BMC Biotechnology

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Fibromodulin-overexpressing fibroblast cells increase wound contraction, improve scar quality and enhance angiogenesis: an in-vivo study

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Abstract

Introduction Fibromodulin, a small leucine rich proteoglycan has been suggested to have prominent role in wound healing. On the other hand, fibroblast cells, due to their ability to secrete growth factors and control inflammation in the wound area, have been proposed as effective approaches in cell therapy for wounds. In the current study we attempted to improve treatment results using a combination of fibroblast and fibromodulin features.

Method Fibroblast cells were isolated from the skin and transfected with a vector carrying the fibromodulin gene. Following the assessment of fibromodulin protein production, the effect of transfected fibroblast cells was studied in an animal wound model.

Results Flow cytometry analysis showed high expression of the CD90 marker (97.2%) and very low expression of the CD34 marker (0.47%). Additionally, enzyme-linked immunosorbent assay (ELISA) findings confirmed high expression of the fibromodulin gene in the transfected fibroblast cells. In vivo studies demonstrated that the animals treated with fibroblast cells transfected with fibromodulin (V + G+) exhibited significantly improved wound contraction on day 7 (i.e., contraction percentage: 21.79 ± 9.96%, compared with 7.23 ± 2.30% in the PBS-treated group). Histopathological studies also indicated improvements in angiogenesis score and collagen density score in the animals treated with the V + G + group.

Conclusion The results of this study showed that fibroblast cells expressing the fibromodulin gene improve wound contraction and some histological parameters in the deep wound model of the rat.

Keywords Fibroblast, Cell isolation, Primary culture, Wound healing, Fibromodulin

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Introduction

Depending on the origin of the damage and the time required for healing, wounds are categorized as either acute or chronic. Acute wounds commonly result from traumatic (physical or chemical) injuries, whereas chronic wounds, which are difficult to manage, are associated with conditions such as infection, diabetes, vascular diseases and cancer [1, 2]. The process of wound healing involves different molecular and cellular events that occur after tissue damage. These events include inflammation, reproduction, and repair/regeneration which are coordinated by soluble mediators, blood cells and parenchymal cells [3]. The healing process in deeper dermal layers can be slow and less efficient, often resulting in scar formation [2]. Various approaches have been developed for wound management, including the use of wound dressings, growth factors, skin grafts, cell therapy and gene therapy [4–6].

The efficacy of cell therapy in the treatment of acute and chronic wounds has been shown previously. Enhancing the wound healing rate as well as reducing scar formation and color mismatch, following the use of different cells, such as fibroblasts, has been reported in clinical settings [7]. Fibroblasts coordinate the entire wound healing process through crosstalk with other cell populations and the production of growth factors, chemokines and components of the extracellular matrix (ECM). They also respond to mechanical signals and transform into myofibroblasts for wound contraction. On the other hand, dysfunction of fibroblasts during the wound healing process can lead to chronic ulcers or fibrotic scars, indicating the important role of fibroblasts during in the wound healing [8].

Fibromodulin is an important protein in the mammalian ECM and plays an important role in tissue repair in various organs [9]. Fibromodulin acts as a modulator of transforming growth factor-β (TGF-β) activity in wound healing and is involved in collagen accumulation [10], matrix organization [11] and cell signaling [12, 13]. Fibromodulin protein has a crucial role in angiogenesis and fibrillogenesis, but its effect in fetal and adult wound repair is not clearly defined. It has been previously shown that a decrease in fibromodulin expression is associated with the transition from scarless fetal-type to scarred adult-type healing [14]. In the wound healing process, TGF-β1 and TGF-β2 both play a stimulatory role in scar formation, while TGF-β3 has been demonstrated to have anti-scarring features. It has also been shown that fibromodulin gene transfer to fibroblast cells increases the expression of TGF-β3 and decreases the expression of TGF-β1 and TGF-β2 [14], which are expected to reduce scarring [15]. Reduced fibromodulin and TGF-β3 levels have also been associated with hypertrophic scarring [16].

Choosing a suitable wound healing approach is of utmost importance in achieving effective wound healing that includes the reduction of complications, acceleration of healing and mitigation of scar formation. To achieve this objective, we employed the overexpression of the fibromodulin gene (using an adenoviral vector) in fibroblast cells that isolated from rat skin. The cells were then utilized as a therapeutic approach to facilitate the healing of deep wounds in rats. To the best of our knowledge, such a fibroblast system has not been reported before for wound healing purposes.

Materials and methods

Fibroblast cell isolation

Fibroblast cells were isolated from the dermis of one-day-old rats. A small piece (3 mm^2) was separated from the dorsal skin of the animal and placed on ice under a laminar hood. The skin was then washed three times with PBS + 1% Pen/Strep and 1% amphotericin B. Subsequently, the epidermal layer and blood vessels were removed from the sample. The sample was crushed into smaller particles and centrifuged (1000 rpm, 2 min). Next, 2 ml of trypsin 1X (containing 0.25% trypsin) was added to the sediment and the sample was incubated at 37 °C for 30 min. To neutralize the trypsin, 4 ml DMEM containing 10% FBS was added and centrifuged (2000 rpm, 5 min). The cell pellet was resuspended in 1 ml of culture medium containing 10% FBS and transferred to a T25 flask, followed by addition of 5 ml culture medium containing 10% FBS and 2% Pen/Strep + 1% amphotericin B and incubation for 72 h at 37 °C. To remove tissue fragments, the culture medium was discarded and the contents of the flask were washed twice with PBS and replaced with 5 ml of fresh culture medium. To identify the cell population, CD90 and CD34 markers were analyzed using a flow cytometry approach at passage 4.

Transfection of fibroblast cells

Transfection of fibroblast cells was performed with the aid of adenovirus carriers. For this purpose, 5×10^5 cells were cultured in each well of a 12-well plate. The adenoviral expression vector containing fibromodulin was gifted by Dr Alireza Biglari, the details of the vector and its efficiency have been provided previously [17]. Twenty-four hours after the initial cell seeding, the cells were carefully exposed to adenovirus containing fibromodulin (multiplicity of infection = 1000) or lacZ cDNA.

