

## Abstract

Fibrillar collagens form the structural and organizational framework for most connective tissues including skin. The supramolecular architecture of the collagen network in normal skin is severely altered in fibrotic diseases. Cells embedded in such an altered matrix perceive mechanical tension which modulates their inherent behavior and leads to dysfunction. Recently, our group and others observed high COMP expression in skin lesions of patients with the fibrotic disease systemic sclerosis, while no COMP was noted in healthy human skin. So far, the function of COMP in skin and related fibrotic diseases remains unknown.

This study demonstrated for the first time that COMP is a component of healthy human skin with a characteristic linear localization in the papillary dermis immediately below the epidermis. COMP is expressed by dermal fibroblasts but not epithelial cells. This study identified collagens XII and XIV as new binding partners for COMP, which closely associate with major collagen I fibrils. The physiological relevance of these interactions was validated by co-localization of COMP with these proteins *in vivo* in healthy human skin.

It is postulated that COMP may function as an organizer of the fibrillar collagen network by binding collagen I fibrils via FACIT collagens XII and XIV and thereby may contribute to the supramolecular arrangement of the dermal collagen network. Further, deposition of all three proteins in anchoring plaques suggested a potential role in maintaining structural integrity of the dermo-epidermal junctional zone.

Besides sclerosis, augmented COMP deposition was also detected in fibrotic plaques underlying chronic, non-healing wounds, and in the fibroproliferative stroma surrounding invasively growing epithelial tumors. These results suggest induced expression of COMP as a characteristic hallmark of fibrotic connective tissue in general.

One distinguished feature of fibrotic diseases is abundance of activated fibroblasts. Stimulation of fibroblasts either with exogenous TGF $\beta$ 1 or via direct contact with carcinoma cells resulted in increased COMP deposition, demonstrating a close correlation of COMP induction with fibroblast activation. A further characteristic unifying feature of fibrotic diseases is a densely packed altered collagen matrix exerting increased biomechanical forces. Aberrant deposition of COMP in fibrotic skin is proposed to alter the dermal collagen suprastructure by disturbing interactions of COMP with fibrillar type I collagen and its associated FACIT collagens XII and XIV, thereby contributing to higher density and increased mechanical tension in affected skin areas, which likely contributes to fibroblast activation. In this way, COMP is thought to be involved in sustaining fibrotic reactions.