Abstract. Long non-coding (Inc)RNA nuclear-enriched transcripts 1 (NEAT1) has been demonstrated to be involved in the inhibition of hypoxia-induced scar fibroblast proliferation, but the specific mechanism remains undetermined. The present study found that with the decrease of oxygen concentration, lncRNA NEAT1 was upregulated in hypoxia-induced scar fibroblasts, which promoted the mRNA and protein expression levels of collagen (COL)-I, COL-III and α-smooth muscle actin, thereby suppressing hypoxia-induced scar fibroblasts proliferation. In addition, the microRNA (miR)-488-3p/COL3A1 axis was involved in lncRNA NEAT1's regulation of the proliferation of hypoxia-induced scar fibroblasts. In conclusion, the knockdown of lncRNA-NEAT1 expression can inhibit hypoxia-induced scar fibroblast proliferation through regulation of the miR-488-3p/COL3A1 axis, which will provide a novel therapeutic target for the treatment of hypertrophic scars.

Introduction

Hypertrophic scar is a type of fibrotic skin disease caused by abnormal healing of skin injuries including skin burns (1), which is characterized by excessive proliferation of fibroblasts, epidermal interstitial transformation and collagen deposition (2). Hypertrophic scars commonly occur in injured skin areas and cause pain, itching and other symptoms, which cause great psychological effects to the patients. At present, the main clinical treatment methods for scars include surgical excision and steroid therapy, but the pathological molecular mechanism of scar formation remains to be elucidated. Therefore, the present study on the pathological mechanism of scar formation may reveal a novel therapeutic target for the treatment of hypertrophic scars.

Long non-coding RNAs (IncRNAs) are a class of non-coding RNAs that contain >200 nucleotides. Studies have demonstrated that IncRNAs significantly affect complicated pathological processes of various diseases, e.g., cardiovascular diseases (3), cerebral ischemic diseases and carcinomas (4). IncRNAs have no protein-coding capability, but they bind to micro (mi)RNA as competitive endogenous RNAs and regulate the expression of downstream target genes, thus serving a critical role in various biological cellular processes and malignant diseases. LncRNA nuclear-enriched transcripts 1 (NEAT1) is a tumor growth regulator that plays an essential role in different types of cancer (5,6) including breast (7), gastric (8) and lung (9) cancer. It has been demonstrated that lncRNA NEAT1 sponges miRNA (miR)-129 to regulate the epithelial-mesenchymal transition (EMT) and inflammatory response of renal fibrosis through regulation of collagen (COL)-I (10). Nonetheless, the molecular regulation mechanism of lncRNA NEAT1 in hypertrophic scar formation remains unclear.

The role of miRNA in the progression of malignant diseases has attracted extensive attention (11). miRNA can competitively block the translation of downstream target genes and negatively regulate the expression level of target genes, thus serving a key part in the treatment of hypertrophic scars (12). Wang et al (13) found that miR-31-5p participates in the formation of hypertrophic scars (HSs) by inhibiting FIH and regulating the expression of HIF-1α. Bi et al (14) found that miR-98 inhibits the proliferation of hypertrophic scar fibroblasts by targeting COL1A1. In addition, Li et al (15) found that IncRNA8975-1 regulates the expression of COL3A1, COL1A1 and α-smooth muscle actin (α-SMA) and inhibits the proliferation of fibroblasts in hypertrophic scars. COL3A1 has been identified as a marker for fibroblast differentiation in hypertrophic scar formation, implying that the expression level of COL3A1 is associated with the pathological process of hypertrophic scars. Given the abnormal proliferation of fibroblasts, it was hypothesized that COL3A1 is involved in the proliferation of fibroblasts during scar formation. The present study aimed to investigate the inhibitive effects of IncRNA NEAT1 on cell proliferation of hypertrophic scars and elucidate the molecular mechanism of the miR-488-3p/COL3A1 axis in regulating scar fibroblast proliferation.
Materials and methods

Cell culture and treatments. Scar fibroblasts purchased from American Type Culture Collection were incubated in Dulbecco's Modified Eagle's Medium (DMEM; Gibco; Thermo Fisher Scientific, Inc.) supplemented with 10% fetal bovine serum (FBS; Gibco; Thermo Fisher Scientific, Inc.) and 1% penicillin-streptomycin in 5% CO₂ at 37°C. The groups of the experiment included the control group (2% O₂), the 10% hypoxia group (10% O₂), the 5% hypoxia group (5% O₂) and the 1% hypoxia group (1% O₂). After 48 h of culture, the experiments were started.