To determine the production of the fibromodulin gene in the transfected cells, an enzyme-linked immunosorbent assay (ELISA) test kit (E91494Ra; USCN Life Sciences, China) was employed.

Fig. 1 The process of shaving and inducing wound on the dorsal surfaces of animals

Table 1 The scale used in the semi-quantitative examination of the samples

Scale	Inflammation cells	Collagen	Fibroblast density	angiogenesis	Re-epithelialization
0	Absence	Absence	Absence	Absence	Thickening of cutting edges
1	Mild (around the tissue)	Mild (granulation tissue)	Mild (around the tissue)	Mild (subcutaneous)	< 50% migration of epithelial cells
2	Mild (granulation tissue)	Mild (granulation tissue)	Mild (granulation tissue)	Mild (granulation tissue)	> 50% migration of epithelial cells
3	Moderate	Moderate	Moderate	Moderate	Bridging over the cut area
4	Marked	Marked	Marked	Marked	Keratosis

Animal studies

All animal experiments were carried out in compliance with guidelines by Research Ethics Committee at the North Khorasan University of Medical Sciences (Ethics approval ID: IR.NKUMS.REC.1399.082). In this study, 36 male Wistar rats weighing 180 g were used, obtained from the animal house of North Khorasan University of Medical Sciences. The rats were maintained on a 12:12 h light: dark schedule with lights on between 6 and 18 h. The temperature ranged between 12 and 16 °C. For surgery, the rats were first anesthetized using ketamine and xylazine. Then, as shown in Fig. 1, a full-thickness section of the skin was cut from the shaved dorsal surfaces of the animals using a square template (dimensions ~ 1.5 × 1.5 cm). After the surgery, each animal was kept in a separate cage. Nutritional conditions, ambient temperature and light-dark cycles were controlled as standard conditions.

Thirty-six animals were divided randomly into four groups, based on the treatment received, as follows: V + G+: fibroblast cells that had been transfected with a vector containing the fibromodulin gene. V + G-: fibroblast cells that had been transfected with a vector containing lacZ cDNA. V-G-: fibroblast cells that had not been transfected. Control: PBS. In this study we used a vector containing lacZ cDNA as a control (viral vector without the fibromodulin gene) to eliminate possible effects of the vector on fibroblast cells.

The treatments were injected subdermally into the four sides of the wound area (10^6 cells/800 µl). Wound healing was assessed with the help of photography and tissue sampling on days 7, 14 and 21. During each sampling, three rats from each study group were removed from the study. The wound area was calculated using Olympus cellSens software. The wound closure rate was calculated using Equation 2.

$$Wound\ closure(\%) = ((A_o - A_x))/A_o \times\ 100$$

where A_o and A_x are the wound areas on day zero and tissue sampling day, respectively.

Histopathological studies

On days 7, 14 and 21 post wound induction, the animals were anesthetized and specimens of fullthickness skin were taken from the shaved back (square shape, 1.5 cm × 1.5 cm × 0.5 mm). The isolated samples were washed with physiological serum and fixed using formalin (10%). The samples were embedded in paraffin, and then cut to obtain 5 µm thick sections using a microtome (Vibroslice, Compelen, UK). For tissue staining, conventional hematoxylin and eosin (H & E) was used, followed by examination of the slides with an optical microscope [18].

Wound healing rate was examined by histopathological indicators including angiogenesis, inflammatory cells, re-epithelialization, fibroblast density, collagen mass volume and collagen maturation rate, as detailed in Table 1.

Data analysis

SPSS v.22 software was used to analyze the data. The data were presented descriptively as mean ± Standard Deviation (SD). To find the significant differences between the groups, a One-way ANOVA test was conducted, followed by Turkey's post hoc test. A p-value < 0.05 was considered significant difference.

Results

Fibroblast cell isolation and culture

Fibroblast cells were isolated from the skin of newborn rats and cultured. After reaching 85% confluence (i.e., day 6), the initial cell passage was performed. The cultivation and passage of cells were conducted several times to adapt the cells to the culture conditions. Figure 2 shows the microscopic image of the fibroblast cells at different time intervals.

Identification of fibroblast cells derived from rat skin

From flow cytometry analysis (Fig. 3), the levels of expressed CD90 (a positive marker of fibroblast cells) and CD34 (a negative marker of fibroblast cells) were 97.2% and 0.47%, respectively.

Cell culture and ELISA test

From Fig. 4, no difference is apparent between the cells transfected with adenovirus containing either fibromodulin or lac Z.

Furthermore, to determine the production of the fibromodulin gene in the transfected cells, an ELISA test was employed. The findings are presented in Fig. 5. As the details show, the secretion of fibromodulin protein in the V + G + group has increased significantly compared to the V + G- and V-G- groups ($p < 0.001$).

In-vivo studies

Figure 6 represent the wound contraction on days 7, 14 and 21 as a function of treatment with V + G+, V + G- and V-G-. The calculations show that on day 7, the V + G + group had the highest wound contraction (i.e., contraction percentage: 21.79 ± 9.96%), indicating a significant increase in the healing process ($p < 0.05$). The contraction percentages in the V + G-, V-G- and PBS treated groups were 9.36 ± 1.13%, 2.30 ± 3.86% and 7.23 ± 2.30%, respectively. Calculation of wound contraction on day 14 of the study (see Fig. 6) indicates a small but not significant increase in wound contraction for the V + G + group (i.e., 91.78 ± 1.70%). The wound contraction studies on day 21 (see Fig. 7) also indicated that the highest contraction belonged to the V + G + treatment, showing a significant difference ($p < 0.05$) compared to the V-G- treatment (i.e., 99.25 ± 1.30% vs. 91.35 ± 3.05%, respectively).

