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# FBXL6 is dysregulated in keloids and promotes keloid fibroblast growth by inducing c-Myc expression

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## Abstract

C-MYC-mediated keloid fibroblasts proliferation and collagen deposit may contribute to the development of keloids. F-box and leucine-rich repeat protein 6 (FBXL6) is reported to be involved in tumour progression, while the role of FBXL6 in keloid fibroblasts is not deciphered. Normal control skins, hypertrophic scars and keloid tissues were collected and prepared for FBXL6 detection. FBXL6 short hairpin RNAs (shRNAs) or FBXL6 over-expression plasmids were transfected into keloid fibroblasts, and then c-MYC plasmids were further transfected. Cell viability was assayed with a Cell-Counting Kit-8 kit. The relative expression of FBXL6, Cyclin A1, Cyclin D2, Cyclin E1 and Collagen I was detected with real-time PCR and Western blot. Elevated FBXL6 expression could be observed in keloid tissues and hypertrophic scars. FBXL6 shRNAs transfection could inhibit the viability of keloid fibroblasts with diminished c-MYC expression and down-regulated Cyclin A1, Cyclin D2, Cyclin E1 and Collagen I expression. At the same time, overexpressed FBXL6 could promote the proliferation of keloid fibroblasts. Overexpression of c-MYC could promote the proliferation of keloid fibroblasts reduced by FBXL6 shRNAs with up-regulated Cyclin A1 and Collagen I expression. FBXL6 could promote the growth of keloid fibroblasts by inducing c-MYC expression, which could be targeted in keloids treatment.

**KEYWORDS**

c-MYC, Collagen I, Cyclin A1, FBXL6, fibroblast

## Key Messages

- C-MYC-mediated keloid fibroblasts (KFs) proliferation and collagen deposit may contribute to the development of keloids
- whether FBXL6 mediated c-MYC expression may contribute to the proliferation of KFs is investigated in this study
- our results indicate the possibility to target FBXL6 to provide corresponding medication or treatment guidance for the clinical treatment of keloids
- FBXL6 inhibition might represent an effective therapeutic option for keloids treatment

## 1 | INTRODUCTION

Skin trauma or inflammation can induce abnormal fibroproliferative wound healing with excessive scar tissue beyond the borders of the original wound, and such phenomenon is defined as keloids, which show a higher incidence in dark-skinned individuals.[1,2] Despite many treatment interventions, such as intralesional corticosteroids, surgery and lasers, keloids continue to pose a challenge for clinicians due to the high recurrence.[3-5] When considering the lacking of effective medical options and the accompanying psychological distress, keloids have become health-related burdens in affected individuals.[6]

Keloid fibroblasts are implicated as principal mediators to remodel the scar tissue, which possesses the overproliferation and apoptosis resistance characteristics to produce collagen fibres and other extracellular matrices.[7-9] C-MYC-mediated fibroblasts proliferation and collagen deposition are vital in keloids.[10,11] On the other hand, the ubiquitin-proteasome system is also reported to be involved in keloid fibroblasts proliferation, differentiation and collagen secretion in keloids.[12] Among the ubiquitin-proteasome system, the SKP1-cullin-F-box complex determines substrate specificity in phosphorylation-dependent ubiquitination,[13,14] which may play an indispensable role in the regulation of cell cycle and tumorigenesis.[15,16] However, only a few F-box-containing proteins have been identified and deciphered.

F-box and leucine-rich repeat protein 6 (FBXL6) could regulate c-MYC to promote hepatocellular carcinoma oncogenesis through ubiquitination and stabilisation of heat shock protein 90 alpha family class A member 1 (HSP90AA1).[17] On the other hand, FBXL6 degrades phosphorylated p53 to promote colorectal cancer growth with diminished cell cycle arrest and apoptosis.[18] Whether FBXL6 mediated c-MYC expression may contribute to the proliferation of keloid fibroblasts is investigated in this study.

## 2 | METHODS AND MATERIALS

### 2.1 | Participants

Normal scars (n = 8; 3 women, aged 25-51, mean 35.7 years), hypertrophic scars (n = 8; 4 women, aged 22-49, mean 35.1 years) and keloid tissues (n = 20; 11 women, age 19-61, mean 37.4 years) were collected during aesthetic plastic or reconstructive surgery. More detailed information about the participants involved in this study was provided in Table 1. Hypertrophic scars are raised cutaneous conditions characterised by excessive amounts of collagen deposits, but not beyond the borders of the original wound observed in keloids. The classification of hypertrophic scars and keloids was performed by trained clinicians. This study was approved by the Ethics Committee of The Affiliated Wuxi No. 2 People's Hospital, and informed and written consent was obtained by all participants enrolled.

