Sports Medicine, Orthopaedics & Pain Management

Amniotic Fluid Cell Therapy to Relieve Disc-Related Low Back Pain and Its Efficacy Comparison with Long-Acting Steroid Injection

Introduction: There are many problems in case of treatment of the patients reporting with degenerated disc with or without disc prolapse, desiccation, bulge, or compression of the adjacent nerves and its implications. Most of the patients with chronic discogenic back pain, without specific history of trauma, are on geriatric age group. In this age group, low back pain is associated with varying degree of age-induced degenerative osteoporosis, spondylosis, spondyloarthrosis, intervertebral disc prolapse, or even compression collapse apart from other problems like diabetic background, hypertension, ischemic heart disease, chronic obstructive pulmonary disorder, dyslipidemia, and hypothyroidism. MRI presentation of a typical geriatric presentation of low back pain is shown (Figs. 19.1, 19.2, and 19.3). Materials and methods: 42 patients participated and randomized in two equal groups. Group A (N = 21, male 10 and female 11, mean age 56.4 ± 8.9 year) was treated with 80 mg methylprednisolone in 10 mL water for injection under C-arm guidance in the operation theater (OT) after 1 % infiltration with Xylocaine at the site of maximum tenderness in the back. Similarly, Group B (N = 21, male 12 and female 9, mean age 59.4 ± 6.4 year) was also treated in the OT with similar protocol with 10 mL of freshly collected amniotic fluid from mothers undergoing hysterotomy and ligation. All the procedures passed through the donor and recipient's informed consent protocol and vetted by the institute-based ethical committee. Result and analysis: Studying and comparing the clinically manifested effect of treatment, it can be easily seen that both steroid (Group A) and cell therapy (Group B) patients showed improvement of pain and distress from the pretreatment value; however, Group B scoring is much better (p, 0.01), as seen and assessed from the value of the VAS (visual analog pain scale), WD (walking distance in meters), and HAQ (Health Assessment Questionnaire). If we see further the clinical assessment of pain relief and patient's satisfaction as seen from Table 19.3 and Graph 19.1 in case of Group A (long-acting steroid group), it was 20/21 cases in 1st month which became 12/21 in 3rd month, 6/21 in 6th month, 4/21 in 12th month, and 2/21 after 24-month follow-up. Similarly in Group B (cell therapy patients), the identical values after the 1st month were 18/21, which became 21/21 in 3rd month, 21/21 in 6th month, 14/21 in 12th month, and 12/24 after 24-month follow-up. Another globally practiced guideline for pain assessment or scoring for comparison is Oswestry low back pain disability questionnaire. Here in Table 19.4 and Graph 19.2, we have again compared the effect of treatment of Group A (steroid) and Group B (cell therapy with fresh amniotic fluid) and followed up the results of Group A and Group B treatment as per scoring by Oswestry low back pain disability questionnaire up to 24 months. Here, postinjection with long-acting steroid (Group A) suggested a mean scoring of 9 ± 1.2 % SD after 3 months, which became mean 1.9 ± 1.2 % SD after 6 months, mean 39 ± 9.2 % SD after 9 months, mean 39 ± 8.2 % SD after 12 months, mean 41 ± 7.2 % SD after 18 months, and then ultimately mean 48 ± 12.2 % SD after 24 months. Similarly in case of cell therapy group (Group B), the mean scoring was 11.7 ± 1.6 % SD after 3rd month follow-up, which became mean 9.4 ± 0.6 % SD after 6th month, mean 9.1 ± 0.96 % SD after 9th month, mean 7.1 ± 0.6 % SD after 12th month, mean 6.7 ± 0.4 % SD after 18th month, and ultimately mean 4.1 ± 0.96 % SD after 24th month follow-up. Discussion and conclusion: If we analyze the results, we can see long-acting steroid, due to its anti-inflammatory and other activities, causes some improvement of the patients; however, it is ill sustained as noted from the follow-up. But freshly collected simple amniotic fluid cell

therapy has a much more sustained effect apart from the remarkable improvement, but the question remains why in long-term follow-up there is reappearance of pain in some of the victims』 Is it psychosomatic aspects or a recurrent cell therapy or increasing the cell dosage that can have a more sustained effect』 These are some of the questions for the future investigators in this frontline area of cellular therapy. But from an overall point of view, regeneration can only treat the root cause of degeneration of the whole lumbosacral region. Cell therapy is the only curative approach for such a generalized multisystemic deterioration of the region, and the palliative approach of pain relief with anti-inflammatory drug including steroid is short lived and has longtime use and may lead to drug-induced problems in addition of the recurrence of the symptoms.

Bhattacharya, Niranjan. (2012, December 5). Human Fetal Tissue Transplantation. Amniotic Fluid Cell Therapy to Relieve Disc-Related Low Back Pain and Its Efficacy omparison with Long-Acting Steroid Injection. 2013, pp 251-264

Amniotic Fluid Stem Cells: a Promising Therapeutic Resource for Cell-Based Regenerative Therapy

Stem cells have been proposed as a powerful tool in the treatment of several human diseases, both for their ability to represent a source of new cells to replace those lost due to tissue injuries or degenerative diseases, and for the ability of produce trophic molecules able to minimize damage and promote recovery in the injured tissue. Different cell types, such as embryonic, fetal or adult stem cells, human fetal tissues and genetically engineered cell lines, have been tested for their ability to replace damaged cells and to restore the tissue function after transplantation. Amniotic fluid -derived Stem cells (AFS) are considered a novel resource for cell transplantation therapy, due to their high renewal capacity, the "in vitro" expression of embryonic cell lineage markers, and the ability to differentiate in tissues derived from all the three embryonic layers. Moreover, AFS do not produce teratomas when transplanted into animals and are characterized by a low antigenicity, which could represent an advantage for cell transplantation or cell replacement therapy. The present review focuses on the biological features of AFS, and on their potential use in the treatment of pathological conditions such as ischemic brain injury and bone damages.

