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ORIGINAL ARTICLE

The Stromal Derived Factor-1 (SDF-1) Secretion Attracts Stem Cells and Accelerates the Skin Wound Healing Against the Background of Its Closure With Dermal Fibroblasts Associated With Polylactide Film

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Abstract

Background/Aim: Chronic skin wounds are a huge clinical problem, leading to the need for prolonged treatment and significant health care expenses. Regenerative engineering using tissue technologies and cellular constructs offers promising alternatives for treatment. The aim of this research was to evaluate the levels of stromal-derived factor-1 (SDF-1) expression and the presence of CD34+ mesenchymal stem cells (MSC) in regenerating skin wounds treated with polylactide films combined with dermal allofibroblasts.

Methods: Forty-seven white mature male mice line C57/B1 were allocated into two groups – control and experimental. In the experimental group, a standard skin wound was created and treated with polylactide films with allofibroblasts. Biopsies were taken at various time points for histological and immunohistochemical analysis of SDF-1 and CD34 expressions. Cellular indices were determined by counting positive cells per 100 cells under a microscope. Statistical analysis was performed using nonparametric tests.

Results: SDF-1 expression peaked on day 7 and then declined, disappearing by day 15, while the number of MSCs followed a similar trend. Delayed and prolonged SDF-1 expression and the presence of MSCs were observed in control wounds. Enhanced epithelialisation and granulation tissue formation were observed in the experimental group, indicating accelerated wound healing.

Conclusion: Transplantation of polylactide films with dermal allofibroblasts promotes early and active secretion of SDF-1, which promotes MSC recruitment and accelerates skin wound regeneration.

Key words: Polylactide, film; Skin; Wound healing; Dermal; Fibroblasts, allofibroblasts; Regenerative medicine; SDF-1; Mesenchymal stem cells.

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Introduction

Long-term skin wounds are a huge clinical problem, leading to the need for prolonged treatment and significant health care expenses.[1] Regenerative engineering, based on tissue technologies, has become an alternative method for healing chronic skin wounds.[2] Using natural skin grafts,

including allotransplants, xenotransplants and autotransplants, involves risks of infection, immune rejection, the incidence of donor sites and the formation of pathological scars.[3] For skin tissue engineering, bioabsorbable complex polyesters such as glycolide (GA), lactide (LA) and caprolactone are preferred due to their biocompatibility and approval by the US Food and Drug Administration (FDA).[4, 5]

The most useful and popular polylactides from which it is possible to create 2D (film) and 3D designs are recognised by Poly(L-lactide) (PLLA) and Poly(D-lactide) (PDLA), respectively.[6] The superficial and mechanical properties of biomaterials are determinants of cellular reactions.[7] Fibroblasts cultivated on such a biodegraded 2D frame are a promising direction of creating a dermis substitute, on which the epidermis (EP) can subsequently naturally be formed.[8] Specialised functionally active fibroblast is the most common cell in the human dermis and one of the most important architects of skin wounds healing, producing all components of the intercellular substance, growth factors, anti -inflammatory chemokines, as well as stem cell attachments.[9]

In addition, fibroblasts are able to change their cell profile and the most common is the transition to myofibroblasts[10] necessary for wound contraction. It was shown that fibroblasts and a number of other stromal cells of various organs under conditions of tissues damage secretes the stromal derived factor-1 (SDF-1, also known as CXCL12).[11] The concentration gradient of the secreted factor SDF-1 is critical for chemotaxis of multipotent stem cells (MSCs) that express CXC chemokine receptor 4 (CXCR4), which interacts with SDF-1.[12] Information on the successful cultivation of cells on a polylactide is rare[3] and information on morphological transformations in the tissues of regenerating skin defects after their closure with a polylactide film with allofibroblasts is few and far between.[4] Publications on the functioning of the CXCL12-CXCR4 chemokine signalling pathway associated with the expression of the SDF-1 factor by cells of a healing skin wound, which attracts mesenchymal haematopoietic stem cells (MSCs) to the damaged area, are absent in the available literature, thereby determining the relevance of the study.

Aim of the study was to assess the levels of SDF-1 expression and the amount of CD34+ MSCs in experimental skin wounds undergoing regeneration treated with polylactide films combined with dermal allofibroblasts.

Methods

Design

The research involved 47 white sexually mature male mice line C57/B1 aged 5-7 months and weighing 40-45 g, which were kept in the vivarium of the S.I. Medical Institute named after S.I. Georgievsky. The animals were allocated into two groups – control (CG) and experimental (EG), as shown in Table 1. The study complied with the humane guidelines of Directive 2010/63/EU and the ICMR animal research principles (2006).