Bioinformatics analysis. Bioinformatics analysis was performed to predict the downstream miRNA and mRNA of lncRNA NEAT1 using Starbase (https://starbase.sysu.edu.cn/).

Cell transfection. Scar fibroblasts underwent transfection with 20 nM miR-488-3p mimic or the corresponding negative control (Shanghai GenePharma Co., Ltd.) by using Lipofectamine® 2000 (Invitrogen; Thermo Fisher Scientific, Inc.) for 48 h at 37°C. For COL3A1 overexpression, the recombinant sense expression vector pCMV-Tag-3A (Thermo Fisher Scientific, Inc.) was constructed by subcloning the cDNA fragment of COL3A1 containing the complete coding sequence between KpnI and BamHI. Short hairpin RNA (shRNA) targeting NEAT1 (sh-NEAT1) and their negative control (sh-NC) were purchased from Shanghai GenePharma Co., Ltd. Sequences were cloned in the pEGFP vector. miR-488-3p mimic (anti-miR-NC; 5'-CAAUUGAUCUUGAUUGUAAGGUGAAGGUGUACUUGACUGUCAA-3') and miR-488-3p inhibitor (anti-miR-488-3p; 5'-UUGAAAAGUCUUGAUUGAUUGUAAGGUGUACUUGACUGUCAA-3') were also purchased from Shanghai GenePharma Co., Ltd. Sequences were cloned in the pEGFP vector.

Reverse transcription-quantitative (RT-q)PCR. A total of 1 µg RNA was extracted from scar fibroblasts by using Trizol® (Thermo Fisher Scientific, Inc.). Reverse transcription was performed using RT Reagent kit (cat. no. RR037A; Takara, Bio, Inc.). qPCR (cat. no. RR820A; Takara, Bio, Inc.) was performed using SYBR Green mix (Takara Bio, Inc.) with primers specific to miR-488-3p (Guangzhou RiboBio Co., Ltd.) according to the manufacturer’s instructions. The PCR conditions were as follows: 95°C for 10 min, followed by 40 cycles of 95°C for 10 s, 60°C for 30 s and 72°C for 1 min. Relative quantification of the mRNA expression was calculated through the 2^−ΔΔCt method (16). Primers: miR-488-3p forward, 5'-ACACTTCCACGTGGTTAAGGCTATTT-3' and reverse, 5'-CTCAACTGTTGTGCTGGATGTCGCAGATCCTGAGAGCAGACAA-3'; NEAT1 forward, 5'-GGGAGAGGTGGTGTTAGAGTATG-3' and reverse, 5'-CCCTAACCTGCTTCTTTCT-3'; U6 forward, 5'-CTCCTCGGACGACAAC-3' and reverse, 5'-AACGCTTCACGATTGCT-3'; and GAPDH forward, 5'-GACCCGCTACGGGTATGCAGAC-3' and reverse, 5'-GGATGAGGTGGTGTTAGAGTATG-3'. U6 and GAPDH were selected as the housekeeping gene to normalize the expression of miRNA and mRNA.