Figure 7 shows images of H&E staining of tissues on day 21. Re-epithelialization, fibroblast density, collagen density, inflammatory cells and angiogenesis based on H&E were evaluated based on H&E images

Figure 8 indicates the re-epithelialization score along with the microscopic images of H&E-stained tissues on day 21. From the details, on day 7, no significant change in re-epithelialization is observed in the studied groups. On day 14, considerable re-epithelialization is observed

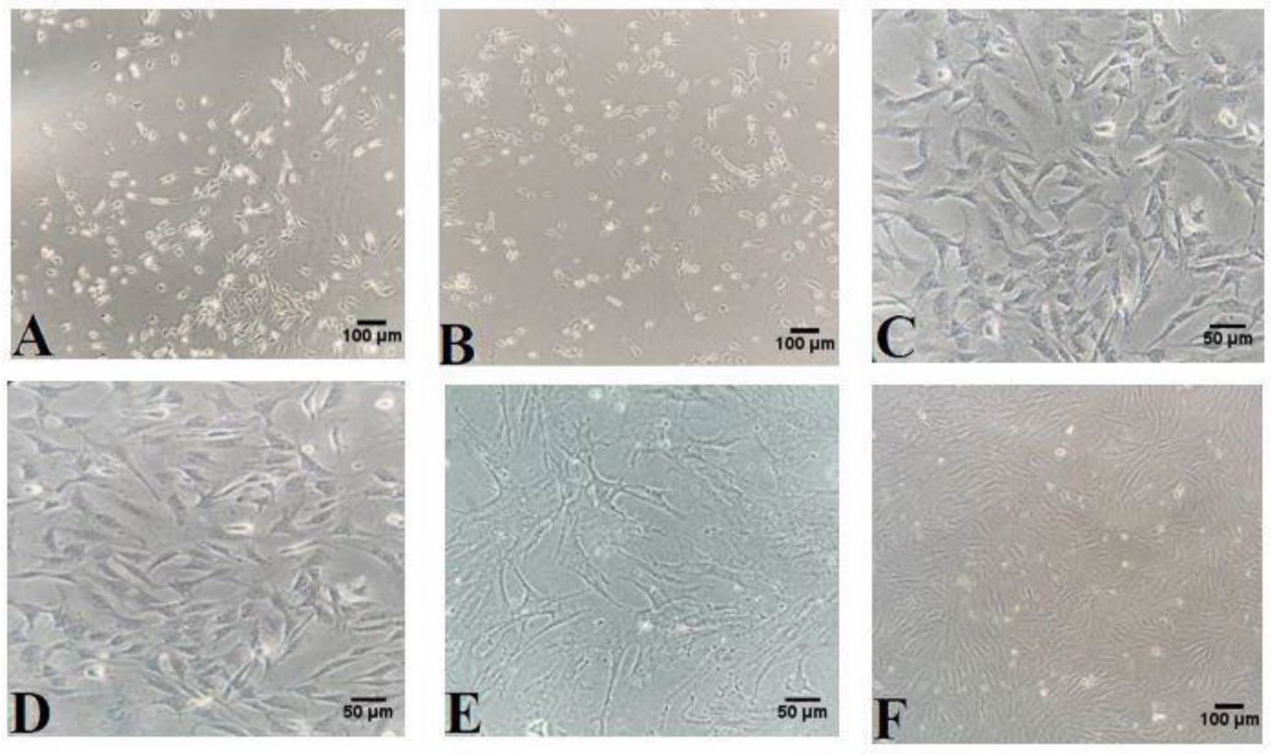

Fig. 2 Microscopic image representing the morphological state of fibroblast cells. **A**&**B**; 48 h after isolation, **C**&**D**; 72 h after isolation, **E**&**F**; 96 h after isolation