Table 1: Allocation of mice according to the timing of sample collection in control (CG) and experimental (EG) group

Time elapsed after surgery (days)	Control group (individuals)	Experimental group (individuals)
4	3	3
7	4	5
10	4	5
12	4	4
15	4	5
23	3	3
Total (n = 47)	22	25

In all animals, the operation to simulate a skin wound in the interscapular region was performed after intraperitoneal administration of a 0.3-0.4 mL of a 2.5 % tribromoethanol (Avertin) solution. The skin was excised to the subcutaneous fat tissue in the form of a circle with a diameter of 12 mm. To the edges of the wound with fascial nodal sutures of "polypropylene" 5-0 were fixed to silicone ring with an external diameter of 12 mm. This was done to exclude the possibility of epithelisation of the wound and closing it with the mobile skin of the area.

In the experimental group dermal fibroblasts were obtained by fermentation and cultivated among DMEM/F12 (Lonza).[13] The suspension of fibroblasts in a solution of Versen was painted with trypan blue, which visualises living cells. The number of cells stained in blue was counted in the Goryaev chamber. Samples in which there were at least 94 % of living cells were used (Figure 1).

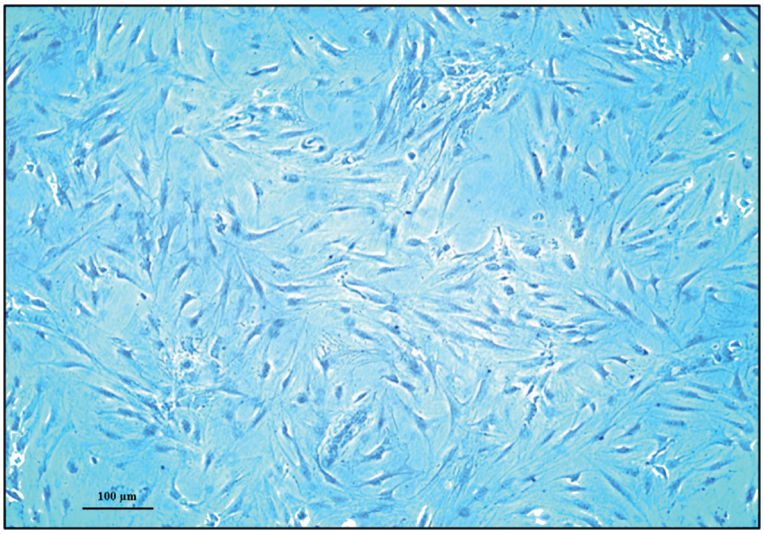

Figure 1: Dermal fibroblasts of the mouse at the stage of confluence. The third passage. Inverted microscope. Magnification ×100

The substrate for applying the poly-L-lactide solution consisted of 15 × 15 mm cover glasses with hydrophilic, untreated surfaces. The polylactide was evenly distributed on the glass substrate by using a polar, well–retaining solvent – acetone. Was applied 30 µL of the polymer solution so that its concentration on the glass was 1.4 µg/mm^2. The optimal concentration of a polymer solution of 50 mg/mL was the optimal when applying 85 µL to the surface of the cover glass. The film thickness was 100 microns.[4] The cover glasses were dried and sterilised by ultraviolet light irradiation for 2 hours.

Cultivation was carried out in a 5 % CO_2 atmosphere at 37 °C. The cell shape in the process of cultivating them on the polymer was observed under the inverted microscope of OLIMPUS CX-41.

After reaching the confluence, the polylactide film was detached from the cover glass and surgically implanted into the experimental wound with the cell side facing inward (Figure 2). The wound margins and the film were fixed to the silicone ring. From above, the wound in the CG and EG was covered with the sterile bandage "Wosko-Pran" containing *Levomekol* (chloramphenicol and methyl-uracil).

