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Multiple Nanosecond Pulsed Electric Fields Stimulation With Conductive Poly (L-lactic acid)/Carbon Nanotubes Films Maintains the Multipotency of Mesenchymal Stem Cells During Prolonged In Vitro Culture

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Abstract

Mesenchymal stem cells (MSCs) gradually lose multipotency when cultured for prolonged durations in vitro, which significantly hinders subsequent clinical applications. Nanosecond pulsed electric fields (nsPEFs) have been recently investigated to overcome this problem in our lab, however, the differentiation potency of MSCs could only be partially and transiently recovered because the nsPEFs can only be delivered to suspended cells once. Here, we develop a new strategy to apply multiple nsPEFs to adherent MSCs with conductive films to mitigate the decreasing multipotency of prolonged cultured MSCs. The poly (L-lactic acid)/graphitized-carboxylated functionalized carbon nanotubes (PLLA/CNT) films were fabricated as conductive cell culture platforms. Both single and multiple nsPEFs stimulation could significantly increase the differentiation potential of MSCs, as evidenced by upregulated expression of chondrogenic, osteogenic and adipogenic-related gene (SOX9, RUNX2, PPAR-γ), as well as increased production of proteoglycans, mineralized calcium and triglycerides. Multiple nsPEFs stimulation demonstrated significant efficacy in upregulating expression of pluripotency genes of OCT4A (3.5~4.5-folds), NANOG (3.5~4.0-

folds) and SOX2 (1.5~2.0-folds), and stably maintaining high expression of these genes for nearly 23 days. Notably, nsPEFs stimulation did not significantly shorten telomere length. In conclusion, multiple nsPEFs stimulation could effectively mitigate decreasing multipotency of MSCs during prolonged in vitro culture

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Co-transplantation of tonsil-derived Mesenchymal Stromal Cells in Bone Marrow Transplantation Promotes Thymus Regeneration and T Cell Diversity Following Cytotoxic Conditioning

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Abstract

Bone marrow (BM) transplantation (BMT) represents a curative treatment for various hematological disorders. Prior to BMT, a large amount of the relevant anticancer drug needed to be administered to eliminate cancer cells. However, during this pre-BMT cytotoxic conditioning regimen, hematopoietic stem cells in the BM and thymic epithelial cells were also destroyed. The T cell receptor (TCR) recognizes diverse pathogen, tumor and environmental antigens, and confers immunological memory and self-tolerance. Delayed thymus reconstitution following pre-BMT cytotoxic conditioning impedes de novo thymopoiesis and limits T cell-mediated immunity. Several cytokines, such as RANK ligand, interleukin (IL)-7, IL-22 and stem cell factor, were recently reported to improve thymopoiesis and immune function following BMT. In the present study, it was found that the co-transplantation of tonsil-derived mesenchymal stromal cells (T-MSCs) with

BM-derived cells (BMCs) accelerated the recovery of involuted thymuses in mice following partial pre-BMT conditioning with busulfan-cyclophosphamide treatment, possibly by inducing FMS-like tyrosine kinase 3 ligand (FLT3L) and fibroblast growth factor 7 (FGF7) production in T-MSCs. The co-transplantation of T-MSCs with BMCs also replenished the CD3+ cell population by inhibiting thymocyte apoptosis following pre-BMT cytotoxic conditioning. Furthermore, T-MSC co-transplantation improved the recovery of the TCR repertoire and led to increased thymus-generated T cell diversity.