### 2.2 | Primary keloid fibroblasts culture

Keloid tissues were aseptically collected and incubated in DMEM medium supplemented with trypsin (0.2 mg/mL) and type-I collagenase (0.5 mg/mL) for 6 hours at 37°C. Low-glucose DMEM medium supplemented with 10% fetal bovine serum and 2 mM L-glutamine (Gibco, Grand Island, NY) was utilised to culture the isolated fibroblasts.

### 2.3 | RNA interference

Human FBXL6 short hairpin RNAs (shRNAs) were ordered from Merck, and the target sequences were indicated as following: FBXL6-shRNA1, TGGAGTGGCTTATGCCCAATC; FBXL6-shRNA2, CACCGGCATCAACCGTAATAG. FBX L6 gene was amplified by a polymerase chain reaction and cloned into the pbabe-Flag vector. C-MYC-PT3EF1a plasmid was obtained from Addgene (plasmid # 92046). The relevant plasmids were transfected into keloid fibroblasts with Lipofectamine 3000 (Invitrogen, Waltham, MA) according to the manufacturer's instructions.

### 2.4 | Cell viability

Cell viability was detected with a Cell-Counting Kit-8 (CCK-8, Dojindo Laboratories, Kumamoto, Japan). Transfected or untransfected keloid fibroblasts ($5 \times 10^5$ cells) were plated into 96-well plates and cultured for 24 hours. Then, 10 μL CCK-8 solution was added and incubated for 2 hours at 37°C. The absorbance was assayed with the SpectraMax Plus 384 Microplate Reader (Molecular Devices, Sunnyvale, CA) at 450 nm.

### 2.5 | Real-time PCR

Total RNA in keloid fibroblasts was extracted with TRIzol (Invitrogen), which was further reverse-transcribed into cDNA with a High Capacity cDNA Reverse Transcription Kit (Applied Biosystems, Foster City, CA). SYBR Green (TaKaRa, Dalian, China) was utilised to

**TABLE 1** Case information for all tissue samples analysed

| Tissue type | Number | Age (Years) | Sex | Type of lesion | Duration (Months) | Location |
|---|---|---|---|---|---|---|
| Normal skin | #1 | 25 | Male | NA | NA | Arm |
| Normal skin | #2 | 26 | Female | NA | NA | Leg |
| Normal skin | #3 | 32 | Female | NA | NA | Breast |
| Normal skin | #4 | 37 | Male | NA | NA | Abdomen |
| Normal skin | #5 | 44 | Female | NA | NA | Breast |
| Normal skin | #6 | 28 | Male | NA | NA | Abdomen |
| Normal skin | #7 | 51 | Male | NA | NA | Face |
| Normal skin | #8 | 43 | Male | NA | NA | Leg |
| Hypertrophic scar | #1 | 27 | Female | Trauma | 27 | Scalp |
| Hypertrophic scar | #2 | 33 | Female | Burn | 71 | Thorax |
| Hypertrophic scar | #3 | 22 | Female | Surgery | 23 | Abdomen |
| Hypertrophic scar | #4 | 36 | Male | Surgery | 26 | Back |
| Hypertrophic scar | #5 | 47 | Male | Trauma | 29 | Scalp |
| Hypertrophic scar | #6 | 29 | Female | Surgery | 42 | Abdomen |
| Hypertrophic scar | #7 | 38 | Male | Surgery | 22 | Face |
| Hypertrophic scar | #8 | 49 | Male | Burn | 102 | Arm |
| Keloid | #1 | 21 | Male | Trauma | 60 | Thorax |
| Keloid | #2 | 35 | Female | Burn | 32 | Abdomen |
| Keloid | #3 | 19 | Male | Burn | 24 | Neck |
| Keloid | #4 | 41 | Male | Ear piercing | 21 | Earlobe |
| Keloid | #5 | 24 | Male | Burn | 69 | Arm |
| Keloid | #6 | 53 | Female | Ear piercing | 26 | Earlobe |
| Keloid | #7 | 33 | Female | Surgery | 39 | Abdomen |
| Keloid | #8 | 48 | Male | Burn | 53 | Thorax |
| Keloid | #9 | 20 | Female | Burn | 33 | Neck |
| Keloid | #10 | 23 | Male | Ear piercing | 31 | Earlobe |
| Keloid | #11 | 55 | Female | Ear piercing | 49 | Earlobe |
| Keloid | #12 | 36 | Female | Surgery | 41 | Abdomen |
| Keloid | #13 | 30 | Male | Burn | 112 | Arm |
| Keloid | #14 | 45 | Male | Burn | 35 | Thorax |
| Keloid | #15 | 31 | Female | Ear piercing | 28 | Earlobe |
| Keloid | #16 | 61 | Female | Surgery | 44 | Abdomen |
| Keloid | #17 | 34 | Male | Ear piercing | 74 | Earlobe |
| Keloid | #18 | 50 | Female | Burn | 45 | Thorax |
| Keloid | #19 | 32 | Female | Burn | 98 | Arm |
| Keloid | #20 | 57 | Female | Trauma | 40 | Neck |

