Tissue Engineering Strategies for Skeletal Repair

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Introduction

There is a strong medical need for biological tissue grafts that could reestablish the structure and function of skeletal tissues lost to congenital abnormalities, trauma, and disease. Both the prosthetic devices and autologous tissue grafts are most helpful in providing the necessary tissue structure, but they each have serious limitations [1]. Tissue engineering offers potential to grow fully biological substitutes of native tissues, through the individual and combined use of cells, biomaterial scaffolds, and culture systems [2–5].

The Potential of Bioengineered Human Tissues

In its most complex incarnation, tissue engineering involves the *in vitro* generation of living, functional tissue grafts by cultivation of cells on biomaterial scaffolds (designed to serve as a template for tissue formation) in bioreactors (providing environmental control and physical signaling). The design of tissue engineering systems has been guided by biological principles and the need to provide native-like (biomimetic) environments in order to unlock the full biological potential of the cells (Fig. 1). Variations of this

approach resulted in engineered cartilage, bone, and osteochondral grafts [2–4] for implantation studies in animal models and eventual translation into clinical use.

One recently developed approach enables the *in vitro* cultivation of living human bone grafts customized to match the exact anatomical features of the specific defect, using the patient's own cells (Fig. 2). Importantly, engineered tissues also find application for *in vitro* screening of cells and regulatory factors and construction of disease models [6]. Furthermore, engineering a tissue under controllable conditions brings new insights into the progression of tissue development and identification of the underlying factors and mechanisms. This knowledge can then also be used to develop therapeutic modalities that involve mobilization and regulation of the host's cells by bioactive acellular implants.

Summary

Bioengineered culture platforms can provide tight environmental control and the physiological transport and signaling, enabling study of cartilage/bone development, regeneration, and disease under conditions that predict the human *in vivo* context [2–4, 6]. The field of bone and cartilage tissue engineering holds significant potential for providing clinically relevant tissue grafts for restoring joint function. These grafts can be personalized using imaging-guided techniques and the patient's own cells. As our ability to grow mechanically functional bone and cartilage grafts has progressed, efforts are focusing at tissue interfaces, vascularization of bone, stratification of cartilage, and “conditioning” of grafts to better tolerate the inflammatory environment of an osteoarthritic joint.

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Fig. 1. Biomimetic paradigm. Stem cell fate and function are regulated by the entire context of the cellular microenvironment, through dynamic interactions of the cells with cascades of multiple factors: molecular, structural, and physical. Native-like (biomimetic) cell environments can be engineered by a combined use of a scaffold (a structural and logistic template for cell differentiation and functional assembly) and a bioreactor (environmental control, molecular, and physical signaling)

Fig. 2. Engineering of personalized osteochondral grafts. The approach involves imaging-guided design of anatomically shaped composite scaffold and bioreactor chamber, for cultivation of human mesenchymal stem cells. An example is shown for human TMJ condyle consisting of fully viable cells and bone tissue matrix. Adapted from [2]

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