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Original Article

Combination of adipose-derived stem cells with platelet-rich plasma gel for wound repair through TGFβ1 in rats

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Abstract: Objective: To analyze the role of TGFβ1 in the combination of adipose-derived stem cells (ADSCs) with platelet-rich plasma (PRP) gel for wound repair in rats. Methods: A total of 100 SD rats were divided into 5 groups: model group, control group, PRP group, ADSCs group, and combined group; with n=20 in each. No treatment was given to the control group, while four 1 cm^2 square wounds were made on the back of the animals in the other four groups and were treated accordingly. Then the four groups were compared at different time points after administration of each treatment in terms of the wound recovery, hydroxyproline level, TGFβ1 level, Smad1 level, Smad3 level, MMP2 level, and MMP-9 level which were determined by enzyme-linked immunosorbent assay. Results: (1) After 3 days of drug delivery, the PRP group and the combined group had better wound dryness than the model group and the ADSCs group. After 7 days of drug delivery, the combined group had the most healing of the wounds, followed by the PRP group, the ADSCs group, and the model group in that sequence. At the same time, the four groups reached a level of wound recovery close to the control group. (2) Although the four groups showed lower levels of hydroxyproline, TGFβ1, Smad1, Smad3, MMP2 and MMP-9 in wound tissue by comparison with the control group, the combined group, PRP group, and ADSCs group had levels that gradually rose after treatment. In addition, each group had significantly different levels of indicators at different time points ($P<0.05$), with the lowest levels in the model group ($P<0.05$). Among the four groups, the combined group experienced the greatest variations in these indicators before and after treatment, as well as significant differences compared with the other groups ($P<0.05$). Conclusion: The combination of ADSCs with PRP can accelerate wound repair involving TGFβ1 in rats and shorten wound repair time, which is worthy of popularization and application.

Keywords: Wounds in rats, ADSCs, PRP, TGFβ1, repair

Introduction

As the largest organ of the body, the skin protects a variety of tissues and organs from direct invasion by pathogenic microorganisms and from chemical and physical invasion as a protective barrier between the external environment and the remainder of the body [1]. Soft tissue defects in the skin caused by high-energy injury or burns are hard to repair and have been the focus of clinical research [2].

Clinically, autologous skin grafts or local flap transposition is frequently-used for repairing soft tissue defects. However, these operations may not always work and other treatments are required for patients with large defects due to the lack of self-sourced skin [3]. It has been found that vascular endothelial cells and vascular smooth muscle cells play important roles in the repair of complicated wounds, and they are the source of tissue cells for regeneration and remodeling of granulation tissue in wounds [4]. Therefore, the question of how to amplify these cells in large quantities outside the body, or how to locally stimulate their regeneration in a wound is a major clinical focus. ADSCs have multi-directional differentiation potential and are similar to embryonic stem cells in terms of proliferation rate, senescence, apoptosis and growth kinetics [5]. On top of that, PRP gels have been found to promote wound recovery as they are effective in angiogenesis, tissue repair, and inflammatory responses [6]. There

have been many previous studies on the application of ADSCs-PRP gel in wound repair, and it has proved to have certain healing effects, but few studies have mentioned transforming growth factor β1 (TGFβ1). In fact, studies have found that TGFβ1 is closely related to the process of skin tissue damage, and Smad protein is also an important participant. Abnormal expression of these factors is closely related to the pathological and physiological processes of different skin tissues [7]. Therefore, it is important to understand the role of TGFβ1 in wound repair.

In the present study, 100 SD rats were divided into 5 groups to analyze the role of TGFβ1 in ADSCs-PRP combination therapy for wound repair in rats, in an effort to find new treatment options.

Materials and methods

Data

A total of 100 pathogen free SD rats weighing between 220 g and 240 g were allowed to acclimate for 1 week, during which they ate freely. After that, the rats were evenly divided into a model group, control group, ADSCs group, PRP group and combined group; with 20 rats in each group. All animal-related operations herein were carried out in accordance with the Regulations on the Management of Laboratory Animals.

Methods

Instrument and reagents: Surgical instruments; ultra-clean workbench; electronic balance; high-speed refrigerated centrifuge; autoclave; ELISA; ELISA plate; PRP gel; TGFβ1 ELISA kits; hydroxyproline assay kits; MMP-9 ELISA kits; MMP-2 ELISA kits; and Smad1 & Smad3 ELISA kits.