Western blotting. Total protein lysates were generated using RIPA lysis buffer supplemented with protease and phosphatase inhibitor mixtures (cat. no. KC-440; Shanghai KangChen Biological Technology Co. Ltd.). Nuclear proteins were extracted by using the NE-PER nuclear and cytoplasmic extraction reagents (Pierce; Thermo Fisher Scientific, Inc.) according to the manufacturer's instructions. The concentration of the protein in cells lysates was detected using a BCA kit (Beijing Solarbio Science & Technology Co., Ltd.).
Proteins (40 µg) were loaded onto a 5‑10% polyacrylamide gel, separated by electrophoresis and transferred onto a poly‑vinylidene difluoride (PVDF) membrane. Then, the PVDF membrane was blocked with a 5% solution of non‑fat milk at room temperature for 3 h and incubated with rabbit polyclonal antibodies to COL‑I (1:1,000 cat. no. ab260043; Abcam) and COL‑III (1:1,000; cat. no. ab7778; Abcam), α‑SMA (1:1,000; cat. no. 19245s; Cell Signaling Technology, Inc.) and GAPDH (1:1,000; cat. no. 5174s; Cell Signaling Technology, Inc.) at 4˚C overnight. Horseradish peroxidase‑conjugated goat anti‑rabbit (cat. no. BA1054) or anti‑mouse (cat. no. BA1050) antibody (1:15,000) (Wuhan Boster Biological Technology, Ltd.) was utilized as a secondary antibody, incubated at 37˚C for 1 h. Proteins were visualized by an enhanced chemiluminescence system using the FluorChem FC system (ProteinSimple). ImageJ software V.1.4 (National Institutes of Health) was used to measure the gray values of the bands and analyze the changes in relative protein expression levels.

**Statistical analyses.** Statistical analyses were performed using SPSS 13.0 software (SPSS Inc., Chicago, IL, USA). The data are shown as mean ± standard error of the mean (SEM) from three independent experiments. Statistical analyses were conducted using Student's t‑test or ANOVA followed by Tukey's post hoc test. P<0.05 was considered to indicate a statistically significant difference.

**Results**

**Upregulated lncRNA‑NEAT1 expression in scar fibroblasts under different hypoxic conditions.** First, the viability of scar fibroblasts under different hypoxic conditions was detected by CCK‑8 kit. As shown in Fig. 1A, the CCK‑8 results indicated that with the decrease of oxygen concentration, the viability of scar fibroblasts was significantly enhanced; the viability of scar fibroblasts in the 5% group was the highest. The expression of lncRNA NEAT1 in scar fibroblasts under different hypoxic conditions was detected. The RT‑qPCR analysis results (Fig. 1B) implied that compared with the 21% group, the expression of lncRNA NEAT1 in scar fibroblasts in the 5% group and the 1% group were markedly increased (P<0.001). Thus, lncRNA NEAT1 can upregulate in the hypoxic environment, which may play a role in the proliferation of scar fibroblasts.

**Effects of lncRNA NEAT1 on hypoxia‑induced scar fibroblast proliferation.** RT‑qPCR analysis was performed to detect the expression of lncRNA NEAT1 in different groups. As shown in Fig. 2A, compared with the NC group, the expression of lncRNA NEAT1 in the lncRNA NEAT1 group and the hypoxia (5%) + lncRNA NEAT1 group was significantly reduced, whereas that in the hypoxia (5%) + NC group was increased. To investigate the effect of lncRNA NEAT1, the hypoxia‑induced scar fibroblasts proliferation was detected by CCK‑8 kit. The results (Fig. 2B) demonstrated that compared with the NC group, the viability of scar fibroblasts in the hypoxia (5%) + NC group was substantially enhanced while that in the hypoxia (5%) + lncRNA NEAT1 group was inhibited. Ki‑67 protein can be used as a proliferation marker for hypertrophic scar fibroblasts, hence RT‑qPCR analysis and immunofluorescence staining were performed to detect the expression of Ki‑67 in scar fibroblasts. The results (Fig. 2C) indicated that compared with the NC group, the expression of Ki‑67 in the hypoxia (5%) + NC group was significantly increased while that in the hypoxia (5%) + lncRNA NEAT1 group was markedly reduced, which is consistent with the immunofluorescence staining results (Fig. 2D). Therefore, lncRNA NEAT1 can inhibit the proliferation of hypoxia‑induced scar fibroblasts.

