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Altered Cellular Mechanics during Osteogenic Differentiation of Human Mesenchymal Stem Cells

I. A. Titushkin [1] and M. Cho [1]

Unique properties of bone-marrow derived stem cells make them a promising candidate for tissue engineering and regenerative medicine. However biochemical and biophysical events taking place during stem cell commitment to a tissue-specific lineage remain to be elucidated for full utilization of recuperative potential. In this study we seek to characterize the biomechanical changes in human mesenchymal stem cell (hMSC) membrane and cytoskeleton in osteogenic differentiation, and show that the prospective use of external physical force to regulate stem cell fate through manipulation of the mechanical properties.

First, we used AFM micro-indentation technique to show that the cytoskeleton elasticity of hMSC (3.2 ± 1.4 kPa) is much higher than that of fully differentiated osteoblasts (1.8 ± 0.8 kPa). Upon 10-day differentiation induction with the osteogenic factors, the hMSC Young's modulus decreased apparently due to actin cytoskeleton reorganization. In native mesenchymal stem cells, cytoskeleton is composed of thick actin stress fibers, whereas in terminally differentiated osteoblasts actin filaments are organized as a dense thin meshwork.

Second, we studied the plasma membrane mechanics using Laser Optical Tweezers (LOT) to extract membrane tethers from the outer cell membrane. The average tether length was much higher in hMSC (10.6 ± 1.1 μm) than in fully committed osteoblasts (4.0 ± 1.2 μm). Our results indicate that this difference is likely due to a weaker membrane/cytoskeleton interaction in hMSCs compared to osteoblasts. As hMSCs undergo osteogenic differentiation, the membrane tether length decreased almost by a 2-fold after 10 days in the osteoinductive media. The temporal dynamics of this process correlates with the change in the cytoskeleton elasticity.

Finally, we explored the effect of electrical stimulation on the stem cell mechanics. Application of a 1 Hz, 2 V/cm stimulation caused a decrease in the stem cell elasticity but had no effect on the hMSC membrane tether length. We hypothesize that electrical stimulation induces an electric field-dependent cytoskeleton remodeling and may be used to control the hMSC proliferation/differentiation. It appears that an external physical force may be used to manipulate the differentiation mechanisms of stem cells through controlled changes in the cellular mechanics to improve the efficacy of stem cell-based tissue construct development.

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[1]Department of Bioengineering, University of Illinois, Chicago, IL 60607