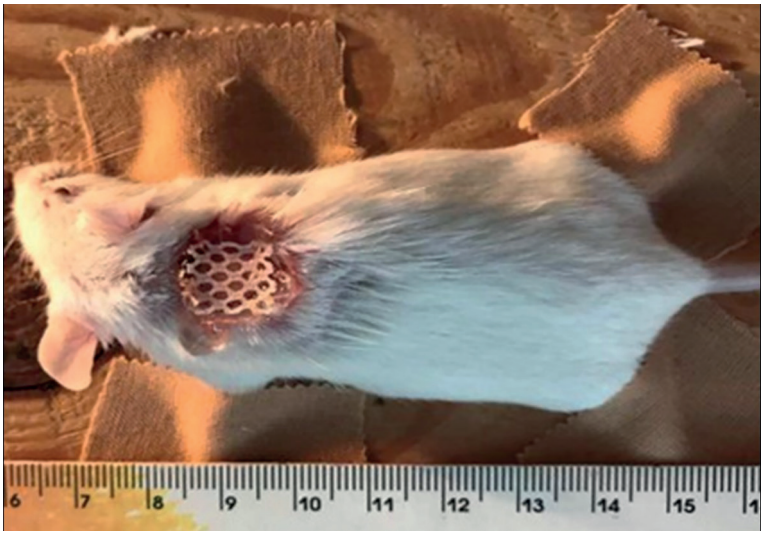

Figure 2: Experimental wound in the intrascapular region. A polylactide film with allofibroblasts was transplanted into the wound and covered with an aseptic dressing "VoskoPran" with "Levomekol".

Morphological examination of scars

On the 4, 7, 10, 12, 15 and 23 days after surgery, the resulting regeneration was excised intraoperatively in both groups and fixed in 10 % buffered formalin solution for morphological examination. The samples were embedded in paraffin and subsequently stained with haematoxylin and eosin (H&E).

Immunohistochemical study

The detection of SDF-1 and CD34+ cells was performed by immunohistochemistry on paraffin sections. Primary antibodies consisted of polyclonal rabbit anti-SDF-1 antibodies (GTX45117, GeneTex Inc., USA) and monoclonal mouse anti-CD34 antibodies (GTX28158, GeneTex Inc) at a 1:100 dilution. Secondary detection was performed using universal antibodies (HiDef Detection™ HRP Polymer system, Cell Marque, USA), enabling the identification of both mouse and rabbit primary antibodies conjugated with an enzyme complex containing horseradish peroxidase. Validation experiments were conducted for every biomarker to eliminate false-positive and false-negative outcomes.

Statistical analysis

The quantification of SDF-1 and CD34-expressing cells was performed by visual enumerating their count per 100 cells under microscopic observation (magnification ×1350), followed by computation of the mean percentage derived from five randomly selected analysed sections of each biopsy specimen in both the control and experimental groups.

The data's distribution normality was assessed using the Shapiro-Wilk test.[14] Pairwise comparisons of the CG and EG of mice were performed as well as a pairwise comparison between the previous and subsequent wound healing periods within the CG and EG, as well as pairwise comparison between the previous and subsequent wound healing periods within the control or experimental groups. Since the data distribution differed from normal, the Mann-Whitney test was used for pairwise comparisons and group data were described using the median, first and third quartiles (interquartile range).[15] All data analysis was carried out using R statistical software version 4.2.3 (R Development Core Team 2024).[15]

Results

On day 4 after the operation, in the biopsy sections of the CG and EG of mice, the wound was limited by a silicone ring sutured to the wound edges. In the CG, the wound was mainly filled with a voluminous scab consisting of fibrin with dead inflammatory cells and exudate. In the EG, an oxyphilic stained polylactide film was present on the surface of the skin defect (Figure 3A). The surface of the biopsy specimens along the wound edges was covered with developing epidermis consisting of 1-2 rows of epidermocytes. In the centre of the biopsy specimens, the epidermal cover was absent (Figure 3A). The entire skin defect in the CG mice and the wound volume under the developing epidermis in the EG mice was filled with white adipose tissue with thin layers of granulation tissue (GT). Between the adipocytes adjacent to the developing epidermis in the EG, there is an accumulation of leukocyte cells.

Tissue samples from both groups contained cells expressing SDF-1 (Table 2). In the control group biopsies, the numerical expression of the median value of the index of such cells in the granulation tissue was 11.52 (11.07-12.10). In similar layers of the EG biopsies (Figure 3B), SDF-1$^+$ cells were numerous and the numerical expression of the median value of their index was reliably three times greater than in the CG (Table 2). CD34-expressing mesenchymal stem cells were not detected in the CG biopsies, but in the EG they were identified in single quantities in the epidermis and in the deep layers of the biopsies, where they were three times more numerous (Table 2).

On day 7, the silicone ring securing wound margins remained firmly in place in both the CG and EG. In the EG, the skin lesion was fully lined by an epidermis composed of multiple layers of cells, including distinct basal and spinous layer cells. There were significantly more rows of cells along the periphery of the biopsy specimens. In the CG, the epidermis contained up to three rows of epidermocytes that were not differentiated into layers. Epidermocytes secreted the SDF-1 factor (Figure 4A). Among the epidermocytes of the CG, such cells appeared for the first time (Table 2). The numerical expression of the median value of the index of such cells had significantly increased over the past three days. The median index of SDF-1-positive epidermal cells in the experimental group was 61.31 % higher than in the CG.

