

The properties of connective tissues vary with biological demand: Thus, the extracellular matrix (ECM) in the skin has to bear tensile forces, while the ECM in cartilage needs to resist compression forces and mechanical pressure. These characteristic properties are conferred by the specific biochemical composition of the matrices, which in turn determine their structural properties.

COMP is a characteristic and abundant component of cartilage ECM in which it interacts with the collagen network. By virtue of its pentameric structure COMP is capable of binding with up to 5 collagen molecules, thereby controlling collagen fibril formation, which strongly depends upon the molar ratio between collagen and COMP.

In healthy skin, COMP is detected in subepidermal regions below the basement membrane and transiently in close proximity to hair follicles. Fibrotic alterations in the dermal ECM are characterized by structural changes of the collagenous matrix which coincide with skin stiffening. These processes are accompanied by changes in the molecular composition of the ECM, and large amounts of COMP are deposited into the fibrotic matrix.

The aim of this dissertation was to characterize which processes contribute to the deposition of COMP into dermal ECM, and whether these are responsible for the structural alterations of fibrotic ECM. These questions were addressed by employing genetically modified mouse models.

Deposition of COMP into the dermal ECM was detected not only in fibrotically altered dermis but also in healthy skin during hair follicle morphogenesis. In both situations enhanced COMP deposition was induced by mechanical forces within the skin, potentially attempting to maintain the integrity of the collagen matrix. In line with this concept, the collagen matrix of COMP-deficient mice was altered with severely reduced spacing between fibrils and with altered fibril morphology. Dermal fibroblasts derived from COMP-deficient mice exhibited ER stress and disturbed protein secretion, which might explain the reduced production of ECM components by these mice upon induction of experimental skin fibrosis.

A mouse line was generated with constitutive, fibroblast-restricted overexpression of COMP. This model was used to investigate whether deviations from the correct molar ratio between COMP and collagen I might lead to changes in the supramolecular organization of the dermal ECM similar to those seen in fibrotic disorders. Ultrastructural analysis indeed revealed morphological abnormalities in the skin of overexpressing mice resembling fibrotic dermis.

Collectively these results suggest that a precisely controlled amount of COMP is required to maintain collagen fibril spacing within the dermal ECM. Secretion of ECM components by COMP-deficient fibroblasts would result in structural matrix defects; in this situation fibroblasts would retain structural ECM components and ER stress builds up.

Development of fibrosis is in part due to fibroblast activation by e.g. TGF β and interleukin-13. These cytokines were shown to enhance COMP expression, thereby leading to aberrant molar ratios between COMP and collagen I and to disturbed collagen I fibrillogenesis. Such alterations were detected in fibrotically altered dermis and in the dermal ECM of COMP overexpressing mice.

This work showed for the first time that COMP does not only regulate collagen fibrillogenesis but has a major impact on the structure of the collagen network and controls protein secretion of fibroblasts. Variations in the expression level of COMP result in an altered structure of the extracellular matrix and are responsible for a characteristic fibrotic arrangement of the collagen fibrils.