Electrophysiological Modulation of Human Mesenchymal Stem Cell Behavior

Sarah Sundelacruz[1], Michael Levin[2], David L. Kaplan[1]
Corresponding author: david.kaplan@tufts.edu
[1] Dept. of Biomedical Engineering, Tufts Univ., Medford, MA, USA
[2] Dept. of Biology & Ctr. for Regenerative and Developmental Biology, Tufts Univ., Medford, MA, USA

Introduction

Electrophysiological signals are potent regulators of cell proliferation, differentiation, migration, and wound healing.[1-3] Modulation of bioelectric properties, such as membrane potential, of stem cells in particular holds great potential for regenerative medicine efforts. Our study has uncovered functional roles for membrane potential (V_{mem}) in human mesenchymal stem cell (hMSC) differentiation, maintenance of differentiated phenotype, and wound healing properties.

Materials and Methods

hMSCs were differentiated in monolayer or on silk scaffolds into which a defect was introduced. Cells were depolarized by ouabain, $BaCl_2$, or elevated K^+; or hyperpolarized by pinacidil or diazoxide. Osteogenic (OS) and adipogenic (AD) differentiation was assessed by qPCR and other tissue-specific assays. Cellularization of the wound was visualized by histology. Student's t-test was used to determine significance ($p<0.05$).

Results

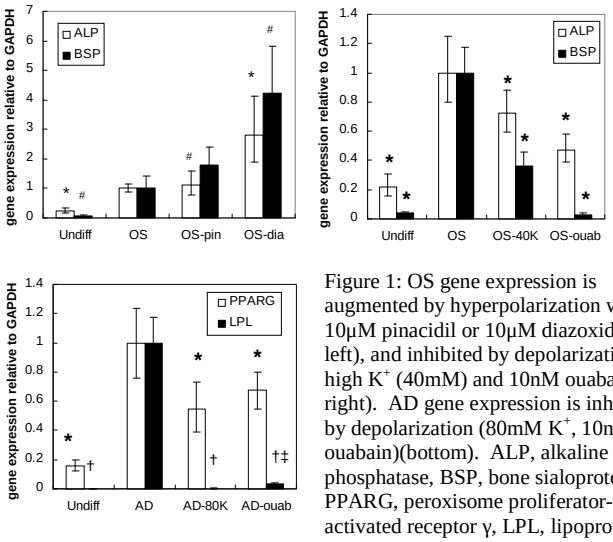

Figure 1: OS gene expression is augmented by hyperpolarization with 10μM pinacidil or 10μM diazoxide (top left), and inhibited by depolarization with high K^+ (40mM) and 10nM ouabain (top right). AD gene expression is inhibited by depolarization (80mM K^+, 10nM ouabain)(bottom). ALP, alkaline phosphatase, BSP, bone sialoprotein, PPARG, peroxisome proliferator-activated receptor γ, LPL, lipoprotein lipase. $p<0.05$

hMSCs exhibited endogenous V_{mem} hyperpolarization during differentiation. V_{mem} disruption by external depolarization inhibited differentiation, while external hyperpolarization augmented OS differentiation (Fig.1).[4] V_{mem} sensitivity was retained in mature OS- or AD-differentiated hMSCs: depolarization diminished key bone and fat markers (Fig.2). These results suggest that hyperpolarization is necessary for both differentiation and maintenance of the differentiated phenotype. The ability to alter differentiated state of mature cells suggests that plasticity can be induced in cells for wound healing applications. In a 3D *in vitro* model of bone wound healing, $BaCl_2$-induced depolarization of OS-differentiated hMSCs improved cell infiltration into the wound (Fig.3).

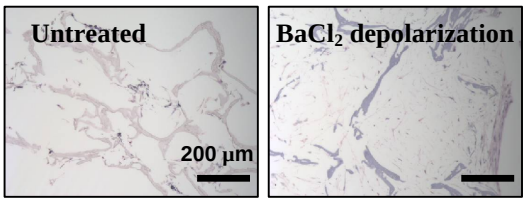

Figure 3: Depolarization of OS-differentiated hMSCs promotes cellularization of a defect introduced into an *in vitro* bone model.

Discussion and Conclusions

This study demonstrates that rational control of V_{mem} can modulate hMSC behavior for improved differentiation and wound healing. Electrophysiological manipulation of stem cells is a novel approach for tissue engineers to develop better *in vitro* tissue models and wound healing strategies. Further characterization of the ionic and molecular species involved in V_{mem} signaling will facilitate our ability to translate this knowledge of stem cell bioelectric properties into regenerative medicine strategies.

References

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Acknowledgments – We gratefully acknowledge funding from the NIH P41 Tissue Engineering Resource Center, NHTSA, DARPA, and NSF.

Disclosures – The authors have nothing to disclose.