Types of tissue wounds and medication: To prepare modified PRP by the Cascade-Esforax method, calcium ions were activated to form a PRP gel. Four square wounds (a=1 cm^2) were made 2 cm from both sides of the posterior spine except in the control group. The marked skin was disinfected with iodophor before it was cut off along the mark. Subsequently, the prepared wound was fixed by a silica gel plate at its edge. The wounded area was treated with 1 ml ADSCs (3×10^6/ml) in the ADSCs group; a PRP gel (2×10^6/ml) in the PRP group; and a PRP gel (2×10^6/ml) combined with 1 ml ADSCs (3×10^6/ml) in the combined group. No medication was given to the the model group despite its wounds, nor the control group which had no skin wounds.

Wound observation followed. On days 3, 5, and 7 after injury, the rats were sacrificed to measure the levels of hydroxyproline, TGFβ1, Smad1, Smad3, MMP2 and MMP-9. On day 14 was the final measurement.

Observation indicators

(1) The control rats were used as a reference for observation of wound recovery in other 4 groups, including wound dryness and size. Wound healing time is the time required for the wound to be completely epithelialized, and the wound healing area to exceed 95% of the wound area indicates complete healing.

(2) The levels of hydroxyproline, TGFβ1, Smad1, Smad3, MMP2 and MMP-9 in the wound tissues were measured in all groups by Enzyme-linked immunosorbent assay (ELISA) on days 3, 5, 7 and 14 days of treatment. Wound tissues were collected at 3, 5 and 7 days after treatment for each index measurement, and wound tissues were collected at 14 days after the rats were sacrificed for each index measurement. ELISA was carried out in strict accordance with the operating instructions.

Statistical analysis

SPSS Statistics V22.0 was used for statistical analysis. A mean plus or minus one standard deviation defines the measurement data, which are compared intra or inter group with the Independent-Samples *t* Test. The count data were expressed as [n (%)] and analyzed between groups and within groups by a chi-squared test whereas multi-point comparison within the group and multi-time comparison between the groups were analyzed by ANVOA and F tests. The results were considered statistically significant at $P<0.05$.

Results

Comparison of wound recovery

Wounds of the PRP and combined groups were significantly drier than those in the model

Table 1. Comparison of hydroxyproline levels at different times of administration ($\bar{x}$ ± s, μg/mg)

	Before administration	3 days after administration	5 days after administration	7 days after administration	14 days after administration
combined group (n=20)	0.38±0.09	1.90±0.27	3.38±0.46	4.77±0.47	7.78±1.34
PRP group (n=20)	0.36±0.09	1.35±0.20	2.77±0.36	3.76±0.37	5.77±1.05
ADSCs group (n=20)	0.37±0.10	0.41±0.09	1.35±0.26	1.96±0.47	3.88±0.47
Model group (n=20)	0.36±0.07	0.38±0.08	0.79±0.12	1.77±0.32	2.90±0.24
Control group (n=20)	8.30±0.90	8.40±0.88	8.40±1.45	8.31±0.99	8.51±0.97
F	1.326	3.854	4.127	3.625	3.317
P	0.312	0.013	0.009	0.037	0.026

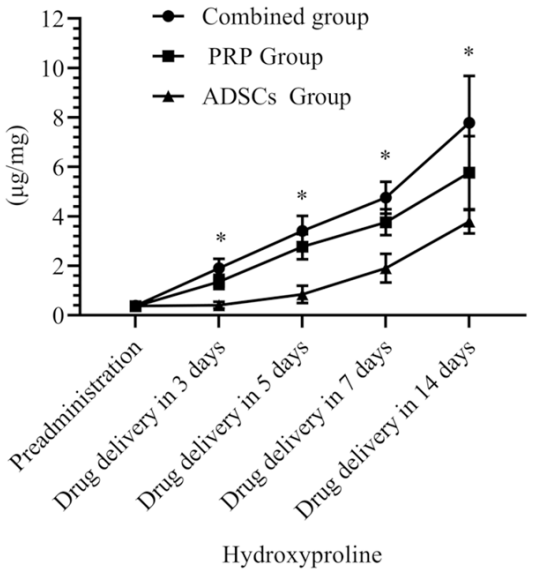

Figure 1. Comparison of hydroxyproline levels in the PRP group, ADSCs group and combined group. No significant difference was found in hydroxyproline levels among the three groups before administration (P>0.05). On day 3 of administration, the combined group did better than the other two, of which the PRP group had a significantly higher level (P<0.05). This was also the case on days 5, 7 and 14. * meant at the same time point, P<0.05 was obtained by comparison among the three groups.

