stromal cells, and hence, is do not have any cytotoxic effects. SEM photographs showed that scaffold provided a suitable surface for attachment, growth and spread of stromal cells. According to in vivo results, the scaffolds enhance the repair of critical bone defect, especially when seeded with marrow stromal cells. In conclusion, we introduce a novel ternary system gelatin-bioactive glass nano-composite with high biocompatibility, which promotes bone tissue repair.

Enhancement of Bone Healing Properties of a Bioglass-Gelatin Composite with Endothelial Cells

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Bone repair is a dynamic process involving recruitment of skeletal stem/progenitor cells followed by cellular differentiation, extracellular matrix deposition, and remodeling. This process could be augmented by delivery of cells and bioactive materials to the site of bone regeneration. The present study aimed to promote the process of bone regeneration with an extracellular matrix substitute and augmentation of angiogenesis using endothelial cells. A three dimensional nanocomposite scaffold composed of gelatin-bioactive glass (SiO_2-CaO-P_2O_5) was fabricated. This scaffold contained the porosity of more than 90% with pore sizes ranging from 200 to 500 µm. To create a tissue-engineered construct, human umbilical vein endothelial cells were seeded on the scaffolds and the constructs were implanted on a critical-size calvarial bone defect in rats. Bone repair was histologically studied after 1, 4 and 12 weeks. SEM and MTT assay showed that the cells were attached and proliferated on the scaffold and the scaffold did not change their proliferation potential. Endothelial cells enhanced angiogenesis and the rate of formation of the new bone. The scaffold was completely replaced by the new bone, three months after implantation. This study demonstrated the importance of angiogenesis in the process of bone repair and suggests that endothelial cells can accelerate bone regeneration through formation of new vessels.

Safety Evaluation of Stem Cells Used for Clinical Cell Therapy in Chronic Liver Diseases

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Attempts have been made to translate in vitro experimental studies into therapeutic strategies for treatment of chronic liver disease. However, less attention has been given to ethical and safety issues in using hepatocytes and progenitor stem cells as an alternative to organ transplantation. Evaluation of safety issues is not limited to the host immune-defense reactions following cell transplantation, assessment of the source of the cells, conditions of cell culture and differentiation methods are also important. The biochemical and molecular assays are useful tools for evaluation of cell therapy procedures. The ability of the cells to home to the target organ and support its repair is as important as the overall well-being of the recipients and donors. As a consequence, it is required to conduct much more well-designed clinical trials to fully establish the long-term safety profile of stem cell therapies and to define the target patient groups by standardized protocols.

The Application of Modified Nano-Fibrous Scaffolds for Soft Tissue Engineering

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Great advances have been made in tissue regeneration by application of engineering techniques in regenerative medicine. A wide variety of synthetic polymers such as polycaprolactone, polylactic acid and polyethersulfone are applied for electrospinning of nanofibrous structures as three dimensional scaffolds for biomedical applications. The surfaces of these structures have been chemically and physically modified by plasma, wet chemical treatment and grafting of natural polymers (collagen, gelatin) after electrospinning. The surface changes were assessed by contact angle measurements and FTIR-ATR analysis. Then, stem cells were seeded for tissue formation. The results of viability assay, scanning electron microscopy and histology showed that the biomimetic microenvironment resulted in cell attachment, infiltration and proliferation. As, the biocompatibility of the polymers used in this study has been already proven, it can be concluded that nanoscaffold structures synthesized with natural bioactive materials have a higher compatibility with body tissues and play a major role on improvement of proliferation and infiltration of stem cells.

