Strategic Directions in Osteoinduction and Biomimetics

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INTRODUCTION*

Strategic Directions in Osteoinduction and Biomimetics

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Treatment of large, critical-sized bone defects remains an important clinical challenge despite the intrinsic regenerative capacity of healthy bone tissue. Indeed, the lack of bone tissue as a result of congenital disorders and loss of bone tissue caused by trauma or disease represent a clinical problem affecting more than 20 million people annually worldwide. This leads to about 5 million orthopedic interventions every year, of which about 60% require bone grafting to ensure bone growth in defect sites.

Conventional methods of bone repair and regeneration employ a patient's own bone graft (autograft) or bone from a donor (allograft); however, there are a number of disadvantages associated with the use of natural bone grafts.[1] The harvest of the graft requires an additional invasive surgical procedure that may lead to donor site morbidity and chronic postoperative pain (in up to 18.7% of all patients after 2 years), hypersensitivity, and infection. The most important disadvantage associated with their use is, however, limited availability, as the total amount of bone that can be harvested from the iliac crest is limited to ∼5 cc.[2]

Therefore, an increasing need exists for effective and affordable bone repair strategies. To meet this need, it is important to develop alternatives for autologous and allogeneic bone grafts. Although various requirements can be defined that a successful bone graft substitute should meet, osteoinductivity is often considered the most critical property in order for the clinical performance of bone graft substitutes to match that of natural bone grafts.

Osteoinduction, initially defined by Friedenstein as the process of the ''induction of undifferentiated inducible osteoprogenitor cells that are not yet committed to the osteogenic lineage to form osteoprogenitor cells,''[3] was recognized as an important mechanism in bone repair strategies after the seminal work by Urist, who showed the ability of hydrochloric acid–decalcified diaphyseal bone to induce *de novo* bone formation upon intramuscular implantation in various animal models.[4] Further research, focusing on describing the mechanisms of this heterotopic bone formation, resulted in the identification of bone morphogenetic proteins (BMPs) as inducer of the cascade of chemotaxis, mitosis, differentiation, callus formation, and finally bone formation.[5] The fact that BMPs, with emphasis on commercially available BMP-2 and BMP-7 (OP-1), have shown clinical successes in spinal fusion and treatment of defects caused by trauma[6–8] has logically strengthened the perception of osteoinduction as being a highly important property of a bone graft substitute.

As a result, research into new, improved bone graft substitutes is often focused on developing constructs that are osteoinductive, while retaining other important properties, such as mechanical strength, handling properties, or degradability. Strategies toward this aim are diverse, varying from addition of osteogenic cells or cells with the potential to differentiate into the osteogenic lineage to appropriate carrier materials, to the use of osteoinductive growth factors, molecules, or bioinorganics and the development of smart synthetic biomaterials capable of triggering *de novo* bone formation *in vivo*, by tuning their physicochemical and structural properties.

In this special issue, many of these different approaches are covered. In a number of studies, the delivery and the osteoinductive capacity of BMP-2 were the topic of investigation. Demineralized bone matrix-based paste was investigated as a carrier of BMP-2 for controlled delivery in time, while retaining the osteoinductive capacity (Huber *et al.*, page 1321). A combined delivery of alendronate and BMP-2 from a collagen carrier (Cho *et al.*, page 1343), of platelet-derived growth factor-ββ end BMP-2 from a calcium phosphate (CaP)/alginate composite (Bayer *et al.*, page 1382), of zoledronic acid and BMP-2 from a commercially available gentamicin-containing calcium sulfate/hydroxyapatite composite carrier (Horstmann *et al.*, page 1403), and a sequential delivery of fibroblast growth factor-2 and BMP-2 from layer-by-layer coatings (Gronowicz *et al.*, page 1490) were also investigated *in vitro* and *in vivo*.

Two novel extracellular matrix-like gels, one based on elastin-like recombinomers, functionalized with BMP-2 or the Arg-Gly-Asp (RGD) cell adhesion motif (Colletta *et al.*, page 1361), and the other on a self-assembling peptide hydrogel SBG-178-Gel (Tsukamoto *et al.*, page 1394), were investigated for their potential to be used in bone regeneration, whereas a jelly collagen was supplemented with lysophosphatidic acid and 1α, 25-dihydroxyvitamin D3 to induce the proliferation, differentiation, and migration of human primary osteoblasts (Bosetti *et al.*, page 1413).

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In yet another study, chondrogenic priming and mechanical stimulation were investigated as combined tools to induce the osteogenic differentiation of human mesenchymal stromal cells (Freeman *et al.*, page 1466).

In two studies, mimicking the process of natural biomineralization was used as an inspiration to develop new biomaterials for bone regeneration (Ramírez-Rodríguez *et al.*, page 1423; Harding *et al.*, page 1452).

Another set of interesting studies focused on fine-tuning of physicochemical and structural properties of synthetic biomaterials, such as CaPs with the aim to improve their bone regenerative potential. A comparison was made between biomimetic and sintered CaPs, having different physicochemical features with regard to their effect on osteoblastic and mesenchymal stromal cells (Sadowska *et al.*, page 1297) and between two types of moldable CaP-based bone graft substitutes, differing in their carrier, regarding their bone-forming capacity *in vivo* (Barbieri *et al.*, page 1310). In another study, an iron chelator deferoxamine, a hypoxia mimicker, was used as an additive to 3D printed CaP implants to stimulate bone formation (Drager *et al.*, page 1372), whereas divalent cations-substituted borosilicate bioactive glasses were developed and tested for their ability to induce the osteogenic differentiation and mineralization of mesenchymal stromal cells (Fernandes *et al.*, page 1331).

Finally, this special issue contains three excellent review articles. Two of these reviews provide a comprehensive overview on the potential of extracellular matrices (Mansour *et al.*, page 1436) and membranes (Caridade and Mano, page 1502) to be used in bone regeneration, whereas one is focused on the importance of surface properties, including hydrophilicity and roughness on peri-implant bone tissue formation (Boyan *et al.*, page 1479).

Taken together, this special issue provides an overview of efforts that have been expended to develop effective bone graft substitutes. Some of these strategies follow a rational approach aimed at mimicking the composition or structure of natural bone, or a microenvironment within bone, whereas other strategies focus on optimizing one property (e.g., accelerating the rate of new bone formation) with the rationale that, by doing so, other limitations of the material (e.g., poor mechanical properties) will be compensated.

Regardless of the strategy taken, it is obvious that the bone regenerative capacity of new bone graft substitutes needs to match that of the natural grafts, to be fully accepted as a comprehensive alternative. It is furthermore important to take into account challenging clinical settings, including elderly patients and patients with systemic or chronic diseases that may significantly affect bone regenerative potential in such patients. Finally, it is imperative that the bone regenerative strategies are affordable, to meet an ever-growing need without presenting a heavy burden on our healthcare system.

In summary, it is evident that continuing research efforts in the field of biomaterials and tissue-engineered constructs for bone regeneration are much needed. This special issue will hopefully stimulate further work in this area, both from a fundamental and from a translational perspective.

Disclosure Statement

No competing financial interests exist.

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