group and ADSCs group on day 3 of treatment. On day 7, the combined group had the smallest wounds, followed by the PRP group, ADSCs group, and the model group in that sequence, and the 4 groups reached an almost full recovery close to the control group.

Comparison of hydroxyproline levels

The expression of hydroxyproline was significantly lower in all wounded rats but rebounded gradually in the combined group, PRP group and ADSCs group after treatment (P<0.05). It differed remarkably at different time points in the same group (P<0.05). The level in the combined group topped the other three groups while the model group had the least, the difference of which was considered statistically significant (P<0.05) (**Table 1**; **Figure 1**).

Comparison of TGFβ1 expression

The expression of TGFβ1 was significantly lower in all wounded rats but rebounded gradually in the combined group, PRP group and ADSCs group after treatment (P<0.05). It differed remarkably at different time points in the same group (P<0.05). The level in the combined group topped the other three groups while the model group had the lowest level, the difference of which was considered statistically significant (P<0.05) (**Table 2**; **Figure 2**).

Comparison of Smad1 expression

The expression of Smad1 was significantly lower in all wounded rats but rebounded gradually in the combined group, PRP group and ADSCs group after treatment (P<0.05). It differed noticeably at different time points within groups (P<0.05). The level in the combined group topped the other three groups while the model group had the lowest level, the difference of which was considered statistically significant (P<0.05) (**Table 3**; **Figure 3**).

Comparison of Smad3 expression

The expression of Smad3 was significantly lower in all wounded rats but rebounded gradually in the combined group, PRP group and ADSCs group after treatment (P<0.05). It differed remarkably at different time points within groups (P<0.05). The level in the combined group topped the other three groups while the model group had the lowest, which was considered statistically significant (P<0.05) (**Table 4**).

Table 2. Comparison of TGFβ1 levels at different times of administration ($\bar{x}$ ± s, β-actin)

	Before administration	3 days after administration	5 days after administration	7 days after administration	14 days after administration
Combined group (n=20)	0.31±0.05	0.42±0.10	0.46±0.06	0.51±0.06	0.55±0.06
PRP group (n=20)	0.32±0.06	0.40±0.09	0.44±0.11	0.48±0.10	0.51±0.13
ADSCs group (n=20)	0.32±0.05	0.37±0.06	0.41±0.08	0.44±0.09	0.46±0.09
Model group (n=20)	0.31±0.07	0.35±0.07	0.40±0.06	0.42±0.06	0.45±0.10
Control group (n=20)	0.37±0.09	0.36±0.08	0.38±0.09	0.37±0.10	0.36±0.08
F	0.238	2.941	3.215	3.561	3.608
P	0.120	0.039	0.025	0.015	0.008