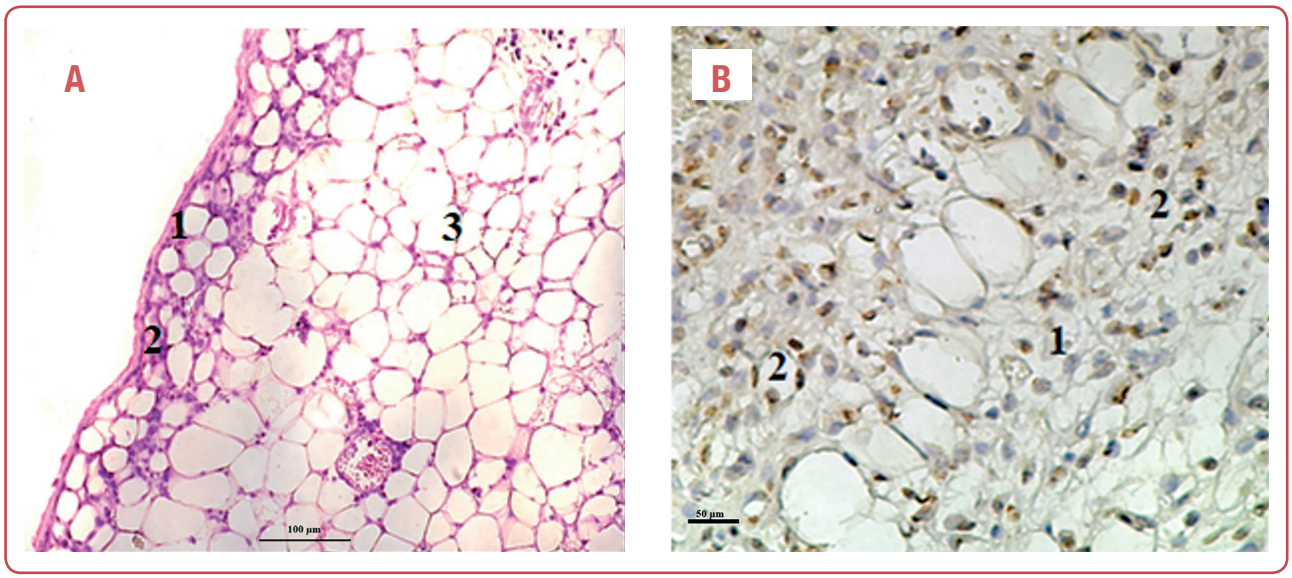

Figure 3: Biopsy on day 4 after transplantation of a polylactide film with allofibroblasts into an experimental skin wound. A – Haematoxylin and eosin staining. 1 – polylactide film; 2 – granulation tissue; 3 – adipose tissue. Magnification: x200. B – Immunohistochemical reaction with antibodies against stromal-derived factor-1 (SDF-1). Staining in the diaminobenzidine with horseradish peroxidase – hydrogen peroxide system. Counterstaining with Mayer's haematoxylin. 1 – granulation tissue; 2 – SDF-1+ cells. Magnification: ×600.

Table 2: Index of stromal-derived factor-1 (SDF-1)+ and CD34+ cells in skin wound tissue samples of the control (CG) and experimental (EG) group

Days after surgery	Control group				Experimental group			
	SDF-1⁺ cells median (1-3 quartiles), interquartile range		CD34⁺ cells median (1-3 quartiles), interquartile range		SDF-1⁺ cells median (1-5 quartiles), interquartile range		CD34⁺ cells median (1-5 quartiles), interquartile range	
	Epidermis	Granulation tissue	Epidermis	Granulation tissue	Epidermis	Granulation tissue	Epidermis	Granulation tissue
4	-	11.52 (11.07–12.10)	0.00	0.00	10.61 (10.18–11.17)*	29.44 (27.68–31.15)*	4.02 (3.83–4.57)	14.97 (13.89–16.04)*
7	12.89 (12.02–13.58)**	15.53 (14.72–16.88)**	0.00	0.00	33.32 (32.26–34.07)*,**	68.26 (65.31–72.31)*,**	11.22 (10.93–12.15)	25.50 (24.48–27.72)*,**
10	21.11 (19.88–22.98)**	18.28 (16.59–20.07)**	0.00	4.95 (4.22–6.01)	23.74 (22.53–25.45)*,**	58.22 (54.91–60.72)*	10.01 (9.62–10.95)**	34.78 (32.36–34.59)*,**
12	69.25 (62.24–71.48)**	22.15 (20.71–25.14)**	1.02 (0.85–1.14)	11.28 (10.24–12.38)**	19.33 (18.26–20.94)*,**	45.11 (42.65–48.27)**	3.86 (3.12–4.26)*	29.07 (26.28–31.51)*,**
15	77.36 (75.21–79.63)**	27.20 (25.62–29.11)**	1.89 (1.42–2.32)	18.19 (16.96–17.29)**	15.28 (14.36–16.17)	38.12 (36.41–41.13)*,**	0.00	18.44 (17.32–20.09)*,**
23	35.28 (32.14–36.52)**	14.11 (12.51–16.32)**	0.00	2.89 (2.12–3.44)**	0.00	5.15 (4.63–5.65)*,**	0.00	8.11 (7.61–8.85)**

