Mesenchymal stem cells

Mesenchymal stem cells (MSCs) are multipotent stem cells found in the bone marrow that are important for making and repairing skeletal tissues, such as cartilage, bone, and the fat found in the bone marrow. With age and disease, MSCs predominantly convert into lipid-accumulating fat cells.

Bone-marrow mesenchymal stem cell

Bone-marrow mesenchymal stem cell.

Human umbilical cord-derived mesenchymal stem cells

Human umbilical cord-derived mesenchymal stem cells.

Nasal Olfactory Mucosa Mesenchymal Stem Cells

Nasal Olfactory Mucosa Mesenchymal Stem Cells.

A critical indicator of the overall survival of patients with high-grade glioma is the successful isolation of tumor mesenchymal stem-like cells (tMSLCs), which play important roles in glioma progression. However, attempts to isolate tMSLCs from surgical specimens have not always been successful, and the reasons for this remain unclear. Considering that the amount of surgical high-grade glioma specimens varies, we hypothesized that larger surgical specimens would be better for tMSLC isolation.

Materials and methods: We assessed 51 fresh, high-grade glioma specimens and divided them into two groups according to the success or failure of tMSLC isolation. The success of tMSLC isolation was confirmed by plastic adherence, presenting antigens, tri-lineage differentiation, and non-tumorigenicity. Differences in characteristics between the two groups were tested using independent two sample t-tests, chi-square tests, or Kaplan-Meier survival analysis.

Results: The mean specimen weights of the groups differed from each other (tMSLC-negative group: 469.9±341.9 mg, tMSLC positive group: 546.7±618.9 mg), but the difference was not statistically significant. The optimal cut-off value of specimen weight was 180 mg, and the area under the curve value was 0.599.

Conclusion: Our results suggested a minimum criterion for specimen collection, and found that the specimen amount was not deeply related to tMSLC detection. Collectively, our findings imply that the ability to isolate tMSLCs is determined by factors other than the specimen amount [1)].

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see also Human adipose tissue derived mesenchymal stem cell.

Mesenchymal stem cells (MSCs) are undifferentiated, multipotent cells that can differentiate into a variety of cell types.

Mesenchymal stem cells (MSCs) and neural stem cells have been regarded also for their clinical therapeutic potential for central nervous system (CNS) pathologies.

Although the word chondroblast is commonly used to describe an immature chondrocyte, the term is imprecise, since the progenitor of chondrocytes (which are mesenchymal stem cells) can differentiate into various cell types, including osteoblasts.

MSC-derived exosomes effectively improve functional recovery after ICH, possibly by promoting endogenous angiogenesis and neurogenesis in rats after ICH. Thus, cell-free, MSC-derived exosomes may be a novel therapy for ICH [2].

Mesenchymal stem cells deliver exogenous miR 21 via exosomes to inhibit nucleus pulposus cell apoptosis and reduce intervertebral disc degeneration [3].

Tumorigenesis

Although mesenchymal stem cells (MSCs) have been implicated as stromal components of several cancers, their ultimate contribution to tumorigenesis and their potential to drive cancer stem cells, particularly in the unique microenvironment of human brain tumors, remain largely undefined.

Studies on gliomas suggested that the microenvironment of human gliomas contains both glioma stem cells (GSCs) and glioma associated (GA)-mesenchymal stem cells (MSCs; (GA-MSCs). Also, studies have suggested that nano- sized vesicles, termed exosomes, have been recently observed to contribute towards intercellular communication within the tumor niche [4].

MSCs have shown therapeutic applications in different medical fields and could represent a successful

treatment of degenerative disc disease (DDD). Several studies have demonstrated, ex vivo or in animal models, the MSCs efficacy in spine surgery [5].

Mesenchymal stem cell therapy is a novel regenerative approach for treating tendinopathy.

Their potential utility is a result of their intrinsic ability to repair damaged tissues, deliver therapeutic proteins, and migrate to sites of pathology within the brain. However, it remains unclear whether the CNS promotes any changes in these potential therapeutic cells, which would be critical to understand before clinical application.

NSCs as well as mesenchymal stem cells (MSCs) have been reported to possess tumor tropism capacities.

Single MSCs application to intramedullary and intradural space is safe, but has a very weak therapeutic effect compared with multiple MSCs injection. Further clinical trials to enhance the effect of MSCs injection are necessary [6].

Animal Studies

Animal studies have shown that MSCs have the potential to treat a variety of diseases and injuries, including osteoarthritis, bone fractures, and heart disease. These studies have primarily been conducted in rodent models, with some studies also being done in larger animals such as sheep and pigs. The results of these studies have been promising, but more research is needed to fully understand the potential therapeutic uses of MSCs in humans.

There is increasing concern that cancer and cancer treatment accelerate aging and the associated cognitive decline.