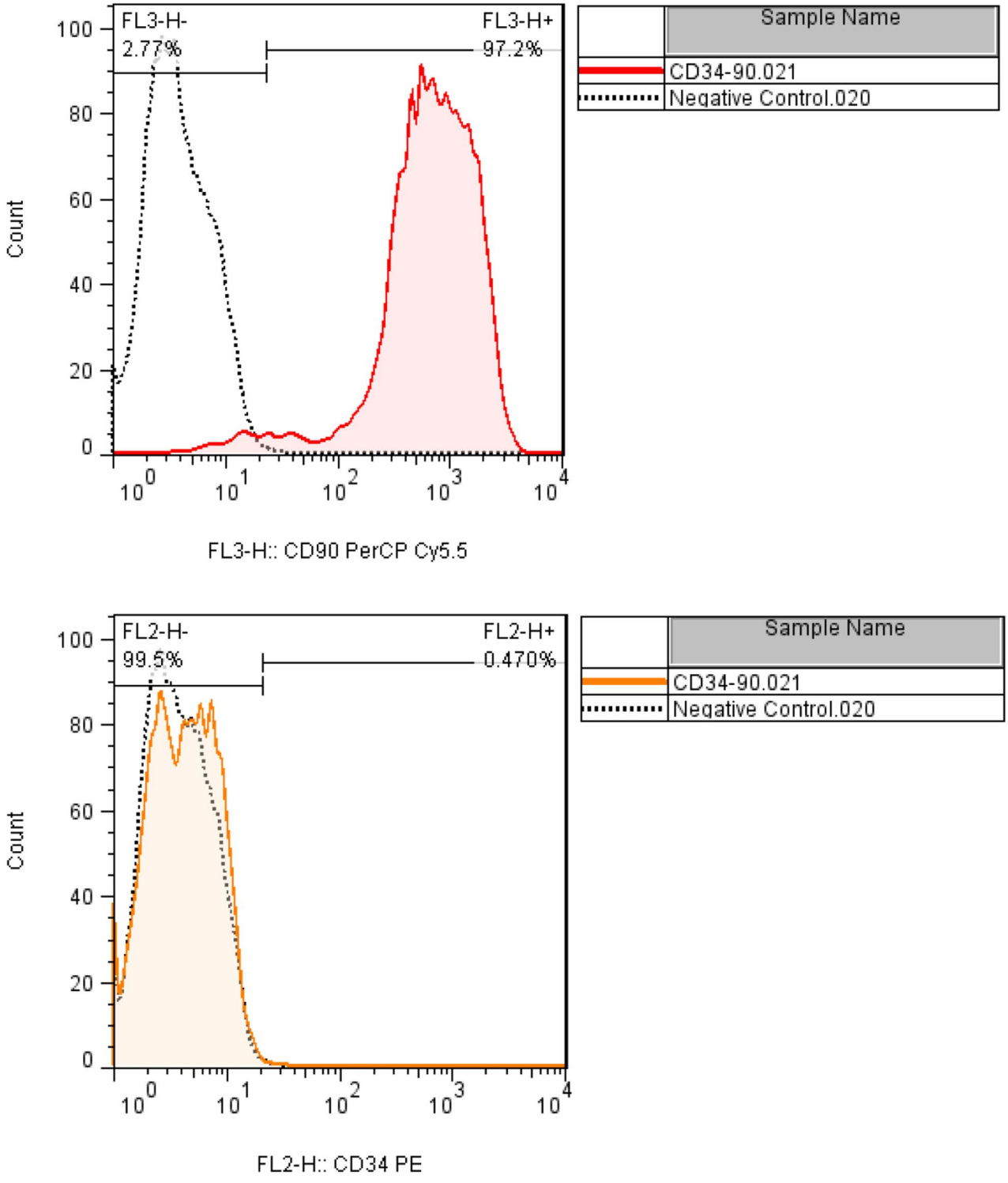

Fig. 3 Flow cytometry analysis of CD90 (top) as positive marker and CD34 (bottom) as negative marker of fibroblast cells

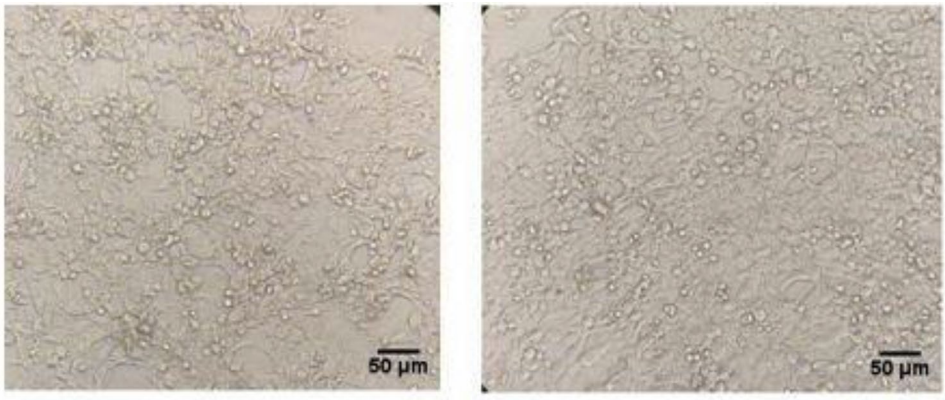

Fig. 4 Microscopic images of fibroblast cells transfected with adenovirus containing the fibromodulin gene (left) and adenovirus containing lac Z (right)

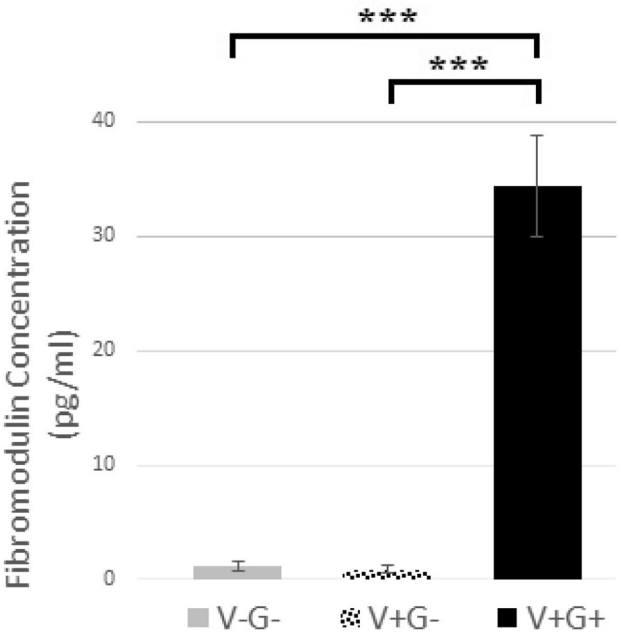

Fig. 5 Fibromodulin protein level, determined using ELISA, in V + G+: fibroblast cells transfected with the vector containing the fibromodulin gene, V + G-: fibroblast cells transfected with the vector without the fibromodulin gene and V-G-: non-transfected fibroblast cells. *** represents $p < 0.001$

in all groups, with the V + G + group having the highest score (3.33 ± 0.57) and the PBS group having the lowest score (1.67 ± 1.15). On day 21, re-epithelialization shows further progress in the V + G+, V + G- and PBS groups. The V + G + treatment had the maximum score, which was significantly higher than that of the V-G- treatment ($p < 0.05$). From the H&E staining results, a complete epithelialization showing dermal appendages such as hair follicles and sebaceous glands in the V + G + group was observed on day 21.

Figure 9 summarizes the density of fibroblast cells as a function of treatment with the cells transfected with V + G+, V + G-, V-G-, or PBS. From the data, except for a significant difference between V + G- and PBS on day 7, no important changes were observed among the groups under study during the study period.

Figure 10. The angiogenesis score in the groups treated with cells transfected with V + G+ (the vector containing the fibromodulin gene), V + G- (the vector without the fibromodulin gene), V-G- (non-transfected fibroblast cells) as well as PBS. ** represents $p < 0.01$ ($n = 3$).

Figure 11 shows the results of the investigation of inflammatory cells following treatment with cells transfected with V + G+, V + G-, V-G- or PBS. On day 7, all groups exhibited a maximum presence of inflammatory cells, with no significant difference between the treatment groups. The level of inflammatory cells dropped suddenly on day 14, with no significant difference between the groups. The level of inflammatory cells on day 21 also decreased slightly further, with no significant difference between the groups.

