Evidence for articular cartilage regeneration in MRL/MpJ mice

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Introduction: Articular cartilage injury and disease in humans is challenging to repair effectively. Existing treatments are often invasive, expensive, vary in outcome and induce repair with fibrocartilage. Regeneration, instead of repair, involves a complete functional restoration of the lost tissue. The regenerative capacity of mammals has been explored through the years and recently Clark et al. (1998) were the first to describe ear punch regeneration in the MRL/MpJ strain of mouse. MRL/MpJ mice show distinct and rapid 2mm through-and-through ear hole closure compared to other strains. Notably, they are able to form islands of genuine newly synthesized cartilage, rather than an extension of existing cartilage1. The mechanisms (and limitations) involved in the healing capacity of MRL/MpJ mice are currently being explored. In an effort to expand our current knowledge and refine our abilities in correcting articular cartilage defects in humans, we studied whether MRL/MpJ mice have an enhanced ability to regenerate full thickness articular cartilage lesions.

Materials and Methods: Articular cartilage lesions were introduced into 8 week old MRL/MpJ and C57Bl/6 mice. Full thickness osteochondral lesions were made in the trochlear groove with a 27g needle penetrating through the articular cartilage and into the subchondral bone. A transverse, partial thickness lesion that did not breach the subchondral bone was made distal to the full thickness lesion on the same knee using an ophthalmic scalpel. At 6 and 12 weeks post-surgery, the knees were harvested, fixed, decalcified, paraffin embedded and serial sagittal sections cut. Average histology scores were generated by two observers blinded to section identity using the worst lesion found in serial sections. The total histology score is the sum of individual parameters including cell morphology, toluidine blue staining, cartilage thickness, surface regularity and extent of integration of new matrix with matrix flanking the wound, as previously described2. Partial thickness lesions were also scored. For histological and immunohistochemical analyses, serial knee sections were stained with 0.03% toluidine blue solution or labeled with mouse anti-chick collagen II (II-II6B3; Developmental Studies Hybridoma Bank), respectively, and visualized by fluorescent microscopy.

Results: Analysis of the full thickness wounds at the 6 week time point revealed that both C57Bl/6 and MRL/MpJ male and female mice had formed proteoglycan rich deposits surrounded by chondrocyte-like clusters of cells within the lesion. C57Bl/6 mice had fewer cells and less proteoglycan deposition overall and MRL/MpJ mice had significantly better total histopathology scores (p = 0.01; data not shown). By 12 weeks the majority of C57Bl/6 males and females lacked significant collagen II and proteoglycan deposition while MRL/MpJ mice had undergone a robust wound repair response (Fig.1).

The MRL/MpJ females, who demonstrated superior healing initially at 6 weeks, were similar to C57Bl/6 mice at 12 weeks. In contrast, the MRL/MpJ males had maintained their cartilaginous repair tissue at 12 weeks and, despite variation in the healing capacity in each strain, had significantly better histopathological cartilage repair (Fig.2).

There was no evidence of repair of the partial thickness cartilage lesions in any strain or sex at any time point.

Discussion: To date, the MRL/MpJ strain of mice has shown a large range of regenerative capacity, depending on which tissue is injured and how the injury is made1,2,3,4,5. We have for the first time investigated articular cartilage regeneration in MRL/MpJ mice. MRL/MpJ mice demonstrated superior cartilage regeneration than their C57Bl6 counterparts however the response was sexually dimorphic. While both sexes showed chondrogenesis at 6 weeks, only the male MRL/MpJ mice were able to maintain the chondrogenic response at 12 weeks. Currently, it is not known why only the MRL/MpJ males showed superior cartilage regeneration, but perhaps activity levels or QTLs associated with male MRL mice may contribute to the extent of healing. Notably, the partial thickness lesion did not translate into repair. This suggests that factors residing in the bone marrow, such as stem cells or immune system components, were not accessed and may be important for a true regenerative process. Through further studies in the MRL/MpJ strain we eventually identify the precise factors involved and recreate them in human therapies.


Representative collagen II immunostaining of MRL and C5 mice showing collagen II in lesions from MRL mice but not C57 mice. The corresponding toluidine blue-stained slide is shown in the bottom panel.

Total histology scores for each experimental group shown in median, maximum, minimum and 25th and 75th percentile. Although there is variation within each group the MRL/MpJ males healed better overall.