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Biologic augmentation of polymer scaffolds for bone repair

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The major clinical challenges in bone repair include large segmental defects, fracture non-unions, spine fusion, and bone-soft tissue integration. Although the use of BMPs is increasing rapidly, bone grafting remains the current clinical standard for osseous reconstruction. Autografts, however, have several disadvantages including limited available tissue for transplantation, lack of structural integrity to withstand functional loads, and significant patient morbidity at the site of harvest. As a result of these limitations, allogeneic bone and synthetic scaffold materials have increasingly been used as substitutes for autografts over the past 20 years. Allografts provide initial structural integrity but suffer from reduced bioactivity and often fail to fully revascularize and remodel, resulting in a high refracture rate 1-2 years after implantation[1,2]. Although possible immunogenicity and the low porosity of structural allografts may contribute to poor clinical outcomes, recent evidence suggests that the absence of viable cells is a critical factor in allograft failure[3]. These problems have led to the search for improved methods to stimulate bone repair, including tissue engineering strategies that augment porous biomaterial scaffolds with bioactive proteins, genes, or cells.

Although a tremendous number of biomaterials have been investigated for bone repair, including a broad range of biodegradable natural and synthetic polymers, bioactive ceramics, composites and permanent or non-resorbable materials, scaffolds alone are typically insufficient to repair challenging bone defects. The bioactivity of biomaterial scaffolds must therefore be enhanced via incorporation of combinations of cells, proteins, peptide sequences, and genes that promote osteoinduction and mineralized matrix formation. Bone morphogenetic protein-2 (BMP-2) is an example of an osteoinductive factor approved by the FDA for non-healing fractures and spine fusion. Angiogenic factor delivery represents a potential complementary therapeutic strategy to enhance bone repair. The short biological half-life of these proteins and concerns regarding use of superphysiologic doses suggest that optimal effectiveness of growth factor-based therapies may require development of improved spatial and temporal delivery strategies[4].

Given the complex sequence of growth factors expressed during normal bone repair, combinations of co-delivered osteoinductive growth factors may more effectively regenerate bone than single growth factor delivery. Moreover, multiple growth factors may promote bone repair at lower total protein doses than single growth factors. Dual delivery of BMP-2 and TGF-β3, for example, synergistically enhances ectopic osteogenesis compared to delivery of either factor alone[5]. In a segmental bone defect model, these two factors show an additive but not synergistic effect on bone repair in a dose-dependent manner. Co-delivery of these growth factors with or without VEGF in a polycaprolactone (PCL)/RGD alginate composite scaffold that provides 4-5 days of sustained release results in consistent bridging of the defect. However, construct integration as measured by biomechanical testing of torsion strength is limited to approximately 50% of intact bone strength at 12 weeks of repair. Factors limiting complete restoration of biomechanical function may include the slow resorption kinetics of PCL or perhaps insufficient biomechanical load sharing between the implanted construct and fixation plate.

Cell-based strategies for engineering bone regeneration involve the implantation of osteoprogenitor or stem cell populations derived from a growing number of tissue sources. Cellular augmentation may be the rate limiting factor for difficult clinical cases involving older patients, smokers, patients receiving chemotherapy or radiation, and those with severely damaged wound beds in which the endogenous availability of osteoprogenitor cells is reduced[6]. The identification of a cell

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source that may be readily harvested, expanded to large numbers, and controllably differentiated would be highly beneficial for the clinical reconstruction of damaged or degenerated bone. The success of cell-based therapies for bone regeneration will also rely on development of delivery strategies that preserve cell viability following implantation. Such strategies require careful consideration of the method of cell delivery and mass transport through the 3-D construct[7]. Electrospun scaffolds or meshes are potential candidates for cell delivery in constructs that mimic the function of the periosteum. Osteoprogenitor cells will attach, proliferate, and differentiate on nanofiber meshes composed of PCL alone or PCL and collagen. Furthermore, cells will migrate off cell-seeded meshes radially into 3-D constructs and maintain high viability.

An important step towards clinical translation of cell-based therapies is to quantitatively evaluate the ability of different cell sources to restore function in challenging pre-clinical bone defect models. Bone marrow is the most common source of mesenchymal stem cells (MSCs) used for bone repair. The osteogenic potential of MSCs derived from sources other than bone marrow has also been evaluated. Adipose tissue in particular has gained attention as it is abundant, suggesting it may be possible to quickly generate the large number of cells needed for clinical bone repair[8]. However, reports of the osteogenic potential of MSCs derived from adipose tissue have been conflicting. Differentiation of MSCs into osteogenic lineages has also been observed in cells derived from amniotic fluid, placenta, umbilical cord, skin, and thymus[9-12]. While these studies suggest that MSCs are relatively ubiquitous in healthy tissues, the comparative abundance, differentiation potential, and clinical utility of the various cell sources remain to be fully determined. In one such recent study, MSCs derived from human amniotic fluid were shown to have a greater capacity for mineralization within 3-D constructs compared to human marrow-derived cells.

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