**Effects of lncRNA NEAT1 on steady‑state protein levels of COL‑I, COL‑III and α‑SMA in scar fibroblasts.** To investigate the regulatory mechanism of lncRNA NEAT1 in scar fibroblasts, RT‑qPCR analysis and western blotting were performed to detect the mRNA and protein expression levels of COL‑I, COL‑III and α‑SMA in scar fibroblasts. The RT‑qPCR results (Fig. 3A‑C) indicated that compared with the NC group, the mRNA expression of COL‑I, COL‑III and α‑SMA in the Hy + NC group was substantially upregulated while that in the Hy + lncRNA NEAT1 group was downregulated, which is consistent with the western blotting results (Fig. 3D). In summary, the RT‑qPCR results and the western blotting results demonstrated that lncRNA NEAT1 can downregulate the expression levels of COL‑I, COL‑III and α‑SMA in hypoxia‑induced scar fibroblasts.
XU et al: KNOCKDOWN OF lncRNA ‑NEAT1 INHIBITS HYPOXIA ‑INDUCED SCAR FIBROBLAST PROLIFERATION

lncRNA NEAT1 directly targeted miR‑488‑3p. Luciferase activity of scar fibroblasts (Fig. 4A and B) transfected with miR‑488‑3p mimics was markedly reduced compared with the mimics control group (P<0.01). In addition, the RT‑qPCR results (Fig. 4C) demonstrated that the expression of miR‑488‑3p in the lncRNA NEAT1 group was significantly increased compared with the NC group. Therefore, it was confirmed that lncRNA NEAT1 directly targets miR‑488‑3p.

miR‑488‑3p directly targets COL3A1. As indicated by the results of the luciferase activity assay (Fig. 5A and B), luciferase activity of scar fibroblasts transfected with miR‑488‑3p mimics was substantially reduced compared with the mimics control group (P<0.01). In addition, compared with the mimics control group, the expression level of miR‑488‑3p in the miR‑488‑3p mimics group was significantly increased. Compared with the inhibitor control group, the expression level of miR‑488‑3p was significantly reduced in the miR‑488‑3p inhibitor group. Furthermore, the RT‑qPCR analysis results (Fig. 5D) indicated that the mRNA expression level of COL3A1 in the miR‑488‑3p mimics group was substantially downregulated compared with the mimics control group, whereas that in the miR‑488‑3p inhibitor group was increased compared with the inhibitor control group. The western blotting results (Fig. 5E) were consistent with the RT‑qPCR results. Given the above results, it was concluded that miR‑488‑3p directly targets COL3A1 in scar fibroblasts.

lncRNA NEAT1 inhibited hypoxia‑induced scar fibroblasts proliferation through regulation of miR‑488‑3p/COL3A1 axis. To detect the mRNA expression level of COL3A1 in scar fibroblasts after transfection, RT‑qPCR analysis was performed. The results (Fig. 6A) demonstrated that compared with the pcDNA3.1 group, the mRNA expression level of COL3A1 in the pcDNA3.1‑COL3A1 group was significantly increased. The western blotting results (Fig. 6B) indicated that...
compared with the Hy + NC group, the protein expression level of COL-III in the Hy + lncRNA NEAT1 group was substantially reduced; compared with the Hy + lncRNA NEAT1 + inhibitor control group, the protein expression level of COL-III in the Hy + lncRNA NEAT1 + miR-488-3p inhibitor group was substantially increased; compared with the Hy + lncRNA NEAT1 + NC group.
NEAT1 + pcDNA3.1 group, the protein expression level of COL-III in the Hy + IncRNA NEAT1 + pcDNA3.1-COL3A1 group was markedly increased. The proliferation of scar fibroblasts was detected by CCK-8 kit. The results (Fig. 6C) suggested that compared with the Hy + NC group, the viability of scar fibroblasts in the Hy + IncRNA NEAT1 inhibitor group was substantially inhibited; compared with the Hy + IncRNA NEAT1 + inhibitor control group, the viability of scar fibroblasts in the Hy + IncRNA NEAT1 + pcDNA3.1-COL3A1 group was increased with statistic difference (P<0.05). Meanwhile, the expression of Ki-67 protein in scar fibroblasts was detected through RT-qPCR analysis and the results (Fig. 6D) were consistent with the CCK-8 assay results. Given the above, IncRNA NEAT1 inhibited hypoxia-induced scar fibroblast proliferation through regulation of miR-488-3p/COL3A1 axis.

