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Mini review

Regeneration of articular cartilage in healer and non-healer mice

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ABSTRACT

Mammals rarely regenerate their lost or injured tissues into adulthood. MRL/MpJ mouse strain initially identified to heal full-thickness ear wounds now represents a classical example of mammalian wound regeneration since it can heal a spectrum of injuries such as skin and cardiac wounds, nerve injuries and knee articular cartilage lesions. In addition to MRL/MpJ, a few other mouse strains such as LG/J (a parent of MRL/MpJ) and LGXSM-6 (arising from an intercross between LG/J and SM/J mouse strains) have now been recognized to possess regenerative/healing abilities for articular cartilage and ear wound injuries that are similar, if not superior, to MRL/MpJ mice. While some mechanisms underlying regenerative potential have been begun to emerge, a complete set of biological processes and pathways still needs to be elucidated. Using a panel of healer and non-healer mouse strains, our recent work has provided some insights into the genes that could potentially be associated with healing potential. Future mechanistic studies can help seek the Holy Grail of regenerative medicine. This review highlights the regenerative capacity of selected mouse strains for articular cartilage, in particular, and lessons from other body tissues, in general.

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1. Introduction

Our research interest focuses on injury and repair of articular cartilage and the relationship between repair (and regeneration) of cartilage and the degeneration seen in osteoarthritis. Recent studies have demonstrated a surprising genetic variability in the capacity for regeneration of cartilage. For these investigations, we and others have turned to

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lessons provided by studies on regeneration of tissues in mouse models. Tissue regeneration in adult mammals is erratic which has led to renewed interests in classical models of tissue regeneration. Interest in this enduring problem is undergoing a resurgence stimulated by the availability of new mouse strains that are providing insights into the mechanisms that participate in tissue regeneration in mammals. To this end, the MRL/MpJ mouse strain has the exceptional potential to recapitulate regenerative abilities, a characteristic that is otherwise limited to amphibians and organisms other than adult mammals. MRL/MpJ has been demonstrated to regenerate an amazing spectrum of organs and body tissues including the articular cartilage of the knee — a tissue that is notoriously poorly healed. Comparison of MRL/MpJ and other unrelated mouse strains has provided some insights into the types of pathways that lead to regeneration. To provide genetic evidence, we and others have used genetic strains derived from the parent of MRL/MpJ, called LG/J (large), and recombinant inbred strains resulting from mating LG/J with SM/J (small). In this review, we will discuss the healing potential of MRL/MpJ, LG/J and other mouse strains for articular cartilage, in particular, and lessons from other body tissues in general along with some mechanistic insights from the available literature and our recent work.

1.1. Mouse strains

1.1.1. MRL/MpJ

The Murphy Roths Large (MRL) lymphoproliferation (lpr) wild type mouse strain was generated from a series of selective interbreeding of the following strains (the composite genome distribution is indicated in parentheses): C57BL/6J (0.3%), C3H/HeDi (12.1%), AKR/J (12.6%) and LG/J (75%) and then maintained by inbreeding (http://jaxmice.jax.org/strain/000486.html) and (Murphy and Roths, 1979). During the selective breeding of this strain a spontaneous mutation *Fas*^{lpr} was found at generation F_{12}, which was associated with a major defect in immune regulation (Adachi et al., 1993). The MRL/lpr mouse strain was originally selected for its large body size (body weight) and was mainly used as an autoimmune model. In contrast to MRL/lpr, the MRL/MpJ (MRL derived by the Murphy group of Jackson Laboratory) mice carry a normal (wild type) Fas gene. In spite of carrying the normal Fas gene, MRL/MpJ still exhibits autoimmune disorders; however, the symptoms are manifested later in life compared to MRL/MpJ-Fas^{lpr} mice. MRL/MpJ-Fas^{lpr} and the MRL/MpJ mice are kept congenic with each other by backcrosses to the MRL/MpJ wild type every 5–10 inbred generations.

