#528 - Experimental Study / Posters

Endochondral Bone Regeneration Using Chondrogenically Differentiated Human Induced Pluripotent Stem Cells

General Topics / Basic Sciences

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Background
Induced pluripotent stem cells (iPSCs) have been demonstrated to be a promising source for tissue regeneration because of their unlimited self-renewal capacity and ability to differentiate into all somatic cell types. Recently, there has been great interest in the use of iPSCs for bone regenerative strategies.

Objectives
The objective of this study was to investigate whether implantation of chondrogenically differentiated iPSC-derived mesenchymal stem cells (MSCs) could lead to bone regeneration of bone defects in nude mice.

Study Design & Methods
Human iPSCs (201B7 and 454E) were used. After generation of undifferentiated iPSCs into MSCs, chondrogenic differentiation was induced by three-dimensional culture. Twenty-eight male BALB/cAJcl-nu/nu mice were used. A 2-mm defect was created at the middle-third of the radius of each mouse. Chodrogenically differentiated iPSC-derived MSC pellets were implanted in the defect. For control animals, saline was implanted as sham treatment. For assessment of gene expression at bone defect sites, animals were euthanized at weeks 2. The newly generated tissues were harvested, and total RNA was extracted. Expression of human and mouse vascular endothelial growth factor (VEGF) and osteocalcin (OC) was analyzed by reverse transcription-polymerase chain reaction (RT-PCR). For radiographic assessment of bone regeneration, micro-computed tomography (μ-CT) imaging analysis was performed at week 8 after transplantation.

Results
In the treated groups, RT-PCR revealed positive expression of human VEGF, mouse VEGF, and mouse OC at the grafted bone defect sites, whereas expression of human OC was not detected at the defect sites. For the rate of bone regeneration assessed by μ-CT at week 8, 11 out of 11 (100%) radius in the 201B7 transplantation group achieved bone healing, and 7 out of 10 (70%) radius in the 454E2 transplantation group achieved bone healing. 2 out of 11 radius (18%) achieved bone healing in the control group. The bone regeneration rates in the treated groups were significantly higher than that in the control group.

Conclusions
Treating large bone defects caused by severe trauma, nonunion, infection, or tumor resection is a major clinical challenge in orthopaedic surgery, and utilizing tissue engineering technology is an attractive

approach. Recently, there have been increasing interest in regenerating bone through a cartilage-mediated process similar to endochondral bone ossification. In the current study, RT-PCR analysis at week 2 suggests that implanted pellets have angiogenic and chemotactic capacities. Histological findings indicate typical bone healing process of endochondral ossification. Our results for the first time demonstrated that grafting bone defects with chondrogenically differentiated iPSC-derived MSCs led to rapid successful bone regeneration through endochondoral bone ossification. Our results provide insights on the development of a promising technology for endochondral bone regeneration using iPSCs. Implantation of chondrogenically differentiated iPSC-derived MSCs could be a novel system to repair large bone defects.