detect the amplification on Light Cycler480 (Roche, Switzerland) with the following reaction: 95°C for 10 minutes, 40 cycles of 95°C for 15 seconds and 60°C for 1 minutes. GAPDH was adopted as an internal control. Differential expression was calculated with the $2^{-\Delta\Delta Ct}$ method. Primers used for real-time PCR analysis were listed in Table 2.

## 2.6 | Western blotting

Keloid fibroblasts were lysed with Cell Extraction Buffer (Invitrogen). The relevant cellular lysates were separated on 12% SDS-PAGE and transferred to NC membrane, which were blocked with 5% non-fat milk in phosphate-buffered saline (PBS) for 2 hours and incubated with

TABLE 2 Primers used for qPCR in the current study

| Gene name | | Sequences |
|---|---|---|
| FBXL6 | Forward | 5′-GAAGTCTCAGGTACACCCCG-3′ |
| | Reverse | 5′-AGTGCTGTAGGTCCAGGCTA-3′ |
| Cyclin A1 | Forward | 5′-AGATTTCGTCTTCCAGCAGCAG-3′ |
| | Reverse | 5′-CCACTGTAGCCAGCACAACT-3′ |
| Cyclin D2 | Forward | 5′-AAGCTGTCTCTGATCCGCAA-3′ |
| | Reverse | 5′-CTGCTCCCACACTTCCAGTT-3′ |
| Cyclin E1 | Forward | 5′-CAGCCAAACTTGAGGAAAT-3′ |
| | Reverse | 5′-TCAGCCAGGACACAATAG-3′ |
| Collagen I | Forward | 5′-AGTGGTTTGGATGGTGCCAA-3′ |
| | Reverse | 5′-GCACCATCATTTCCACGAGC-3′ |
| GAPDH | Forward | 5′-GGTATCGTGGAAGGACTCATGAC-3′ |
| | Reverse | 5′-ATGCCAGTGAGCTTCCCGTTCAG-3′ |

primary antibody overnight at 4°C and secondary antibody at room temperature for 1 hours. GE Healthcare ECL system was utilised to develop the signal, and the intensity of the interest bands was calculated with NIH-Image J1.51p 22 by correcting with GAPDH expression. Primary antibodies utilised were indicated: anti-FBXL6 (1:1000 dilution, SAB1407299, Sigma, St. Louis, MO), anti-c-MYC (1:1000 dilution, MA1-980, Invitrogen), anti-Collagen I (1:2000 dilution, PA5-95137, Invitrogen), and anti-GAPDH (12 000 dilution, MA1-16757, Invitrogen).

### 2.7 | Statistical analysis

One/two-way ANOVA followed Dunn's multiple comparisons test or Tukey's multiple comparisons test was utilised to estimate the difference. The significance level was set as $P$-value < .05. All statistical analyses were performed with GraphPad Prism.