From the data in Fig. 12 which compares the collagen density between the groups, all the groups indicated a gradual increase in the collagen density score on day 14. On day 7, the V + G + group showed a significant increase in collagen density compared with the other groups. additionally, on day 14, the score of the PBS group was significantly lower compared with the V + G- and V + G + groups ($p < 0.05$). On the same day, the score of the V + G + group was significantly higher than that of the V-G- group as well ($p < 0.05$).

Discussion

Our results showed that the combined use of fibroblast and fibromodulin had positive effects on the wound healing process. Fibroblasts and keratinocytes are the main skin cells that play a key role in skin homeostasis and wound healing; therefore, they are well studied in skin wound healing experiments. Fibroblasts play an important role in all three stages of wound healing. they coordinate the entire healing process by producing regulatory molecules and interacting with other cells

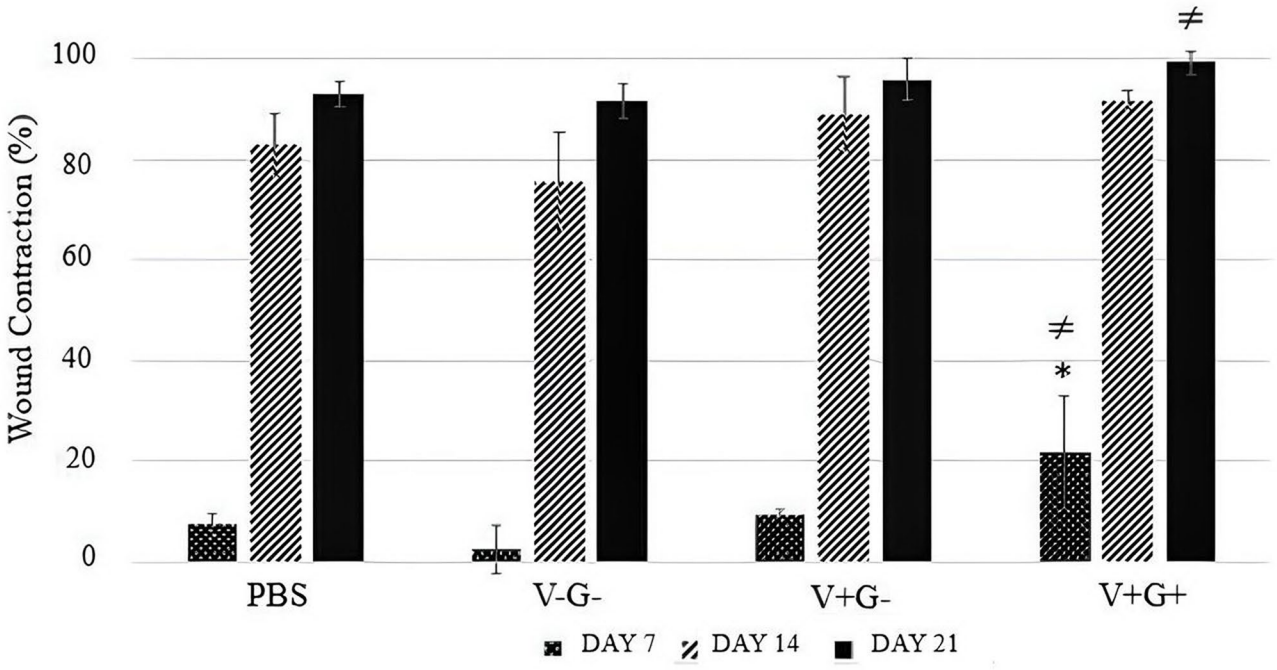

Fig. 6 Wound contraction percentage on days 7, 14 and 21 of the study as a function of treatment with cells transfected with V + G+ (the vector containing the fibromodulin gene), V + G- (the vector without the fibromodulin gene) and V-G- (non-transfected fibroblast cells). * represents $p < 0.05$ in comparison with PBS and ≠ represents $p < 0.05$ in comparison with V-G-

involved in wound healing mechanisms [8]. Probably the most important role of fibroblasts is their ability to produce the rich extracellular matrix in connective tissues. The matrix includes adhesive and structural proteins as well as proteoglycans and glycosaminoglycans that act as space-filling substances [19]. In subdermal injection of fibroblast cells in wounds of diabetic rats, after 7 and 21 days of treatment, the wound healing rate and collagen synthesis showed a significant increase ($p < 0.01$) in the group treated with fibroblast cells, compared to the control group. The group treated with fibroblasts indicated complete wound closure and appearance of hair growth on day 21, while wounds were not healed in the control group [20].

Fibromodulin as an important part of the extracellular matrix has been successfully employed in wound healing. In pig animal model of skin wound, intradermal injection of fibromodulin protein significantly reduced the scar size (up to 57%) and increased the tensile strength of the scar (up to 27%) [21]. Fibromodulin also significantly reduced scar formation in adult skin wounds by inducing a fetal-like phenotype [22]. The presence of fibromodulin is mandatory for correct temporospatial coordination in wound healing steps as well as for the regular activity of TGF-β [23]. Inhibition of TGF-β1 signal transduction has been a major strategy to reduce scarring. Fibromodulin acts as a modulator of TGF-β activity in wound healing. It is important for normal collagen fibrillogenesis; it significantly reduces scar formation and simulates human cutaneous scar repair in adult cutaneous wounds by creating a fetal-like phenotype [22].

