STEM CELLS

New insights into meniscal regeneration by stem cells

Injection of mesenchymal stem cells (MSCs), which can differentiate into cartilage and bone-forming cells, has been shown to enhance regeneration of the meniscus of the knee. “How MSCs produce these beneficial effects has been difficult to establish, in part because these cells do not engraft in large numbers or persist in the knee for long periods of time,” explains Darwin Prockop, corresponding author. Now, Prockop and colleagues have started to define how MSCs promote meniscal regeneration.

The investigators used a rat model of a hemi-meniscectomy in which half of the meniscus was removed surgically. Rat MSCs (rMSCs), human MSCs (hMSCs) or control saline were injected into the knee joints following surgery; joints were then compared macroscopically and histologically at 2, 4 and 8 weeks.

“Our findings confirmed that injection of MSCs into the knee joints of rats greatly enhanced regeneration of the meniscus,” explains Prockop. “Our novel observation, however, was that although the number of hMSCs decreased with time, both hMSCs and rMSCs enhanced meniscal regeneration in rats in a similar manner.”

The expression of rat and human genes was then analysed using species-specific

microarray and real-time reverse transcriptase PCR to determine exactly how hMSCs responded to the injured tissue after injection into the damaged rat joints. The most significant finding was that hMSCs started to express a new set of genes once injected into the new joint. 93 human genes were upregulated shortly after the hMSCs had engrafted. Moreover, hMSCs expressed high levels of Indian hedgehog (encoded by *IHH*), parathyroid hormone-like hormone (*PTH1LH*) and bone morphogenetic protein 2 (*BMP2*)—proteins previously shown to have essential roles in the generation of cartilage.

The injected hMSCs also induced expression of rat collagen II, in a manner dependent on hedgehog signalling, and prevented the progression of osteoarthritis in the knee. hMSCs therefore induce changes in gene expression that stimulate rat cells in the damaged meniscus to regenerate by forming new cartilage.

Furthermore, a drug previously shown to enhance the effect of *IHH* duplicated some of the beneficial effects of injecting hMSCs: a hedgehog antagonist inhibited rat collagen II expression in the absence of hMSCs, whereas an agonist

promoted expression of this protein. The investigators now plan to conduct further studies to fully characterize the effects of drugs that enhance expression of *IHH* on cartilage formation. “A long-term aim of our research is to identify the full therapeutic potential of hMSCs by carrying out clinical trials in patients with meniscal damage and, potentially, those with osteoarthritis,” says Prockop.

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Original article Horie, M. *et al.* Intra-articular injection of human mesenchymal stem cells (MSCs) promote rat meniscal regeneration by being activated to express Indian hedgehog that enhances expression of type II collagen. *Osteoarthritis Cartilage* doi:10.1016/j.joca.2012.06.002