** Statistically significant differences from control group, p = 0.05*
*** Statistically significant differences from the previous day, p = 0.05*

The numerical expression of the median value of the MSC index in the epidermis of the EG increased threefold compared to day 4 of wound healing (Figure 4A) (Table 2). Such cells were absent in the epidermis of the CG. In the GT of both groups, a reliable increase in the numerical expression of the median value of the index of cells synthesising the MSC chemoattractant factor SDF-1 continues. In the EG after transplantation of a polylactide film in combination with allofibroblasts into the wound, the numerical expression of the median value of the index of such cells was 77.25 % greater compared to the control group (Figure 4B).

On day 10 of skin defect on the back of mice healing after transplantation of a polylactide film with dermal allofibroblasts, the scab covering the surface of the wound biopsy specimens disintegrated into separate thin fragments. Under

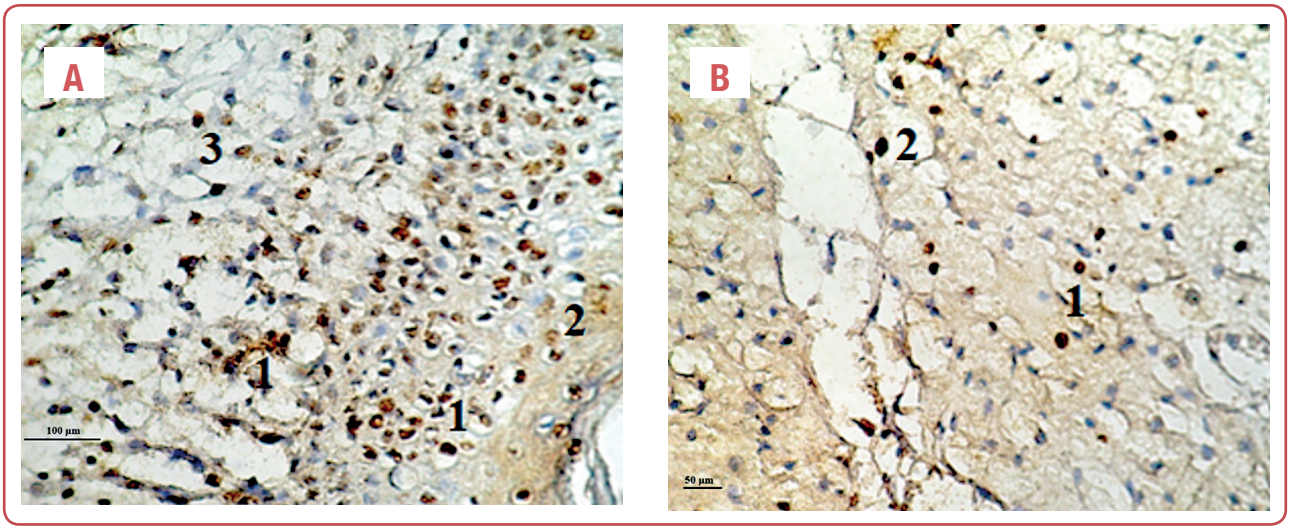

Figure 4: Biopsy of the experimental skin wound on the day 7 after surgery. Control group. A – Epidermis and granulation tissue of the scar. Immunohistochemical reaction with antibodies against stromal-derived factor-1 (SDF-1). 1 – SDF-1+ cells; 2 – epidermis; 3 – granulation tissue. Magnification: x200. B – Granulation tissue of the scar. Immunohistochemical reaction with antibodies against CD34. 1 – CD34+ cells (MSC); 2 – blood vessel. Staining in the diaminobenzidine with horseradish peroxidase – hydrogen peroxide system. Counterstaining with Mayer's haematoxylin. Magnification: x200.