## 3 | RESULTS

### 3.1 | Elevated FBXL6 expression in keloid tissues

The relative mRNA and protein expression of FBXL6 in the normal skin tissues, hypertrophic scars and keloid tissue were detected. Significantly higher mRNA expression of FBXL6 was observed in hypertrophic scars and keloid tissues compared with normal skin tissues (Figure 1A), while its expression in keloid tissue was the highest. At the same time, significantly increased FBXL6 protein expression was also observed in hypertrophic scars and keloid tissues compared with normal skin tissues (Figure 1B,C), and FBXL6 protein expression in keloid tissue was also the highest.

### 3.2 | FBXL6 promotes keloid fibroblasts proliferation

Fibroblast proliferation and excessive collagen secretion are the characteristic pathological features of keloids. FBXL6 shRNA was transfected into keloid fibroblasts, and the significantly down-regulated FBXL6 mRNA expression (Figure 2A) and protein expression (Figure 2B) were observed, which testified the success of FBXL6 shRNA transfection. It was further revealed that FBXL6 shRNA could inhibit the growth of keloid fibroblasts (Figure 2C). While FBXL6 over-expression (Figure 2D) significantly promoted the cell proliferation of keloid fibroblasts (Figure 2E). These results demonstrated that FBXL6 played an essential role in keloid fibroblasts proliferation.

### 3.3 | Knockdown of FBXL6 promotes c-MYC and cyclin molecules expression

To evaluate the regulatory mechanism of FBXL6, the expression of potential downstream molecules were detected. As expected, the diminished c-MYC expression could be observed in FBXL6 shRNA transfected keloid fibroblasts as revealed by Western blot assay, as well as FBXL6 protein expression (Figure 3A). At the same

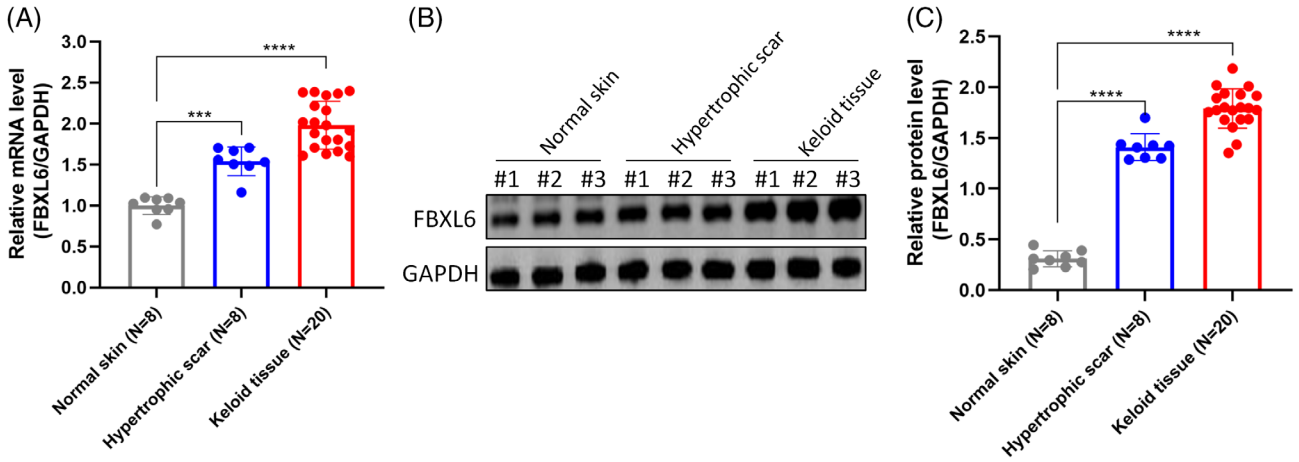


**FIGURE 1** FBXL6 is elevated in keloid tissues. (A) Control normal skins, hypertrophic scars and keloid tissues were prepared for real-time PCR for FBXL6. GAPDH was used as an internal control. (B) Representative tissues were prepared for Western blot analysis against FBXL6. GAPDH was used as a loading control. (C) Statistical analysis for Western blot. One-way ANOVA followed Dunn's multiple comparisons test was used. ***$P < .001$, ****$P < .0001$

