Osteoporotic Changes and Alteration of Osteoblast and Osteoclast Distribution in Aging Syndecan-4 Deficient Mice

Introduction:
Osteoporosis today turns out to be one of the most cost intensive musculoskeletal diseases worldwide. Recent research contributes to our understanding of the regulatory mechanism of bone biology and osteoporotic pathogenesis, but many details remain unclear. In this study, a member of the transmembrane heparan sulfate proteoglycan family of Syndecans, Syndecan-4, appears to function as a co-regulator in bone formation and remodelling. Syndecans play important roles in cell adhesion and cell communication by serving as receptors for both extracellular matrix molecules and growth factors. It has been demonstrated that Syndecan-4 knockout mice show a delay in wound healing and that Syndecan-4 is involved in cartilage breakdown during osteoarthrosis. Recently we showed an osteoporotic phenotype with impaired bone stability and reduced trabecular bone structure of 12 month old Syndecan-4 deficient mice. No changes in proliferation, differentiation or functionality of isolated osteoblasts in vitro were found resulting from the lack of Syndecan-4.

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Materials and Methods:
C57BL/6 females, wild type (wt) and Syndecan-4 knockout (Sdc4−/) (4 (n=10)/12 (n=10)/18 (n=5) month each), were investigated. Spines and right femurs were dissected in paraffin. Sections were used for histochemical staining of osteoblasts and osteoclasts. A look onto the cellular level of bone revealed further consequences of a Syndecan-4 deficiency in young mice at the age of 4 month.

Results:
Biomechanical testing: The results of the torsional testing of the femurs demonstrate an increase in maximum torque between 4 month and 12 month and a striking decrease within 12 and 18 month in both genotypes. But compared to wild type the maximum torque measured for the Syndecan-4 knockout group is lower (highly significant for group)

Additionally, distribution of osteoclasts in this tissue was significantly different than in wild type bones. Osteoclasts were found more within the region of the basis of the vertebra body whereas in wild type cells they were scattered across the whole section. Similar results were found concerning osteoblasts in Syndecan-4 deficient vertebra although the differences were not that clear. The cell density of bone building cells was reduced in Sdc4−/− cells about 16% (0.38 mm/mm²) compared to wild type (0.45 mm/mm²) and osteoblast distance to the vertebra basis was lower (7%).

Discussion: At first sight, biomechanical stability of bone was not affected strikingly by the lack of Syndecan-4 in young and adult mice. Histomorphometric analyses revealed age dependant differences especially concerning trabecular bone structure. Trabecular number and thickness was reduced in older animals compared to wild type. Cortical thickness was higher in young mice which may give reason for the missing differences between wild type and knockout group in biomechanical measurements. A lowered trabecular and cortical thickness in old Sdc4−/− animals seemed to be compensated partly by a constant trabecular number, but bone stability was significantly reduced compared to old wild type mice. The lack of Syndecan-4 influenced bone structure during growth and our data supposed that compensatory mechanisms were used to assure a right bone development and bone stability as far as possible. During aging these mechanism slowly fail and effects on bone structure become visible.

A look onto the cellular level of bone revealed further consequences of a Syndecan-4 deficiency in young mice at the age of 4 month. Determination of the amount and distribution of osteoclasts and osteoblasts showed a reduction of both bone building and absorbing cells which was not expected from experiments with isolated cells before. Additionally, an uncommon vertebra basis orientated localization of the cells was found. These results suggest a reduced remodelling taking place within the center of the bone and causing changes in bone structure like more, but thinner trabeculae. This strongly indicate an important function of Syndecan-4 within the complex interaction of bone cells and tissue.

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