

Intervertebral Disc Repair: Mesenchymal Stem Cells to the Rescue?

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The use of mesenchymal stem cells (MSC) as cell-based therapeutics is by no means a new concept. Indeed, MSC are currently in clinical trials for a number of autoimmune diseases, including Crohn's disease and type I diabetes, and as part of regimens for solid organ transplantation. In addition to the exploitation of the immune modulatory characteristics, the capacity for MSC to participate in tissue repair and regeneration is also being translated to the clinic. In particular, MSC therapy has been utilized with some success for bone and cartilage repair. The true advantage of MSC therapy seems to be in a complex combination of immune suppressive/anti-inflammatory effects with a capacity to coordinate tissue repair; however, it remains unclear how MSC exert these effects *in vivo*.

In this issue of *Transplantation*, Orozco et al. (1) provide a first pilot study report of the safety and efficacy of MSC therapy for intervertebral disc degeneration (IDD) in man. Severe low back pain is a significant consequence of degenerative disc disease for many patients, and the current gold standard therapy is surgical intervention consisting of spinal fusion or arthroplasty. Although surgical intervention is efficacious in treating the symptoms by reducing pain, the underlying problem (disc degeneration) is not resolved, leading to increased strain on surrounding discs.

Clearly, the utility of a less invasive therapy that incorporates a regenerative component for IDD is appealing. Orozco et al. demonstrate that autologous MSC therapy is safe and comparably efficacious in reducing pain and disability when compared with surgical intervention in other trials. As this pilot study had a follow-up time of just 1 year, it remains unclear whether these effects will be maintained long term. MSC are not the only candidate for cell therapy in IDD, a clinical trial using autologous chondrocytes isolated from surgically removed degenerated discs also dem-

onstrated promising results when compared with patients undergoing surgical intervention (spinal fusion) without cell therapy (2). However, this approach required the isolation of cells from the degenerated disc postsurgery, and clearly MSC represent a more accessible and less invasive source for cell therapy. Although both studies demonstrated a positive effect for cell therapy in reducing pain and disability, including some evidence of improvements in disc water content (i.e., preservation of normal biomechanics), disc height was not recovered.

While this is an important study highlighting the potential for MSC therapy in IDD, it leaves many open questions. Do MSC engraft or persist after transplantation in man? How do MSC exert their effects in IDD? Do MSC reduce the inflammation associated with damaged discs? Are MSC secreting bioactive factors that encourage repair? What effect does the damaged disc environment have on MSC? Do MSC differentiate into disc-like cells? Will allogeneic MSC be equally beneficial?

Although, it is difficult to answer these questions from the present study, animal models of IDD should allow their investigation. Although it is important to note that animal models of IDD do not provide an exact model of human IDD, such models can provide information on the survival of therapeutic cells, allow histologic examination to determine the capacity for regeneration, and permit the interrogation of the mechanisms involved. Indeed, autologous MSC have been shown to be efficacious in IDD repair with recovery of disc height in rabbit and canine models (2–4). The disparity in the observed recovery in disc height between animal models and humans could be associated with the differences in the degenerative disease etiology. Ideally, cell therapy for IDD would address the symptoms (through alleviation of pain and disability) and regeneration of degenerated disc (recovery of disc height). Perhaps, the key to this will be the enhancement of MSC cell therapy delivery, and improved survival and function through the provision of suitable scaffolds. The other issue in translating these advances to the clinic will be in the capacity for such autologous therapies to be scalable. A side by side comparison would be beneficial to see whether allogeneic MSC are equally effective, and if so, the latter may provide a more commercially attractive and feasible route for therapeutic development.

Overall, it seems that cell therapy may reduce inflammation and halt disc degeneration (in the follow-up time); however, it seems unlikely that MSC cell therapy, at least in this form, has the capacity to regenerate the damaged disc.

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This is not surprising given that it is now widely believed that prereparative effects of MSC are mediated by the immunosuppressive characteristics and secretion of bioactive factors rather than direct regeneration (5).

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