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Physical Regulation of Human Mesenchymal Stem Cells through Altered Calcium Dynamics

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The role of cytosolic calcium oscillation has long been recognized in the regulation of cellular and molecular interactions. Information embedded in calcium oscillation can provide molecular cues for cell behaviors such as cell differentiation. Although calcium dynamics is versatile and likely to depend on the cell type, the calcium dynamics in human mesenchymal stem cells (hMSCs) and its role in differentiation are yet to be fully elucidated. This study is therefore aimed at elucidation of hMSC differentiation through altered calcium signaling in response to electrical stimulation.

The calcium oscillation under various electrical stimulations in the medium with or without osteoinductive factors was monitored and recorded using the calcium-sensitive dye, Fluo-4. In addition, we used real-time RT-PCR and colorimetric techniques to quantify the extent of osteogenic differentiation. The typical markers, including alkaline phosphatase activity (ALP), calcium mineralization and genes decoding the osteogenic proteins, were measured. Additionally, potential calcium channel-dependent signaling pathways were also investigated using selective channel inhibitors.

Our findings indicate that the frequency of calcium oscillations decreased rapidly with osteodifferentiation to the level observed in terminally differentiated human osteoblasts, whereas the amplitude of each oscillation remained essentially unchanged. Moreover, the calcium oscillations appear to serve as a bidirectional signal during hMSC differentiation. While an altered calcium oscillation pattern may be an indicator for hMSC differentiation, it is also likely involved in directing hMSC differentiation. Treatment of hMSCs with a non-invasive electrical stimulation, for example, not only altered the calcium oscillations but also facilitated osteodifferentiation. We hypothesize that electrocoupling to the phospholipase C molecules near the cell surface likely mediates the altered calcium dynamics and subsequent hMSC differentiation in response to non-invasive electrical stimulation. Regulation of the calcium oscillation by external physical stimulation could amplify hMSC differentiation into a tissue-specific lineage, and may offer an alternate biotechnology to harness the unique properties of stem cells.

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