Targeted Disruption and Aging-related Loss of the Cartilage Surface-Specific Protein HMGB2 Leads to Early Onset Osteoarthritis

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Introduction: Osteoarthritis (OA) typically begins with an aging-related disruption of the articular cartilage surface, followed by progressive destruction and loss of cartilage. In normal articular cartilage the superficial zone possesses 3.5 fold more cells compared to radial zone and a decrease in cell number, along with surface fibrillation, are the earliest indicators of OA development (1). However, the mechanisms leading to the aging-related surface degeneration remain to be determined. In this study we demonstrate that the chromatin protein HMGB2 is uniquely expressed in chondrocytes in the superficial zone of articular cartilage and determine the impact of Hmgb2 deficiency on cartilage homeostasis and OA pathogenesis.

Materials and Methods: Immunostaining was used to assess HMGB2 expression in human articular cartilage from younger (17-39 y.o.) and older (61-85 y.o.) donors (N=6); and in C57Bl/6J mouse knee joints at 3, 6, 9 and 15 months of age (N=6), respectively. Using adult Hmgb2-/- mice at 3, 6, 9, 12 months old, knee joints were examined by safranin O staining and OA grades were evaluated by Mankin scoring. Cell death in articular cartilage was examined by immunohistochemistry for apoptosis markers active caspase-3 and PARP-p85 and compared with the matrix degradation markers MMP-3 and MMP-13. Superficial zone protein (SZP) in murine joints was examined by in situ hybridization.

Results: In normal human and murine knee articular cartilage HMGB2 is exclusively expressed in the superficial zone (Fig. 1). In both species there is an aging-related decline in HMGB2 expression, ultimately leading to its complete absence and this is associated with the development of structural lesions in the cartilage surface. Mice with a targeted disruption of the HMGB2 gene have normal development of the skeleton and joints, which is a distinct phenotype from Hmgb1-/- mice (2). However, HMG2 deficient mice show early onset of osteoarthritis joint pathology. In Hmgb2-/- mice there is increased PARP-p85 at 6 months associated with a reduction in cellularity in cartilage surface (Fig. 2). MMP-3 is increased in Hmgb2-/- at 6 months and reduced at 9 months while MMP-13 is strongly expressed at 9 months. In Hmgb2-/- mice there is also a reduction and early loss of SZP (Fig. 3).

Discussion: These findings identify HMGB2 as a factor specifically expressed in superficial zone chondrocytes and required for cell survival and cartilage homeostasis. The aging-associated loss of HMGB2 may represent a novel trigger for the onset of OA. The HMG2 deficient mouse represents a novel OA model that recapitulates central features of the human disease.


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