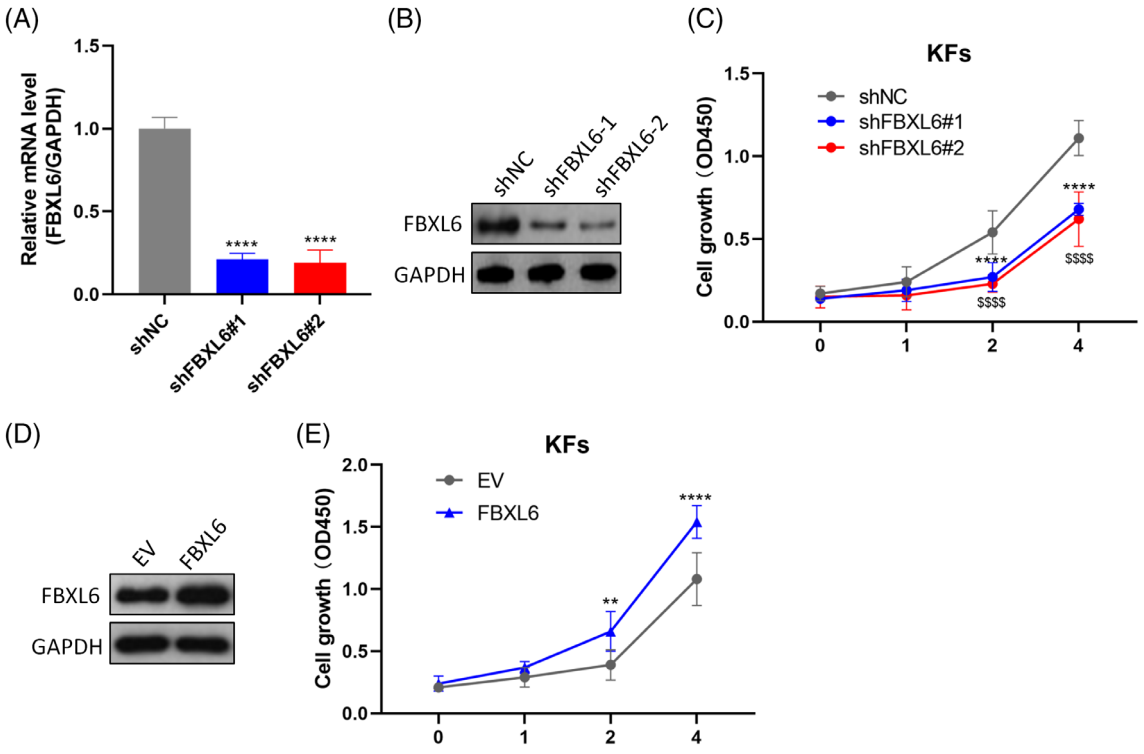


**FIGURE 2** FBXL6 promotes cell proliferation in keloid fibroblasts. (A and B) Keloid fibroblasts (KFs) were infected with FBXL6 shRNAs for 2 days, and then cells were lysed for real-time PCR (A) and Western blot (B). One-way ANOVA followed Dunn's multiple comparisons test was used. ****$P < .0001$. (C) FBXL6 shRNAs infected keloid fibroblasts were cultured for 0, 1, 2, or 4 days, followed by a CCK-8 assay. Two-way ANOVA followed Tukey's multiple comparisons test was used. ****$P < .0001$, $^{\$\$\$\$}P < .0001$. (D and E) FBXL6-overexpressing plasmids transfected keloid fibroblasts were cultured for 2 days, followed by Western blot analysis (D) and CCK-8 assay (E). Two-way ANOVA followed Tukey's multiple comparisons test was used. **$P < .01$, ****$P < .0001$

time, the relative mRNA expression of Cyclin A1 (Figure 3B), Cyclin D2 (Figure 3C) and Cyclin E1 (Figure 3D) was significantly decreased after FBXL6 shRNA transfection. All of these indicated that FBXL6 functioned as the upstream molecules to regulate cell-cycle relevant molecules.

