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Novel Effect of Biphasic Electric Current on *In Vitro* Osteogenesis and Cytokine Production in Human Mesenchymal Stromal Cells

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About

Abstract

Electrical stimulation (ES) can activate diverse biostimulatory responses in a range of tissues. Of various forms of ES, the application of biphasic electric current (BEC) is a new approach to bone formation. This study is to investigate the effects and mechanism of action of BEC in osteoblast differentiation and cytokine production in human mesenchymal stromal cells (hMSCs). Using an *in vitro* culture system with a modified version of the BEC stimulator chip used in our previous study, we exposed hMSCs to a 100Hz ES with a magnitude of 1.5/15 $\mu A/cm^2$ for 250/25μs. hMSCs showed increased proliferation during static BEC stimulation for 5 days. However, alkaline phosphatase activity and calcium deposition were enhanced in hMSCs 7 days after the stimulation, rather than during the period of ES. BEC induced vascular endothelial growth factor (VEGF) and BMP-2 production; the former can enhance the proliferation of human umbilical vein endothelial cells in culture

using conditioned media from BEC cultures. Treatment with selective inhibitors of p38 MAPK (SB203580) or Erk (PD98059), as well as calcium channel blockers (verapamil and nifedipine), reduced the BEC-mediated increase of VEGF expression and cell proliferation. These findings reveal that BEC is involved in the osteoblast differentiation of hMSCs through enhancement of cell proliferation and modulation of the local endocrine environment through VEGF and BMP-2 induction through the activation of MAPK (Erk and p38) and the calcium channel. Thus, local stimulation using BEC might be most beneficial in promoting osteogenic differentiation of hMSCs, resulting in enhanced bone formation for bone tissue engineering.