Zamorano et al. showed that treatment of 9-month-old male mice with cisplatin causes cognitive deficits that are associated with formation of tau deposits in the hippocampus. They explored the capacity of mesenchymal stem cells (MSC) given via the nose to prevent age-related brain tau deposits. Moreover, they more closely examined the cellular distribution of this hallmark of accelerated brain aging in response to treatment of 9-month-old female and male mice with cisplatin.

They showed that cisplatin induces tau deposits in the entorhinal cortex and hippocampus in both sexes. The tau deposits colocalize with syndecan-2. Astrocytes surrounding tau deposits have increased glial fibrillary acidic protein (GFAP) expression. Most of the cisplatin-induced tau deposits were located in Microtubule-associated protein 2+ neurons that were surrounded by aquaporin 4+ (AQP4)+ neuron-facing membrane domains of astrocytes. In addition, some tau deposits were detected in the perinuclear region of GFAP+ astrocytes and in CD31+ endothelial cells. There were no morphological signs of activation of ionized calcium binding adaptor molecule-1+ (Iba-1)+ microglia and no increases in brain cytokine production. Nasal administration of MSC at 48 and 96 hours after cisplatin prevented formation of tau deposits and normalized syndecan-2 and GFAP expression. Behaviorally, cisplatin-induced tau cluster formation was associated with reduced executive functioning and working/spatial memory and nasal administration of MSC at 48 and 96 hours after cisplatin prevented these cognitive deficits. Notably, delayed MSC administration (1 month after cisplatin) also prevented tau cluster formation and cognitive deficits, in both sexes.

In summary, nasal administration of MSC to older mice at 2 days or 1 month after completion of

cisplatin treatment prevents the accelerated development of tau deposits in entorhinal cortex and hippocampus and the associated cognitive deficits. Since MSC are already in clinical use for many other clinical indications, developing nasal MSC administration for treatment of accelerated brain aging and cognitive deficits in cancer survivors should be feasible and would greatly improve their quality of life [7)].

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Mesenchymal precursor cells (MSC) were obtained from the iliac crest of 8-week-old sheep. Intervertebral disc degeneration (IVD) was induced by postero-lateral annulotomy at three lumbar levels in eight 2-year-old sheep. Six months later, each degenerated IVD was randomized to one of three treatments: Injection of MSC into (i) previously incised annulus fibrosus, (ii) NP (NPI), or (iii) no injection (negative control, NC). The adjacent IVD received injection of phosphate buffered saline into NP (positive control, PC). Radiographs and magnetic resonance imaging scans were obtained at baseline, 6, 9, and 12 months. Discs were harvested at 12 months for biochemical and histological analyses.

IVD degeneration was consistently observed postannulotomy, and characterized by reduced disc height index (DHI), disc height (DH), glycosaminoglycan (GAG) content, and increased grade of disc degeneration.Six months after stem cell injection, DHI and DH had recovered in AFI and NPI groups when compared with NC group ($P<0.01$). Mean Pfirrmann grading system improved from 3.25 to 2.67 (AFI group) and from 2.96 to 2.43 (NPI group). Mean histopathological grade improved for both AFI ($P<0.002$) and NPI ($P<0.02$) groups. Both AFI and NPI groups demonstrated spontaneous repair of the postero-lateral annular lesion.

In this large animal model, injection of MSCs into the annulus fibrosus or the nucleus pulposus of degenerated IVD resulted in significant improvements in disc health [8)].

Twenty-four sheep had annular incisions made at L2-3, L3-4, and L4-5 to induce degeneration. Twelve weeks after injury, the nucleus pulposus of a degenerated disc in each animal was injected with ProFreeze and PPS formulated with either a low dose (0.1 million MPCs) or a high dose (0.5 million MPCs) of cells. The 2 adjacent injured discs in each spine were either injected with PPS and ProFreeze (PPS control) or not injected (nil-injected control). The adjacent noninjured L1-2 and L5-6 discs served as noninjured control discs. Disc height indices (DHIs) were obtained at baseline, before injection, and at planned death. After necropsy, 24 weeks after injection, the spines were subjected to MRI and morphological, histological, and biochemical analyses. RESULTS Twelve weeks after the annular injury, all the injured discs exhibited a significant reduction in mean DHI (low-dose group 17.19%; high-dose group 18.01% [$p < 0.01$]). Twenty-four weeks after injections, the discs injected with the low-dose MPC+PPS formulation recovered disc height, and their mean DHI was significantly greater than the DHI of PPS- and nil-injected discs ($p < 0.001$). Although the mean Pfirrmann MRI disc degeneration score for the low-dose MPC+PPS-injected discs was lower than that for the nil- and PPS-injected discs, the differences were not significant. The disc morphology scores for the nil- and PPS-injected discs were significantly higher than the normal control disc scores ($p < 0.005$), whereas the low-dose MPC+PPS-injected disc scores were not significantly different from those of the normal controls. The mean glycosaminoglycan content of the nuclei pulposus of the low-dose MPC+PPS-injected discs was significantly higher than that of the PPS-injected controls ($p < 0.05$) but was not significantly different from the normal control disc glycosaminoglycan levels. Histopathology degeneration frequency scores for the low-dose MPC+PPS-injected discs were lower than those for the

PPS- and Nil-injected discs. The corresponding high-dose MPC+PPS-injected discs failed to show significant improvements in any outcome measure relative to the controls.