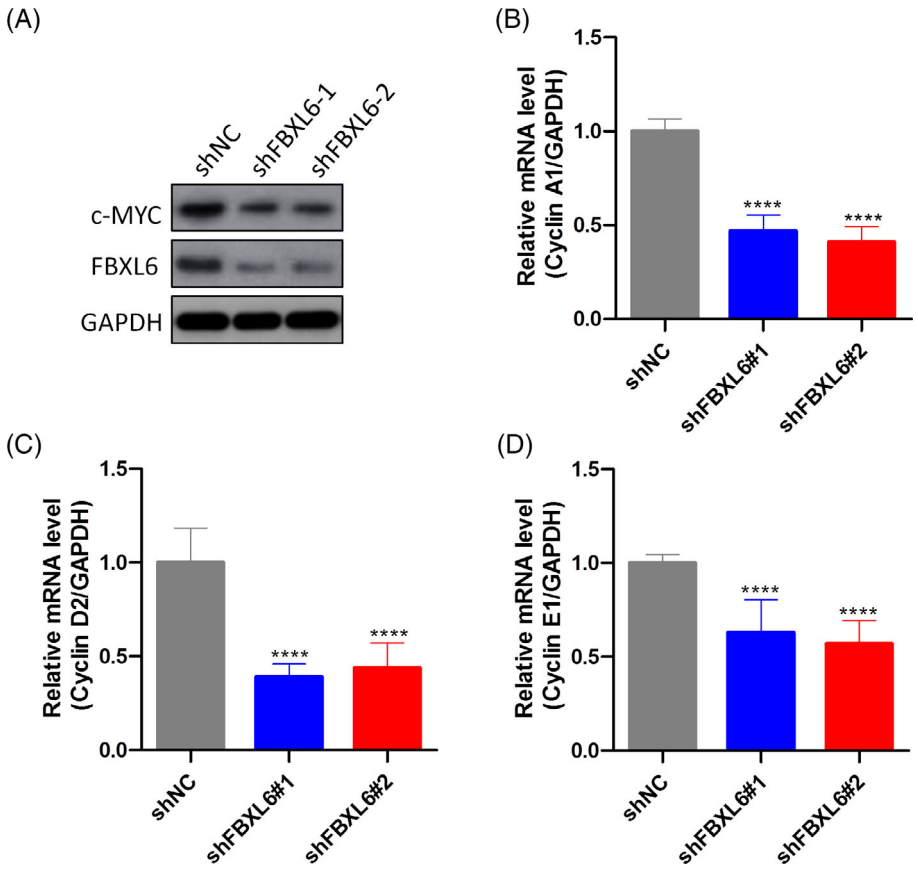


**FIGURE 3** Knockdown of FBXL6 suppresses c-MYC and its downstream genes' expression in keloid fibroblasts. (A) Keloid fibroblasts (KFs) were infected with FBXL6 shRNAs for 2 days, and then cells lysates were prepared for Western blot against c-MYC and FBXL6. (B-D) Keloid fibroblasts were infected with FBXL6 shRNAs for 2 days, and then cells were prepared for real-time PCR against Cyclin A1 (B), Cyclin D2 (C), and Cyclin E1 (D). One-way ANOVA followed Dunn's multiple comparisons test was used. ****$P < .0001$

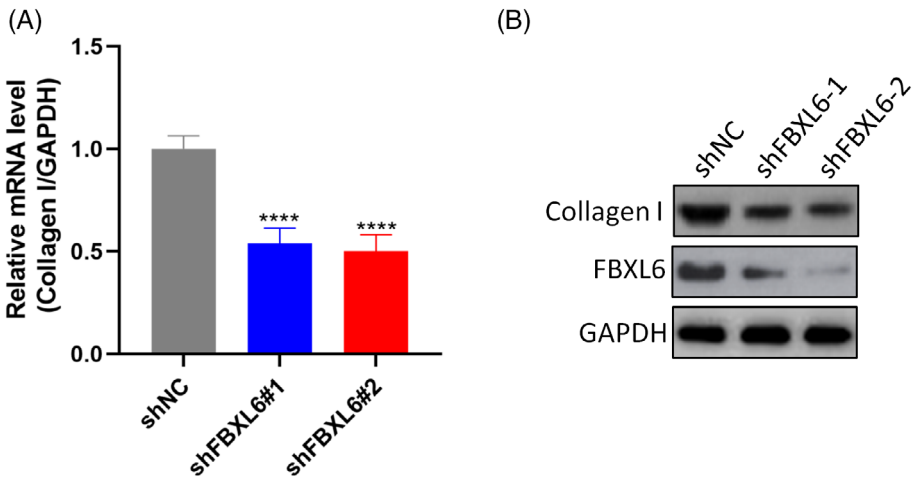


**FIGURE 4** Knockdown of FBXL6 suppresses collagen production in keloid fibroblasts. (A and B) Keloid fibroblasts were infected with FBXL6 shRNAs for 2 days, and then cells were prepared for real-time PCR (A) and Western blot (B). One-way ANOVA followed Dunn's multiple comparisons test was used. ****$P < .0001$

### 3.4 | FBXL6 promotes collagen production in keloid fibroblasts

We also further detected the relative expression of Collagen I. It was found that the inhibition of FBXL6 could significantly inhibit the relative mRNA expression (Figure 4A) and protein expression (Figure 4B) of Collagen I in keloid fibroblasts. It was further suggested that FBXL6 could regulate the transcription and translation of Collagen I and play a vital role in keloid fibroblasts mediated collagen deposit.