the scab there is a stratified squamous partially keratinised epithelium typical of the thin skin of the back of mice. It consists of four layers of epidermocytes, in which the keratinisation process was observed. The third granular layer was thin, discontinuous and was present at the edges of the biopsy specimens. The superficial horny layer of flattened cells was also localised there. The keratinisation strip was thin. In the CG, the wound was also covered by fragments of the original scab, but they were more voluminous and the epidermis was thinner. The epidermis lags behind in development compared to the EG. In stratified squamous partially keratinised epithelium forming the epidermis of the CG, up to four rows of prismatic epidermocytes were visible in the centre of the wound biopsy specimens. There were more rows of cells along the edges of the biopsy specimens, but their morphological differentiation characteristic of keratinisation processes was absent. Secretion of the stem cell chemoattractant SDF-1 by the epidermocytes of the CG and EG had a multidirectional character: in the CG, the numerical expression of the median value of the index of such cells continued to increase (Figure 5A) and in the EG it decreased (Table 2). MSC were present only in the epidermis of the EG, where the numerical expression of the median value of their index did not change compared to 7 days of wound regeneration. The dynamics of secretion of the stem cell chemoattractant SDF-1 by the granulation tissue cells of the biopsy specimens had a similar character. In the CG, the numerical expression of the median value of their index increased and in the EG it decreased. In the granulation tissue of the CG, the presence of MSCs was recorded for the first time (Figure 5B) and the numerical expression of the median value of their index was 4.95 (4.22-6.01) (Table 2), which is 85.77 % less than in the granulation tissue after transplantation of a polylactide film with dermal allofibroblasts.

On day 12 of wound healing in EG the scab disappeared from the wound surface. The surface of the wound biopsy specimens was completely covered by a stratified squamous partially keratinised epithelium, which contained all four necessary layers of epidermal cells (Figure 4). The cells of the superficial rows had not achieved morphological differentiation to form full-fledged granular and horny layers. The keratinisation band on the epidermal surface remained thin. In CG, scab remnants were preserved on the surface of the epidermis. In the epidermis of CG biopsy specimens covering the central areas, differentiation of epidermal cells characteristic of the basal and spinous layers was observed. There were more rows of cells along the periphery of the biopsy specimens, but they did not have signs of morphological differentiation into granular and horny layers. The numerical expression of the median value of the index of epidermal cells secreting the SDF-1 factor in the control group continued to increase, while in the EG it continued to decrease (Figure 6A) (Table 2). The numerical

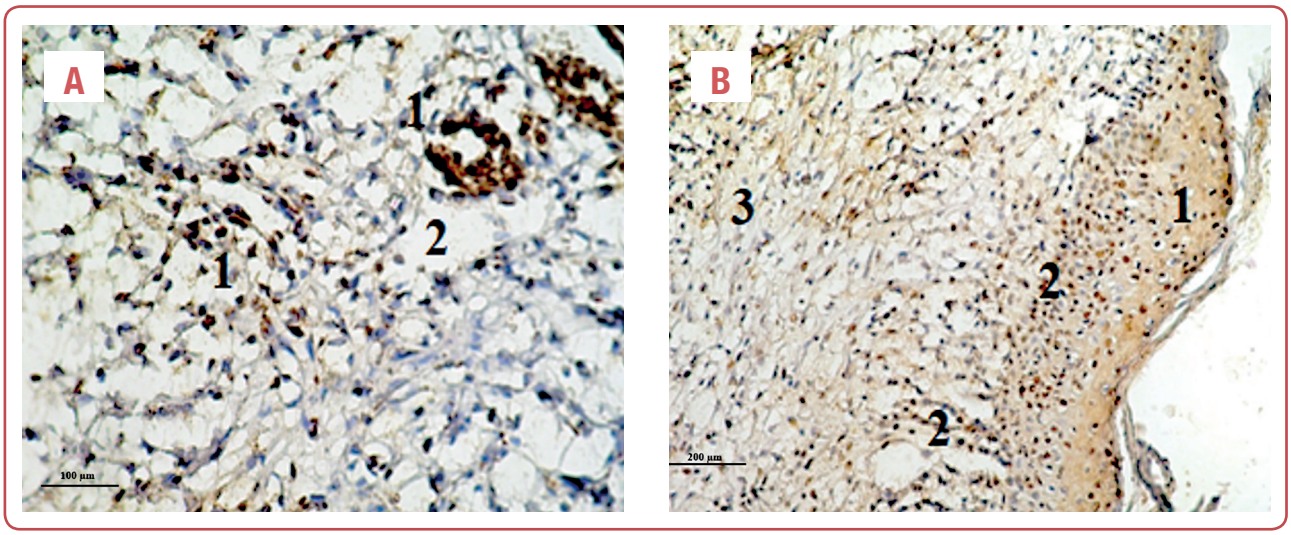

Figure 5: Biopsy of the experimental skin wound on the day 7 after surgery. Control group. A – Epidermis and granulation tissue of the scar. Immunohistochemical reaction with antibodies against stromal-derived factor-1 (SDF-1). 1 – SDF-1+ cells; 2 – epidermis; 3 – granulation tissue. Magnification: x100. B – Granulation tissue of the scar. Immunohistochemical reaction with antibodies against CD34. 1 – CD34+ cells (MSC); 2 – blood vessel. Staining in the diaminobenzidine with horseradish peroxidase – hydrogen peroxide system. Visualisation in the diaminobenzidine with horseradish peroxidase – hydrogen peroxide system. Counterstained with Mayer's haematoxylin. Magnification: x200.

