Collagen and Extracellular Matrix Remodeling: Understanding the role of Collagen in the Remodeling of the Extracellular Matrix During Wound Repair

Mahajan, Naresh PhD*; Alexa Rivera del Rio Hernandez MD; Egro, Francesco M. MBChB, MSc, MRCS; Rubin, J. Peter MD, FACS, MBA; Ejaz, Asim PhD
University of Pittsburgh, Pittsburgh, PA, USA

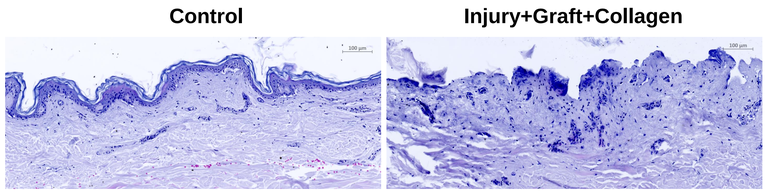
INTRODUCTION

Wound healing is a complex biological process involving hemostasis, inflammation, tissue proliferation, and remodeling, which ultimately restores skin integrity. Immune cell recruitment to the site of injury is crucial for initiating inflammation, controlling infection, and facilitating tissue repair. Collagen, a vital extracellular matrix (ECM) component, plays a key role in wound healing by providing structural support and influencing cellular behavior and immune response. While collagen's potential to enhance tissue repair is well-documented, its role in immune cell infiltration during wound healing remains less explored. This study investigates the impact of collagen powder on immune cell recruitment and wound healing using an ex vivo human skin model.

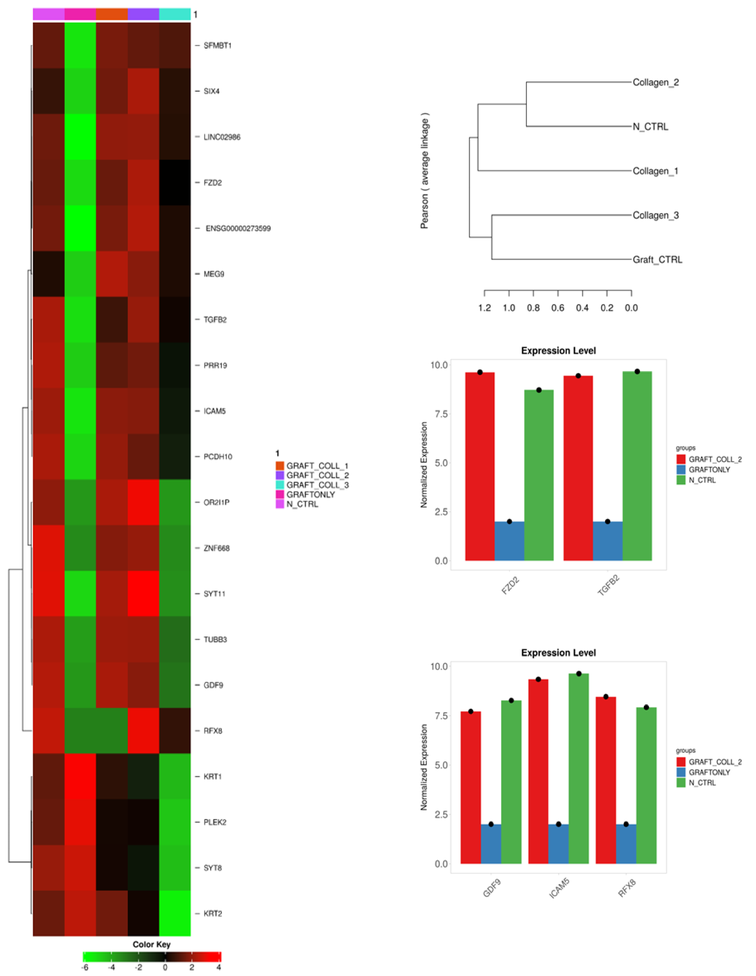
MATERIALS & METHODS

Human skin flaps were maintained on a perfusion system to simulate in vivo conditions and subjected to controlled wound creation using a dermatome. Three experimental groups were established: (1) Injury + Graft Only: epidermal graft without collagen treatment, (2) Injury + Graft + Collagen: epidermal graft with collagen powder applied to the wound bed before graft placement, and (3) Control: no injury or grafting. Wound sites were bandaged and left undisturbed for 10 days. Biopsies were then taken for histological analysis and RNA extraction. Hematoxylin and eosin (H&E) staining was performed to evaluate immune cell infiltration and tissue integration.

RESULTS



H&E stained images of Control and Injury + Graft + Collagen groups.



Heatmap displaying gene distribution across groups. Linkage map illustrating clustering of groups. Differentially expressed genes showing significantly increased expression in the Graft + Collagen group compared to the Graft Only and Control groups.

RESULTS

- Collagen-treated wounds demonstrated increased immune cell infiltration and active extracellular matrix (ECM) remodeling, as observed in H&E-stained tissue sections.
- Collagen enhanced wound healing by promoting a more uniform and mature matrix organization. RNA sequencing analysis identified the top 20 deregulated genes, and Gene Ontology (GO) enrichment revealed significant involvement in biological processes such as membranous septum morphogenesis.
- Notably, genes associated with tissue repair and ECM regulation, including *TGFB2* and *FZD2*, were upregulated in the collagen-treated group, highlighting collagen's regulatory influence.
- The gene expression profile of collagen-treated tissues closely resembled that of healthy skin, in contrast to the collagen-free group.
- Furthermore, the expression of key regenerative markers, including *GDF9*, *ICAM5*, and *RFX8*, was restored with collagen treatment, supporting its role in promoting tissue regeneration.

CONCLUSIONS

- Collagen treatment improves wound healing by promoting immune cell infiltration and extracellular matrix (ECM) remodeling, leading to better matrix organization and a more mature tissue structure. It upregulates regenerative genes like ***TGFB2*** and ***FZD2***, which play critical roles in tissue repair and ECM regulation.
- The treatment also restores the expression of markers such as ***GDF9***, ***ICAM5***, and ***RFX8***, aligning gene profiles of treated wounds with those of healthy skin. These findings highlight collagen's therapeutic potential for accelerating tissue regeneration, restoring homeostasis, and advancing wound care strategies.

Collagen enhances ECM remodeling, immune infiltration, and regenerative gene expression, accelerating wound healing and restoring skin homeostasis, with potential for advanced wound care solutions.