In histopathological studies, the V + G + group (i.e., fibroblast containing the fibromodulin gene) indicated improved scores in re-epithelialization, angiogenesis and collagen, while scores of inflammation and fibroblast density did not change significantly. The findings showed an enhanced presence of inflammatory cells in the early days of injury, without significant differences between the treatment groups. During the inflammatory phase, the activated fibroblasts engage in crosstalk that enhances the local immune response and activates immune cells via the production of pro-inflammatory cytokines (e.g. tumor necrosis factor-α (TNF-α), interferon gamma (IFN-γ), interleukin-6 (IL-6), and interleukin-12 (IL-12)) and the release of a wide range of chemokines (e.g., CXCL1, CX3CL1 and CCL2). Such agents aim to further recruit immune cells to the injury site [24]. Fibroblasts and fibromodulin can modulate the recruitment of immune cells and regulate their behavior, maintenance, and survival in damaged tissue. Furthermore, the interaction between fibroblasts and macrophages is particularly important in regulating the transition from the inflammatory phase to the subsequent proliferative phase, ensuring the correct progress of the healing process [25, 26]. Additionally, it has been documented that wounds in adult fibromodulin-deficient mice indicate

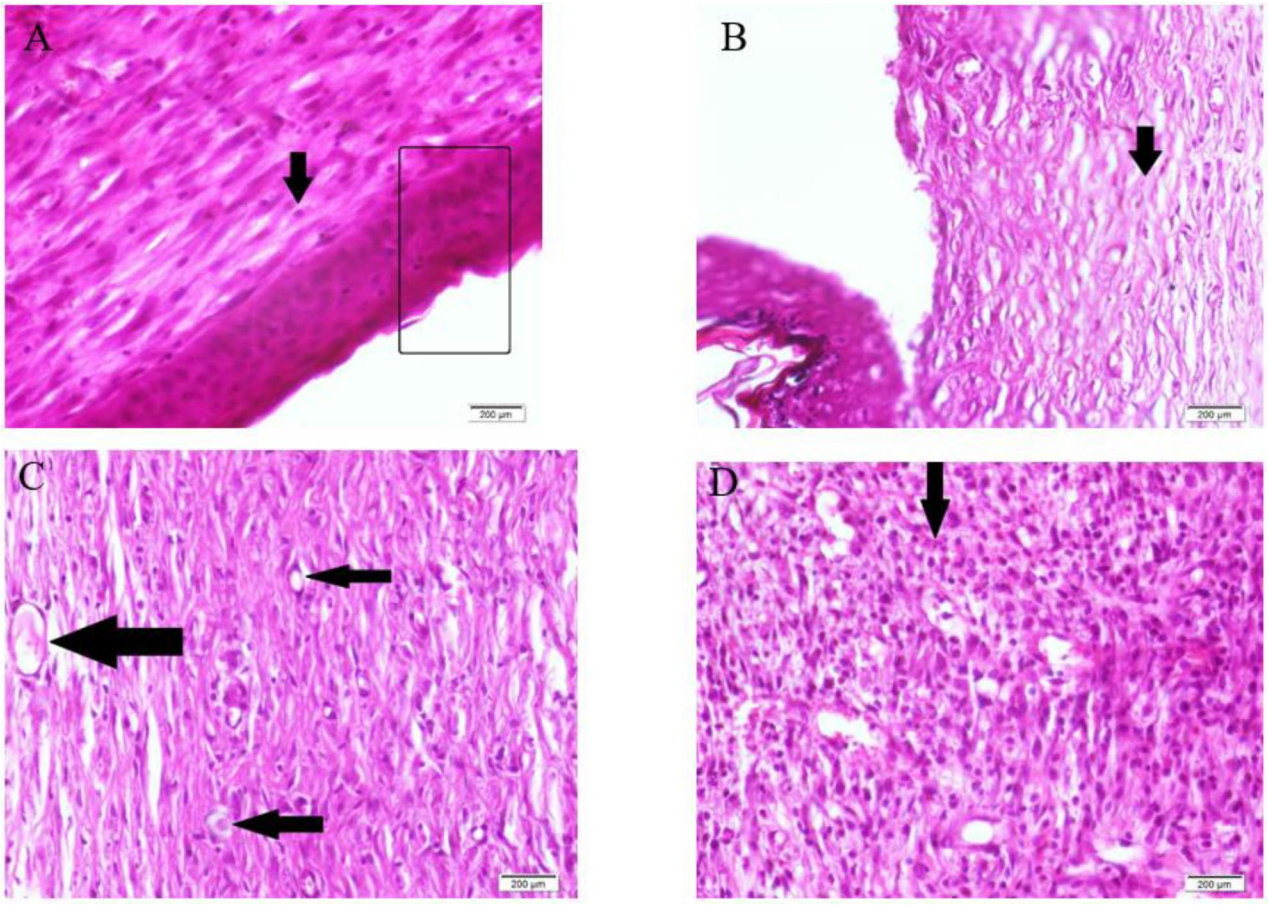

Fig. 7 Selected images of H&E-stained tissue sections (magnification 400×) on day 21: **A**: The rectangle indicates re-epithelialization. The arrow in the image points to spindle-shaped fibroblast cells (fibroblast density). **B**: The arrow indicates developed collagen fibers. **C**: Arrows in the image indicate angiogenesis in the tissue. **D**: The arrow in this image indicates inflammatory cells. Scale bar = 200 µm.

