# THE MECHANOTRANSDUCTION OF HYDROSTATIC PRESSURE BY MESENCHYMAL STEM CELLS

Abstract

By

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Understanding the underlying mechanisms of mesenchymal stem cell (MSC) mechanotransduction has important implications for tissue engineering and regenerative medicine. Hydrostatic pressure (HP) is the dominant load bearing mechanism in joints; however, the mechanotransductive pathways utilized in response to HP are not well understood. Cell-matrix interactions, cytoskeletal organization, and calcium ion ($Ca^{++}$) signaling have all been proposed to regulate MSC mechanotransduction. This dissertation aims to provide insight into the roles of these pathways in the response of MSCs to HP.

To test whether the response of MSCs to HP depends on cell-matrix interactions, MSCs were seeded into either agarose or fibrin hydrogels and exposed to cyclic HP. Agarose hydrogels were found to support a spherical cellular morphology, while MSCs seeded into fibrin hydrogels attached and spread. While agarose hydrogels better supported chondrogenesis of MSCs, HP only enhanced chondrogenesis in fibrin hydrogels. This study demonstrates that a complex relationship between cell-matrix interactions and HP mechanotransduction plays a key role in regulating the chondrogenic differentiation of MSCs.

Next, the roles of integrins and the cytoskeleton in the mechanotransduction of HP were examined. Matrix stiffness and/or density modulated the development of the pericellular matrix

and consequently integrin binding and cytoskeletal structure. This study suggests that physiological cues such as HP enhance chondrogenesis of MSCs as the pericellular environment matures and the cytoskeleton adapts, and points to a novel role for vimentin in the mechanotransduction of HP.

Intracellular $Ca^{++}$ concentrations have been found to increase with application of HP, yet the role of $Ca^{++}$ signaling in the mechanotransduction of HP had yet to be investigated. $Ca^{++}$ signaling was found to regulate the chondrogenic response of MSCs and modulate the reorganization of vimentin in response to HP. Further, HP was found to initiate $Ca^{++}$ signaling by activating the purinergic signaling pathway.

These results suggest a complex interplay between cell-matrix interactions and $Ca^{++}$ signaling may transduce HP via vimentin adaptation to loading, indicating that the mechanotransduction of HP is distinct from other loading modalities. Overall, the understanding gained about the mechanisms regulating the chondrogenic response to HP could have important implications for tissue engineering and regenerative medicine.