Antonucci, I., Pantalone, A., Tete, S., Salini, V., Borlongan, C., Hess, D., & Stuppia, L. (2012). Amniotic fluid stem cells: A promising therapeutic resource for cell-based regenerative therapy. Current Pharmaceutical Design, 18(13), 1846-1863.

Mesenchymal stem cells in arthritic diseases

Mesenchymal stem cells (MSCs), the nonhematopoietic progenitor cells found in various adult tissues, are characterized by their ease of isolation and their rapid growth in vitro while maintaining their differentiation potential, allowing for extensive culture expansion to obtain large quantities suitable for therapeutic use. These properties make MSCs an ideal candidate cell type as building blocks for tissue engineering efforts to regenerate replacement tissues and repair damaged structures as encountered in various arthritic conditions. Osteoarthritis (OA) is the most common arthritic condition and, like rheumatoid arthritis (RA), presents an inflammatory environment with immunological involvement and this has been an enduring obstacle that can potentially limit the use of cartilage tissue engineering. Recent advances in our understanding of the functions of MSCs have shown that MSCs also possess potent immunosuppression and anti-inflammation effects. In addition, through secretion of various soluble factors, MSCs can influence the

local tissue environment and exert protective effects with an end result of effectively stimulating regeneration in situ. This function of MSCs can be exploited for their therapeutic application in degenerative joint diseases such as RA and OA. This review surveys the advances made in the past decade which have led to our current understanding of stem cell biology as relevant to diseases of the joint. The potential involvement of MSCs in the pathophysiology of degenerative joint diseases will also be discussed. Specifically, we will explore the potential of MSC-based cell therapy of OA and RA by means of functional replacement of damaged cartilage via tissue engineering as well as their anti-inflammatory and immunosuppressive activities.

Chen, F. H., & Tuan, R. S. (2008). Mesenchymal stem cells in arthritic diseases. Arthritis Research & Therapy, 10(5), 223-223. doi:10.1186/ar2514

Amniotic fluid-derived stem cells in regenerative medicine research

The stem cells isolated from amniotic fluid present an exciting possible contribution to the field of regenerative medicine and amniotic fluid-derived stem (AFS) cells have significant potential for research and therapeutic applications. AFS cells are multipotent, showing the ability to differentiate into cell types from all three embryonic germ layers. They express both embryonic and adult stein cell markers, expand extensively without feeder cells, double in 36 h, and are not tumorigenic. The AFS cells can be maintained for over 250 population doublings and preserve their telomere length and a normal karyotype. They differentiate easily into specific cell lineages and do not require human embryo tissue for their isolation, thus avoiding the current controversies associated with the use of human embryonic stem (ES) cells. The discovery of the AFS cells has been recent, and a great deal of work remains to be performed on the characterization and use of these cells. This review describes the various differentiated lineages that AFS cells can form and the future of these promising new stem cells in regenerative medicine research.

Joo, S., Ko, I. K., Atala, A., Yoo, J. J., & Lee, S. J. (2012). Amniotic fluid-derived stem cells in regenerative medicine research. Archives of Pharmacal Research, 35(2), 271-280. doi:10.1007/s12272-012-0207-7

Mesenchymal Stromal Cells in Rheumatoid Arthritis: Biological Properties and Clinical Applications

Mesenchymal stromal cells (MSC) isolated from a variety of adult tissues including the bone marrow (BM), have the capacity to differentiate into different cell types such as bone and cartilage and have therefore attracted scientific interest as potential therapeutic tools for tissue repair. MSC display also immunosuppressive and anti-inflammatory properties and their putative therapeutic role in a variety of inflammatory autoimmune diseases is currently under investigation. Joint destruction, caused by persistent inflammation, renders rheumatoid arthritis (RA) a possible clinical target for cartilage and bone repair using BM MSCs for their tissue repair and immunoregulatory effects. A number of studies, based mainly on experimental animal models, have recently provided interesting data on the potential of BM-MSCs to suppress local inflammation and tissue damage in RA whereas tissue engineering and cell-scaffold technology represents an emerging field of research. This review deals with the biological repair/regeneration of joint tissues in RA via MSC-based therapies. In view of the current interest in the autologous usage of BM MSC in RA, all available data on the biological properties of patient MSCs including the immunoregulatory characteristics, differentiation capacity towards osteocytes/chondrocytes,

clonogenic/proliferative potential and molecular/protein profile and the possible influence of the RA milieu will be also summarized.