1.1.2. Recombinant inbred lines from LG/J and SM/J

The LG/J mouse strain, a parent of MRL/MpJ, was selected for its large body size while another strain namely SM/J was selected for its small body size in two separate experiments performed in the first half of the 20th century. Both strains have been maintained by brother–sister mating for over 200 generations. These two inbred strains have obvious differences in body size and growth and are also known to differ in a wide range of other traits (Hrbek et al., 2006). The LGXSM intercross is a model for studying the genetics of complex traits segregating many interacting genes of small effect. Each LGXSM recombinant inbred strain is a unique recombination of the parental genomes. As in ordinary inbred strains, recombinant inbred strains are genetically identical, but each strain is a different 50:50 mix of the parental genotypes so that phenotypic and genotypic differences between strains allow gene mapping to a 10 cM (centimorgan) resolution containing a few hundred genes (Hrbek et al., 2006). We now have 45 recombinant inbred strains (JM Cheverud, personal communication). The ear wound healing and articular cartilage regeneration phenotypes studied in recombinant inbred strains and in several common inbred mouse strains will be highlighted in this article.

2. MRL/MpJ healing

Since 1998, first serendipitously discovered for their rapid ability to heal 2-millimeter through-and-through external ear wounds, MRL/MpJ mice have gained substantial popularity among investigators interested in tissue regeneration in mammals (Clark et al., 1998). Then, over the course of the next decade several investigators reported the reproducibility of ear wound healing in this mouse strain (McBrearty et al., 1998; Kench et al., 1999; Masinde et al., 2001; Gourevitch et al., 2003; Rajnoch et al., 2003; Davis et al., 2005; Beare et al., 2006; Colwell et al., 2006; Metcalfe et al., 2006; Naseem et al., 2007; Fitzgerald et al., 2008; Rai et al., 2012). After the discovery of this exceptional healer mouse strain, it was natural for other investigators to explore whether tissues other than external ears also regenerate in MRL/MpJ mice. Accelerated regeneration in amputated digit tips (Han et al., 2005; Chadwick et al., 2007), peripheral nerves (Buckley et al., 2011), alkali-burned corneas (Ueno et al., 2005), and cardiac wounds (Leferovich et al., 2001; Bedelbaeva et al., 2004; Naseem et al., 2007) has been shown in MRL/MpJ mice. In contrast to the ear wound phenotype, surgically induced skin wounds on the dorsum did not show accelerated healing. All four studies conducted so far (Beare et al., 2006; Colwell et al., 2006; Metcalfe et al., 2006; Buckley et al., 2011) have collectively shown that there was slow re-epithelialization without the formation of hair follicles and sebaceous glands, along with the formation of granulation tissue and scarring at the site of injury. A summary of regenerative phenotypes in MRL/MpJ mice is provided in Table 1.

Two other phenotypes (articular cartilage regeneration and intraarticular fracture healing) are discussed separately.

Table 1
Summary of regenerative phenotypes reported in MRL/MpJ mice.

Phenotype	Outcome	Reference
Ear wound healing	Complete closure along with full restoration of all structures of 2-millimeter diameter wounds in the ear pinna	(Clark et al., 1998; McBrearty et al., 1998; Kench et al., 1999; Masinde et al., 2001; Gourevitch et al., 2003; Rajnoch et al., 2003; Davis et al., 2005; Beare et al., 2006; Colwell et al., 2006; Metcalfe et al., 2006; Naseem et al., 2007; Fitzgerald et al., 2008; Rai et al., 2012)
Digit tip regrowth	Digit tip amputated neonatally happened to regrow along with complete structural and functional restoration (including nail)	(Han et al., 2005; Chadwick et al., 2007)
Peripheral nerve regeneration	Higher proximal wound nerve density	(Buckley et al., 2011)
Alkali-burned cornea	Rapid re-epithelialization along with restoration of complete functional capacity of the eye without any loss of corneal transparency	(Ueno et al., 2005),
Cardiac wound	Accelerated healing, increased mitosis, increased function by echo, less collagen deposition along with restoration of the function	(Leferovich et al., 2001; Bedelbaeva et al., 2004; Naseem et al., 2007)
Articular cartilage regeneration	Significant regeneration of full-thickness articular cartilage lesions with maximum restoration of matrix staining and hyaline nature of cartilage	(Fitzgerald et al., 2008; Rai et al., 2012)
Intraarticular fracture	Rapid fracture healing along with decreased cartilage degeneration	(Ward et al., 2008)
Surgical skin wound	Slow re-epithelialization, absence of hair follicles and sebaceous glands	(Beare et al., 2006; Colwell et al., 2006; Metcalfe et al., 2006; Buckley et al., 2011)