Chitosan/PVA/HEC Electrospun Scaffold for Skin Tissue Engineering

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Nanofibrous structures made from natural polymers with 3D fibrillar network can resemble the structure of natural fibrillar ECM. They have been fabricated with several techniques including electrospinning as the most attractive method. Skin wounds result from various conditions for which various treatments exist. The standard treatment of some specific skin wounds includes autologous or cadaveric skin transplantations. But, these methods are associated with the potential risk of donor site morbidity and transmission of pathogenic organisms. To avoid these potential disadvantages, an alternative approach is to use a tissue engineered skin for replacement of the damaged skin using electrospun scaffolds. In this study, the blend solution of three polymers including polyvinylalcohol (PVA), chitosan, and hydroxyethyl cellulose (HEC) in different weight ratio was electrospun and crosslinked using sebacic acid solution in methanol. In the next step, viability, attachment and proliferation of fibroblast cells on the surface of scaffold were evaluated using MTT assay and SEM observation, respectively. The results showed that this mat had high capacity to support adhesion and growth of skin cells and could be a potential candidate scaffold for skin tissue engineering or wound dressing applications.

Engineering of Transforming Growth Factor Beta 3-producing Mesenchymal Stem Cells for Tissue Engineering Applications

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Transforming growth factor beta 3 (TGF-β3) is a regulatory cytokine that affects cellular differentiation, adhesion and formation of extracellular matrix. It has a major role in palate and lungs development and regulates skin wound healing and scar formation. Delivery of TGF-β3 to the site of injury in lungs, skin or an epithelial tissue can regulate the regenerative process and the behavior of the contributing cells. As mesenchymal stem cells (MSCs) have been shown to promote regenerative activities in the above tissues, it was hypothesized that engineering of TGF-β3-secreting MSCs can add a new regenerative modality for repair of the above tissues. Rat TGF-β3 cDNA was cloned in the plasmid vector of pcDNA3.1 using competent *E. coli* cells. The cloned product was sequenced and matched with the reference sequence in GenBank website. Mesenchymal stem cells were isolated from rat femur using

flushing method and culture on a cell culture-treated plastic surface. In flow cytometry, they were positive for CD90 and CD106 and were capable of differentiation into osteoblasts, chondroblasts and adipocytes. Using Lipofectamine 2000 transfection reagent, Mesenchymal stem cells were transfected with the cloned cDNA and expression of TGF-β3 protein was confirmed by Western blotting. The transfected MSCs preserved their ability for the triple differentiation into osteoblasts, chondroblasts and adipocytes. In this study, we have successfully engineered transforming growth factor beta 3-secreting mesenchymal stem cells with preservation of their stemness characteristics. There are several implications for application of these cells in regenerative medicine.

Structural Stability and Cytotoxicity of Genipin-Crosslinked Electrospun Chitosan/PEO nanofibers

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Owing to their biocompatibility, biodegradability, anti-bacterial activity, and similarity to natural extracellular matrix, chitosan nanofibers have gained much attention for their application as a tissue engineering scaffold and a wound dressing. However, chitosan nanofibers suffer from structural instability in biological media because of their solubility and high swelling ratio. To overcome this problem, glutaraldehyde, a cytotoxic agent, is commonly used for crosslinking of chitosan nanofibers. In this study, we aimed to crosslink chitosan-based nanofibers by genipin, a biocompatible and nontoxic agent. For this purpose, different amount of genipin were added to the chitosan solutions, chitosan/PEO weight ratio 90/10 in 80% acetic acid, and the solutions were then electrospun to form nanofibers. The spun nanofibers were exposed to water vapor to complete crosslinking. SEM images of nanofibers showed that genipin-crosslinked nanofibers maintained their fibrous structure after immersing in PBS for 24 h, while the uncrosslinked samples lost their fibrous structure, indicating the water stability of genipin-crosslinked nanofibers. The genipin-crosslinked nanofibers also showed no significant change in swelling ratio in comparison with uncrosslinked fibers. FTIR-ATR spectrum of uncrosslinked and genipin-crosslinked chitosan nanofibers revealed the reaction between genipin and amino groups of chitosan. Cytotoxicity of genipin-crosslinked nanofibers was examined by MTT assay on human fibroblast cells in the presence of nanofibers extraction media. The genipin-crosslinked nanofibers did not show any toxic effects on fibroblast cells at the lowest and moderate amount of genipin. The fibroblast cells also showed a good adhesion on genipin-crosslinked nanofibers.

