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MINIREVIEWS

Stem cells for spine surgery

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Abstract

In the past few years, stem cells have become the focus of research by regenerative medicine professionals and tissue engineers. Embryonic stem cells, although capable of differentiating into cell lineages of all three germ layers, are limited in their utilization due to ethical issues. In contrast, the autologous harvest and subsequent transplantation of adult stem cells from bone marrow, adipose tissue or blood have been experimentally utilized in the treatment of a wide variety of diseases ranging from myocardial infarction to Alzheimer's disease. The physiologic consequences of stem cell transplantation and its impact on functional recovery have been studied in countless animal models and select clinical trials. Unfortunately, the bench to bedside translation of this research has been slow. Nonetheless, stem cell therapy has received the attention of spinal surgeons due to its potential benefits in the treatment of neural damage, muscle trauma, disk degeneration and its potential contribution to bone fusion.

Key words: Stem cell; Spine surgery; Spinal cord injury; Peripheral nerve damage; Intervertebral disk regeneration; Fusion; Skeletal muscle regeneration

Core tip: Stem cells have become an increasingly feasible option for the future treatment of spinal disorders. Recent scientific advances have allowed researchers and spinal surgeons alike to investigate the potential of stem cells in the regeneration of degenerated disks, healing spinal cord injury and helping bone growth in spinal fusion.

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INTRODUCTION

In recent years, stem cells have become a focus of regenerative medicine. Adult stem cells, harvested directly from bone marrow, adipose tissue or blood have the ability to undergo mitosis as well as multipotent differentiation into a variety of cell lineages. The goal of stem cell therapy is to replace or replenish diseased tissue through the localized differentiation of transplanted stem cells into cells which advance the healing process or directly restore the tissue physically. Despite the years of research elucidating the physiology and the processes of stem cell differentiation, both the survival as well as the physical

and biochemical control over the stem cells when implanted into a body remains a challenge. Advances in material sciences have aided tremendously in providing a three-dimensional environment for the cells within a scaffold which allows for both the local retention of cells where they are intended to operate and simultaneously allowing the diffusion of nutrients to enable cell survival. Advances in genetic engineering on the other hand have allowed the modification of stem cells to induce the expression of selective growth factors to further aid in tissue reconstruction. Several challenges in spine surgery have been addressed by experimental ventures into stem cell therapy. Degenerative spinal disorders such as Degenerative Disk Disease have been sought to be addressed through the biological reconstruction of the disk by a variety of stem cells and growth factors, thereby potentially circumventing the need for surgery. The potentially devastating consequences of Spinal Cord Injury have been moderated through the implantation of stem cells to aid in the recovery of nerve cells. Spine surgery itself has been the focus of tissue engineers primarily to achieve bony fusion in the spinal fusion of vertebrae to attain stability. The iatrogenic injury of peripheral nerves and skeletal muscle surrounding the spine, which inevitably occurs during spine surgery whilst access to the spine is being prepared, although not as dramatic in its effect on the disability of the patient in the long-term has been addressed by many scientists. Overall, stem cell therapy, despite being in the experimental phase in most sub-disciplines, promises exciting opportunities to improve spine care and decrease the morbidity due to spine surgery in the future.

