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Cross-Talk between bone morphogenetic protein and canonical Wnt pathways during osteoblast differentiation

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Bone morphogenetic proteins (BMPs) and Wnts play essential roles in modeling and remodeling of bones. The evolutionarily conserved BMP and Wnt pathways are independent signaling mechanisms with different ligands, receptors and intracellular signal transducers. However, these two pathways control bone formation cooperatively. Activation of canonical Wnt signaling induces the differentiation of pluripotent MSCs into osteoblast progenitors and signals them to maintain their precursor status. Activation of BMP signaling stimulates these osteoprogenitor cells to further differentiate into mature osteoblasts. After becoming osteoblasts, both the Wnt and BMP signaling pathways promote further differentiation. The focus of the present study is to focus on the cross-talk of BMP and canonical Wnt pathways and define how they cooperate synergistically in osteoblast differentiation. Utilizing our previously validated in silico and *in vitro* screening process, we identified multiple FDA approved and novel small molecules that are able to inhibit sclerostin's interaction with its receptor, thus potentiating the canonical Wnt pathway. We next confirmed that these small molecules result in the expected known effects of sclerostin blockade, including: (1) Enhancement of canonical Wnt signaling, (2) Enhancement of BMP signaling intensity, (3) Enhancement of mineralization *in vitro* and (4) Produce dose-dependent ectopic mineralization in a challenging in vivo subcutaneous environment. We finally show that the small molecule sclerostin blockers are able to directly regulate BMP/Smad1 signal termination, thus further potentiating the BMP pathway by extending the duration of BMP signaling *in vitro*.

Biography

Sreedhara Sangadala has completed his PhD from University of Georgia, Athens, Georgia, the USA in 1990, M.Phil. from Jawaharlal Nehru University, New Delhi in 1985. He has developed several novel methods: (i) Production and characterization of monoclonal antibodies to various cell surface receptors and (ii) Cloning and characterization of several genes from prokaryotic and eukaryotic systems (iii) Development of novel biochemical purification methods for several proteins, peptides, and compounds. (iv) Performed extensive protein and enzyme engineering to derive recombinants with desired properties, (v) Performed structural determination of oligosaccharides and oligopeptides on several mammalian cell surface glycoproteins. (vi) Performed various structure-based drug designing to address specific regulation of several biological pathways. (vii) Successfully developed several structure-based and ligand-based drug molecules with osteogenic properties.

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