Discussion

Hypertrophic scar is a common proliferative disease associated with abnormal wound healing responses (17), so clarifying its pathological mechanism is conducive to determining appropriate treatment strategies. Abnormal proliferation and apoptosis of scar fibroblasts directly or indirectly affect
their collagen deposition and scar formation (18). With the development of biomedical science, increasing evidences have demonstrated that lncRNAs play a regulatory role in the pathogenesis of various diseases including cancer, myocardial infarction, pulmonary fibrosis and hypertrophic scars by regulating key proteins with competing endogenous (ce) RNAs (19‑21). LncRNA NEAT1 regulates FRS2 by targeting miR‑29‑3p in hypertrophic scar fibroblasts, thereby exacerbating the pathological process of scar formation (22). The results of the present study indicated that lncRNA NEAT1 serves an important role in hypertrophic scars by mediating miR‑488‑3p/COL3A1 axis. Therefore, it was hypothesized that lncRNA NEAT1 acts as a mediator in the progression of hypertrophic scars.

Hypertrophic scar formation is a complicated pathological process characterized by inflammation, collagen deposition and fibroblast dysfunction. Activated fibroblasts are the main effector cells in this fibrosis process (23). The abnormal proliferation of scar fibroblasts and the inflammation-mediated fibrosis directly affect scar formation. Bai et al (24) found that loureirin B suppresses scar fibroblasts proliferation and fibrosis induced by TGF‑β1 by downregulating the expression of fibrosis-related molecules by regulating MMPs. Liu et al (25) found that miR-6836-3p promotes the proliferation of scar fibroblasts by upregulating the expression of connective tissue growth factor, hence miR-6836-3p may be a potential target in the treatment of hypertrophic scars. The present study investigated the effects of lncRNA NEAT1 on the function of hypoxia-induced scar fibroblasts.

As the main participants of scar formation in wound healing, scar fibroblasts are involved in biological processes including collagen synthesis, extracellular matrix (ECM) formation and deposition (26) and skin fibrosis. TGF-β1 recruits macrophages to release inflammatory factors, promotes the chemotaxis of fibroblasts and smooth muscle and regulates the collagen gene expression in fibrosis (27). Collagens are known to regulate the migration, proliferation and gene expression of cells (28). In hypertrophic scars, fibroblasts synthesize excessive ECM proteins, among which the deposition of collagens, especially COL-I and COL-III, is significantly increased (29).
Consistent with previous studies, the results of the present study confirmed that collagen deposition is significantly increased in hypoxia-induced hypertrophic scars. The present study found that silencing IncRNA NEAT1 targeted miR-488-3p to downregulate the expression levels of COL-I, COL-III and α-SMA in hypoxia-induced fibroblasts under hypoxic pathological conditions. Zhang et al. (30) concluded that Flt1 activates the PI3K/Akt/mTOR signaling pathway and promotes the expression levels of COL1A1 and COL3A1, thereby stimulating fibroblast proliferation and myofibroblast differentiation and accelerating wound healing. The present study found that silencing IncRNA NEAT1 mediated miR-488-3p/COL3A1 axis, downregulated collagen expression levels and attenuated the process of hypertrophic scarring.

In summary, the knockdown of IncRNA NEAT1 expression inhibited scar fibroblast proliferation through regulation of the miR-488-3p axis and regulated a series of collagens including COL3A1 to serve protective roles in hypertrophic scar formation. The results demonstrated that IncRNA NEAT1 may be a novel therapeutic target for the treatment of hypertrophic scars. Nonetheless, the limitation of this study lies in the fact that the underlying regulatory mechanism of IncRNA NEAT1 in hypertrophic scar formation remains unconfirmed in vivo experiments.

