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Bone morphogenetic protein-independent induction of osteogenesis by FK506

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Osteoinductive Bone Morphogenetic Proteins (BMP), including BMP-2, have a unique capability of inducing bone formation and a regenerative response. While they are an effective alternative to autografts and allografts, the supraphysiological doses of rhBMP-2 have led to clinically-adverse side effects. The immunophilin FK-binding-protein-12 (FKBP12) is an intracellular BMP repressor and serves as a "guardian" to prevent leaky signaling under sub-optimal ligand concentrations. FKBP12 prevents the type II receptor from phosphorylating the type I receptor and thus prevents the association and subsequent phosphorylation of intracellular signaling molecules, Smads. In an, in silico targeted drug design project we screened and identified small molecules that would interact with the cytosolic portion of the BMPRI and disrupt FKBP12 binding. Our targeted design process identified several FDA-approved macrolides that are known immunosuppressive agents (including FK506, and rapamycin). Here, we show an osteogenic activity of FK506 as a stand-alone agent both in vitro and in vivo. We tested the paradigm of transient activation of BMP signaling through FK506 delivery to initiate the local osteoinductive cascade for induction of bone without adjunctive recombinant BMP or implanted MSCs. For in vivo bone induction, FK506 was applied without any exogenously added rhBMP-2 on collagen disks and surgically placed. Bone formation ectopically induced by rhBMP-2 was significantly increased by FK506-mediated augmentation. Our findings suggest that the use of FK506 enhances the osteoblastic differentiation of BMP-responding cells in vitro and new bone formation induced by rhBMP-2 in vivo. These data present a novel approach to induce bone formation through small molecule delivery and could have significant clinical implications in a variety of bone regeneration applications.

Biography

Sreedhara Sangadala has completed his Ph.D. from University of Georgia, Athens, Georgia, 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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