### 3.5 | C-MYC mediates FBXL6 induced cell cycle-related molecules regulation

FBXL6 shRNA transfected keloid fibroblasts were further transfected with c-MYC plasmid, and the transfection

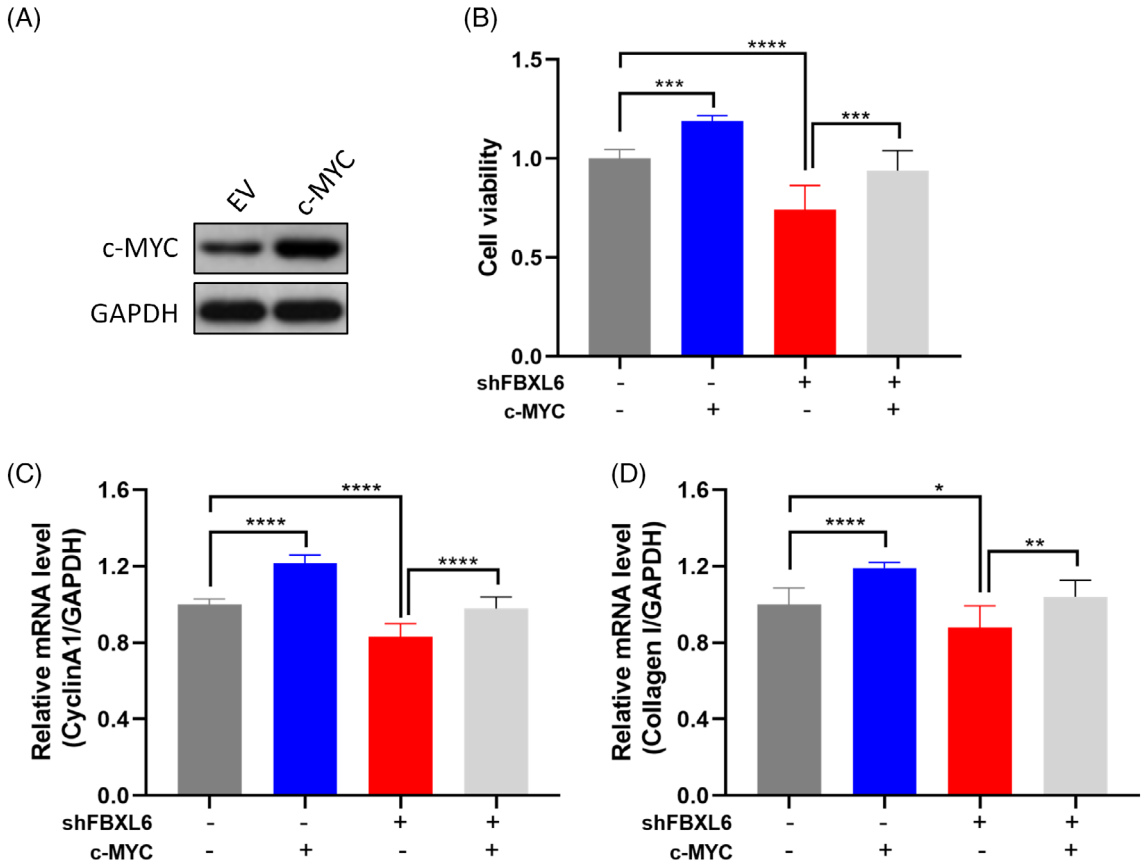


**FIGURE 5** C-MYC overexpression blocks the function of FBXL6 shRNAs in keloid fibroblasts. (A) The overexpressing efficacy for c-MYC. (B) keloid fibroblasts were transfected with FBXL6 shRNAs or FBXL6-overexpressing plasmids for 2 days, followed by a CCK-8 assay. (C & D) Keloid fibroblasts were transfected with FBXL6 shRNAs or FBXL6-overexpressing plasmids for 2 days, followed by real-time PCR analysis for Cyclin A1 (C) and Collagen I (D). GAPDH was used as an internal control. One-way ANOVA followed Dunn's multiple comparisons test was used. *$P < .05$, **$P < .01$, ***$P < .001$, ****$P < .0001$

