Interactive Roles of Activin A in Epidermal Regeneration

Jee Woong Choi, Kyung Mi Nam¹, Hye Ryung Choi¹, Chang Hun Huh¹, Kyung Chan Park¹

Department of Dermatology, Ajou University School of Medicine, Suwon, ¹Department of Dermatology, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, Korea

Dear Editor:

Recently, various stem cell lines have been widely used in tissue engineering. Among them, the mesenchymal stem cell (MSC) has been reported to stimulate wound healing. In particular, the bone marrow mesenchymal stem cell (BMSC) migrates directly towards a wound, differentiates into various cells and provides a favorable environment where other cells can regenerate quickly. The adipose-derived stem cell (ADSC) is another line that has features of the MSC. Although these two types of MSCs have great potential for treating wounds, few studies have investigated how they function in skin regeneration. Activin A, a homodimer of two inhibitin βA subunits linked by a disulfide bond, is a cytokine produced by various cell types including stem cells. It participates in regulation of stem cell maintenance, and also plays an important role in the wound healing process. Because the mesenchymal-epithelial interaction is a critical process for tissue regeneration, we focused on activin A as an important factor of dermal-epidermal interaction.

Recent studies have revealed that the epithelialization process of living skin equivalent (LSE) was similar to that occurring during the re-epithelialization process after wounding. Therefore, in our study, we compared three different LSE models that were cultured with ADSC, BMSC, and fibroblast. This study was approved by Seoul

Fig. 1. Effects of the stem cells in the living skin equivalents (LSE) reconstruction. Sections of LSE were stained for H&E (A, B, and C), activin A (D, E, and F), integrin β1 (G, H and I; white arrows indicating basement membrane), PCNA (J, K, and L; yellow arrows indicating basal keratinocytes), and p63 (M, N and O; yellow arrows indicating basal keratinocytes). Original magnification: ×400 in (A∼C) and ×200 in (D∼O). Fb: fibroblast, ADSC: adipose-derived stem cell, BMSC: bone marrow mesenchymal stem, PCNA: proliferating cell nuclear antigen.
Table 1. Comparison of the level of protein expression by image analysis

| Protein   | Signal intensity | p-value | Main location |
|-----------|------------------|---------|---------------|
|           | Fb-based LSE     | ADSC-based LSE | BMSC-based LSE |       |
| Activin A | 26.7±12.9        | 137.5±35.4 | 112.8±33.9   | 0.002 | E    |
| Activin A | 2.7±2.0          | 16.8±6.7   | 20.9±8.1     | 0.006 | D    |
| Integrin β1 | 31.0±10.2    | 128.0±45.6 | 70.8±28.9    | 0.002 | BM   |
| PCNA      | 16.7±7.6         | N/D       | 43.9±12.2    | 0.000 | BL   |
| p63       | 5.1±3.2          | 35.6±10.1  | N/D          | 0.000 | BL   |

Values are presented as mean±standard deviation. The Kruskal-Wallis test was used to compare the signal intensity among the three LSE models. Fb: fibroblast, LSE: living skin equivalent, ADSC: adipose-derived stem cell, BMSC: bone marrow mesenchymal stem, PCNA: proliferating cell nuclear antigen, E: epidermis, D: dermis, BM: basement membrane, BL: basal layer, N/D: not detected.
In the study, we used LSE models to investigate the effects of MSCs during skin regeneration. The results showed that epidermal proliferation and basement membrane formation were improved by the presence of these cells. This improvement can be explained by the paracrine effects of stem cells and their derivatives to secrete various factors including antioxidant mediators and cytokines. Among them, we postulated that activin A could be an important factor in the wound healing process. In a mouse model, activin A promoted healthy granular tissue formation, regenerated epidermal keratinocytes, and influenced keratinocyte migration. In hair follicles, this pathway is also related to the hair regeneration cycle. Previous reports and our findings suggest that activin A serves an important function for maintaining homeostasis of skin tissue. Activin A is mainly produced in keratinocytes and the MSCs, and we also verified that activin A was largely expressed in both epidermal and dermal layers of the LSE. It seems that activin A produced from the MSCs in the dermis affects the basal keratinocytes through paracrine effects, and contributes to epidermal proliferation and keratinocyte migration.

In summary, it was concluded that activin A may have an important role in wound healing as a mediator in dermal-epidermal interaction.

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**CONFLICTS OF INTEREST**

The authors have nothing to disclose.

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