REVIEW ARTICLE

Cell therapy for the degenerating intervertebral disc

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Spinal conditions related to intervertebral disc (IVD) degeneration cost billions of dollars in the US annually. Despite the prevalence and soaring cost, there is no specific treatment that restores the physiological function of the diseased IVD. Thus, it is vital to develop new treatment strategies to repair the degenerating IVD. Persons with IVD degeneration without back pain or radicular leg pain often do not require any intervention. Only patients with severe back pain related to the IVD degeneration or biomechanical instability are likely candidates for cell therapy. The IVD progressively degenerates with age in humans, and strategies to repair the IVD depend on the stage of degeneration. Cell therapy and cell-based gene therapy aim to address moderate disc degeneration; advanced stage disease may require surgery. Studies involving autologous, allogeneic, and xenogeneic cells have all shown good survival of these cells in the IVD, confirming that the disc niche is an immunologically privileged site, permitting long-term survival of transplanted cells. All of the animal studies reviewed here reported some improvement in disc structure, and 2 studies showed attenuation of local inflammation. Among the 50 studies reviewed, 25 used some type of scaffold, and cell leakage is a consistently noted problem, though some studies showed reduced cell leakage. Hydrogel scaffolds may prevent cell leakage and provide biomechanical support until cells can become established matrix producers. However, these gels need to be optimized to prevent this leakage. Many animal models have been leveraged in this research space. Rabbit is the most frequently used model (28 of 50), followed by rat, pig, and dog. Sheep and goat IVDs resemble those of humans in size and in the absence of notochordal cells. Despite

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this advantage, there were only 2 sheep and 1 goat studies of 50 studies in this cohort. It is also unclear if a study in large animals is needed before clinical trials since some of the clinical trials proceeded without a study in large animals. No animal studies or clinical trials completely restored IVD structure. However, results suggest cause for optimism. In light of the fact that patients primarily seek medical care for back pain, attenuating local inflammation should be a priority in benchmarks for success. Clinicians generally agree that short-term back pain should be treated conservatively. When interventions are considered, the ideal therapy should also be minimally invasive and concurrent with other procedures such as discography or discectomy. Restoration of tissue structure and preservation of spinal motion are desirable. (Translational Research 2016;■:1–10)

Abbreviations: ■ = ■■

CLINICAL SIGNIFICANCE

The annual costs of spinal conditions related to intervertebral disc (IVD) degeneration exceed $190 billion in the US.[1] In industrialized countries, low back pain is extremely common with a prevalence of 60%–90%.[2] Despite this prevalence and soaring cost, there is no specific treatment that restores the physiological function of the degenerate IVD. Thus, developing new treatment strategies to repair the degenerating IVD is vital.

Current treatments for disc-related pain include surgical and nonsurgical approaches,[3] and often result in incomplete symptomatic relief. A key limitation of current treatments for disc degeneration is that they do not maintain or restore native tissue structure and mechanical function. Therefore, there is a pressing need for new therapies to treat disc degeneration that retain and/or restore disc structure and mechanical function by directly addressing the underlying causes and mechanisms.

The IVD is an elegant structure, with a gelatinous inner core (the nucleus pulposus [NP]) that functions as a shock absorber converting axial loads into radial forces. The

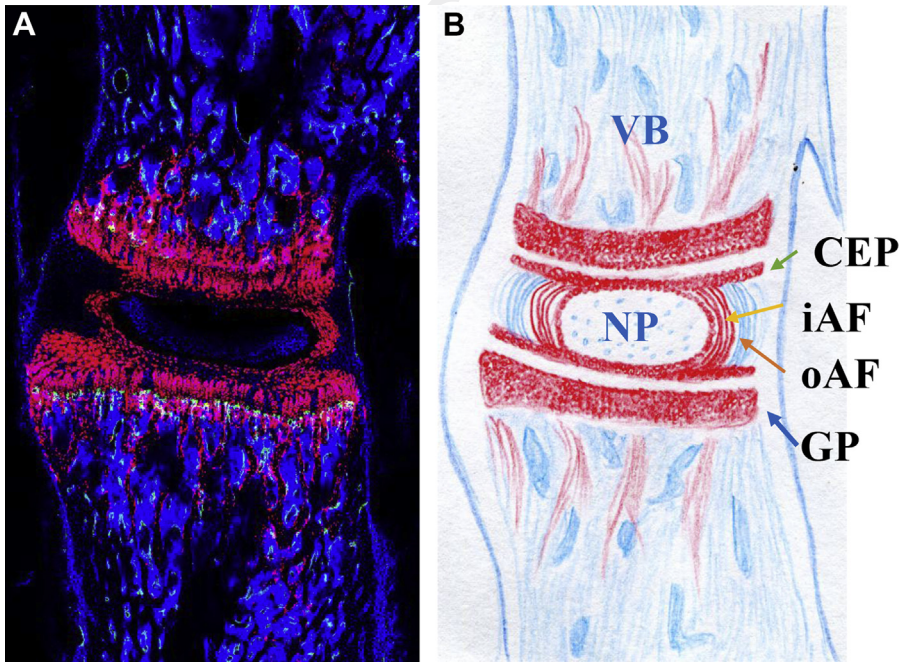

Fig 1. Mouse lumbar intervertebral disc (IVD). **A,** Sagittal section of a *Col2CreER;R26-tdTomato* mouse IVD. **B,** Schematic drawing of the vertebral body (VB)-IVD-VB motion segment. Red: type II collagen expressing cells; Blue: cell nuclei stained with DAPI. NP, nucleus pulposus; CEP, cartilaginous endplate; iAF, inner annulus fibrosus (AF); oAF, outer AF; GP, growth plate.