Effect of Allogeneic Bone Marrow-mesenchymal Stem Cells (BM-MSCs) to Accelerate Burn Healing of Rat on the Expression of Collagen Type I and Integrin α2β1

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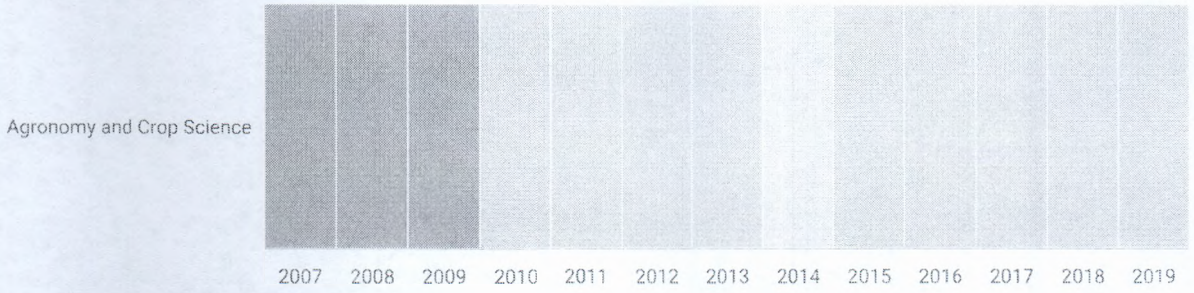

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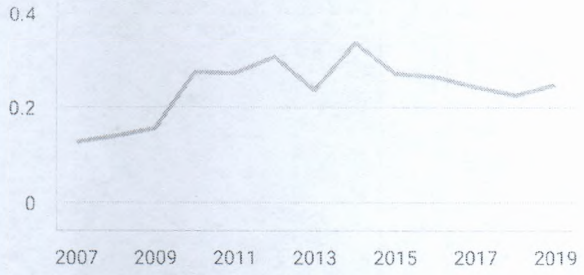

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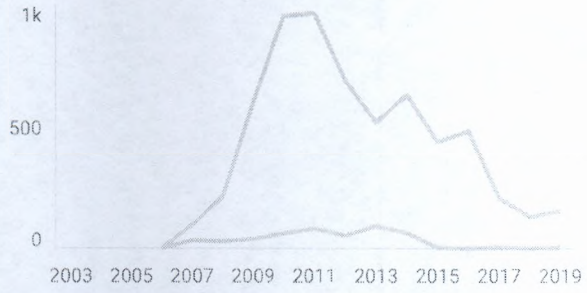

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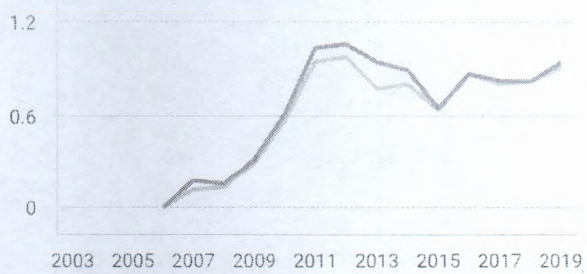

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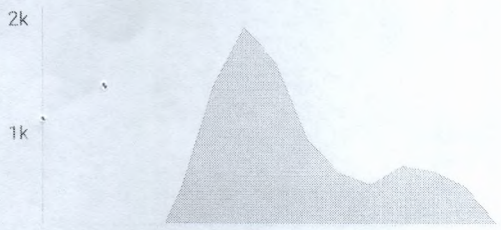

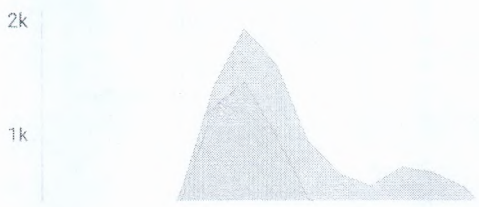

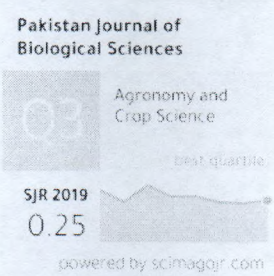

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Research Article

Effect of Allogeneic Bone Marrow-mesenchymal Stem Cells (BM-MSCs) to Accelerate Burn Healing of Rat on the Expression of Collagen Type I and Integrin α2β1

