

Bone morphogenetic proteins, tissue engineering and regeneration

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Among the many tissues in the human body bone has the highest potential for regeneration and repair. Bone grafts have been used by surgeons to aid in the repair of recalcitrant bone fractures. Urist made the key discovery that demineralized lyophilized segments of rabbit bone induced new bone formation when implanted in an intramuscular site. Studies in my laboratory dissected the bone morphogenetic cascade into distinct steps such as chemotaxis, mitosis and differentiation of cartilage and replacement by bone. The sequential morphogenetic cascade is reminiscent of cartilage and bone morphogenesis in the embryonic limb bud with implications for isolation of morphogens for bone induction. It is traditional to isolate morphogens in fly and frog embryos by genetic approaches, expressed sequence tags, expression cloning, differential displays and subtractive hybridization. The information from flies and frogs are then extended to mice and men. I will demonstrate a non-traditional approach of morphogen isolation from adult bone by the biochemical approach. This type of approach has resulted in a superfamily of bone morphogenetic proteins (BMPs) and cartilage-derived morphogenetic proteins (CDMPs). BMPs are pleiotropic molecules with discrete thresholds for their biological actions. The motogenic, mitogenic and morphogenetic actions

of BMPs are concentration dependent. BMPs have actions beyond bone as gleaned from gene knockout experiments with homologous recombination. BMPs have a pivotal role in heart, kidney, skin, eye and tooth development. BMPs elicit their actions via specific BMP receptors I and II. These are membrane bound serine/threonine protein kinases. The cytoplasmic substrates for BMP-receptor kinases are Smads 1, 5 and 8 which associate with Smad 4 prior to nuclear translocation to activate the transcriptional machinery. Thus BMPs appear to play multiple roles from initial pattern formation, cell differentiation, morphogenesis and maintenance of adult tissues and in regeneration and repair of damaged tissues. The cloning of BMPs and related morphogens has led to clinical applications in orthopaedic surgery, dentistry, plastic and reconstructive surgery. Examples of clinical applications in orthopaedics, craniofacial and periodontal surgery will be exemplified. The emerging advances in BMPs will facilitate the design and manufacture of spare parts for human skeleton based on tissue engineering principles. Tissue engineering is the science of manufacture of spare parts for the human body based on morphogens, stem cells, extracellular matrix-based biomimetic biomaterials and bioengineering.