APPLICATION OF STEM CELLS IN SPINE SURGERY

Spine fusion

Spine fusion is performed to address the pain, deformity or neurologic deficit caused by degenerative conditions, spinal tumor, vertebral fractures and spinal deformities such as scoliosis and kyphosis amongst other indications. The bony fusion between two or more vertebrae eliminates the pain caused by aberrant motion of the vertebrae through immobilization. Lumbar fusion has been reported to have increased at a rate of 220% from 1990, more than the increases for knee and hip arthroplasty combined[1]. Ambulatory lumbar spine surgery has been demonstrated to increase at a larger rate relative to inpatient surgery[2]. Cervical and thoracolumbar fusions have also reportedly increased at a rate of 89% and 31%, respectively, mirroring the rapid increase in the utilization of the procedure[3]. The introduction of new surgical technology has not proven to reduce reoperation rates[4]. The vital elements in bony fusion are an adequate quantity of bone-forming cells (osteogenesis), an appropriate microenvironment directing bone synthesis through a variety of growth factors (osteoinduction), and a scaffold or cage in which the growth of bone is well positioned (osteoconduction). Despite the recent advances in cage design and bone fusion extender materials, pseudoarthrosis remains a pressing issue occurring in 13%-41.4% of patients[5-8]. Risk factors for pseudoarthrosis have been reported to be older age, thoracolumbar kyphosis, smoking, diabetes mellitus, metabolic bone disease and female gender[6,8-11]. As patients more than 60 years old represent the demographic with the largest increase in the rate of fusion surgery, the medical community has begun investigating alternatives to support the process of bone growth and fusion, for example with the implantation of stem cells[1]. The gold standard for creating a bony fusion is the use of autograft bone from the iliac crest; however, this has been associated with increased morbidity. Allograft or synthetic bone graft extenders carry the osteoconductive, and to a different extent, the osteoinductive properties, but no cells that will bring the fusion together. Mesenchymal stem cells (MSCs) harvested from the bone marrow, adipose tissue, periosteum or skeletal muscle have been confirmed to differentiate into osteoblasts both *in vitro* and *in vivo*[12-17]. Adipose derived stem cells (ADSCs) harvested from fat pads, although less commonly utilized in experimental models, are multipotent cells that can differentiate into adipocytes, osteoblasts, chondrocytes, or myocytes when cultivated in the correct microenvironment[17-21]. Both types of cells have been demonstrated to have a significant effect on spinal fusion in a multitude of settings including a variety of culturing mechanisms, scaffolds and added growth factors. Bone morphogenetic protein-2 (BMP-2) is a growth factor which is increasingly used in spinal fusion, mostly on an off-label basis, which may be the reason for the increased incidence of complications associated with its utilization[22]. Genetically modified MSCs which were induced to express BMP-2 were reported to induce spinal fusion in mice after injection into the paraspinal musculature comparable, in terms of rigidity, to the fusion achieved with instrumentation[23,24]. Fu *et al*[25] addressed the concern of complications associated with BMP-2 by examining if a reduced amount combined with MSCs would still yield acceptable fusion rates. They found that the group with MSCs seeded on alginate with a low dose of BMP-2 achieved equal fusion rates to the group treated with an iliac crest autograft in a rabbit model[25]. Additional evidence that MSCs may potentially serve as a substitute for autograft or BMP-2 has been presented, however, slightly lower fusion rates were reported for the group treated with MSCs *vs* the group treated with BMP-2 in a rabbit model[26]. Seo *et al*[27] attempted to induce higher fusion rates in a rat model by transplanting MSCs seeded on hydroxyapatite in addition to fibroblast growth factor-4, but found that the group treated without the addition of the growth factor achieved the highest fusion rate[27]. Other than selection of the appropriate growth factor, the level of osteogenic differentiation of the cells may also play a role. One study reported that 80% of rabbit spines treated with MSCs cultured in osteogenic differentiation medium fused *vs* only 33.3% of spines treated with cells that had been cultured without

the addition of differentiation medium[28]. The efficacy of MSCs transplanted without amendments to culturing protocols, the addition of genetic engineering or growth factors has been less encouraging in a variety of animal models utilizing beta-tricalcium phosphate graft or porous ceramics[29-31]. Recently, stem cells derived from adipose tissue have become popular in the tissue engineering community, in part due to the ease of cell harvesting from fat pads through liposuction. ADSCs expressing bone morphogenic proteins have proven effective for spinal fusion in animal models of metabolic bone disease[32,33]. In a study comparing MSCs and ADSCs expressing BMP-2 seeded on collagen sponges, fusion rates were encouraging and not significantly different in the two groups of rat models[34]. Due to the relatively easier clinical access to ADSCs in the patient, greater attention to their potential role in spinal fusion is warranted. Overall, the use of stem cells in clinical spine fusion has been restricted due to the limited number of cells which may be harvested through liposuction or bone marrow puncture. Cellular *in vitro* expansion is necessary to increase the number of viable pluripotent cells. This represents the greatest burden in the bench to bedside translation of stem cells in spine fusion, as two separate procedures, the availability of sophisticated instrumentation and educated personnel decrease the cost-effectiveness of the intervention[35-37].