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Abstract

Background and Objective: Burn is a public health problem, it causes physical disability even death. Treatment of burn wound has been conducted in various ways, but the satisfactory healing has not been provided. Bone marrow-derived mesenchymal stem cells (BM-MSCs) treatment is one of attempt to burn recovery, accelerate wound healing and angiogenesis. This study aimed to investigate the effect of allogeneic BM-MSC treatment on the expression of collagen type I and integrin α2β1 in burn skin tissue of rat observed on day 14. **Materials and Methods:** Twelve Wistar rats divided into two groups, control group (injected with phospate buffer solution) and treatment group (injected with BM-MSC). Rat was anaesthetized with xylazine and ketamine (ratio 1:1), fur of rat's back was shaved and full thickness burn was made by boiling plate in hot water for 30 min and patched on the back for 20 min. The burns were covered by tegaderm film and elastomult haft. Antalgin as an analgetic was injected to rats during observation process. Burns of rat was observed on day 14. In this study one-way analysis of variance test and Tukey as a further test were analyzed. **Results:** The results showed that the healing time of allogeneic BM-MSC treatment on burn skin tissue rats was faster, the thickness of collagen type I in burn skin tissue of rats was thicker (0.977 μm) than controls (0.475 μm) and statistically demonstrated significant differences ($p = 0.000$). The average percentage of integrin α2β1 expression was higher (2.94%) than control group (2.34%), but the differences were not statistically significant ($p = 0.176$). **Conclusion:** The study concluded that BM-MSC treatment was able to accelerate the healing process of burns by increasing the thickness of the collagen and the percentage of integrin α2β1, thus accelerated the cell migration involved during wound healing.

Key words: Bone marrow-derived mesenchymal stem cells, collagen type I, integrin α2β1, wound healing, burns

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Bone marrow-derived mesenchymal stem cells (BM-MSCs) are non-haematopoeitic progenitor cells that have the ability to self-renew, proliferate and differentiate into chondrocytes, osteoblasts, adipocytes, myocytes, fibroblast myofibroblast epithelial cells, endothelial and neuronal cells[1,2]. The BM-MSCs also have strong potential in regeneration of skin tissue[3,4]. The BM-MSCs differentiation ability to bring into stem cells as candidate cells in tissue technologies that are useful to regenerate damaged tissue. The BM-MSCs can also provide an excellent effect on the improvement of tissues through local environmental modulation and activation of endogenous progenitor cells[5]. These have led the researchers interested in using BM-MSCs cell therapy for various diseases, including burns healing therapy.

The use of mesenchymal stem cells for healing burns has been reported since 2003 by Shumakov *et al*.[6]. The use of BM-MSCs for the treatment of burns in many studies has been continued and has been generated 21 kinds of study, but the most of studies were about radiation burns. Previous studies showed that BM-MSCs were able to accelerate wound healing time, reduce inflammatory cell infiltration in place injuries, accelerate the formation of new blood vessels (angiogenesis) and granulation tissue[7] and reduce wound contraction[8], epithelialization and collagen deposits[9]. Study about the administration of allogeneic BM-MSCs showed that BM-MSCs could differentiate into epidermal skin, formation of new blood vessels (angiogenesis), blood vessel density became much denser[10] and released cytokines to accelerate the wound healing process, but the benefit of BM-MSC administration has been completely known[11].

Wound healing is a complex process, occurs in three phases: The inflammatory phase, proliferation and maturation (remodeling) and each phase is interrelated (overlapping), this condition begins from the start of wound, until resolution of injury. In phases of wound healing, cellular elements and extracellular elements are involved. Cellular elements are inflammatory cells (neutrophils and macrophages), fibroblasts, endothelial and others. The components of extracellular consist of fibronectin, laminin and collagen including collagen type I that plays a role in all 3 phases of wound healing in initiating the process of homeostasis[12] and involves in immune cell migration and angiogenesis[13,14], increases the cellular components and encourages the process of fibroplasias[15]. Cellular elements need adhesion molecule to migrate. Those are selectin, integrins, ICAM and VCAM. Integrin plays a role in all three phases of wound healing. Integrin is a transmembrane receptor finding on the extracellular on membrane and intracellular. There are 24 kinds of integrins, integrin $\alpha2\beta1$ is predominant in wound healing.