Articular Cartilage Repair using PDGF-Stimulated Chondrocyte/PCL Constructs in Rabbit

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Articular cartilage has a limited capacity for repair. Osteoarthritis (OA) is characterized by cartilage degradation induced by pro-inflammatory cytokines. Current treatment options for OA result in fibrocartilage formation without adequate improvement of joint function. As metabolism of hyaline cartage is regulated by different growth factors, in this study we evaluated whether a technique of allograft cartilage transplantation using PDGF-stimulated chondrocyte/seeded polycaprolactic acid (PCL) in rabbit articular cartilage defect can enhance matrix synthesis and integrity. Cartilage was harvested from knee joints of a New Zealand white rabbit. Chondrocytes were isolated, expanded in monolayer culture, treated with 10 ng/mL PDF and then seeded onto PCL scaffolds. Identical 4 mm diameter defects were created surgically in the articular cartilage of both knees. In total, 12 defects were equally allotted to experimental and control groups that were filled with PDGF-stimulated chondrocyte/PCL construct or left empty. Healing of defects were assessed 12 weeks post-surgery on the basis of macroscopic appearance and microscopic scores using the International Cartilage Research Society (ICRS) score. By gross evaluation, complete or partial filling of lesion sites with new thin cartilage-like tissue were observed in cell/scaffold treated defects in comparison to whitish fibrous tissue observed in controls. Histological evaluations showed newly formed repair tissue with hyaline characteristics in PDGF-stimulated cell/scaffold transplanted groups compared with fibrous connective tissue observed in untreated knee joints. This study demonstrates that it is possible to stimulate chondrocytes/PCL scaffolds with PDGF and subsequently produce in vivo repaired cartilage

Nerve Growth Factor and Basic Fibroblast Growth Factor Induce Human Endometrial Stem Cells Differentiation into Cholinergic Neuron-Like Cells

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The potential of cell therapy in nerve regeneration is promising, but is limited by the availability of suitable cell sources. Here, we introduce endometrial stem cells (EnSCs) as a potential cell source for this purpose and show that using nerve growth factor (NGF) and basic fibroblast growth factor (bFGF) signaling, human EnSCs can be efficiently differentiated into cholinergic neurons. Endometrial stem cells were isolated from donated biopsy specimens of human endometrial tissue by positive selection for CD146, CD105, CD90 and CD 44 markers using magnetic cell sorting. The cells were cultured under adherent condition and were induced to differentiate into cholinergic neuron-like cells in a chemically defined medium supplemented by a combination of bFGF and NGF. The differentiated cells were characterized by immunocytochemical detection of choline acetyltransferase (ChAT), microtubule associated protein 2 (MAP2) and neurofilament L. Although, these results need further in vitro and in vivo functional characterization, they demonstrate that endometrial stem cells could be considered as a potential source of cells for regenerative therapy of nervous system.

How Fluoride and Silver Make Bioactive Glasses Good Candidates for Regenerative Dentistry?

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Bioactive glasses have recently gained specific attentions in dentistry for treatment of dentine hypersensitivity. Fluoride-containing bioactive glasses are known to prevent dental caries by formation of fluorapatite in physiological solutions and reduction of dentine demineralization. This makes them good candidates for regenerative dentistry. Also, incorporation of silver into bioactive glasses can be used as an effective way to synthesize bone-bonding materials with combined bioactive and antimicrobial properties. In this study, the 58S glasses consisting of fluoride and silver were synthesized. The effects of molecular interactions on the formation of fluorapatite layer at the surface of samples in simulated body fluid were investigated. The results indicated that silver ions in the hydration layer of apatite crystals bound phosphate ions and formed clusters of silver phosphate, which were uniformly dispersed on the newly formed apatite crystals. Due to the high amount of fluoride release into the surrounding medium, these clusters could act as the nucleation sites for the formation of fluorapatite. All samples had antibacterial effects against different types of bacteria, which demonstrated their possible benefits for application in contaminated areas. These results show that bioactive glasses have the potential to be tailor-made for specific applications.