Disc regeneration

Degenerative Disk Disease results from a complex process regulated by biomechanical forces and molecular changes within the disk. A healthy disk consists of the nucleus pulposus rich in collagen type Ⅱ fibers with a high content of proteoglycan and aggrecan to aid in the resistance to compression[38,39]. It is surrounded by the annulus fibrosus, rich in collagen type Ⅰ fibers which are arranged in a parallel fashion to withstand bending and twisting forces. A healthy disk is aneural and avascular due to the high proteoglycan content of the nucleus pulposus, receiving most of its nutrients by diffusion through the vertebral endplate[40]. Starting at the second decade of life, the progressive calcification of the endplate results in a decrease in the nutrient supply to the disk[41]. This has been hypothesized to result in phenotypic changes leading to decreased synthesis of proteoglycan and collagen type Ⅱ, and increased synthesis of collagen type Ⅰ and Ⅲ as well as an increase in matrix metalloproteinase activity[41-44]. Overall, the change in the biochemical composition of the disk results in gross morphologic changes and decreased disk height which contribute to the impingement of nerves[45-47]. The clinical manifestation of Degenerative Disk Disease in the form of lower back pain is usually focused on conservative management including lifestyle- or work modifications, physical therapy, pain medication, acupuncture and epidural injections. If the symptoms are persistent, cause progressive deformity or neurologic compromise, surgery in the form of disc replacement or spinal fusion is considered[48]. Growth factors, inflammatory cytokine antagonists and intracellular regulatory proteins are among the factors which have been demonstrated to result in encouraging regeneration of nucleus pulposus cells *in vitro* and *in vivo*[49-53]. The utility of these therapies in humans may be limited due to the rapid *in vivo* degeneration of the molecules used for the treatment. Gene therapy, although successfully utilized in animal studies, has significant risks concerning the vectors used for gene transduction. Stem cell therapy for Degenerative Disk Disease is based on the premise of reconstruction of the nucleus pulposus matrix. Nishimura and Mochida were the first to reimplant autologous nucleus pulposus cells in a disk herniation rat model and reported decreased degeneration of the annulus fibrosus, the endplate and the remaining nucleus pulposus when compared to the control group[54]. As with bony fusion, most scientists have focused on MSCs for Degenerative Disk regeneration. MSCs can differentiate into cell lineages populating bone, cartilage, skeletal muscle and ligamentous tissue[15]. As the exact phenotype of nucleus pulposus cells has yet to be determined, confirmation of the possibility of MSCs to differentiate into nucleus pulposus cells capable of proteoglycan production does not exist. Nonetheless, researchers have demonstrated that various environmental stimuli and genetic manipulations may result in an MSC differentiating into a nucleus pulposus-like cell. Richardson *et al*[55] transfected MSCs using the transcription factor, SOX-9, and found that they differentiated into chondrocyte-like cells with the deposition of nucleus pulposus matrix markers collagen type Ⅱ and aggrecan[55]. Risbud *et al*[56,57] experimentally cultured immobilized MSCs under hypoxic conditions with transforming growth factor-beta and found that these conditions prompted MSC differentiation towards nucleus pulposus-like cells[56,57]. Similar differentiation of stem cells into cells which expressed nucleus pulposus-like phenotypic markers has been observed in rabbit studies. Sakai *et al*[58,59] studied the effect of the transplantation of MSCs into both healthy and degenerated disks. They found that the implanted cells differentiated into nucleus pulposus-like cells, producing collagen type Ⅱ and proteoglycan without harm to the rabbit[58,59]. The degenerated disks showed significant improvement in height and hydration[60]. Allogenic MSCs were transplanted into the intervertebral disk in a rat model, and demonstrated viability and proliferation[61]. However, concerns regarding an immune reaction to allogenic stem cells in humans have limited the utilization of such cells in clinical trials. Orozco *et al*[62] transplanted autologous MSCs into ten patients diagnosed with Degenerative Disk Disease[62]. They found improvements in pain and disability within three months of treatment. Their study had severe limitations regarding the average age of the patients (35 years) and the number of patients (10). Nonetheless, these results exemplify the importance of arranging larger clinical trials to ease the translation of stem cell therapy from bench to bedside for patients suffering from Degenerative Disk Disease.

Spinal cord injury

Spinal cord injury (SCI) results from traumatic damage to the spinal cord which may have devastating consequences