Integrin has two functions. First, as cell adhesion to the extracellular matrix and as signal transduction, integrin as cell adhesion associate with extracellular matrix, including type I and III collagen, laminin and fibronectin. Integrin and collagen integration accelerate wound healing process by helping cells migration, including assisting with the migration of keratinocytes of the basal membrane. Collagen interacts with endothelial cells via $\alpha2\beta1$ integrin ligation which is important for angiogenesis[16]. Second, as signal transduction, integrin convey a signal into cell affecting intracellular activity. Intracellular activity of integrin affects a variety of processes, such as proliferation, differentiation, survival and apoptosis of cells[17,18].

Collagen type I and integrin $\alpha2\beta1$ have cooperative skills to accelerate wound healing, this study was performed to investigate the effect of allogeneic BM-MSC intradermal in full thickness burns by observing the expression of collagen type I and integrin $\alpha2\beta1$.

MATERIALS AND METHODS

Material and apparatus

Material: Rat BM-MSCs, 12 Wistar rats.

Main reagent: The Phosphate Buffer Saline (PBS), xylazine, ketamine, antalgin, tegaderm film, elastomult haft, xylol solution, ethanol absolute, ethanol 70%, H_2O_2 3%, methanol, rabbit anti-mouse biotinilated antibody label, streptavidine HRP label, chromogen solution hematoxylin Mayer.

Apparatus: Waterbath (Memmert), micropipette (Eppendorf), plate (made from aluminum with 15 mm diameter and 150 g in weight), pap pen (Thermo), microscope and computer equipments.

Method

Preparation of rat bone marrow-mesenchymal stem cell: Rat BM-MSCs was derived from Stem Cell Laboratory, Institute of Tropical Disease (ITD), Airlangga University, Surabaya. Number of dose of BM-MSCs cells used for one rat was 2×10^6 cells mL^{-1}.

Preparation of rat: Twelve Wistar rats divided into 2 groups: Control group (injected with PBS) and treatment group (injected with BM-MSCs). Rats used were about with 180-200 g in weight. The lightning and humidity of rat cage

were arranged in such a manner for well-established conditions. Rats were put in 1 place during treatment administration, rats did not move out from laboratory during application performed.

Preparation of burn rat: Burn-making of rats were applied based on Paramonov and Chebotarev method[19,20]. Rat was anaesthetized with xylazine and ketamine (ratio 1:1), fur of rat's back was shaved. Full thickness burn of rat was made by boiling the plate in hot water for 30 min and patched it on the back of rats for 20 min. Rats in control group was injected with PBS and treatment group was injected with BM-MSCs. The burns were covered by tegaderm film and elastomult haft. Antalgin as an analgetic was injected to rats during observation process. Skin tissue of rats was taken at day 14 to investigate the expression of collagen type I and integrin α2β1 (merck, Bios output, USA) by immunohistochemical methods.

Immunohistochemical staining of collagen type I and integrin α2β1: Immunohistochemical staining for collagen type I and integrin α2β1 was begun with deparafinasion by dipping the slides into xylol solution, 3 times for 5 min. Dehydration was performed by sticking the slides into xylol twice for 3-5 min, continued with soaking slides in ethanol absolute 3 times for 2 min, ethanol 70% twice for 2 min, then slides was rinsed with distillated water 3 times and the edge of slides was wiped with a tissue. Slides was soaked into H_2O_2 3% in methanol for 5 min, rinsed with distillated water and PBS 3 times (mouse anti rat 1:50) for 30 min at room temperature and then rinsed with PBS 3 times, each was done for 2 min. The cut-tissues were marked with pap pen for daubing. Slides were dipped in secondary antibody (rabbit anti-mouse biotinilated antibody label) for 30 min, slides were rinsed with PBS 3 times for 2 min. Slides was soaked into streptavidine HRP label for 30 min, then rinse in PBS solution 3 times, each was performed for 2 min. Slides was rinsed into chromogen solution for 3-10 min, rinsed with distillated PBS 3 times, each was done for 2 min, then rinsed with distillated water. Slides were dipped in hematoxylin Mayer for 6-12 min, finally slides were rinsed with running water and mounting.

