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Bone Graft Substitutes in the Upper Extremity

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Orthobiologics is an expanding discipline within the field of musculoskeletal surgery. In 1965, Urist and colleagues [1] first reported that extracts from demineralized bone matrix induced new bone formation when implanted in muscle. Scientists have thereafter endeavored to develop demineralized bone matrix-based bone graft substitutes to induce bone healing. Advances in bone graft substitute development are now revolutionizing surgical practice. The ability to stimulate bone healing and restore structural integrity while avoiding donor site morbidity has the potential to improve patient outcomes and satisfaction while decreasing morbidity and costs in the management of bone defects.

In 1972, Reddi and Huggins [2] first reported that bone morphogenetic proteins (BMPs) were involved in bone formation. Sampath and Reddi [3] developed an assay to analyze bone morphogenetic protein activity in rats in 1983, and determined that BMPs initiated a cascade of events leading to bone healing through the modulation of interactions in the mesenchymal stem cells of adjacent tissues (ie, fascia, peripheral blood, bone marrow, periosteum, and cancellous bone). More than 15 BMPs have now been identified that bind to stem cell receptors and trigger proliferation and differentiation, resulting in bone regeneration and repair [4].

In addition to bone morphogenetic proteins, there is an extensive array of other bone graft substitutes available that may serve as gap fillers and restore structural integrity [5]. These bone graft substitutes can provide structural support and act as a scaffold for new bone formation. Popular demand and the potential economic benefits of using graft substitutes are likely to increase routine usage of these materials in the future.

Physicians may now choose among a wide variety of bone graft substitutes. These substitutes include bone allograft, injectable demineralized bone matrix with the entire cascade of bone morphogenetic proteins, recombinant gene-produced BMP-7 and BMP-2, and synthetic ceramic mineral substitutes that provide structural support [6]. The high market value of these materials has provided the commercial incentive for their development. The purpose of this article is to help the practicing hand surgeon to understand the differences among these products, so that he or she can make informed decisions regarding product selection.

Fracture healing is a complex physiological process that involves several cell types [7]. An understanding of the cells that participate in fracture healing and the signaling molecules that direct cellular function will aid scientists and physicians in understanding the methods used to promote fracture healing. Stable reduced extremity fractures undergo direct primary bone healing. Less stable fractures heal by secondary endochondral ossification. Endochondral bone formation occurs as undifferentiated cells from the periosteum and adjacent soft tissues form chondroblasts at the fracture site. The bone marrow may also supply cells that contribute to endochondral ossification. Chondrocytes extrude a matrix rich in Type II collagen and proteoglycans. At approximately 3 weeks after fracture, the matrix is modified as phosphatidate enzymes (alkaline phosphatase) hydrolyze phosphate esters to provide phosphate groups in order to allow calcium accretion. The initial calcium deposits form an early immature callus. Once the matrix is calcified, osteoclasts

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begin to absorb the calcified cartilage, making way for penetration of the tissue by blood vessels. Mesenchymal cells accompany the penetrating blood vessels and differentiate into osteoblasts to lay down woven bone.

What is bone?

Bone is the composite tissue comprised of bone matrix and mineral. Type I collagen comprises 90% of the bone matrix. Various growth factors permeate the bone matrix [7]. These growth factors include insulinlike growth factor (IGF)-1, IGF-2, transforming growth factor (TGF)-B, platelet-derived growth factors (TDGFs), basic fibroblast growth factor (bFGF), and BMPs. These growth factors regulate osteoblast differentiation, development, and function.

The mineral component of bone is comprised of hydroxyapatite [3Ca3(PO4)2(OH)2] [8]. Hydroxyapatites are the spindle- or plate-shaped crystals found on the Type I collagen fibers. Cortical bone is densely calcified. Approximately 80% to 90% of the volume of cortical bone is calcified. Cancellous bone in the intermedullary canal and metaphyses is only 15% to 20% calcified. Woven bone is the immature bone of fracture healing. Woven bone has little cellular organization and lacks strength. It gradually remodels along the lines of stress to form stronger organized lamellar mature bone.

Osteoblasts produce collagen and osteoid ground substance (matrix) before calcification. Osteoblasts never appear individually, but form in clusters and line the layer of bone matrix that they are producing. Calcification of the osteoid matrix begins in earnest at approximately 10 days after injury. Mesenchymal stem cells from the endosteum or periosteum first differentiate to become periosteoblasts and then evolve into osteoblasts. There are three correlating processes involving bone formation. The osteoblasts initially rapidly deposit collagen as a thick unmineralized osteoid seam. Following the deposition of collagen, mineralization begins at a rate equal to the collagen synthesis. The collagen synthesis then decreases while mineralization continues. Collagen cross-linking occurs concurrently with calcium deposition during early immature bone formation. Osteoblasts trapped in the bony matrix become osteocytes (bone maintenance cells). Osteocytes derive their nourishment from canaliculi, long cell processes that interconnect the osteocytes. At this point, osteocyte metabolic activity decreases although matrix proteins are still produced.

Howship's lacunae are vascularized, three-dimensional, microscopic cutting cones that invade immature woven bone. Osteoclasts form the border of vascularized Howship's lacunae. Osteoclastics create an acidic environment that dissolves hydroxyapatite crystals. Cathepsins resorb and digest the residual collagen matrix by proteolysis [9]. Osteoblasts then accrete organized mature lamellar bone that further aligns during modulation by mechanical stress.

Terms

When discussing bone graft substitutes, three terms are commonly involved, and the definitions need to be understood. Osteoconduction is the process, sometimes termed "creeping substitution," whereby decalcified bone matrix (DBM) provides a passive structural scaffold for invasion by surrounding osteoprogenitor cells to form new bone. Examples include tri-calcium phosphate crystals, calcium sulfate crystals, and hydroxyapatite or coral. Osteoinduction uses blood-borne proteins, growth factors, and cytokines to stimulate and signal undifferentiated host cells to form new bone. Examples of osteoinduction are the various demineralized bone matrix putties that include bone morphogenetic proteins. Osteogenesis is cellular new bone formation from the transfer of live cells that have the capacity to induce new bone formation. Live cells may be derived from autograft bone or bone marrow aspirant.

Autograft bone is considered the "gold standard" for filling bone defects, although this may change in the future. The advantages of autograft bone are that it is osteoinductive, osteoconductive, and osteogenic. Autograft bone is available in cancellous, cortical, and combined forms. It provides structural support and is biocompatible [10]. It readily incorporates into the host graft site and has the ability to remodel to become normal bone.

The disadvantages of autograft bone are the increased operative time required for its harvest, and donor-site morbidity. Pain, morbidity, and the length and cost of hospitalization are often increased when the iliac crest is used as a donor site. Patients may complain of more pain from the iliac crest donor site than at the recipient site in the extremity. Chronic pain may persist at the iliac donor site. To decrease patient's complaints of