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Biomaterial-based endochondral bone regeneration: a shift from traditional tissue engineering paradigms to developmentally inspired strategies

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ABSTRACT

There is an urgent, clinical need for an alternative to the use of autologous grafts for the ever increasing number of bone grafting procedures performed annually. Herein, we describe a developmentally inspired approach to bone tissue engineering, which focuses on leveraging biomaterials as platforms for recapitulating the process of endochondral ossification. To begin, we describe the traditional biomaterial-based approaches to tissue engineering that have been investigated as methods to promote in vivo bone regeneration, including the use of three-dimensional biomimetic scaffolds, the delivery of growth factors and recombinant proteins, and the in vitro engineering of mineralized bone-like tissue. Thereafter, we suggest that some of the hurdles encountered by these traditional tissue engineering approaches may be circumvented by modulating the endochondral route to bone repair and, to that end, we assess various biomaterials that can be used in combination with cells and signaling factors to engineer hypertrophic cartilaginous grafts capable of promoting endochondral bone formation. Finally, we examine the emerging trends in biomaterial-based approaches to endochondral bone regeneration, such as the engineering of anatomically shaped templates for bone and osteochondral tissue engineering, the fabrication of mechanically reinforced constructs using emerging three-dimensional bioprinting techniques, and the generation of gene-activated scaffolds, which may accelerate the field towards its ultimate goal of clinically successful bone organ regeneration.

Introduction

Bone is a dense, connective tissue that functions to produce blood cells, store minerals, facilitate locomotion, and support and protect the vital organs of the body. As a highly dynamic material, bone possesses an intrinsic capacity for regeneration and constantly undergoes a remodeling process involving the resorption of old bone and deposition of new bone. However, clinical situations exist, whereby bone regeneration is required in large quantities, such as for reconstruction of large bone defects caused by trauma, infection, tumor resection, and skeletal abnormalities, or in cases where the regenerative process is compromised, such as in avascular necrosis, atrophic non-unions, and osteoporosis [1]. As a result, bone is the second most implanted tissue in the body after blood [2].

The gold standard treatment to promote regeneration of large bone defects is an autologous bone graft. This involves harvesting a section of a patient's own bone, usually from the anterior or posterior iliac crest of the pelvis, and then implanting the harvested bone back into the defect site. While this is a well-established approach, there are a number of drawbacks associated with the therapy; harvesting of the bone, for example, requires an additional surgical procedure, which can result in donor site morbidity, and there is a limitation on the quantity of bone available for harvest. Such limitations can be addressed through the use of an allogeneic bone graft, which can be obtained from human cadavers or living donors. However, as allogeneic bone grafts are devitalized prior to implantation, they may not possess the same osteoinductive potential as autologous bone grafts and complications can also arise due to immunogenicity and potential infection transmission [3]. Therefore, there is an urgent need for alternatives to autologous and allogeneic grafts in order to promote the regeneration of bone.

Tissue engineering has emerged as a multidisciplinary field which utilizes materials science, as well as aspects of cell biology and

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