

## Topical application of hyaluronidase accelerates cutaneous wound healing

Chronic wound care poses a significant biomedical burden. The management and treatment of chronic wounds affect millions of people annually; these numbers are rapidly growing worldwide owing to the increase in the aging population and a sharp increase in the incidence of pathologies such as diabetes, obesity, and cardiovascular diseases. Current therapies usually fail to achieve complete healing.

Hyaluronidases (HYALs) are enzymes that degrade hyaluronan, an important constituent of the extracellular matrix, generating fragments of different sizes and with distinct roles. In the recent past, important biological properties of HYALs have been described, such as the ability to recruit mesenchymal-like cells to the lung, thereby reducing bleomycin-induced lung injury and fibrosis, involvement in cancer progression, thereby promoting tumor cell invasion, anti-inflammatory activity, and expression in keloid disease.

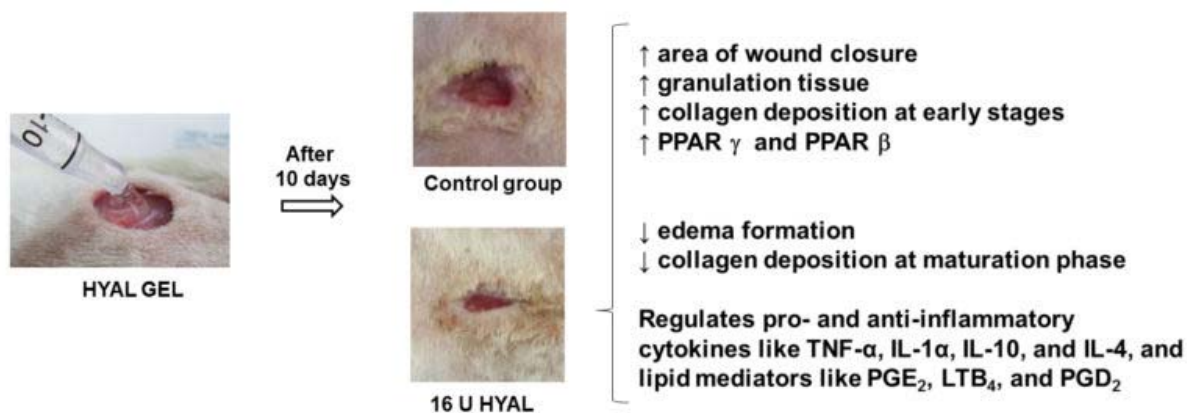


Fig. 1.

In this context, we investigated the influence and the mechanisms of action of HYAL from bovine testes HYAL in different stages of cutaneous wound healing in *in vitro* and *in vivo* assays. The ability of HYAL to stimulate fibroblast proliferation and/or migration was analyzed using the scratch assay. We demonstrated that HYAL increased the migration and proliferation of fibroblasts *in vitro* at low concentrations, e.g., 4 U of HYAL enhanced the cell number count by 70%.

HYAL induced faster and higher greater reepithelialization in *in vivo* full-thickness excisional wounds generated on the back skin of adult Wistar rats back skin already in the early phase on post-operation day 2 compared to that in the vehicle-control group. The area of wound closure, observed after topical application of 16 U of HYAL reached about 38% compared to 19% in the controls (Fig. 1).

Histological and biochemical analyses supported the clinical observations. Histological analysis of the skin revealed significantly increased cellularity in the wounds of the rats treated with 16 U of HYAL at days 2 and 7 compared to that observed in the controls. In addition, HYAL contributed to a balance between synthesis and deposition of collagen. However, after 21 days of wound treatment with 16 U of HYAL, the collagen content significantly reduced compared to that in the control group, which may have contributed to anti-fibrotic scar formation and better distribution and organization of collagen fibers. HYAL also regulated the inflammatory response by mediating pro- and anti-inflammatory cytokines such as TNF- $\alpha$ , IL-1 $\alpha$ , IL-10, and IL-4, and lipid mediators such as PGE<sub>2</sub>, LTB<sub>4</sub>, and PGD<sub>2</sub>. Moreover, HYAL increased the gene expression of peroxisome proliferator-activated receptors (PPAR)  $\gamma$  and PPAR  $\delta$ .

Under *in vivo* conditions, we were able to show that HYAL accelerates wound closure in the full-thickness excisional model in Wistar rats and provided further insights on how the wound-healing properties of HYAL can be explained at the molecular level. Thus, topical application of HYAL may have potential as a wound healing-promoting strategy for cutaneous injuries.

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## **Publication**

[Hyaluronidase modulates inflammatory response and accelerates the cutaneous wound healing.](#)

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