Kastrinaki, M., & Papadaki, H. (2009). Mesenchymal stromal cells in rheumatoid arthritis: Biological properties and clinical applications. CURRENT STEM CELL RESEARCH & THERAPY, 4(1), 61-69. doi:10.2174/157488809787169084

Local Adherent Technique for Transplanting Mesenchymal Stem Cells as a Potential Treatment of Cartilage Defect

Introduction Current cell therapy for cartilage regeneration requires invasive procedures, periosteal coverage and scaffold use. We have developed a novel transplantation method with synovial mesenchymal stem cells (MSCs) to adhere to the cartilage defect. Methods For ex vivo analysis in rabbits, the cartilage defect was faced upward, filled with synovial MSC suspension, and held stationary for 2.5 to 15 minutes. The number of attached cells was examined. For in vivo analysis in rabbits, an autologous synovial MSC suspension was placed on the cartilage defect, and the position was maintained for 10 minutes to adhere the cells to the defect. For the control, either the same cell suspension was injected intra-articularly or the defects were left empty. The three groups were compared macroscopically and histologically. For ex vivo analysis in humans, in addition to the similar experiment in rabbits, the expression and effects of neutralizing antibodies for adhesion molecules were examined. Results Ex vivo analysis in rabbits demonstrated that the number of attached cells increased in a time-dependent manner, and more than 60% of cells attached within 10 minutes. The in vivo study showed that a large number of transplanted synovial MSCs attached to the defect at 1 day, and the cartilage defect improved at 24 weeks. The histological score was consistently better than the scores of the two control groups (same cell suspension injected intra-articularly or defects left empty) at 4, 12, and 24 weeks. Ex vivo analysis in humans provided similar results to those in rabbits. Intercellular adhesion molecule 1-positive cells increased between 1 minute and 10 minutes, and neutralizing antibodies for intercellular adhesion molecule 1, vascular cell adhesion molecule 1 and activated leukocyte-cell adhesion molecule inhibited the attachment. Conclusion Placing MSC suspension on the cartilage defect for 10 minutes resulted in adherence of >60% of synovial MSCs to the defect, and promoted cartilage regeneration. This adherent method makes it possible to adhere MSCs with low invasion, without periosteal coverage, and without a scaffold.

Koga, H., Shimaya, M., Muneta, T., Nimura, A., Morito, T., Hayashi, M., . . . Sekiya, I. (2008). Local adherent technique for transplanting mesenchymal stem cells as a potential treatment of cartilage defect. Arthritis Research & Therapy, 10(4), R84-R84. doi:10.1186/ar2460

Human Amnion Tissue Injected with Human Umbilical Cord Mesenchymal Stem Cells Repairs Damaged Sciatic Nerves in Rats

Human umbilical cord mesenchymal stem cells, incorporated into an amnion carrier tubes, were assessed for nerve regeneration potential in a rat nerve defect model. Damaged nerves were exposed to human amnion carriers containing either human umbilical cord mesenchymal stem cell (cell transplantation group) or saline (control group). At 8, 12, 16 and 20 weeks after cell implantation, the sciatic functional index was higher in the cell transplantation group compared with the control group. Furthermore, electrophysiological examination showed that threshold stimulus and maximum stimulus intensity gradually decreased while compound action potential amplitude gradually increased. Hematoxylin-

eosin staining showed that regenerating nerve fibers were arranged in nerve tracts in the cell transplantation group and connective tissue between nerve tracts and amnion tissue reduced over time. Gastrocnemius muscle cell diameter, wet weight and restoration ratio were increased. These data indicate that transplanted human umbilical cord mesenchymal stem cells, using the amnion tube connection method, promote restoration of damaged sciatic nerves in rats.

Li, D., Wang, C., Shan, W., Zeng, R., Fang, Y., & Wang, P. (2012). Human amnion tissue injected with human umbilical cord mesenchymal stem cells repairs damaged sciatic nerves in rats. NEURAL REGENERATION RESEARCH, 7(23), 1771-1778. doi:10.3969/j.issn.1673-5374.2012.23.002

Tendon Regeneration and Repair with Stem Cells

The use of stems cells in tendon repair is of particular interest given the frequency of tendon injuries worldwide together with the technical difficulty often encountered when repairing or augmenting tendons. Stems cells have the capability to differentiate into a variety of different cell types including osteocytes and tenocytes, and if normal architecture of damaged tendon (either macroscopic or microscopic) could be restored, this would significantly improve the management of patients with these injuries. There is already encouraging research on the use of stems cells clinically although considerable further work is required to improve knowledge and clinical applications of stem cells in tissue engineering.

MacLean, S., Khan, W. S., Malik, A. A., Snow, M., & Anand, S. (2012). Tendon regeneration and repair with stem cells. Stem Cells International, 2012, 316281. doi:10.1155/2012/316281

Effects of Human Amniotic Fluid on Cartilage Regeneration From Free Perichondrial Grafts in Rabbits

After the chondrogenic potential of free grafts of perichondrium was shown in several experimental studies, perichondrium has been used to reconstruct cartilage tissue in various clinical situations. This study investigates the effects of human amniotic fluid on neochondrogenesis from free perichondrial grafts in a rabbit model. Since this fluid contains high concentrations of hyaluronic acid, hyaluronic acid-stimulating activator, growth factors, and extracellular matrix precursors during the second trimester, it may have a stimulating effect on neochondrogenesis. Perichondrial grafts, measuring 20x20 mm super(2) were obtained from the ears of 144 New Zealand young rabbits and were sutured over the paravertebral muscles. The rabbits were randomly divided into three groups with 48 rabbits per group. In group 1, 0.3 ml human amniotic fluid, and in group 2, 0.3 ml saline were injected underneath the perichondrial grafts. Group 3 formed the control group in which no treatment was given. Histologically, neochondrogenesis was evaluated in terms of cellular form and graft thickness at 2, 4, 6, and 8 weeks after surgery. In group 1, the mature cartilage was generated quickly and the cartilage plate in this group was significantly thick and extensive when compared with groups 2 and 3 at 8 weeks ($p<0.05$, ANOVA). In conclusion, our study shows that human amniotic fluid enhances neochondrogenesis from free perichondrial grafts. The rich content of hyaluronic acid and growth factors possibly participate in this result.

