Introduction: Cartilage is primarily composed of aggrecan and type II collagen. When type II collagen is cleaved by collagenases, the triple helix unwinds generating gelatin. Gelatin is then cleaved by gelatinases including matrix metalloproteinase-2 and -9 (MMP-9). MMP-9 has also been described as type IV collagenase of neutrophils and has a MW of 92kD in most species, but additional base pairs in exons 9 and 13 making the MW 103kDa in the mouse. MMP-9 is broadly expressed in many normal and diseased tissues and has a multitude of functions including cleavage of gelatin, structural proteins, type IV collagen of basement membranes, and antiproteases. MMP-9 can also regulate cytokines and matrix-bound growth factors affecting a change in cell functions. MMP-9 is expressed by articular chondrocytes and the levels are up-regulated in osteoarthritis (OA). In order to investigate the role MMP-9 plays in the pathogenesis of OA, MMP-9 KO mice were challenged in a surgically-induced model and evaluated via histology.

Materials and Methods: MMP-9 KO mice on various backgrounds (derived from the same initial mouse1) along with their respective wild-type (WT), underwent Destabilization of the Medial Meniscus (DMM) at 10 weeks of age. The FVB/n MMP-9 and WT mice were obtained from Jackson Laboratories (Bar Harbor, ME). 129SvEv MMP-9 KO mice were also evaluated and backcrossed for 8 generations onto a BALB/cAnNTac background. All mice were sacrificed at 8 weeks after surgery and Safranin-O histology evaluated throughout the entire tibiofemoral joint via a semi-quantitative system where greater summed scores reflect a greater burden of degenerative cartilage changes.

Results: The MMP-9 KO on the FVB/n background developed significantly more OA than the WT controls and also developed spontaneous OA. Both the 129SvEv and BALB/c lines of mice showed a contrasting result to the FVB/n, with decrease in OA severity in the MMP-9 KOs relative to their respective WTs. Four of 18 MMP-9 KO mice on the BALB/c background had evidence of cruciate degeneration and severe medial MTP osteophytes and were removed from the analysis (note: discarded scores were not higher than the group mean). None of these abnormalities were observed with the MMP-9 KO on the 129SvEv background.

Discussion: This study indicates that MMP-9, and possibly other compensatory enzymes or natural inhibitors, interact with the genetic background to produce differences in OA susceptibility. Conflicting observations of exacerbation2 and protection3 in an OVA-induced asthma model have also been reported for the MMP-9 KO mouse with the same common origin1 (as used in our studies) that have partly been attributed to differences in background2. These observations indicate that the results from any KO study should be interpreted with caution if only one background strain is evaluated. Alternately, if further evaluations show that the results in the FVB/n are not representative of the majority of mouse strains, it may indicate that the FVB/n strain should be avoided as a background for investigating KOs in OA models.

The current study also found that the level of OA observed in the BALB/c mice is the highest we have observed for any strain in the 8-week DMM model of OA. This is extremely interesting since the BALB/c mouse is also very susceptible to models of RA. Further studies are required to elucidate the commonality of mechanisms in this strain, and how they vary with other strains.


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