Abstract

Matrilin-3 is a cartilage specific, non-collagenous extracellular matrix protein and one of the four members of the matrilin family. Matrilin-3 is known to act as an adapter protein, because it interacts with collagens and non-collagenous proteins, e.g. COMP to form a unique fibrillar network. Recent studies show, that matrilin-3 also has regulatory functions. Mutations in matrilin-3 lead to severe skeletal diseases, such as chondrodysplasias and osteoarthritis. This dissertation focuses on the T298M mutation (human T303M), which is located in the first EGF-domain of matrilin-3 and is associated with the development of hand osteoarthritis and spinal disc degeneration in humans. Bioinformatic studies predicted an altered secondary structure in the mutated EGF-domains which could result in a disturbance of protein function. The wildtype and mutated EGF-domains only be sufficiently expressed only in a tandem of more than two domains. The recombinant mutant proteins showed a reduced mobility in SDS polyacrylamide gel electrophoresis.

Since the underlying pathomechanism is unknown, a matrilin-3 T298M knock in mouse model was generated to investigate the influence of the T298M mutation on the development of osteoarthritis. Studies of primary chondrocytes revealed a pericellular localization of matrilin-3 in both wildtype and T298M mutant. Since loading also plays an important role in development of osteoarthritis, investigations were performed not only on the forepaw but also on the knee joint. Thereby, an altered tissue distribution of matrilin-1 and matrilin-3 was detected in both tissues of two weeks old T298M mice. Analysis of the unchallenged forepaw and knee did not show signs of osteoarthritis, but more pronounced osteoarthritis could be detected after destabilization of the medial meniscus (DMM) in knee joints in T298M mice compared to wildtype mice. Moreover, in unchallenged T298M mice altered fibrillogenesis within the articular cartilage of the tibia of could be observed. Furthermore, measurements of the biomechanical properties revealed an increased stiffness of the tissue and a premature ossification of the secondary ossification center of the tibia was observed. Moreover, for the first time the involvement of matrix metalloproteinases (MMPs) in the proteolytic processing of matrilin-3 protein was detected

In summary, these results display the impact of the matrilin-3 T298M mutation on the development of osteoarthritis and provides insight into its underlying pathomechanism.