expression of the median value of the MSC index in the EG had similar dynamics. In the CG on day 12 the presence of single MSC was recorded for the first time in the epidermis of biopsies and the numerical expression of the median value of their index is 1.02 (0.85-1.14) (Table 2). Granulation tissue was present under the developing epidermis in the biopsies of both groups, the cells of which also continued to secrete the SDF-1 factor. The numerical expression of the median value of their index in the CG and EG decreased compared to that on day 10 of wound healing. At the same time, the numerical expression of the median value of the index of SDF-1+ cells in the granulation tissue of the EG was 50.9 % higher than in the CG. The numerical expression of the median value of the index of MSC attracted by the chemoattractant increased in the CG, while it decreased in the EG (Figure 6B). However, in the EG, the numerical expression of the median value of the MSC index was 61.2 % higher than in the CG.

On day 15 after the surgical formation of a skin defect in mice and transplantation of a polylactide film with dermal allofibroblasts, in the epidermis of biopsies the differentiation of the cellular composition of all four layers of the stratified squamous partially keratinised epithelium was completed. Among the cellular composition of the epidermis, the numerical expression of the median value of the index of epidermocytes secreting the chemoattractant MSC factor SDF-1 decreased (Table 2). MSC completely disappeared from the composition of the cellular population of the epidermis. In the CG, in the epidermis that did not complete the differentiation of the cells of the granular and horny layers, the numerical expression of the median value of the index of SDF-1+ cells went up and became 5 times greater than in the EG. Also, among epidermocytes, the numerical expression of the median value of the MSC index increased in absolute figures, although there were no reliable differences between the MSC indices on days 12 and 15 (Table 2). Similar dynamics of these indicators are also recorded in the granulation tissue of biopsies. The numerical expression of the median value of the SDF-1-positive cell index and the MSC index in the GT of the EG decreased, while in the CG it went up.

By day 23, a white normotrophic scar covered with epidermis consisting of fully formed stratified squamous partially keratinised epithelium is formed in the EG. Among the cells of this epidermis, cells secreting the chemoattractant SDF-1 and MSC were not detected (Table 2). Incomplete formation of the spinous, granular and horny layers was preserved in the CG. Epidermocytes secreting the chemoattractant SDF-1 were preserved in the population, but their numerical expression of the median index value had decreased by 2 times compared to day 15 of wound healing. MSC had completely disappeared from the EP. In the GT, the numerical expression of the median

