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Three-dimensional Spheroid Culture Enhances Multipotent Differentiation and Stemness Capacities of Human Dental Pulp-derived Mesenchymal Stem Cells by Modulating MAPK and NF-kB Signaling Pathways

Ya-Hui Chan[#1], Yu-Chieh Lee[#2], Chia-Yi Hung[3], Pi-Ju Yang[4], Pin-Chuang Lai[5], Sheng-Wei Feng[6,7,8]
Affiliations expand

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Abstract

Background: Three-dimensional (3D) culture of mesenchymal stem cells has become an important research and development topic. However, comprehensive analysis of human dental pulp-derived mesenchymal stem cells (DPSCs) in 3D-spheroid culture remains unexplored. Thus, we evaluated the cellular characteristics, multipotent differentiation, gene expression, and related-signal transduction pathways of DPSCs in 3D-spheroid culture via magnetic levitation (3DM), compared with 2D-monolayer (2D) and 3D-aggregate (3D) cultures.

Methods: The gross morphology and cellular ultrastructure were observed in the 2D, 3D, and 3DM experimental groups using scanning electron microscopy (SEM) and transmission electron microscopy (TEM). Surface markers and trilineage differentiation were evaluated using flow cytometry and staining analysis. Quantitative reverse transcription-polymerase chain reaction and immunofluorescence staining (IF) were performed to investigate the expression of differentiation and stemness markers. Signaling transduction pathways were evaluated using western blot analysis.

Results: The morphology of cell aggregates and spheroids was largely influenced by the types of cell culture plates and initial cell seeding density. SEM and TEM experiments confirmed that the solid and firm structure of spheroids was quickly formed in the 3DM-medium without damaging cells. In addition, these three groups all expressed multilineage differentiation capabilities and surface marker expression. The trilineage differentiation capacities of the 3DM-group were significantly superior to the 2D and 3D-groups. The osteogenesis, angiogenesis, adipogenesis, and stemness-related genes were significantly enhanced in the 3D and 3DM-groups. The IF analysis showed that the extracellular matrix expression, osteogenesis, and angiogenesis proteins of the 3DM-group were significantly higher than those in the 2D and 3D-groups. Finally, 3DM-culture significantly activated the MAPK and NF-kB signaling transduction pathways and ameliorated the apoptosis effects of 3D-culture.

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In Vitro Anti-cancer Activity of Adipose-Derived Mesenchymal Stem Cells Increased after Infection with Oncolytic Reovirus

Abouzar Babaei[1], Hossein Bannazadeh Baghi[2,3], Akram Nezhadi[4], Zahra Jamalpoor[1]
Affiliations expand

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Abstract

Purpose: Reovirus type 3 Dearing (ReoT3D), a wild type oncolytic virus (OV) from the *Reoviridae* family, kills KRAS mutant cancer cells. However, the use of OVs has faced

with some limitations such as immune responses, and delivery of OVs to the tumor sites in systemic therapy. To solve this, and also to increase the anti-cancer effects of these OVs, mesenchymal stem cells (MSCs) might be used as an effective vehicle for OVs delivery. In this study, we examined the anti-cancer effects of human adipose derived-MSCs (AD-MSCs) as a vehicle of ReoT3D against human glioblastoma cells. ***Methods:*** Here, AD-MSCs were characterized and toxicity of ReoT3D on them was determined by 3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide (MTT) assay. Then, capability of AD-MSCs for virus production was assessed by real-time polymerase chain reaction (PCR), and different in vitro anti-cancer experiments were applied for our anti-cancer purposes. ***Results:*** Our results from toxicity assay revealed that the isolated and provoked AD-MSCs were resistant to nontoxic concentration multiplicity of infection (MOI) >1 pfu/cells of ReoT3D. In addition, the results indicated that AD-MSCs were susceptible for virus life cycle complementation and were capable for production of virus progenies. Furthermore, our results showed that AD-MSCs had oncolysis effects and increased the anti-cancer effects of ReoT3D. ***Conclusion:*** AD-MSCs as a susceptible host for oncolytic reovirus could increase the anti-cancer activity of this OV against glioblastoma multiforme (GBM) cell line.