ACCELERATION OF WOUND HEALING BY A GROWTH HORMONE RELEASING HORMONE AGONIST IN THE AGED MURINE MODEL

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Introduction

In 2020, approximately 1 in 6 people in the United States were aged 65 years and older, totaling 55.8 million people nationally, and this number is expected to continue to rise with time.[1] This demographic often faces a variety of age-related ailments. As such, it is important that as medicine evolves it considers the critical need to care for these age-related diseases, including chronic wounds. With age, the complex, dynamic processes of wound healing become dysregulated which leads to non-healing, chronic wounds such as venous leg ulcers, diabetic foot ulcers, arterial ulcers, and pressure ulcers.[2,3] This impairment is due to age related factors including, but not limited to, structural changes in the skin, impaired keratinocyte proliferation and migration, attenuated fibroblast functions, decreased extracellular matrix production, metabolic dysfunction, and a diminished microvascular response.[2,3] Growth hormone releasing hormone (GHRH) modulates the release of growth hormone from the pituitary gland. However, the significance of its biologic activity extends beyond its endocrine functions. GHRH and its analogs affect a variety of tissue types in an autocrine/paracrine fashion.[4] The current study follows a previous study by our group which demonstrated that the GHRH agonist MR-409 significantly accelerated wound healing in 12-weeks old mice.[5] The present study aims to investigate if the therapeutic benefits of MR-409 apply to the aged murine model.

Materials & Methods

Thirty 78-weeks old male C57/BL6 mice were purchased from Jackson Laboratory (Bar Harbor, ME, USA). All animal care and use procedures were approved by the University of Miami Institutional Animal Care and Use Committee.

After anesthesia, one wound was made per animal. To evaluate effects of MR-409 on wound healing, 3 groups of 10 animals each were treated topically with the following: Control, MR-409 1 µg/day, or MR-409 10 µg/day for 12 days. Mice were observed daily to assess wound healing and closure, and 8 mm skin punch biopsies were obtained on day 12 for histologic evaluation.

Results

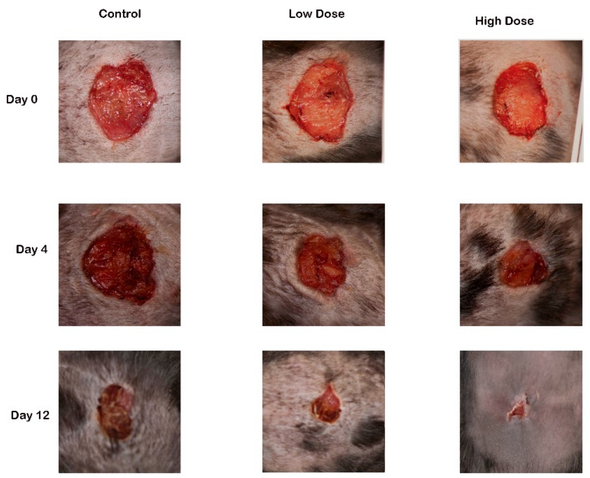

Figure 1. Digital images of the wounds at 0, 4 and 12 days after treatment with 1 µg/day or 10 µg/day of MR-409, or vehicle

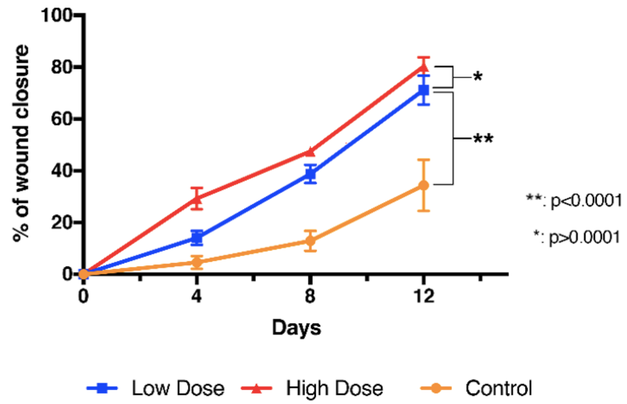

Figure 2. Photographs were taken on days 0, 4, 8, and 12 and analyzed to evaluate the percentage of wound closure. Error bars represent SEM; **p<0.0001 and *p>0.0001.

Results Cont'd

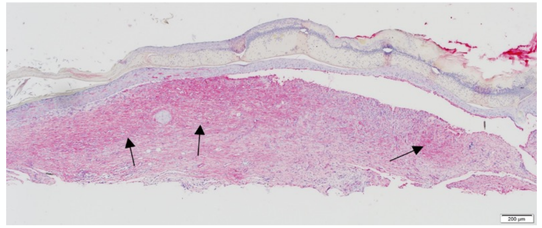

Figure 3. There are areas highlighted in the wound area (arrows) which indicate an elevated presence of myofibroblasts. The arrangement of these collections suggest that they are involved in contracting the wound

Conclusion

In this study, we provided evidence that MR-409 treatment accelerated wound healing on 78-weeks old, aged mice in a dose-dependent manner. GHRH-R activation *in vivo* likely accelerated the differentiation of fibroblasts into contractile myofibroblasts which aided in closing the wounds. Under high dose MR-409 treatment, the wounds on 78-weeks old aged mice required 12 days for near-complete closure whereas closure of the same wounds only required 10 days in our previously published study of wound healing on 12 weeks old mice.[5] This shows that our aged skin model does in fact reflect the age-related cutaneous changes which influence wound healing. Our group also demonstrated separately that MR-409 synthetic GHRH analogue is a potent stimulator of senescent fibroblast survival, proliferation, mobility, and collagen synthesis. These mechanisms likely underlie the acceleration in wound healing observed in the present study.

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