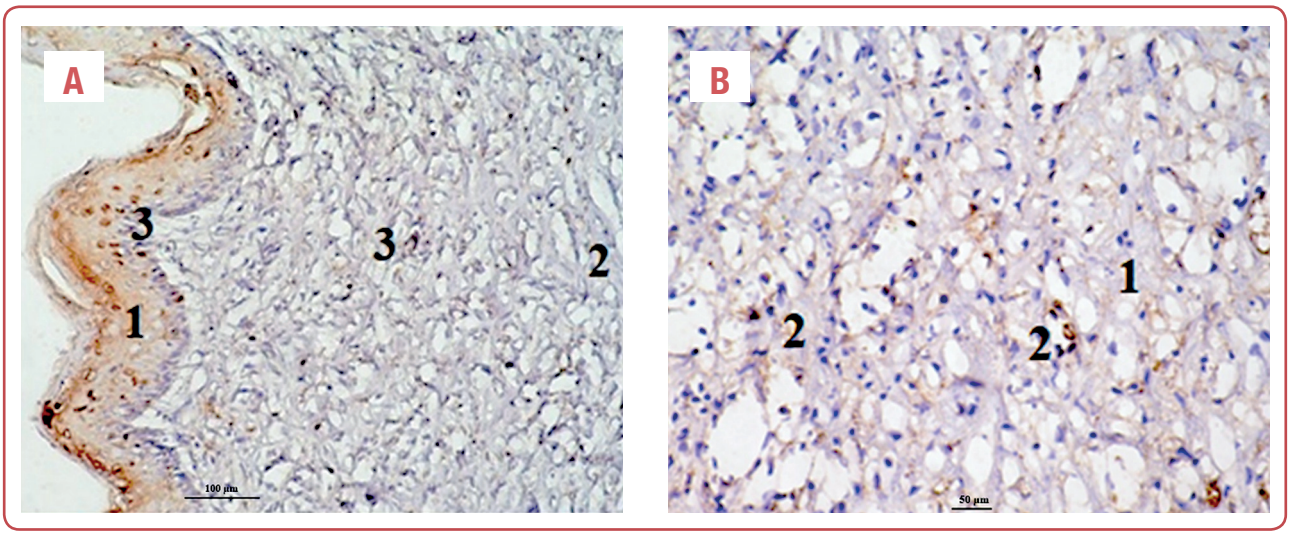

Figure 6: Biopsy specimen on day 12 after transplantation of polylactide film with allofibroblasts into an experimental skin wound. A – immunohistochemical reaction with antibodies against stromal-derived factor-1 (SDF-1). Staining in the diaminobenzidine with horseradish peroxidase – hydrogen peroxide system. 1 – epidermis; 2 – granulation tissue; 3 – SDF-1+ cells. Magnification: x200. B – immunohistochemical reaction with antibodies against CD34. Staining in the diaminobenzidine with horseradish peroxidase – hydrogen peroxide system. Counterstained with Mayer's haematoxylin. 1 – granulation tissue; 2 – CD34+ cells. Magnification: ×400.

value of the SDF-1-positive cells in the CG and EG had decreased compared to day 15 to single cells in the EG. The numerical expression of the median value of the SDF-1-positive cell index in the CG was 63.5 % higher than in the EG.

Discussion

In authors' previous work[16] and the works of other authors,[17] it was shown that transplantation of polylactide film associated with dermal allofibroblasts reduces the healing time of even ischaemic, long-term non-healing skin defects by reducing the inflammatory response highly effectively. It was shown that cell proliferation and growth on 2D polymer matrices help maintain the native intercellular connections and membrane receptors when creating cellular products and transplanting them.[6] It is possible that problems with disruption of their spatial organisation and functional properties arise when transferring cultured cells into wounds. They are associated, first of all, with unavoidable harm inflicted on cultured cells during enzymatic treatment used to detach cell layers from the vessel surfaces, resulting in decreased intercellular adhesion and strength, as well as partial degradation of surface receptors.[18]

Skin wound cells produce many signalling molecules like CXCL12 (SDF-1), which attract mesenchymal stem cells[19] via the CXCL12-CXCR4 chemokine signalling pathway. MSCs are mature multipotent progenitor cells derived from hematopoietic sources that play a beneficial role in chronic wound regeneration and have the capacity to develop into functional fibroblasts.[20] They also have the property of plasticity, expressed in the fusion of MSCs with fibroblasts to form polyploid fibroblasts with high synthetic activity, providing accelerated healing of skin defects.[21] Obviously, the introduction of allofibroblasts into the wound effectively increases the local concentration of the SDF-1 factor secreted by them, which attracts hematogenous MSCs along the concentration gradient. This ensures faster wound healing.

Conclusion

On the fourth day following the implantation of a biodegradable polylactide film combined with dermal allofibroblasts into a chronic skin lesion, the median numerical value of cells expressing SDF-1, which effectively attract MSCs, was higher in both the epidermis and dermis compared to the CG. Subsequently, the numerical expression of the median value of the index of SDF-1+ cells in the EG increases in the epidermis and dermis of biopsies up to day 7, decreases by day 10 and after 15 days of wound healing, such cells disappear from the popu-

lation. In the CG, SDF-1+ cells increase quantitatively up to day 15, significantly exceeding those in the EG and decrease by day 23. Active production of the chemoattractant SDF-1 by transplanted cells in EG biopsies from the first day of wound regeneration ensures the presence in the regenerate an increasing number of MSCs up to 7 days of healing in the epidermis and up to 10 days in the dermis, exceeding the number of those in the CG, which is obvious and ensures accelerated and high-quality healing of the skin defect.

Transplantation of polylactide films with dermal allofibroblasts promotes early and active secretion of SDF-1, which promotes MSC recruitment and accelerates skin wound regeneration.

Ethics

The Ethics Commission of V.I. Vernadsky Crimean Federal University approved this study (Protocol No 12), dated 10 May 2020. All procedures were conducted in strict compliance with the ILAR guidelines for the care and use of laboratory animals, the "International recommendations for conducting biomedical research using animals" (EEC, Strasbourg, 1985) and the "European convention for the protection of vertebrate animals for experimental and other scientific purposes" (EEC, Strasbourg, 1986).

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None.

Conflicts of interest

The authors declare that there is no conflict of interest.

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Data access

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

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