Acknowledgements
Not applicable.

Funding
The study was supported by the hospital level project of Children's Hospital of Shanxi (grant no. 202028)

Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions
HX wrote the manuscript, designed experiments and analyzed the data. XG and YT participated in experiments and data analysis. JW participated in experiments and literature review. HX and XG confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate
Not applicable.

Patient consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

References
1. Chen L, Li J, Li Q, Yan H, Zhou B, Gao Y and Li J: Non-coding RNAs: The new insight on hypertrophic scar. J Cell Biochem 118: 1965-1968, 2017.
2. Lee HJ and Jang YJ: Recent understandings of biology, prophylaxis and treatment strategies for hypertrophic scars and keloids. Int J Mol Sci 19: 711, 2018.
3. Zhang J, Yu L, Xu Y, Liu Y, Li Z, Xue X, Wan S and Wang H: Long noncoding RNA upregulated in hypothermia treated cardiomyocytes protects against myocardial infarction through improving mitochondrial function. Int J Cardiol 266: 213-217, 2018.
4. Li X, Wu Z, Fu X and Han W: IncRNAs: Insights into their function and mechanics in underlying disorders. Mutat Res Rev Mutat Res 762: 1-21, 2020.
5. Shan G, Tang T, Xia Y and Qian HJ: Long non-coding RNA NEAT1 promotes bladder progression through regulating miR-410 mediated HMGB1. Biomed Pharmacother 121: 109248, 2020.
6. Zhang X, Guan MX, Jiang QH, Li S, Zhang HY, Wu ZG, Cong HL and Qi XH: NEAT1 knockdown suppresses endothelial cell proliferation and induces apoptosis by regulating miR-638/akt/mTOR signaling in atherosclerosis. Oncol Rep 44: 115-120, 2020.
7. IncRNA NEAT1 facilitates cell proliferation, invasion and migration by regulating CBX7 and RTCB in breast cancer (retraction). Onco Targets Ther 13: 7807, 2020.
8. Zhang J, Zhao B, Chen X, Wang Z, Xu H and Huang B: Silence of long noncoding RNA NEAT1 inhibits malignant biological behaviors and chemotherapy resistance in gastric cancer. Pathol Oncol Res 24: 109-113, 2018.
9. Gu G, Hu C, Hui K, Chen T, Zhang H and Jiang X: NEAT1 knockdown enhances the sensitivity of human non-small-cell lung cancer cells to anlotinib. Aging (Albany NY) 13: 13941-13953, 2021.
10. Li C, Liu YF, Huang C, Chen XY, Xu CY and Chen Y: Long noncoding RNA NEAT1 sponges miR-129 to modulate renal fibrosis by regulation of collagen type I. Am J Physiol Renal Physiol 319: F93-F105, 2020.
11. Chen X, Xie D, Zhao Q and You ZH: MicroRNAs and complex diseases: From experimental results to computational models. Brief Bioinform 20: 515-539, 2019.
12. Wu X, Li J, Yang X, Bai X, Shi J, Gao J, Li Y, Han S, Zhang Y, Han F, et al: miR-155 inhibits the formation of hypertrophic scar fibroblasts by targeting HIF-1α via PI3K/AKT pathway. J Mol Histol 49: 377-387, 2018.
13. Wang X, Zhang Y, Jiang BH, Zhang Q, Zhou RP, Zhang L and Wang C: Study on the role of Hsa-miR-31-5p in hypertrophic scar formation and the mechanism. Exp Cell Res 361: 201-209, 2017.
14. Bi S, Chai L, Yuan X, Cao C and Li S: MicroRNA-98 inhibits the cell proliferation of human hypertrophic scar fibroblasts via targeting Coll1A1. Biol Res 50: 22, 2017.
15. Li J, Chen L, Cao C, Yan H, Zhou B, Gao Y, Li Q and Li J: The long non-coding RNA LncRNA8975-1 is upregulated in hypertrophic scar fibroblasts and controls collagen expression. Cell Physiol Biochem 40: 326-334, 2016.
16. Livak KJ and Schmittgen TD: Analysis of relative gene expression data using real-time quantitative PCR and the 2(N-Delta Delta C(T)) method. Methods 25: 402-408, 2001.
17. Kirkpatrick LD, Shupp JW, Smith RD, Alkhalil A, Moffatt LT and Carney BC: Galectin-1 production is elevated in hypertrophic scars. Histol Histopathol 40: 326-334, 2016.
18. Tian S, Zheng Y, Xiao S, Luo P, Sun R, Liu J and Xia Z: Ivermectin inhibits cell proliferation and the expression levels of type I collagen, α-SMA and CCN2 in hypertrophic scar fibroblasts. Mutat Res 762: 1-21, 2014.
19. Wang C: Study on the role of Hsa-miR-31-5p in hypertrophic scar formation and the mechanism. Exp Cell Res 361: 201-209, 2017.
20. Peng Q, Li L and Bi X: Long noncoding RNA small nuclear RNA (lncRNA)-mediated competing endogenous RNA networks provide novel potential biomarkers and therapeutic targets for cardiovascular cancer. Int J Mol Sci 20: 5758, 2019.
21. Tu L, Huang Q, Fu S and Liu D: aberrantly expressed long noncoding RNAs in hypertrophic scar fibroblasts in vitro: A microarray study. Int J Mol Med 41: 1917-1930, 2018.
22. Wu Q, Chen J, Tan Z, Wang D, Zhou J, Li D and Cen Y: Long non-coding RNA (lncRNA) nuclear enriched abundant transcript 1 (NEAT1) regulates fibroblast growth factor receptor substrate 2 (FRS2) by targeting microRNA (miR)-29-3p in hypertrophic scar fibroblasts. Bioengineered 12: 5210-5219, 2021.