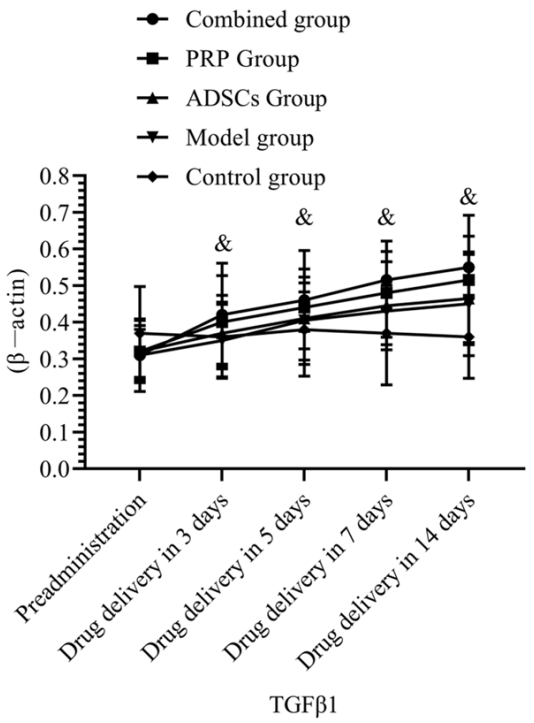

Figure 2. Comparison of TGFβ1 levels. There was no significant difference in TGFβ1 levels between the above-mentioned three groups before administration (P>0.05). Within 3 days of drug delivery, the combined group topped the rest groups (P<0.05). This was also the case after 5 days, 7 days and 14 days of administration. & indicated that at the same time, the comparison between groups showed P<0.05.

Comparison of MMP2 expression

The expression of MMP2 was significantly lower in all wounded rats but rebounded gradually in the combined group, PRP group and ADSCs group (P<0.05). It differed significantly at different time points within groups (P<0.05). The combined group had higher levels than the other three groups while the model group was at the bottom, which was considered statistically significant (P<0.05) (**Table 5**; **Figure 4**).

Comparison of MMP9 expression

The expression of MMP9 was significantly lower in all wounded rats compared with the control group but rebounded gradually in the combined group, PRP group and ADSCs group (P< 0.05). It differed noticeably at different time points within groups (P<0.05). The level in the combined group was greater than in the other three groups while the model group was at the bottom, which was considered statistically significant (P<0.05) (**Table 6**).

Discussion

Stem cells are found in most mature tissues, and are important participants in the process of tissue injury repair. It was ten years ago when ADSCs were isolated from adipose tissue and now they are widely applied in preclinical and clinical models [8]. ADSCs can provide various angiogenic factors such as stem cell growth factors, fibroblast growth factors and vascular endothelial growth factors to promote neovascularization of the lesion site [9]. A single growth factor will not be effective in cell proliferation and metastasis unless it is bound to a different cytokine, and then it can promote wound healing [10, 11]. PRP is obtained by spinning whole blood in a centrifuge, and collecting the concentrated platelets. It can be activated by calcium ions to release insulin-like growth factor 1 (IGF-1) in large quantities, transforming growth factor-β (TGF-β), and platelet-derived growth factors (PDGF) [12].

Notoriously, collagen in the dermis is closely associated with the endurance and strength of the skin, of which Type I and Type III matter most [13]. The combined application of adipose stem cells and a platelet-rich plasma gel can promote the synthesis of collagen and thus help enhance the endurance and strength of

Table 3. Comparison of Smad1 levels at different times of administration ($\bar{x} \pm s$, β-actin)

	Before administration	3 days after administration	5 days after administration	7 days after administration	14 days after administration
combined group (n=20)	0.23±0.05	0.37±0.10	0.42±0.09	0.49±0.14	0.54±0.13
PRP group (n=20)	0.22±0.07	0.33±0.08	0.40±0.09	0.43±0.10	0.49±0.12
ADSCs group (n=20)	0.21±0.06	0.28±0.05	0.32±0.06	0.36±0.08	0.44±0.07
Model group (n=20)	0.21±0.07	0.25±0.04	0.28±0.07	0.34±0.07	0.40±0.06
Control group (n=20)	0.29±0.05	0.29±0.06	0.28±0.08	0.27±0.06	0.28±0.05
F	1.871	2.679	2.935	3.057	3.521
P	0.168	0.029	0.018	0.020	0.009

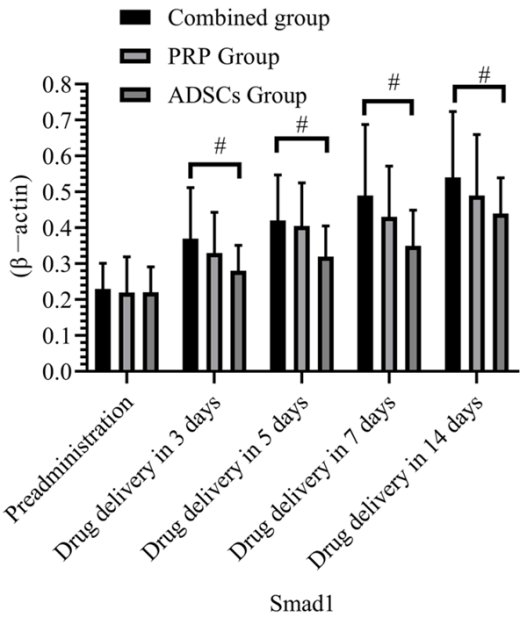

Figure 3. Comparison of Smad1 levels. There was no significant difference in Smad1 levels among the three groups before administration (P>0.05). After 3 days of treatment, the combined group topped the rest groups (P<0.05). This was also the case after 5 days, 7 days and 14 days of treatment. # indicated that at the same time, the comparison between groups showed P<0.05.