Design of study: This study was an experimental study with post test only controls design.

Observation of collagen type I expression and adhesion molecule of integrin α2β1: Quantitative assessment of collagen type 1 expression was the measurement of collagen thickness, which gave a positive reaction to anti-collagen 1 in the skin tissue of burns rats by using a microscope that was directly connected to a computer screen. Percentage of integrin α2β1 expression was done by counting the No. of cells that gave a positive reaction to the anti-integrin α2β1. Positive reaction was calculated by counting cells which expressed with integrin and divided with a total No. of cells per 15625 μm^2 on skin tissue of burns rats.

Analysis of data: The effect of MSC stem cells to the thickness of collagen type I and percentage of integrin α2β1 were analyzed with one-way ANOVA test, with Tukey test as an advanced test.

Ethical clearance: This study has received approval from the Ethics Committee of the Faculty of Medicine, Andalas University, Padang.

RESULTS AND DISCUSSION

Effect of BM-MSCs on burns rat injury improvement: The results of administration of BM-MSC allogeneic in skin tissue burns rats showed that BM-MSCs accelerated wound healing time compared with control group which injected with PBS (Fig. 1), demonstrated with an increasing in the thickness of the collagen type 1, the percentage of integrin α2β1 expression and there were no infection on burn rat found.

Acceleration of healing of burns rats could be show in the increase of collagen type I thickness and the percentage of integrin α2β1 after BM-MSC administration.

Expression of collagen type I: The results of immunohistochemical test of the expression of collagen type I showed that the average thickness of collagen type I in burnt-skin tissue of rat group injected with BM-MSC was 0.977 μm, higher than the control group 0.475 μm (Fig. 2).

The average of collagen type I thickness showed statistically significant difference ($p = 0.000$) between treatment and control group. The thickness of collagen fibers expression of each group (control and BM-MSC) by immuno-histo-chemistry on burns skin tissue of rat was demonstrated in Fig. 3. Rats in control group injected with PBS in burns skin tissue showed that the expression of collagen type I fibers formed only a thin brownish color shade (400x). Besides, treatment group injected with BM-MSC in

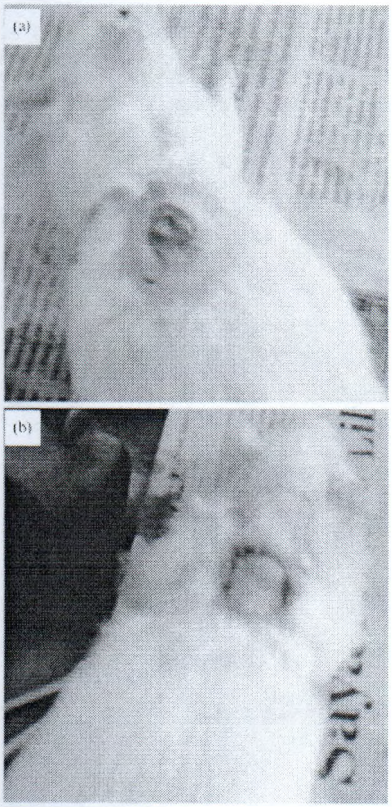

Fig. 1(a-b): Injury improvement of burns rat at day 14 after being given (a) BM-MSC and (b) PBS injection, infection of burns wound occurred in control group

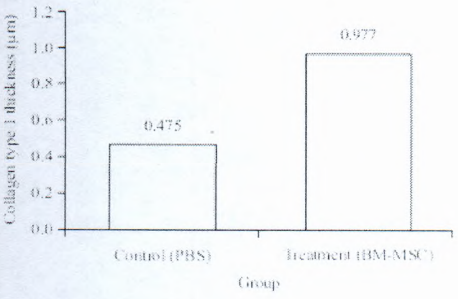

Fig. 2: Average of collagen type I expression level in control and BM-MSC group

burns skin tissue showed the thicker of collagen type I expression than the control group were positive visible brownish color.