23. Wang J, Dodd C, Shankowsky HA, Scott PG, Tredget EE and Wound Healing Research Group: Deep dermal fibroblasts contribute to hypertrophic scarring. Lab Invest 88: 1278-1290, 2008.

24. Bai X, He T, Liu J, Wang Y, Fan L, Tao K, Shi J, Tang C, Su L and Hu D: Loureirin B inhibits fibroblast proliferation and extracellular matrix deposition in hypertrophic scar via TGF-β/Smad pathway, Exp Dermatol 24: 355-360, 2015.

25. Liu F, Chen WW, Li Y, Zhang JQ and Zheng QB: MiR-6836-3p promotes proliferation of hypertrophic scar fibroblasts by targeting CTGF. Eur Rev Med Pharmacol Sci 22: 4069-4074, 2018.

26. Deng J, Shi Y, Gao Z, Zhang W, Wu X, Cao W and Liu W: Inhibition of pathological phenotype of hypertrophic scar fibroblasts via coculture with adipose-derived stem cells. Tissue Eng Part A 24: 382-393, 2018.

27. Hamed S, Ullmann Y, Egozi D, Daod E, Hellou E, Ashkar M, Gilhar A and Teot L: Fibronectin potentiates topical erythropoietin-induced wound repair in diabetic mice. J Invest Dermatol 131: 1365-1374, 2011.

28. Wang X, Song Z, Hu B, Chen Z, Chen F and Cao C: MicroRNA-642a-5p inhibits colon cancer cell migration and invasion by targeting collagen type I α1. Onco Rep 45: 933-944, 2021.

29. Wang Q, Peng Z, Xiao S, Geng S, Yuan J and Li Z: RNAi-mediated inhibition of COL1A1 and COL3A1 in human skin fibroblasts. Exp Dermatol 16: 611-617, 2007.

30. Zhang E, Gao B, Yang L, Wu X and Wang Z: Notoginsenoside Ft1 promotes fibroblast proliferation via PI3K/Akt/mTOR signaling pathway and benefits wound healing in genetically diabetic mice. J Pharmacol Exp Ther 356: 324-332, 2016.

This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0) License.