the skin to accelerate wound repair [14]. This study showed that before treatment, the PRP group, ADSCs group, combined group and model group had significantly lower expressions of hydroxyproline, TGFβ1, Smad1, Smad3, and MMP2 than the control group. On days 3, 5, 7 and 14 of corresponding treatment, these levels rebounded gradually and each revealed a significant difference from that collected at the former time points within groups (P<0.05). Furthermore, among the four groups, the model group had significantly lower levels (P< 0.05) whereas the combined group topped the rest (P<0.05). It manifested in a time-dependent manner of recovery, and the longer the treatment time, the higher the levels.

TGFβ is among the major regulators of skin tissue physiological and pathological processes. The TGFβ1-Smad signaling pathway is an participant in the formation and repair of skin injuries, and it has a close influence on the efficacy of medication [15, 16]. A study on wound recovery in rats reported that TGF-β1 is time-dependent during the whole process of skin wound repair, and it can help a forensic doctor to infer when an injury was made on the skin [17]. Zhang S et al [18] confirmed that the traditional Chinese prescription Danggui Sini Decoction can effectively ameliorate skin sclerosis and reduce the level of TGF-β in model mice, while Yan J et al [19] found that hydrolyzed pearl solution regulates the secretion of bFGF and TGF-β1, and significantly reduces scarring of the skin. If abnormal regulation of TGFβ1-Smad signaling pathway is successfully restored, skin injury can heal [20]. In the current study, the levels of TGFβ1, Smad1, and Smad3 significantly increased after treatment, especially in rats receiving the combination therapy, of which these animals showed a greater increase. This suggests the high value of the combination treatment. The expression of matrix metalloproteinases and its inhibitors is connected with the occurrence and repair of tissue wounds [21]. Huang XY et al [22] showed that UVB can induce the formation of human fibroblasts and promote their changes, using irradiation with UVB for 24 hours, human fibroblasts gradually became round, wrinkled, and disorganized, with matrix metalloproteinases MMP-3 and MMP-1 becoming significantly greater expressed and telomeres being significantly shortened. Additional findings of high-

Table 4. Comparison of Smad3 levels at different times of administration ($\bar{x}$ ± s, β-actin)

	Before administration	3 days after administration	5 days after administration	7 days after administration	14 days after administration
Combined group (n=20)	0.24±0.07	0.36±0.08	0.44±0.07	0.48±0.13	0.56±0.15
PRP group (n=20)	0.23±0.08	0.32±0.07	0.38±0.08	0.41±0.07	0.50±0.14
ADSCs group (n=20)	0.24±0.06	0.28±0.05	0.33±0.07	0.38±0.09	0.46±0.09
Model group (n=20)	0.22±0.05	0.26±0.05	0.30±0.08	0.35±0.08	0.39±0.08
Control group (n=20)	0.28±0.06	0.30±0.07	0.29±0.08	0.29±0.08	0.30±0.07
F	0.933	2.867	3.621	2.785	2.468
P	0.162	0.039	0.024	0.031	0.018

Table 5. Comparison of MMP2 levels at different times of administration ($\bar{x}$ ± s, β-actin)

Grouping	Before administration	3 days after administration	5 days after administration	7 days after administration	14 days after administration
Combined group (n=20)	0.25±0.07	0.39±0.10	0.43±0.11	0.47±0.12	0.54±0.13
PRP group (n=20)	0.25±0.08	0.37±0.08	0.40±0.06	0.43±0.09	0.48±0.12
ADSCs group (n=20)	0.26±0.10	0.34±0.07	0.37±0.08	0.40±0.08	0.44±0.08
Model group (n=20)	0.25±0.07	0.31±0.06	0.33±0.06	0.36±0.07	0.40±0.09
Control group (n=20)	0.30±0.08	0.32±0.07	0.31±0.07	0.30±0.06	0.31±0.07
F	0.682	2.784	3.131	2.874	2.968
P	0.135	0.027	0.011	0.023	0.019