or result in death[63]. The most common causes of traumatic SCI are motor vehicle accidents, sports injuries, falls at home, and traumatic injury in the workplace[64]. A total of 15-40 cases per million people are estimated to suffer a SCI every year, with most cases occurring in males 16-30 years of age[65-67]. SCI consists of several complex phases which are yet to be elucidated fully on a molecular level. The primary or acute phase consists of the physical disruption and contusion of the nerves and the tissues surrounding the spinal cord[68]. The force of the traumatic disturbance correlates directly with the amount of cell death[69]. As a consequence, the spinal cord swells and concomitantly with the commonly associated hemorrhage impedes blood flow, causing hypoxia[70-74]. The second or sub-acute phase of SCI is characterized by overlapping phases of sustained inflammation, oxidative and immune events. Excessive glutamate levels, the formation of reactive oxygen species and lipid peroxidation cause widespread neuronal and glial death, and axonal degeneration[75-79]. The scar tissue which is generated during the third or chronic phase presents a physical and biochemical barrier for axonal regeneration, complicating recovery[80,81]. Scientists have experimented with stem cell transplantation in the hope of promoting functional recovery after SCI. The intervention may be targeted at different phases, but should ideally enhance neuron and axon regeneration and remyelination through the creation of a favorable microenvironment or the direct physical replacement of cells[82]. This may best be achieved through suppression of the inflammatory cascade resulting in cell apoptosis and necrosis[83]. Embryonic stem cells, pluripotent cells derived from the inner cell mass of an embryo, have been considered as a treatment option for SCI[84]. Although these cells can divide infinitely and have greater differentiation potential than adult stem cells, their use is highly controversial[85-89]. A Chinese surgeon who claimed to have cured SCI in hundreds of patients without complications by injecting them with olfactory ensheathing cells isolated from aborted fetuses was received with great skepticism and sparked fierce debates about the ethicality of such research[90-93]. The Gevron Corporation is the first company to have received approval to initiate a clinical trial assessing a human embryonic stem cell-derived candidate therapy for severe spinal cord injuries in the United States[94]. Adult stem cells have more commonly been used in both *in vitro* and *in vivo* experimentation due to the ethical concerns regarding embryonic stem cells. MSCs are favored by many scientists due to the ease of cell harvest, isolation, expansion, and preservation[35,95-97]. To date, no reports of immunologic reactions to allogeneic *vs* autologous cell transplants have been observed, making MSCs a very practical solution for cellular therapy[98,99]. MSCs have been demonstrated to promote axonal regeneration and suppress demyelination[100]. Several different studies in rat models found that MSCs induce nerve regeneration, modulate the production of inflammatory cytokines such as TNF-α and IL-6 and reduce myeloperoxidase activity[101-105]. Menezes *et al*[106] hypothesized that laminin may play a pivotal role in neuron and axon preservation and regeneration after finding deposits of the glycoprotein on the lesion site in a rat SCI model[106]. All of these studies reported that transplanted MSCs operate mainly through the creation of a favorable microenvironment by means of the secretion of a variety of neurotrophic factors[107-111]. However, the *in vivo* differentiation of MSCs into neuron-like cells has been documented to be inefficient[108-110]. Therefore, MSCs are as of now, not capable of directly repopulating and physically restoring the damaged tissue in SCI. Neural stem cells (NSCs) were sought as an option for stem cell therapy, specifically for their ability to overcome this deficit. NSCs are harvested from the subventricular zone and are capable of differentiation into neurons, oligodendrocytes and most commonly astrocytes[112,113]. Nemati *et al*[114] reported that the transplantation of NSCs into a contusion SCI in a monkey model facilitated hind limb performance recovery[114]. Lee *et al*[115] documented similar functional recovery in terms of hind limb recovery paired with reduced lesions and an increased density of axons and dendritic spines surrounding the transplanted NSCs in a rat model[115]. Piltti *et al*[116] examined the survival rates, migration and sensory fiber sprouting of transplanted NSCs in a rat model in the secondary or subacute phase *vs* the tertiary or chronic phase of SCI. They found that the number of surviving transplanted cells was lower in the group treated during the tertiary phase, but that these cells had a stronger effect by increasing the number of mature oligodendrocytes[116]. The experimental utilization of stem cell therapy in SCI has been very limited to date. Several studies have reported sensory and motor improvements after 1-3 mo of stem cell transplantations combined with various other cells and growth factors[117-121]. In contrast, Karamouzian *et al*[122] stated that despite the feasibility and safety of cellular transplantations, the improvements in terms of functional recovery were not statistically significant in their study[122]. The low numbers of patients in these studies make it difficult to provide a definitive statement on the clinical potential of stem cell transplantation for SCI.

CONCLUSION

Additional areas of interest which have not been clinically addressed with stem cell therapy are iatrogenic nerve and muscle injury caused by spinal surgery. Additional considerations are warranted with respect to the ethics and the cancerogenous risk of embryonic stem cell therapy, the potential immune reaction to autologous cell transplantation as well as the clinical morbidity of adult stem cell harvest. Overall, greater standardization of *in vitro* experimentation and animal models may aid the speed of translation of stem cell therapy in spinal surgery from bench to bedside.

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