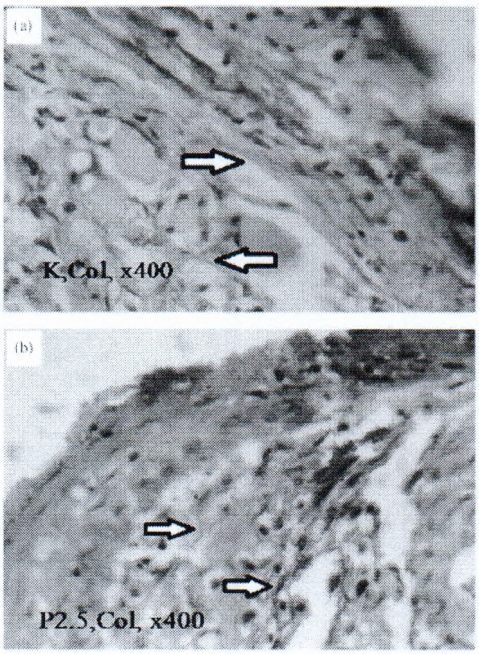

Fig. 3(a-b): Positive reaction of immunohistochemical staining of collagen type I in (a) Control group, arrow showed that the layer of collagen formed only thin brownish color shade (400x) and (b) Treatment group, arrow showed thick layer of collagen type I formed (400x)

Collagen is a component of the extracellular matrix produced by fibroblasts and integrin α2β1 is one of adhesion molecules that cooperate with the extracellular matrix to assist the migration of cellular components that play a role during wound healing. In this study, an increase of collagen type 1 thickness occurred after BM-MSC was given on burns rat skin tissue on day 14, which significantly different when compared with the control group.

The increasing of collagen thickness after administration of allogeneic BM-MSC were also found by Yan *et al.*[21] and Liu *et al.*[22], an increase of accumulation of the amount and concentration of collagen type I and II as well as regulation of the ratio of collagen occurred after being given human umbilical cord-blood mesenchymal stem cells (HUC-BMCS). This increase may be due to BM-MSC produced mediators with paracrine effects, thus it could increase the number and fibroblast migration in wound rat skin tissue[23] and BM-MSC were able to differentiate into fibroblasts[24]. The increase of collagen thickness affected the wound healing phase among the phases of inflammation, proliferation and remodeling. Collagen in the inflammatory phase helped the

monocyte cells to migrate from the peripheral blood to extravascular to perform its function as phagocytosis and the ability of bactericidal activity[25]. In the proliferative phase, collagen played a role in the formation of granulation tissue and wound strength. This situation accelerated the closure and healing of burns. In the remodeling phase, synthesis and degradation of collagen were necessary to accelerate the wound healing process. In this phase, BM-MSC regulated collagen deposition and regulated MMP/TMMP, so that the strength and integrity of burns tissues were well-formed[26].

Percentage of integrin α2β1: The results of percentage calculation of integrin α2β1 expression average in burns rat skin tissue on BM-MSC group was 2.94%, higher than the percentage of control group 2.34%. The average percentage and integrin α2β1 expression in burns skin tissue of rat in both groups were demonstrated in Fig. 4 and 5.

Result of immunohistochemical staining in integrin α2β1 expression in cells showed only a thin shadow of brownish color in control group, whereas the staining result showed more brown color in cells in treatment group.

The percentage of integrin α2β1 expression in the burns rat skin tissue showed an increase but it did not show significantly differences ($p = 0.176$) compared with the control group. Integrin α2β1 expression generally increased at the time of injury because integrin affected the functioning of migration and proliferation of inflammatory cells, keratinocytes and fibroblasts.

In this study, the expression of integrin α2β1 at day 14 increased, but the elevation did not show any significant difference, it may be due to burns skin tissue has entered the remodeling phase of wound healing and the number of migrating cells have reduced. Integrin α2β1 is only needed by keratinocytes to bind with collagen, so that the migrations can occur[27]. Increasing the percentage of integrin α2β1 expression was also necessary to regulate cell migration and proliferation of platelets. In immunohistochemical assay, integrin expression may have been reduced because the wound closure process has been well-occurred.

