

THE BIGLYCAN/FIBROMODULIN DOUBLE-DEFICIENT MOUSE: CHARACTERIZATION OF A NEW ANIMAL MODEL OF OSTEOARTHRITIS

L. Ameye^{1,2} & M.F. Young²

¹ Nestlé Research Center, Lausanne, Switzerland

² Craniofacial and Skeletal Diseases Branch, National Institute of Dental and Craniofacial Research, National Institutes of Health, Bethesda, Maryland, USA

INTRODUCTION: Biglycan and fibromodulin are two extracellular small leucine-rich proteoglycans co-expressed in tendon, cartilage and bone [1]. Collagen fibrils in tendons from mice deficient in biglycan and fibromodulin are structurally and mechanically altered resulting in unstable joints. As a result, the mice develop successively and progressively: gait impairment, ectopic tendon ossification and severe premature knee osteoarthritis (OA) [2]. Forced use of the joints increases ectopic ossification and OA in the double-deficient mice further indicating that structurally weak tendons may cause the phenotype. In the knees, the articular cartilage lesions recapitulate the histological features of human OA. In order to further characterize and validate the use of the biglycan/fibromodulin double deficient mouse as an animal model of OA, other joints were processed for histology and an immunohistochemical characterization of the cartilage lesions was initiated.

METHODS: Knees, hands, feet, hips, shoulders, and elbows were fixed in Z-fix, decalcified in Immucal and processed for histology. Immunostaining for cartilage oligomeric matrix protein (COMP), decorin and type II collagen was performed on wild type and double deficient knees. Two and 6 month-old knees, corresponding respectively to an early and an advanced stage of the disease in the double deficient mice, were analyzed.

RESULTS: All the observed joints develop OA although the severity of OA differs from joint to joint, with knees joints being affected first and most severely.

In two month-old wild-type knees, the expression of COMP was low and restricted to the extracellular matrix above the tidal mark. Comparatively, this area was more strongly stained in the two month-old double deficient knees. In addition, in the double deficient knees, the calcified matrix and its chondrocytes were also stained but at a lower level. At 6 months, the level of expression of COMP had increased in the wild-type mice but decreased in the double deficient mice.

Type II collagen stained the whole articular cartilage matrix and the chondrocytes in wild-type knees. In double deficient knees, type II collagen was not detected at the articular surface at 2 months, and by 6 months its absence had spread to the matrix surrounding the chondrocytes. Similar, but not identical, patterns of expression were observed for decorin.

DISCUSSION & CONCLUSIONS: Our data demonstrate that the biglycan/fibromodulin double deficient mouse develop polyarthritis. Because each joint develop OA at its own time and pace, the biglycan/fibromodulin double deficient mouse will provide a great deal of flexibility as an animal model to test the *in vivo* actions of molecules on OA. In addition, the immunohistochemical results reported here are similar to immunostainings performed on samples from natural OA and other animal models. The transient increase in COMP level observed here has also been reported in Dell mice, a transgenic model of OA and in natural OA in horses. Superficial loss of decorin occurs in human OA and the collagen loss pattern reported here mimic the degradation pattern of type II collagen in human OA. Taken together, our data support the use of the biglycan fibromodulin deficient mouse as an animal model of OA.

REFERENCES: ¹ L. Ameye and M.F. Young (in press) *Glycobiology* Mice deficient in small leucine-rich proteoglycans. Novel *in vivo* models for osteoporosis, osteoarthritis, Ehlers-Danlos syndrome, muscular dystrophy and corneal diseases. ² L. Ameye, D. Aria, K. Jepsen et al. (in press), *FASEB J* Abnormal Collagen Fibrils in Tendons of Biglycan/Fibromodulin Deficient Mice Lead to Gait Impairment, Ectopic Ossification and Osteoarthritis.

ACKNOWLEDGEMENTS: We thank Drs. Tianshun Xu and Ake Oldberg (Dept. Cell & Molecular Biology, Lund University, Lund, Sweden) for generating and providing the single deficient mice used to generate the biglycan/fibromodulin double deficient mouse.