-PVT1 is deemed to act positively and contribute to cell proliferation as well as migration.[36] In recent years, LncRNA PVT1 is also reported to stimulate cardiac fibrosis in mice by regulating the miR-145/HCN1 signaling.[37]

As for the regulation mechanism of cell pathobiological behavior, the predominant view is that PVT1 regulates the associated signal pathway through competing endogenous RNA (ceRNA). That is, PVT1 competitively binds microRNAs, which can bind and silence mRNA with functional messenger RNA. In this study, miR-29a-3p was identified as a possible downstream gene, which was verified by a dual luciferase reporting experiment. In addition, upregulated expression of miR-29a-3p inhibited cell activity, migration and reinforced apoptosis. The miR-29a-3p knockdown was beneficial for elevating the activity and migration. Besides, miR-29a-3p could rescue the negative influence of lncRNA PVT1 silencing on human HSFs.

Previous research findings have discovered that miR-29a-3p can suppress the proliferation and migration of hepatocellular carcinoma via decreasing IGF1R level.[38–40] A study in endometrial cancer cells shows that miR-29a-3p plays a vital role in proliferation and migration by targeting VEGFA/CD C42/PAK1.[41] Some research shows that miR-29a-3p is closely associated with keloid progression and has been identified as an underlying biomarker for keloid treatment.[42] Evidence in mice makes it clear that exosomes with miR-29a highly expressed attenuate scar formation.[43] There is also other evidence that miR-29a-3p closely engages in reduced pulmonary adventitial fibrosis.[44]

Further investigation focused on the role of lncRNA PVT1 in HS. STAT3 was identified as a potential downstream target gene of miR-29a-3p in our study. Moreover, our rescue experiments also confirmed the regulatory effects of lncRNA PVT1 and miR-29a-3p on STAT3 expression. Emerging reports show that STAT3 is a key transcription factor involved in cell growth, differentiation, survival, immune response, and inflammation.[45] Studies show that STAT3 is overexpressed in hypertrophic scar fibroblasts, driving fibroblast proliferation, migration, and fibrosis.[46] In burn-induced scars, elevated STAT3 increases ECM production by binding to promoters and upregulating collagen I and fibronectin.[47] Additionally, inhibiting STAT3 reduces collagen I and III levels.[48] These findings highlight the critical role of STAT3 in the fibrotic process of scar tissue. We identified STAT3 as a downstream target of miR-29a-3p and the target relationship has been previously confirmed in studies on sepsis.[49] Collectively, we hypothesized that highly expressed lncRNA PVT, acting as a molecular sponge for miR-29a-3p, promoted STAT3 expression thereby facilitating the progression of HS through enhanced cell proliferation, migration, fibrosis, and accumulation of extracellular matrix. A substantial amount of evidence from existing studies also provides powerful support for our findings.

Our study also has limitations. The cell experiments used in vitro-cultured myofibroblast lines, which differ from the in vivo cellular microenvironment. This may bias our results. Future in vivo experiments, including animal models, are needed to clarify the role of lncRNA PVT1 in hypertrophic scar progression.

## Conclusion

Our research suggested that miR-29a-3p bounded with lncRNA PVT1 covalently, and there was a negative correlation between them. Repressed miR-29a-3p reverted the negative effect of lncRNA PVT1 on human HSFs. The downstream STAT3 was the direct target of miR-29a-3p.

Results above demonstrated that lncRNA PVT1 accelerated the progress of HS via targeting miR-29a-3p/STAT3.

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## Disclosure

The authors report no conflicts of interest in this work.

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