Ozgenel, G. Y., Filiz, G., & Ozcan, M. (2004). Effects of human amniotic fluid on cartilage regeneration from free perichondrial grafts in rabbits. British Journal of Plastic Surgery, 57(5), 423-428. doi:10.1016/j.bjps.2003.12.021

Meniscal Tears Respond to Cell Injections

Vangsness reported that a few patients in the low-dose MSC group also showed evidence of meniscal regeneration in MRI scans taken after one year.

Young, B. (2012) Meniscal Tears Respond to Cell Injections. ORTHOPEDICS THIS WEEK. Retrieved from Single Source Surgical: http://www.singlesourcesurgical.com/wp-content/uploads/2014/01/amniotic-tissue.pdf

Platelet-Rich Plasma Therapy - Future or Trend?

Chronic complex musculoskeletal injuries that are slow to heal pose challenges to physicians and researchers alike. Orthobiologics is a relatively newer science that involves application of naturally found materials from biological sources (for example, cell-based therapies), and offers exciting new possibilities to promote and accelerate bone and soft tissue healing. Platelet-rich plasma (PRP) is an orthobiologic that has recently gained popularity as an adjuvant treatment for musculoskeletal injuries. It is a volume of fractionated plasma from the patient's own blood that contains platelet concentrate. The platelets contain alpha granules that are rich in several growth factors, such as platelet-derived growth factor, transforming growth factor-β, insulin-like growth factor, vascular endothelial growth factor and epidermal growth factor, which play key roles in tissue repair mechanisms. PRP has found application in diverse surgical fields to enhance bone and soft-tissue healing by placing supra-physiological concentrations of autologous platelets at the site of tissue damage. The relative ease of preparation, applicability in the clinical setting, favorable safety profile and possible beneficial outcome make PRP a promising therapeutic approach for future regenerative treatments. However, there is a large knowledge gap in our understanding of PRPs mechanism of action, which has raised skepticism regarding its potential efficacy and use. Thus, the aim of this review is to describe the various factors proposed to contribute to the biological activity of PRP, and the published pre-clinical and clinical evidence to support it. Additionally, we describe the current techniques and technology for PRP preparation, and review the present shortcomings of this therapy that will need to be overcome if it is to gain broad acceptance.

Dhillon, R. S., Schwarz, E. M., & Maloney, M. D. (2012). Platelet-rich plasma therapy - future or trend? Arthritis Research & Therapy, 14(4), 219-219. doi:10.1186/ar3914

Human Stem Cell Delivery for Treatment of Large Segmental Bone Defects

Local or systemic stem cell delivery has the potential to promote repair of a variety of damaged or degenerated tissues. Although various stem cell sources have been investigated for bone repair, few comparative reports exist, and cellular distribution and viability postimplantation remain key issues. In this study, we quantified the ability of tissue-engineered constructs containing either human fetal or adult stem cells to enhance functional repair of nude rat critically sized femoral defects. After 12 weeks, defects treated with cell-seeded polymer scaffolds had significantly higher bone ingrowth and torsional strength compared to those receiving acellular scaffolds, although there were no significant differences between the cell sources. Next, stem cells were labeled with fluorescent quantum dots (QDs) in an attempt to noninvasively track their distribution after delivery on

scaffolds. Clear fluorescence was observed at implantation sites throughout the study; however, beginning 7-10 days after surgery, signals were also observed at contralateral sites treated with acellular QD-free scaffolds. Although immunostaining for human nuclei revealed retention of some cells at the implantation site, no human cells were detected in the control limb defects. Additional histological analysis of implantation and control defect tissues revealed macrophages containing endocytosed QDs. Furthermore, QD-labeling appeared to diminish transplanted cell function resulting in reduced healing responses. In summary, augmentation of polymeric scaffolds with stem cells derived from fetal and adult tissues significantly enhanced healing of large segmental bone defects; however, QD labeling of stem cells eliminated the observed therapeutic effect and failed to conclusively track stem cell location long-term in vivo.

Dupont, K. M., Sharma, K., Stevens, H. Y., Boerckel, J. D., García, A. J., & Guldberg, R. E. (2010). Human stem cell delivery for treatment of large segmental bone defects. Proceedings of the National Academy of Sciences, 107(8), 3305-3310. doi:10.1073/pnas.0905444107

Metabolic Functions of Myostatin and GDF11

Myostatin is a member of the transforming growth factor β superfamily of secreted growth factors that negatively regulates skeletal muscle size. Mice null for the myostatin gene have a dramatically increased mass of individual muscles, reduced adiposity, increased insulin sensitivity, and resistance to obesity. Myostatin inhibition in adult mice also increases muscle mass which raises the possibility that anti-myostatin therapy could be a useful approach for treating diseases such as obesity or diabetes in addition to muscle wasting diseases. In this review I will describe the present state of our understanding of the role of myostatin and the closely related growth factor growth/differentiation factor 11 on metabolism.