efficiency was testified by the up-regulated c-MYC expression (Figure 5A). C-MYC overexpression could promote the diminished cell viability induced by FBXL6 shRNA transfection (Figure 5B) with up-regulated Cyclin A1 (Figure 5C) and Collagen I (Figure 5D) expression. All of these indicated that FBXL6 dependent c-MYC mediated keloid fibroblasts proliferation may contribute to the development of keloids.

## 4 | DISCUSSION

Significantly highly expressed FBXL6 is observed in keloid tissues compared with normal skins and hypertrophic scars. Silenced or overexpressed FBXL6 could inhibit or promote the proliferation of keloid fibroblasts, and FBXL6 silencing could significantly inhibit the protein expression of c-MYC, Cyclin A1, Cyclin D2 and Cyclin E1. On the other hand, FBXL6 silencing can significantly down-regulate collagen I expression in keloid fibroblasts. C-MYC overexpression could substantially reverse the decreased cell viability and Cyclin A1 and collagen I expression induced by FBXL6 silencing, all of these indicate that the functional recovery of FBXL6 could be obtained by overexpression of c-MYC in keloid fibroblasts. All of these indicate the possibility to target FBXL6 to provide corresponding medication or treatment guidance for the clinical treatment of keloids.

As an oncogenic pleiotropic transcription factor, c-MYC participates and regulates multiple biological processes, such as survival, cell cycle control and cell proliferation.[19,20] On the other hand, FBXL6 induced c-MYC mediated cellular reprogramming could promote somatic cells to convert into pluripotent stem cells and maintain pluripotency in both mouse and human systems.[21,22] As one kind of benign skin disorder, keloid can be attributed to fibroblasts hyperplasia and myofibroblast mediated collagen fibrils. Myofibroblasts could be derived from skin resident fibroblasts or keloid progenitor stem cells.[23] It is worth noting that mesenchymal stem cells derived from fetal skins might participate the scarless healing.[24]

The precise mechanism mediated by c-MYC leading to fibroblasts differentiation and activation needs further detailed analysis.

Accumulated FBXL6 could stabilise and activate c-MYC by preventing HSP90AA1 degradation. In addition to function as a component of the SKP1-cullin-F-box complex, F-box proteins have been testified to have multiple other cellular functions.[25-27] Previous research also demonstrates that c-MYC might directly bind to the promoter region of FBXL6 to promote the transcription, suggesting the positive feedback relationship between FBXL6 and c-MYC.[17]

As downstream molecules of cyclin-dependent kinases, Cyclins could phosphorylate well-defined enzymatic and structural targets to coordinate cell cycle progression.[28] Mitogen-stimulated signal transduction could induce c-MYC mediated Cyclin D1 expression to promote the cell cycle without de novo protein synthesis,[29] and c-MYC might acetylate histone H4 to regulate the CDK1/Cyclin B1-dependent G2/M cell cycle progression in Raji cells.[30]

Some limitations should be indicated here. Whether the positive feedback about FBXL6 and C-MYC happens in keloid fibroblasts needs further detailed analysis. Only in vitro study was performed, the transgenic animal model should be constructed to testify the in vivo reaction pattern. More precise ChIP and luciferase assays should be designed to testify the direct interaction between FBXL6 and C-MYC.

## 5 | CONCLUSION

Elevated FBXL6 expression was found in keloid tissues. Furthermore, FBXL6 could regulate keloid fibroblasts proliferation. Knockdown of FBXL6 promoted c-MYC and Cyclin molecules expression. In addition, FBXL6 promoted collagen production in keloid fibroblasts. Mechanically, C-MYC was demonstrated to mediate FBXL6 induced cell cycle-related molecules regulation. In summary, FBXL6-c-MYC axis might promote the proliferation of keloid fibroblasts. It is proposed that FBXL6 inhibition might represent an effective therapeutic option for keloids treatment.

### CONFLICT OF INTEREST

The author declare no conflicts of interest.

### DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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