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P02-056

3D Bioprinting of Multi-layered Tubular Constructs using Esophageal Tissue-derived Bioinks for Esophageal Regeneration

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The esophagus is located between the pharynx and stomach. It has a hollow passageway structure that allows food to pass into the stomach. The incidence of esophageal diseases such as esophageal cancer, esophageal stenosis, and esophageal atresia is increasing, but recovery is difficult because of the weak esophageal regenerative ability. So, the treatments are performed esophageal resection and reconstruction with a gastric pull-up, jejunal free flap. These methods are prone to necrosis, sepsis, other complications, and in severe cases, death. [1] Therefore, an alternative to existing treatments is needed. A tissue engineering-based approach has been spotlighted recently. Most of the hollow structures being researched are manufactured by electrospinning on the drum collector. However, it is difficult to produce free-form and multi-layer structures and has poor mechanical properties. [2]
In this study, we developed an esophageal alternative construct by a new 3D printing technique that stretches when the material is ejected through the nozzle. Moreover, the decellularized esophageal bioinks were fabricated that mimic the composition of the esophageal tissue and the microenvironment of each layer and were printed. The construct has not only to produce a porous, free-form, multi-layered, and hollow structure but also mimic the morphological and structural characteristics of the actual esophagus.

Keywords
Esophagus, 3D bioprinting, Dragging technique, Decellularized bioink

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[2] Karbasi S, Fekrat F, Semnani D, Razavi S, Zargar EN (2016) Evaluation of structural and mechanical properties of electrospun nano-micro hybrid of poly hydroxybutyrate-chitosan/silk scaffold for cartilage tissue engineering, *Advanced biomedical research*, 5.

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STEM CELL 03

P02-057

The Angiogenic Potentials of Extracellular Vesicles Derived from Tissue-Resident Stem Cells

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Extracellular vesicles (EVs) play significant roles in intercellular communications. EVs released from various cell types deliver angiogenic mediators that regulate cardiovascular homeostasis and have opened up the perspectives for therapeutic angiogenesis. Their angiogenic potentials largely relie on their cellular source, therefore, one of the critical points to consider is the choice of an appropriate cell type for generating EVs. This study aimed to compare the anigogenic potentials of EVs derived from tissue-resident stem cells residing in cardiac (CSC) and adipose (ASC) tissue with bone marrow (BM-MSC). CSCs released the six times higher levels of EVs than that of BM-MSCs or ASCs, yet their size distribution was not differ according to mother cell types. Key angiogenic factors, such as VEGF, Ang-1, HGF, EGF, and bFGF, were significantly higher in EVs of CSCs than MSCs-BM or ASCs. The cytoprotective ability of EVs-CSC from from apoptotic signals and mitogenic ability to promote cell proliferation, migration, and tubulogenesis of HUVEC were significantly higher in EVs-CSCs than that of BM-MSCs and ASCs. Of note, these proangiogenic abilities of EVs derived from CSCs were prominent compared with those of EVs from MSCs. Ischemic hind limbs received EVs from CSCs showed the meaningful recovery of microcirculation, increased limb salvage and motor function, indicating their proangiogenic properties. Taken together, CSCs might be a promising cell source to produce therapeutic EVs for cardiovascular regeneration.

Keywords
Extracellular vesicles, Angiogenesis, Cardiac stem cells

P02-058

Combined treatment with a CHIR99021 and Forskolin reduces cell mass formation of human-induced neural stem cells transplanted into the injured spinal cord

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Patient-derived stem cells avoid the risk of transplantation rejection, and have been used to treat various intractable diseases. However, most stem cell-related research in regenerative medicine has focused on the manipulation of patient-specific stem cells, such as induced neural stem cells (iNSCs), not on their side effects, including overgrowth in tissue. We inhibited the proliferation of iNSCs using a small-molecule cocktail containing the glycogen synthase kinase 3 inhibitor CHIR99021 and the cyclic adenosine monophosphate activator forskolin. After 1 week after spinal cord injury, iNSCs ($4x10^4$ cells) were injected into the spinal cord injury site. After cell transplantation, 10 mg/kg forskolin and 12.5 mg/kg CHIR99021 were treated daily for 7 days. The iNSCs, which were positive for neural stem cell markers such as Nestin and Sox2, differentiated into neuronal cells positive for neuron-specific markers such as Tuj1, MAP2, and NeuN. We confirmed that CHIR99021 and forskolin combination treatment diminished the frequency of cell mass formation after transplant into sites of spinal cord injury, and extended axon outgrowth. The results suggest that CHIR99021 and forskolin combination treatment may represent a promising adjuvant strategy for stem cell therapy.

Keywords
induced neural stem cells, spinal cord injury, small molecules, transplantation, proliferation

P03-059

Effect of Osteogenic Peptide on Tonsil-derived Mesenchymal Stem Cells (TMSCs)

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Tonsil-derived mesenchymal stem cell (TMSC) is an alternative MSC source that is generally obtained from tonsils of children under 10 years old. As its name suggests, TMSCs retain characteristics of MSCs, differentiating into osteocytes, adipocytes or chondrocytes. It is considered as an appealing MSC source for clinical/research applications due to its relatively high proliferation rate and low immunogenicity. For an effective application of TMSCs in cell therapy such as bone regeneration, it is essential to shorten the time required for differentiation, minimizing the use of expensive differentiation factors. In this study, we tested synthetic osteogenic peptides denoted as PEP1, 2, 3, 4 to determine their potential inducibility on osteogenesis using TMSCs. The PEP1 and 4 induced osteogenesis of TMSCs in the range of 10 nM - 100 μM. In contrast, PEP2 and 3 inhibited osteogenesis at 100 μM but induced at around 10 nM. When we tested various concentrations of PEPs, PEP4 induced osteogenicity of TMSCs as the concentrations decreased, retaining the highest osteogenicity at 100 pM as evidenced by the increased staining of Alizarin red S and alkaline phosphatase as well as osteocalcin protein expression. We also found that the PEP4 itself could not initiate osteogenic differentiation of TMSCs, but it was rather functioning as an inducer of osteogenesis. This study demonstrates that osteogenic peptides specifically PEP4 facilitated the highest osteogenicity of TMSCs, but further investigation is required to determine their potential mechanism of action in promoting osteogenesis of TMSCs.

Keywords
Tonsil-derived mesenchymal stem cells (TMSCs), Differentiation, Osteogenesis, Osteogenic peptide

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Abstract

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Conclusion

We have fabricated an innovative artificial esophageal construct that mimics the native esophagus using 3D bioprinting. It is an advanced multilayered construct and esophageal mucosal and muscular bioinks that are morphologically, environmentally similar to the original esophagus using the dragging 3D printing and decellularized technique.

Also, we are currently applying this construct to confirm its suitability as a clinical esophageal construct through an animal test. The developed construct is a very promising approach that can be applied to the treatment of full-thickness circumferential esophageal defects and expected to be suitable for esophageal regeneration.

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