Genetics of Development and Disease Branch, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland USA.(2010) Metabolic Functions Of Myostatin AND GDF11. Immunol Endocr Metab Agents Med Chem. 2010 Dec;10(4):217-231.

Potential Applications for Using Stem Cells in Spine Surgery

While the use of biologics as adjuncts for spine surgery is growing annually stem cells have yet to be approved for this clinical application. Stem cells have the unique ability to differentiate into a variety of musculoskeletal tissues including bone or cartilage. Moreover they have been shown to secrete growth factors that promote matrix repair and regeneration and can down regulate inflammation and immune cell functions. It is these combined activities that make stem cells attractive candidates for advancing current techniques in spine surgery and possibly mitigating those pathologies responsible for tissue degeneration and failure thereby minimising the need for surgical intervention at a later date. This review focuses on the characteristics of progenitor cells from different sources and explores their potential as adjuncts for both current and future applications in spine surgery. Where possible we draw on the experimental outcomes from our own preclinical studies using adult mesenchymal progenitor stem cells, as well as related studies by others to support our contention that stem cell based therapies will play a significant role in spine surgery in the future.

Goldschlager, T., Jenkin, G., Ghosh, P., Zannettino, A., & Rosenfeld, J. (2010). Potential applications for using stem cells in spine surgery. CURRENT STEM CELL RESEARCH & THERAPY, 5(4), 345-355. doi:10.2174/157488810793351686

Initial Clinical Experience with The Use of Human Amniotic Membrane Tissue During Repair of Posterior Tibal and Achilles Tendon

The demonstrated anti-adhesive, anti-inflammatory and anti-microbial properties of amniotic membrane tissue make this a potentially unique alternative to biologically inert collagen matrix products currently available for use in foot and ankle surgery and possible for tendon repair surgery of the upper extremities.

Jay, R. (n.d.). Amniotic Tissue. Retrieved from Single Source Surgical: http://www.singlesourcesurgical.com/wp-content/uploads/2014/01/amniotic-tissue.pdf

Applying Stem Cells to Orthopaedic Conditions: using bone marrow stromal cells to treat nonunions and osteonecrosis

... of infection, makes stem cell therapy appealing to both patients and physicians. Although not yet widespread in orthopaedics, the use of adult stem cells to address...

Kelly, F. B., & Porucznik, M. A. (2014). Applying stem cells to orthopaedic conditions: Using bone marrow stromal cells to treat nonunions and osteonecrosis. AAOS Now, , 1.

Effects of Human Amniotic Fluid on Fracture Healing in Rat Tibia

Human amniotic fluid (HAF), including hyaluronic acid (HA) and several growth factors, has been used experimentally in tendon, nerve, and cartilage regeneration and in bone defects because of its positive stimulating effects on regeneration potential. This study was performed to investigate whether HAF was effective on fracture healing.

Kerimoğlu, S., Livaoğlu, M., Sönmez, B., Yuluğ, E., Aynacı, O., Topbas, M., & Yarar, S. (2009). Effects of human amniotic fluid on fracture healing in rat tibia. Journal of Surgical Research, 152(2), 281-287. doi:10.1016/j.jss.2008.02.028

Summary of Clinical Outcome Related to The Use of Human Amnion Soft Tissue Allograft in Right L4-L5 Decompression Procedure

The use of the nonadherent barrier significantly reduced both scar tissue formation and adherence to the underlying dura in this patient. The lack of scar tissue and associated plane preservation between the dural sac and the surrounding soft tissue significantly decreased the operative time required to perform the revision procedure.

Ploska, P. (2010) Summary of Clinical Outcome Related to The Use of Human Amnion Soft Tissue Allograft in Right L4-L5 Decompression Procedure. Retrieved from Single Source Surgical: http://www.singlesourcesurgical.com/wp-content/uploads/2014/01/amniotic-tissue.pdf

Implantation of Amniotic Membrane to Reduce Postlaminectomy Epidural Adhesions

Postlaminectomy epidural adhesion is implicated as a main cause of "failed back surgery syndrome" and associated with increased risk of complications during revision surgery. Various materials acting as mechanical barriers to reduce fibroblasts infiltration into epidural space have met with limited success. In present research, amniotic membrane (AM) was studied to investigate its effects on reducing epidural scar adhesion after laminectomy in a canine model. Laminectomy sites were created at L-1, L-3, L-5, and L-7 levels in 24 adult mongrel dogs. Freeze dried AM (FAM), cross-linked AM (CAM), and autologous free fat (AFF) were implanted, respectively, at a randomly assigned site in each dog with the remaining untreated site serving as internal control. The animals were sacrificed at 1, 6, and 12 weeks postoperatively. Then, gross pathologic observation including scar amount and adhesion tenacity, qualitative histology evaluation, and quantitative histology analysis were compared. Gross observation demonstrated that scar amount and adhesion tenacity of CAM group were significantly lower in comparison with those of FAM and non-treatment groups. A white, slightly vascularized CAM layer covered the dura mater without tenacious scar adhesion. The histology analysis also indicated reduced fibroblasts infiltration and consequent epidural fibrosis, which were similar to the results of AFF group. In conclusion, the CAM is effective in reducing epidural fibrosis and scar adhesion after laminectomy in canine model. It is a promising biomaterial for future clinical applications.