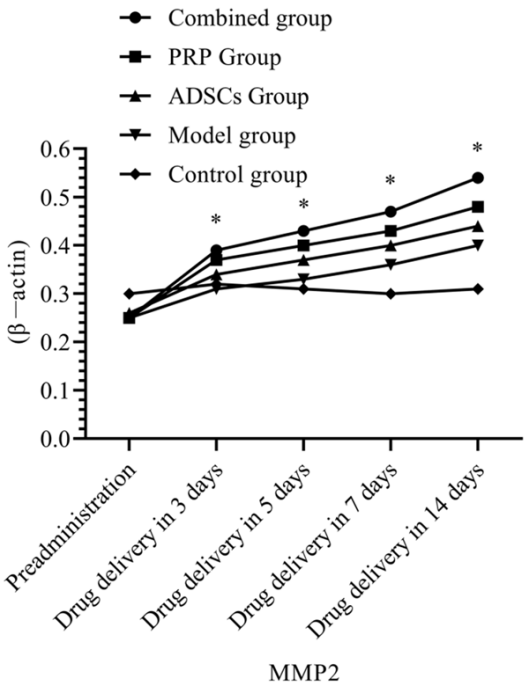

Figure 4. Comparison of MMP2 levels. There was no significant difference in MMP2 levels among the three groups before administration (P>0.05). After 3 days of treatment, the combined group topped the rest groups (P<0.05). This was also the case after 5 days, 7 days and 14 days of treatment. * indicates that at the same time, the comparison between groups showed P<0.05.

er expression of MMP-3 and MMP-1 may be initiators of early photoaging. Abd-Allah SH et al [23] confirmed that, by lowering the levels of MMP-3 and MMP-13 with the retinoic acid receptor (RAR), all-trans retinoic acid can inhibit the photoaging-caused degradation of collagen. Nguyen TT et al [24] found that in patients with diabetic foot ulcers, MMP-8 and MMP-9 levels increased significantly, and as such the levels of both may be associated with the recovery of diabetic foot ulcers. According to Hardy E et al [25], HSP47 and MMP-2 are important players in the repair of scar-less skin wounds. In this study, the levels of MMP2 and MMP9 were significantly increased after treatment, especially in the rats receiving the ADSCs-PRP combination therapy which showed a greater increase. It was confirmed that the combination could accelerate wound healing in rats due to the abnormal expression of matrix metalloproteinases.

In summary, TGFβ1 is involved in ADSCs-PRP combination treatment, and it can help accelerate wound repair in rats, which is of great evidence for the high value of the combination therapy and the important role of TGFβ1 in skin wound repair. However, this study did not investigate the cellular localization of TGFβ1

Table 6. Comparison of MMP9 levels at different times of administration ($\bar{x} \pm s$, β-actin)

	Before administration	3 days after administration	5 days after administration	7 days after administration	14 days after administration
combined group (n=20)	0.22±0.09	0.43±0.09	0.47±0.12	0.52±0.12	0.57±0.12
PRP group (n=20)	0.21±0.08	0.41±0.08	0.44±0.09	0.49±0.11	0.54±0.13
ADSCs group (n=20)	0.22±0.09	0.39±0.09	0.42±0.10	0.46±0.13	0.49±0.09
Model group (n=20)	0.23±0.07	0.35±0.08	0.38±0.07	0.40±0.06	0.43±0.12
Control group (n=20)	0.32±0.10	0.31±0.07	0.32±0.09	0.31±0.06	0.30±0.08
F	0.528	2.976	3.612	3.457	2.867
P	0.136	0.018	0.023	0.018	0.007

and other indicators in cells, nor did it cover the mechanism of TGFβ-1. So future studies will focus on the changes of cellular localization of various proteins during wound injury and repair by means of immunohistochemistry, and on the relevant molecular mechanisms.

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Disclosure of conflict of interest

None.

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