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WHAT'S NEW

Vitamin A metabolism in fibroblasts identified as a key pathway in wound healing

This section is a contribution from the SKINTEGRITY.CH interdisciplinary research consortium. The collaborative work was performed by Dr. Till Wüstemann and colleagues, under the lead of SKINTEGRITY.CH co-chair Prof. Sabine Werner with colleagues from the consortium as well as colleagues in Germany and France. Dr. Wüstemann recently received the consortium's Young Investigator Award for his work.

Maarten Schledorn
Scientific coordinator SKINTEGRITY.CH

Till Wüstemann. *Wound healing is a highly coordinated process that restores tissue integrity after injury. During the proliferative phase, fibroblasts migrate into the wound bed, deposit extracellular matrix, and shape the granulation tissue that supports keratinocyte migration and reepithelialization. While fibroblast heterogeneity has been studied extensively, their metabolic adaptations during repair have remained largely unexplored. In our study, we set out to define the metabolic landscape of wound fibroblasts in an unbiased manner. By integrating transcriptomics, metabolomics, and proteomics, we identified retinol (vitamin A) metabolism as a central pathway activated during skin repair.*

A multiomics view of wound fibroblasts

We isolated Pdgfrα-positive fibroblasts from unwounded skin and from day-5 excisional wounds in mice, corresponding to peak granulation tissue formation. RNA sequencing and untargeted metabolomics comparing wound fibroblasts with normal skin fibroblasts revealed that retinol metabolism was one of the most strongly impacted pathways.

Wound fibroblasts showed elevated levels of retinol and increased expression of genes involved in retinol uptake and intracellular transport, including *Stra6*, *Rbp1*, *Rbp4*, and *Crabp1*. At the same time, enzymes mediating the conversion of retinal to retinoic acid were downregulated, suggesting tight control of downstream signaling. Analysis of published single-cell datasets confirmed that this pathway is particularly active in fibroblasts during the proliferative phase of healing.

Serum retinol drives fibroblast gene expression

Because fibroblasts in wounds are exposed to serum components, we asked whether circulating factors induce this transcriptional program. In cultured primary human fibroblasts, serum robustly upregulated retinol metabolism genes. Removal of lipophilic serum components markedly reduced this effect, which could be restored by adding retinol.

Direct treatment with retinol or retinoic acid similarly induced key pathway genes, including the retinoic acid receptor *RARB*, whereas inflammatory stimuli had only minor effects. These findings identify retinol itself as a major driver of the wound-associated gene expression changes.

Mild vitamin A deficiency impairs reepithelialization

To test the functional relevance of this pathway, we examined a mouse line

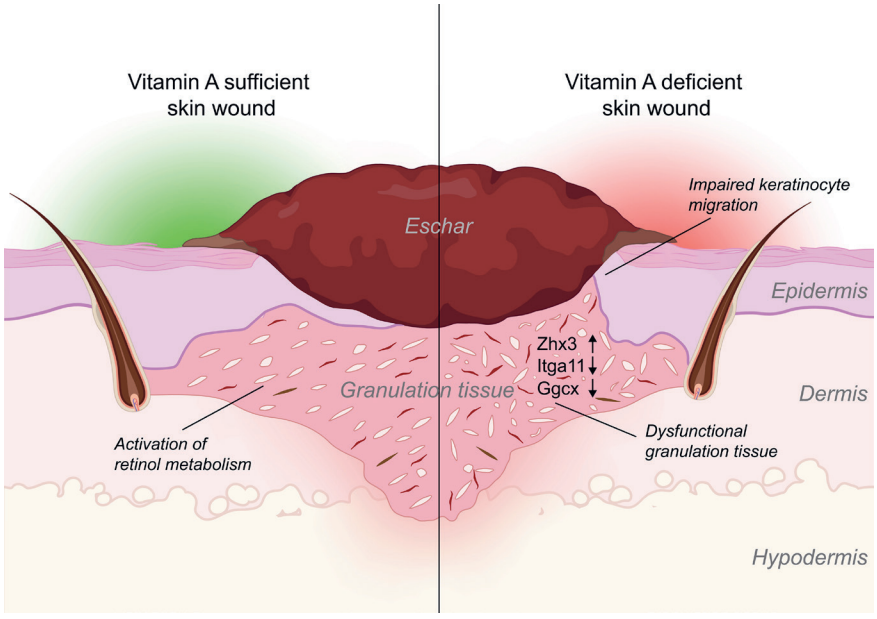

Figure 1: Schematic representation of a skin wound without and with a Vitamin A deficiency.

with a genetic deletion of *Stra6*, the receptor facilitating retinol uptake. However, this deletion did not cause major wound healing defects, indicating that alternative uptake mechanisms are sufficient under physiological conditions.

Instead, we subjected mice to a vitamin A–deficient (VAD) diet prior to wounding. Although the deficiency was mild and did not cause systemic illness, VAD-fed mice exhibited delayed wound closure and reepithelialization. While wound contraction and keratinocyte proliferation were not significantly impaired, we observed a specific failure in directional migration toward the wound center. As illustrated in *Fig. 1*, vitamin A deficiency resulted in dysfunctional granulation tissue and misdirected keratinocyte migration.

Altered granulation tissue composition

While histology revealed no dramatic structural abnormalities, quantitative proteomics uncovered reduced levels of several fibroblast-enriched proteins in VAD-treated wounds, including Itga11, Zhx3, and Ggcx.

Itga11, a collagen-binding integrin, is involved in fibroblast–matrix interactions and myofibroblast differentiation. Consistently, we detected lower levels of α–smooth muscle actin, suggesting impaired myofibroblast differentiation and altered matrix organization. Such changes likely compromise the structural environment required for efficient keratinocyte migration.

Together, our data identify retinol metabolism as a key pathway in wound fibroblasts and demonstrate that even mild vitamin A deficiency can impair tissue repair by altering fibroblast function and granulation tissue quality. These findings highlight metabolic regulation as an important lever for improving healing outcomes.

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Reference

Wüstemann T, Madzharova E, Wietecha MS, Ghyselinck NB, Höring M, Liebisch G, Zamboni N, Auf dem Keller U & Werner S (2025). A multiomics analysis identifies retinol metabolism in fibroblasts as a key pathway in wound healing. JCI Insight, 10(22), e194188. https://doi.org/10.1172/jci.insight.194188