Fibroblast-specific overexpression of collagen XII leads to delayed wound healing in skin

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Background

Collagen XII is a fibril-associated collagen with interrupted triple helices (FACIT) expressed in all stiff connective tissues that, together with other extracellular matrix (ECM) proteins, decorates larger collagen fibrils. It thus has the potential to influence the mechanical properties of the ECM by interconnecting structural molecules, transmitting signals between matrix and cells or by modulating the bioavailability of growth factors. In humans, increased collagen XII deposition has been observed in many pathological conditions involving fibrotic stiffening of the tissue like in systemic sclerosis (SSc) lesions and hypertrophic scars, indicating its vital role during ECM reestablishment and homeostasis in these tissues.

We aim to study the roles of collagen XII deposition during physiological and pathological events in skin that involve remodeling of the ECM, using as model wound healing and fibrosis.

Questions

- How can altered amounts of collagen XII affect skin homeostasis?
- What is the role of collagen XII during skin repair?

Differential deposition of collagen XII in homeostatic and challenged skin

Increased deposition of collagen XII upon development of fibrosis

Accumulation of collagen XII upon wound healing and scar formation

Collagen XII mutant skin exhibits an inconspicuous morphology and tissue stability

Fibroblast-specific collagen XII overexpression Global ablation of collagen XII

Collagen XII has a dose-dependent effect on wound healing

Collagen XII overexpression causes delayed wound healing and higher cell density in the granulation tissue

Collagen XII overexpressing wounds show higher macrophage density but normal myofibroblast numbers

Wound macrophages from collagen XII overexpressing mice have a more early, M1-like gene expression pattern

Collagen XII substrate does not alter macrophage polarization but causes preferential adhesion of M1 polarized macrophages

Working model & Summary

In wild type mice, we observed an increased deposition of collagen XII into the granulation tissue after injury that persisted throughout the healing process. Deletion or overexpression of collagen XII had no effect on morphology and mechanical properties of unchallenged skin. After wounding, the overexpressing mouse model showed delayed healing with enlarged, highly cellularized granulation tissue. Overall cell proliferation and macrophage numbers were increased but the number of proliferative macrophages compared to total amount was unaltered. Myofibroblasts were not affected by overabundance of collagen XII. Gene expression profiling of wound macrophages showed upregulation of early wound macrophage marker genes in the collagen XII overexpressing mice. *In vitro* interaction studies between collagen XII and macrophages revealed that only M1 polarized macrophages were able to adhere to collagen XII, but not unstimulated and M2 polarized macrophages and polarization was not altered by contact to collagen XII.

This led to the hypothesis that over-production of collagen XII favors a selective adhesion of M1-like, pro-inflammatory early wound macrophages leading to an overall delay in resolution of the inflammatory response.