Tao, H., & Fan, H. (2009). Implantation of amniotic membrane to reduce postlaminectomy epidural adhesions. European Spine Journal : Official Publication of the European Spine Society, the European Spinal Deformity Society, and the European Section of the Cervical Spine Research Society, 18(8), 1202-1212. doi:10.1007/s00586-009-1013-x

Mesenchymal Stem Cells for Bone Repair and Metabolic Bone Diseases

Human mesenchymal stem cells offer a potential alternative to embryonic stem cells in clinical applications. The ability of these cells to self-renew and differentiate into multiple tissues, including bone, cartilage, fat, and other tissues of mesenchymal origin, makes them an attractive candidate for clinical applications. Patients who experience fracture nonunion and metabolic bone diseases, such as osteogenesis imperfecta and hypophosphatasia, have benefited from human mesenchymal stem cell therapy. Because of their ability to modulate immune responses, allogeneic transplant of these cells may be feasible without a substantial risk of immune rejection. The field of regenerative medicine is still facing considerable challenges; however, with the progress achieved thus far, the promise of stem cell therapy as a viable option for fracture nonunion and metabolic bone diseases is closer to reality. In this review, we update the biology and clinical applicability of human mesenchymal stem cells for bone repair and metabolic bone diseases.

Undale, A. H., Westendorf, J. J., Yaszemski, M. J., & Khosla, S. (2009). Mesenchymal stem cells for bone repair and metabolic bone diseases. Mayo Clinic Proceedings, 84(10), 893-902. doi:10.4065/84.10.893

Birth Tissue / Ankle Tendon Repair Study Released

The white, slighlty vascularized membrane was found between the dura matter and surrounding tissues to reduce scar intrusion. Furthermore, the CAM layer seldom adhered to the dura mater and was easily removed.

Young, R. (2012) Birth Tissue/Ankle Tendon Repair Study Released. ORTHOPEDICS THIS WEEK - EXTREMITIES. Retrieved from Single Source Surgical: http://www.singlesourcesurgical.com/wp-content/uploads/2014/01/amniotic-tissue.pdf

Using Birth Tissue in Spine Surgery

Fascia is one of the most important covering materials in the body and serves to protect virtually every structure in the body—bones, nerves, muscles, tendons, organs, the spinal cord and the brain. So when trauma or surgery disrupts that natural, protective fascia covering, amniotic membranes are structurally and by composition, extremely similar if not precise transplants

Young, R. (2012, August 20). Using Birth Tissues in Spine Surgery. Retrieved from Orthopedics This Week: http://ryortho.com/2012/08/using-birth-tissues-in-spine-surgery/

Anti-Aging

Inflammation Links Aging to the Brain

The authors go on to show that this feed-forward loop leads to epigenetic changes (chemical and structural modifications that alter gene expression without changing the DNA sequence) in the gene that encodes gonadotropin-releasing hormone (GnRH), leading to its reduced expression. [...]their studies in mice suggest that reduced hypothalamic release of GnRH could contribute to several systemic attributes of ageing, including declining muscle strength, skin atrophy, bone loss, reduced neurogenesis and memory impairment. A decrease in gonadal sex steroids is a well-established marker of ageing, but many other hormonal changes occur as well; and some of these ageregulated hormones (such as dehydroepiandrosterone) also regulate inflammation and other immune responses. [...]interplay between the hormonal and immune systems occurs at multiple levels.

Gabuzda, D., & Yankner, B. A. (2013). Inflammation links ageing to the brain. Nature, 497(7448), 197.

Aging

Overview of Human Aging

Ganz, P. (2014) Aging. Retrieved from http://www.goldlabcolorado.com/2014/Ganz_slides.pdf

Inflammation Links Aging to the Brain

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decrease in gonadal sex steroids is a well-established marker of ageing, but many other hormonal changes occur as well; and some of these ageregulated hormones (such as dehydroepiandrosterone) also regulate inflammation and other immune responses. [...]interplay between the hormonal and immune systems occurs at multiple levels.

Gabuzda, D., & Yankner, B. A. (2013). Inflammation links ageing to the brain. Nature, 497(7448), 197.

Other Therapies

Amniotic Fluid as a Rich Source of Mesenchymal Stromal Cells for Transplantation Therapy

Stem cells isolated from amniotic fluid are known to be able to differentiate into different cells types, thus being considered as a powerful tool for cellular therapy of different human diseases. In the last 4 years, amniotic fluid-derived stem (AFS) cells have been shown to express embryonic and adult stem cell markers. These cells can be considered an intermediate stage between embryonic stem cells and adult stem cells. AFS cells can give rise to adipogenic, osteogenic, myogenic, endothelial, neurogenic, and hepatic lineages, inclusive of all embryonic germ layers. AFS cells have a high renewal capacity and can be expanded for over 250 doublings without any detectable loss of chromosomal telomere length. Taken together, all these data provide evidence that amniotic fluid represents a new and very promising source of stem cells for research, as well as clinical applications. Certainly stem cells from amniotic fluid will be useful both for a customized cell supply for newly born children and for banking cells to be used for therapeutic cell transplantation in immunogically matched recipients. Further investigations are also warranted to fully explore the amniotic cells' potential for adult human disorders.