The percentage of integrin α2β1 expression did not show significantly difference, because several types of integrin found on the surface of keratinocytes, such as α3β1, α6β4, αvβ6 and α5β1. Further study will be needed to investigate other integrin expression in the healing of burns. Integrins that exist in keratinocytes play a role in its migration

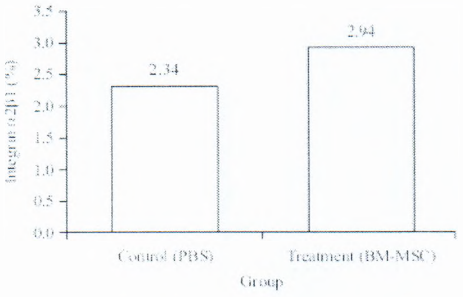

Fig. 4: Average percentage of integrin α2β1 expresssion in control and treatment group

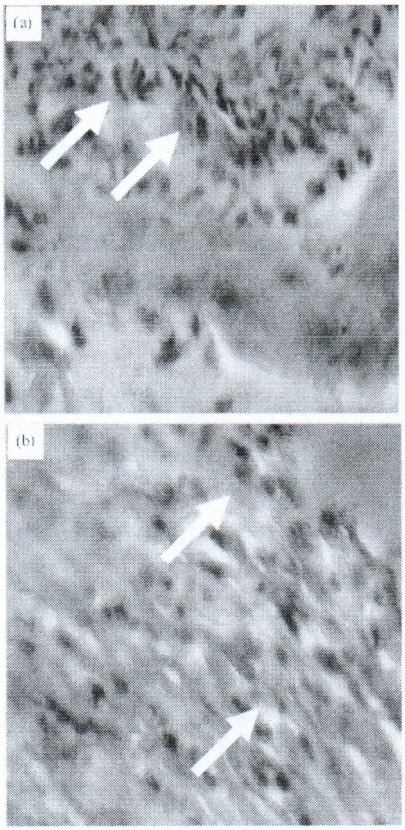

Fig. 5(a-b): Positive reaction of immunohistochemical staining of integrin α2β1 in (a) Control group, arrow showed thin (+) layer of staining in the cell with only the form of brownish color shade (400x) and (b) Treatment group, arrow showed positive reaction of staining with thick layer in the cell with intensity of color was more brown (400x)

from the edge of the wound and the proliferation of keratinocytes, so that re-epithelization process occurs[28,29].

CONCLUSION

Administration of BM-MSCs injected in burns rat accelerated healing time of burns in day 14, compared with control group injected with PBS.

The BM-MSCs elevated the average thickness of collagen type I 0.977 μm, higher than PBS injection 0.475 μm, thickness of collagen fibers was showed with the thicker of collagen type I expression with positive visible brownish color. The average of collagen type I thickness showed statistically significant difference ($p = 0.000$) between treatment and control group.

Integrin $\alpha2\beta1$ expression average in burns rat skin tissue on BM-MSC administration was 2.94%, higher than the percentage of PBS injection 2.34%. The percentage of integrin $\alpha2\beta1$ expression in the burns rat skin tissue did not show significantly differences ($p = 0.176$) compared with the control group. Integrin $\alpha2\beta1$ expression in cells showed only a thin shadow of brownish color in PBS administration, whereas the staining result showed more brown color in cells in BM-MSCs administration.

The increased of collagen type I thickness and percentage of integrin $\alpha2\beta1$ expression showed that administration of BM-MSC accelerated burns healing by assisting the inflammatory cells migration, accelerated the re-ephitelization and elevated synthesis process, deposit and degradation in the remodeling phase of healing of burns.

SIGNIFICANT STATEMENT

The BM-MSCs have ability to regenerate damaged tissue, most of study emphasized on regenerating damaged tissue due to burns of radiations, this study investigated the ability of BM-MSCs to heal wound burns on rat. This study found that administration of BM-MSC increased the expression of collagen type I thickness and percentage of integrin $\alpha2\beta1$, accelerated burns healing by assisting the inflammatory cells migration, accelerated the re-ephitelization and elevated synthesis process, deposit and degradation in the remodeling phase of healing of burns. These results were same with previous studies, further investigations are needed to apply BM-MSCs to human.

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