Laminin-5 promotes intracellular signaling pathways resulting in the osteogenic differentiation of human mesenchymal stem cells

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ABSTRACT

The function of laminins in bone, in particular laminin-5, is not well characterized. Moreover, little is known about the molecular mechanisms governing osteogenic stem cell differentiation *in vivo*. This thesis focuses on the intracellular signaling pathways that link extracellular matrix (ECM) binding, via integrins and other cell surface receptors, to the stimulation of osteogenic transcription factors, genes, and resulting matrix mineralization. We discovered that focal adhesion kinase (FAK) signaling pathways represent an early commitment step in the differentiation of human mesenchymal stem cells (hMSC) toward an osteogenic lineage when plated on laminin-5. This activation was followed by phosphorylation of extracellular signal-related kinase (ERK) 1/2 which resulted in phosphorylation of the Runx2/Cbfa-1 transcription factor that regulates osteogenic gene transcription. Distinct studies using either the MEK inhibitor PD98059 to inhibit ERK 1/2 or small inhibitory RNAs (siRNA) specific to FAK caused a significant decrease in the osteogenic potential of hMSC on laminin-5, measured by decreases in protein phosphorylation, osteogenic gene expression, alkaline phosphatase activity, and matrix mineralization. This study will provide novel insight into a field in which the potential role of laminin-5 has been neglected.