Antonucci, I., Stuppia, L., Kaneko, Y., Yu, S., Tajiri, N., Bae, E. C., . . . Borlongan, C. V. (2011). Amniotic fluid as a rich source of mesenchymal stromal cells for transplantation therapy. Cell Transplantation, 20(6), 789-795. doi:10.3727/096368910X539074

Culture of Human Amniotic Fluid Stem Cells in 3D Collagen Matrix

Most of the researchers attribute amniotic fluid stem cells (AF SCs) to mesenchymal stem cells (MSCs). However, AF SCs express both mesenchymal and epithelial markers, which distinguishes them from postnatal MSCs. Cultivation in the three-dimensional (3D) matrix provides a different look at the nature of the cells. We showed that in 3D collagen gel AF SCs form epithelial structures (tubules and cysts). The active contraction of the gel during the first days of cultivation, which is characteristic of mesenchymal cells, does not occur. Electron microscopic study showed that adherent junctions typical to epithelial cells are formed between AF SCs. On the other hand, during culturing in the gel AF SCs continue to express MSCs markers. Thus, AF SCs may be not true mesenchymal cells because they can display properties of epithelial cells. Perhaps these cells undergo epithelial-mesenchymal transition, a process which actively takes place during embryogenesis.

Davydova, D. A., Vorotelyak, E. A., Bragina, E. E., Terskikh, V. V., & Vasiliev, A. V. (2011). Culture of human amniotic fluid stem cells in 3D collagen matrix. Cell and Tissue Biology, 5(4), 339-345. doi:10.1134/S1990519X11040031

Isolation of Amniotic Stem Cells Lines with Potential for Therapy

Stem cells capable of differentiating to multiple lineages may be valuable for therapy. We report the isolation of human and rodent amniotic fluid-derived stem (AFS) cells that express embryonic and adult stem cell markers. Undifferentiated AFS cells expand extensively without feeders, double in 36 h and are not tumorigenic. Lines maintained for over 250 population doublings retained long telomeres and a normal karyotype. AFS cells are broadly multipotent. Clonal human lines verified by retroviral marking were induced to differentiate into cell types representing each embryonic germ layer, including cells of adipogenic, osteogenic, myogenic, endothelial, neuronal and hepatic lineages. Examples of differentiated cells derived from human AFS cells and displaying specialized functions include neuronal lineage cells secreting the neurotransmitter L-glutamate or expressing G-protein-gated inwardly rectifying potassium channels, hepatic lineage cells producing urea, and osteogenic lineage cells forming tissue-engineered bone.

De Coppi, P., Bartsch, J., Georg, Siddiqui, M. M., Xu, T., Santos, C. C., Perin, L., . . . Atala, A. (2007). Isolation of amniotic stem cell lines with potential for therapy. Nature Biotechnology, 25(1), 100-106. doi:10.1038/nbt1274

Effects of Platelet Growth Factors on Human Mesenchymal Stem Cells and Human Endothelial Cells In Vitro

The aim of the present in vitro study has been to investigate the effects of a enriched platelet derived growth factors on proliferation and migration of human endothelial and mesenchymal stem cells and on osteogenic differentiation of stem cells. Platelet rich plasma has been produced, yielding a four time higher number of thrombocytes than normal plasma. Degranulation of platelets has been performed by means of calcium and thrombin. Plasma has served as a control, whereas plasma in combination with calcium and thrombin was used to distinguish the difference between calcium and/or thrombin mediated effects and growth factor induced effects on the cells. The observed enhanced proliferation and migration of endothelial cells towards the platelet derived growth factors was driven by the plasma component of these preparations. However PDGF solely stimulated the migration and proliferation of mesenchymal stem cells. The increased osteogenic differentiation of growth factor treated mesenchymal stem cells was mostly driven by the high level 4 calcium used for the platelets degranulation. In summery, the different components of platelet derived growth factors work together to influence human endothelial and mesenchymal stem cells. This is of special clinically interest regarding the stimulation of bone healing in orthopaedic and traumatic surgery.

Kilian, O., Flesch, I., Wenisch, S., Taborski, B., Jork, A., Schnettler, R., & Jonuleit, T. (2004). Effects of platelet growth factors on human mesenchymal stem cells and human endothelial cells in vitro. European Journal of Medical Research, 9(7), 337-344.

Effect of Basic Fibroblast Growth Factor and Alpha-Melanocytic Stimulating Hormone on Nerve Regeneration Through a Collagen Channel

An experimental study on the rat sciatic nerve was performed to evaluate nerve regeneration through a collagen guide and to study the effects of -melanocytic stimulating hormone (-MSH) and basic fibroblast growth factor (b-FGF) in accel erating axonal elongation. After transection, nerves were repaired over a 7 mm gap using a placental collagen type IV guide. The channel was filled with either a b-FGF solution or an -MSH

solution or was produced with b-FGF incorporated into the guide. Four weeks later, only

groups in which b-FGF had been injected or incorporated displayed a significant somatosensory evoked potential response. Histological and quantitative analysis of nerve fibres confirmed the existence of nerve continuity in groups receiving an -MSH solution or a channel containing b-FGF. These results demonstrate that -MSH in solution and b-FGF incorporated into a collagen type IV channel enhance peripheral nerve regeneration. However, at 4 weeks, only b-FGF (3 ng) restores functional activity.