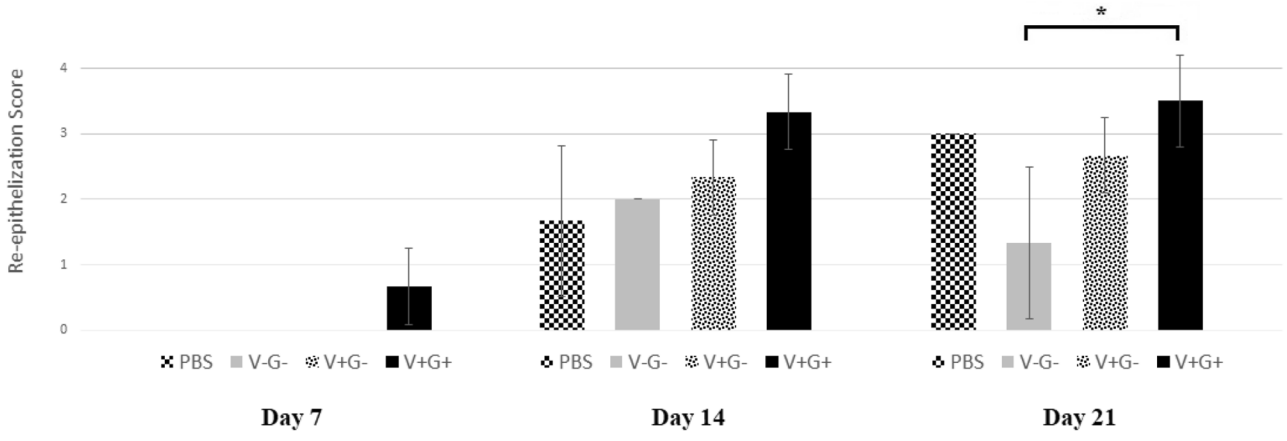

Fig. 8 The results of re-epithelialization assay the animals were treated with cells transfected with V + G+ (the vector containing the fibromodulin gene), V + G- (the vector without the fibromodulin gene), V-G- (non-transfected fibroblast cells) as well as PBS. * represents $p < 0.05$ ($n = 3$)

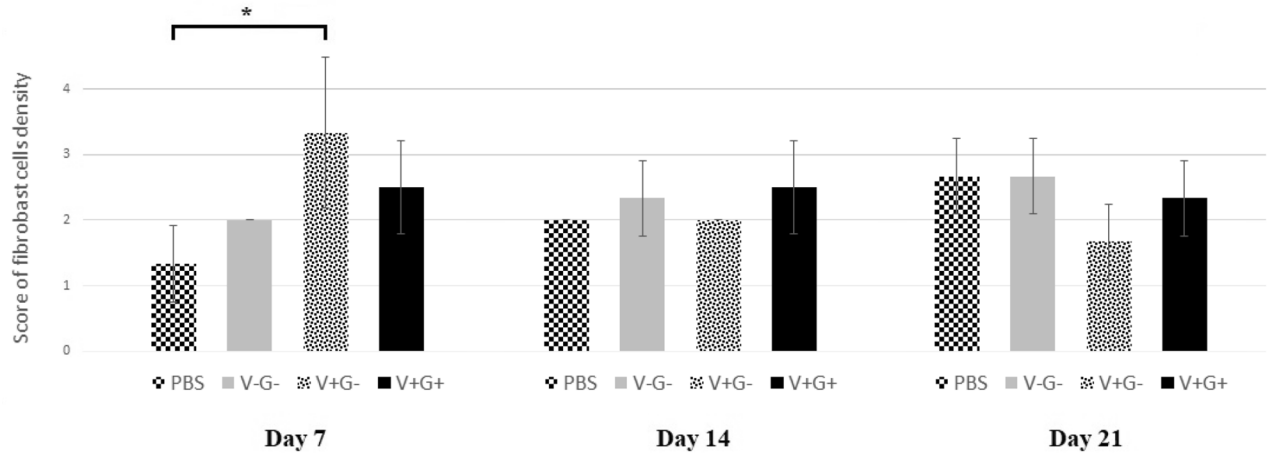

Fig. 9 The fibroblast density score in the treated groups: treatments were performed with cells transfected with V + G+ (the vector containing the fibromodulin gene), V + G- (the vector without the fibromodulin gene) and V-G- (non-transfected fibroblast cells). * indicates $p < 0.05$ ($n = 3$)

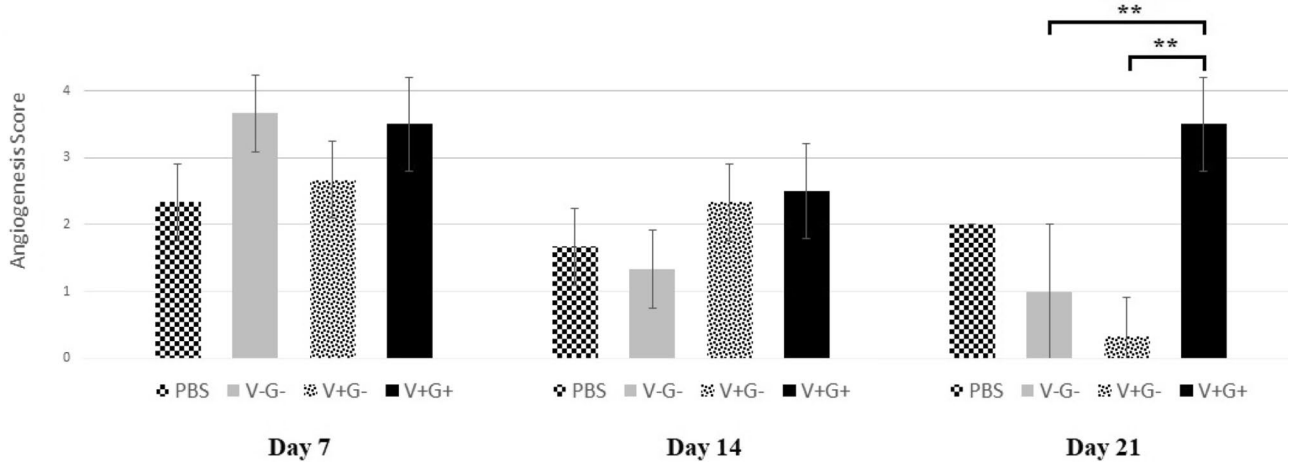

Fig. 10 Shows the scores of angiogenesis studies. On day 21, a significant increase in angiogenesis in the V + G + treatment group is observed compared to the V-G- and V + G- treatment groups ($p < 0.01$)