Intradiscal injections of a formulation composed of 0.1 million MPCs combined with PPS resulted in positive effects in reducing the progression of disc degeneration in an ovine model, as assessed by improvements in DHI and morphological, biochemical, and histopathological scores [9].

While several articles describe isolating MSCs from various human tissues, there are no reports of isolating MSCs from human spinal ligaments, and their localization in situ. If MSCs are found in human spinal ligaments, they could be used to investigate hypertrophy or ossification of spinal ligaments. To isolate and characterize MSCs from human spinal ligaments, spinal ligaments were harvested aseptically from eight patients during surgery for lumbar spinal canal stenosis and ossification of the posterior longitudinal ligament. After collagenase digestion, nucleated cells were seeded at an appropriate density to avoid colony-to-colony contact. Cells were cultured in osteogenic, adipogenic or chondrogenic media to evaluate their multilineage differentiation potential. Immunophenotypic analysis of cell surface markers was performed by flow cytometry. Spinal ligaments were processed for immunostaining using MSC-related antibodies. Cells from human spinal ligaments could be extensively expanded with limited senescence. They were able to differentiate into osteogenic, adipogenic or chondrogenic cells. Flow cytometry revealed that their phenotypic characteristics met the minimum criteria of MSCs. Immunohistochemistry revealed the localization of CD90-positive cells in the collagenous matrix of the ligament, and in adjacent small blood vessels. We isolated and expanded MSCs from human spinal ligaments and demonstrated localization of MSCs in spinal ligaments. These cells may play an indispensable role in elucidating the pathogenesis of numerous spinal diseases [10].

The facet joints and interspinous ligaments may provide alternative sources of MSCs for tissue engineering applications. The facet joints and interspinous ligaments-derived MSCs are part of the microenvironment of the human ligaments of the spinal column and might play a crucial role in the development and progression of degenerative spine conditions [11].

Traditional Chinese medicine can promote the proliferation of bone marrow-derived mesenchymal stem cells (BMSCs). We chose four “Kidney-tonifying” Chinese herbal medicines, Radix Astragali, Salvia, Herba Epimedii, and Saussurea Involucrata, to evaluate whether they had positive effects on the proliferation of BMSCs and TGF-β1-induced chondrogenic differentiation of BMSCs. The four Chinese herbal medicines were intragastrically administered to Sprague-Dawley rats, respectively, to prepare drug-containing serums of corresponding Chinese herbs. BMSCs were isolated, cultured, and exposed to culture solution containing 1%, 5%, 10%, and 15% (v/v) Radix Astragali-, Salvia-, Herba Epimedii-, and Saussurea Involucrata-containing serum, respectively. TGF-β1-induced BMSCs were addressed in the same manner. Collagen type II protein was assessed by immunofluorescence methods. To assess whether the drug-containing serums had positive effects on the proliferation of BMSCs and TGF-β1-induced BMSCs, MTT method was assessed. The proliferation of BMSCs was significantly enhanced when exposed to culture solutions containing 1% and 5% Radix Astragali-, 1% and 5% Salvia-, 5% Herba Epimedii-, and 1%, 5%, and 10% Saussurea Involucrata-containing serum. The proliferation of TGF-β1-induced BMSCs was significantly enhanced when exposed to 1%, 5%, and 15% Radix Astragali-, 10% and 15% Salvia-, 5%, and 15% Herba Epimedii-, and 1%, 5%, and 10% Saussurea Involucrata-containing serum [12].

see Mesenchymal Stem Cell Allograft

Case series

Twenty-two consecutive patients, who suffered of spine degenerative disc disease DDD, were submitted: in 11 cases the MSCs were harvested from red bone marrow, 11 from fat tissue. The red bone marrow withdrawal was performed from the vertebral bodies; processed by a fully-automated, mobile system. The fat tissue withdrawal was acted from the subcutaneous adipose tissue; processed through a microfluidic fractioning procedure. MSCs were implanted in the central part of the nucleus pulposus of the DDD or added to bone chips to accelerate posterolateral arthrodesis.

All the 14 posterolateral fusions and MSCs implantations showed at three months a complete bone bridge, stable at follow-up. The one intersomatic implantation gained a complete interbody fusion after one month; while 80% black discs treated with MSCs presented a new T2-W hyperintensity at postoperative MRI. The mean Visual Analogue Scale Pain Score improved from 70±20 to 10±5 at 12 months, as the ODI score from 70±5% to 20±10%.

There are several questions that need to be answered but MCSs look promising in lumbar spine surgery, both to block the aging of the disc both to accelerate the fusion processes in arthrodesis [13].

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