Cyclic Tensile Strain Promotes COL-I Induced Osteogenic Differentiation and Enhances Lineage Commitment Gene Focusing of Human Mesenchymal Stem Cells

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ABSTRACT

Mechanical forces are vital to bone formation *in vivo*, but relatively little is known about the osteogenic responses of human mesenchymal stem cells (hMSCs) to mechanical forces exerted on them via their integrin attachment to specific extracellular matrix proteins, and the molecular mechanisms regulating this osteogenesis. This thesis investigates the osteogenic effects of cyclic tensile strain on hMSCs attached to collagen type 1 (COL-I). Osteogenesis was measured by altered expression levels of key osteogenic marker genes and subsequent matrix mineralization. We discovered that cyclic tensile strain promotes COL-I-induced osteogenic differentiation of hMSCs through increased activation of signaling proteins, resulting in osteogenic gene upregulation leading to increased mineralization of the matrix. Integration of external signals regarding a cell's microenvironment occurs via specific heterodimeric integrin pairings, bound both to extracellular matrix proteins and a network of cytosolic proteins, including signaling proteins such as focal adhesion kinase (FAK). We showed that specific tyrosine residues of FAK (Y397, Y576/7, and Y925) are responsible for downstream osteogenic effects using retrovirally infected mutant cell lines, and that osteogenesis is also dependent on extracellular signal-related kinase (ERK) 1/2, which activates key bone gene transcription factors. Additionally, our results show that osteogenic differentiation is associated with a downregulation of key marker genes from potential alternative lineages for hMSCs through an ERK-dependent pathway. This study provides novel insights into the pro-osteogenic effects of a cyclic mechanical strain stimulus on hMSCs attached to COL-I, deepening the understanding in this area to further develop the potential of hMSCs in therapeutic tissue regeneration applications.