Mechanical Regulation of Wnt/β-catenin Signaling in Bone Cells

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The Wnt/β-catenin signaling pathway is an important regulatory pathway in development and maintenance of various tissues, including bone. Active Wnt interacts with the frizzled/LRP receptor activating dishevelled, which in turn inactivates the GSK-3β complex and allows β-catenin to accumulate in the cytoplasm. β-catenin translocates to the nucleus where it activates a wide number of developmental target genes. Wnt can be sequestered by soluble frizzled related protein causing the inactivation of dishevelled, allowing for activation of the GSK-3β complex. This activated complex binds β-catenin and targets it for degradation. In addition to its other major role as a linker between cadherins and the actin cytoskeleton, β-catenin accumulation in the cytoplasm and subsequent translocation to the nucleus is a key step in the wnt/β-catenin signaling pathway. In bone, wnt/β-catenin signaling regulates skeletal formation, limb development and osteoblast maturation. Both active and inactive wnt/β-catenin signaling regulate bone cell development, active wnt/β-catenin signaling promotes osteoblast formation, while inactive wnt/β-catenin signaling inhibits osteoclast differentiation. Mechanical regulation of bone cells occurs through a process known as mechanotransduction which can be induced by fluid shear stress that occurs across the surfaces of osteoblasts and osteocytes, the effector cells of mechanotransduction. We hypothesize that knocking down β-catenin expression in mouse osteoblasts and osteoprogenitors will change the way these cells respond to fluid shear stress and regulate expression of relevant bone target genes. The future aims of this project are to assess the role of β-catenin during fluid shear stress induced osteoprogenitor cell differentiation by examining the expression of important osteoblast differentiation markers including: runx2, COX-2, osteopontin, and osteocalcin and evaluate the significance of β-catenin during differentiation of bone marrow stromal cells.