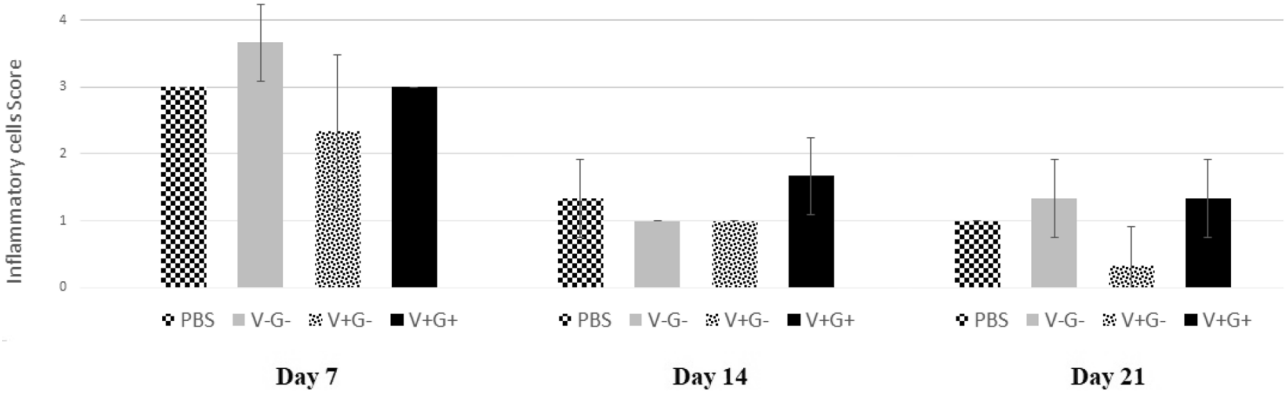

Fig. 11 The inflammatory score in the treated groups: treatments were performed with cells transfected with V + G+ (the vector containing the fibromodulin gene), V + G- (the vector without the fibromodulin gene) and V-G- (non-transfected fibroblast cells). $n = 3$

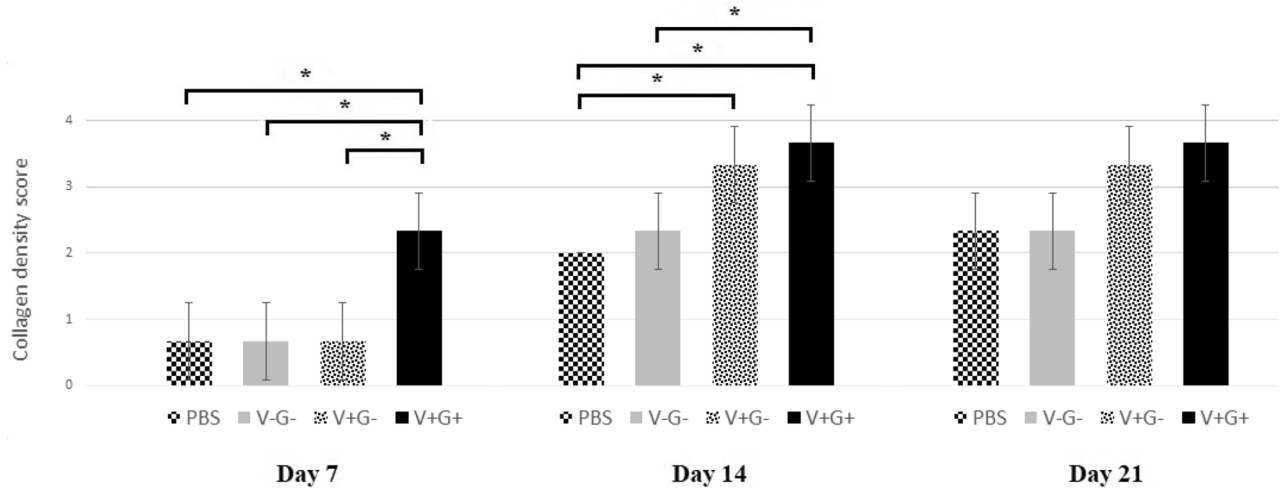

Fig. 12 The collagen density score in the groups under study: treatments were performed with cells transfected with V + G+ (the vector containing the fibromodulin gene), V + G- (the vector without the fibromodulin gene) and V-G- (non-transfected fibroblast cells). * indicates $p < 0.05$ ($n = 3$)

delayed wound healing, enhanced scar formation, as well as decreased angiogenesis, while exogenous fibromodulin can partially resolve the effects [23, 27].

Conclusion

In the present study, improved wound healing was shown by leveraging the properties of fibroblasts and fibromodulin. Our results demonstrated that fibroblasts and fibromodulin reduce scar size, improve scar appearance and increase angiogenesis in a rat model of skin wounds. In conclusion, our findings describe an enhancing effect of cell-based gene therapy in accelerating the wound healing process.

Abbreviations

ELISA	Enzyme-linked immunosorbent assay
ECM	Extracellular matrix
TGF-β	Transforming growth factor-β
H & E	Hematoxylin and eosin

Acknowledgements

N/A.

Author contributions

Negar Abdollahzadeh: Investigation, Writing – Original Draft Preparation. Mehran Vatanchian: Methodology, Supervision, Writing – Review & Editing. Fatemeh Oroojalian: Methodology, Supervision, Writing – Review & Editing. Seyed Ehsan Enderami: Supervision, Writing – Review & Editing. Amir Amani: Formal Analysis, Funding Acquisition, Methodology, Project Administration, Resources, Writing – Review & Editing. Reza Salarinia: Conceptualization, Methodology, Resources, Supervision, Validation, Writing – Review & Editing.

Funding

North Khorasan University of Medical Sciences funded the costs of materials of this study through grant number 980190.

Data availability

data is available upon request from corresponding authors.

Declarations

Ethics approval and consent to participate

All animal experiments were carried out in compliance with guidelines by Research Ethics Committee at the North Khorasan University of Medical Sciences (Iran) Ethics approval ID: IR.NKUMS.REC.1399.082, Approval date: 2020-10-31).

Consent for publication

The authors give their consent for the publication of the manuscript including Figures.

Competing interests

The authors declare no competing interests.

Received: 5 August 2024 / Accepted: 5 May 2025
Published online: 19 May 2025

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