LAQUERRIERE, A., PEULVE, P., JIN, O., TIOLLIER, J., TARDY, M., VAUDRY, H., . . . TADIE, M. (1994). EFFECT OF BASIC FIBROBLAST GROWTH-FACTOR AND ALPHA-MELANOCYTIC STIMULATING HORMONE ON NERVE REGENERATION THROUGH A COLLAGEN CHANNEL. Microsurgery, 15(3), 203-210. doi:10.1002/micr.1920150312

Properties of the Amniotic Membrane for Potential Use in Tissue Engineering

An important component of tissue engineering (TE) is the supporting matrix upon which cells and tissues grow, also known as the scaffold. Scaffolds must easily integrate with host tissue and provide an excellent environment for cell growth and differentiation. Most scaffold materials are naturally derived from mammalian tissues. The amniotic membrane (AM) is considered an important potential source for scaffolding material. The AM represents the innermost layer of the placenta and is composed of a single epithelial layer, a thick basement membrane and an avascular stroma. The special structure and biological viability of the AM allows it to be an ideal candidate for creating scaffolds used in TE. Epithelial cells derived from the AM have the advantages of stem cells, yet are a more suitable source of cells for TE than stem cells. The extracellular matrix components of the basement membrane of the AM create an almost native scaffold for cell seeding in TE. In addition, the AM has other biological properties important for TE, including anti-inflammatory, anti-microbial, anti-fibrosis, anti-scarring, as well as reasonable mechanical property and low immunogenicity. In this review, the various properties of the AM are discussed in light of their potential use for TE.

Niknejad, H., Peirovi, H., Jorjani, M., Ahmadiani, A., Ghanavi, J., & Seifalian, A. M. (2008). Properties of the amniotic membrane for potential use in tissue engineering. European Cells & Materials, 15, 88-99.

Pigs' Bladder Helps Patients' Stem Cells Grow Missing Muscles

Putic, G., (2014, August 04) Pigs' Bladder Helps Patients' Stem Cells Grow Missing Muscles. Retrieved from Voice of America News: http://www.voanews.com/content/pig-bladder-helps-patients-stem-cells-grow-missing-muscles/1971525.html

Amniotic Fluid Stem Cells: Future Perspectives

The existence of stem cells in human amniotic fluid was reported for the first time almost ten years ago. Since this discovery, the knowledge about these cells has increased dramatically. Today, amniotic fluid stem (AFS) cells are widely accepted as a new powerful tool for basic research as well as for the establishment of new stem-cell-based therapy concepts. It is possible to generate monoclonal genomically stable AFS cell lines harboring high proliferative potential without raising ethical issues. Many different groups have demonstrated that AFS cells can be differentiated into all three germ layer lineages, what is of relevance for both, the scientific and therapeutical usage of these cells. Of special importance for the latter is the fact that AFS cells are less tumorigenic than other

pluripotent stem cell types. In this paper, we have summarized the current knowledge about this relatively young scientific field. Furthermore, we discuss the relevant future perspectives of this promising area of stem cell research focusing on the next important questions, which need to be answered.

Rosner, M., Schipany, K., Shanmugasundaram, B., Lubec, G., & Hengstschläger, M. (2012). Amniotic fluid stem cells: Future perspectives. Stem Cells International, 2012, 741810. doi:10.1155/2012/741810Yes

Biochemical and Biological Characterization of a Crude Growth Factor Extract (EAP) From Human Term-Placental Tissue

Trophoblast Resea~ 6:19-37, 1992 BIOCHEMICAL AND BIOLOGICAL CHARACTERIZATION OF A CRUDE GROWTH FACTOR EXTRACT (EAP) FROM ~ TERM-PLACENTAL TISSUE Sylvie...

Uhlrich, S., Tiollier, J., Chirouze, V., Tardy, M., & Tayot, J. (1992). Biochemical and biological characterization of a crude growth factor extract (EAP) from human term-placental tissue. Placenta, 13, 19-37. doi:10.1016/S0143-4004(05)80306-6

Regenerative Medicine Market on Growth Spurt

According to a new market research report published by Transparency Market Research, the regenerative medicine (bone and joint) market was valued at $2.6 billion in 2012 and is estimated to reach a market worth of $6.5 billion by 2019. That is a growth rate of 12.8% from 2013 to 2019...Young, B. (2013, July 30).

Regenerative Medicine Market on Growth Spurt. Retrieved from Orthopedics This Week: http://ryortho.com/breaking/regenerative-medicine-market-on-growth-spurt/

Human Maternal Placentophagy

Maternal placentophagy, although widespread among mammals, is conspicuously absent among humans cross-culturally. Recently, however, advocates for the practice have claimed it provides human postpartum benefits. Despite increasing awareness about placentophagy, no systematic research has investigated the motivations or perceived effects of practitioners. We surveyed 189 females who had ingested their placenta and found the majority of these women reported perceived positive benefits and indicated they would engage in placentophagy again after subsequent births. Further research is necessary to determine if the described benefits extend beyond those of placebo effects, or are skewed by the nature of the studied sample.

Selander, J., Cantor, A., Young, S. M., & Benyshek, D. C (2013)