Consideration of Mechanical Factors

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The basic elements required for tissue engineering include an extracellular matrix scaffold, cells, and tissue-specific bioactive factors. Whether these elements are provided by the host or must be implanted in some combination within a construct depends critically on the \textit{in vivo} biochemical, vascular, and mechanical environments. Using bone tissue engineering as an example, the initial repair response to a construct will vary substantially according to the local availability of osteoprogenitor cells, the vascularity of the wound bed, and the mechanical stability of the defect site. \textit{In vivo} remodeling will subsequently reinforce, maintain, or degrade the tissue formed during repair. Thus, the initial and long-term biological responses to tissue-engineered constructs are strongly influenced by interactions between construct design parameters and the \textit{in vivo} environment. The variability of these interactions among different species, patients, and anatomic sites represents a key challenge in tissue engineering.

Successful tissue regeneration must go beyond reproducing shape and structure to restore biological and mechanical function and long-term integration with surrounding native tissues. Initially, an implanted construct should be immune-acceptable and biocompatible and, in many cases, promote angiogenesis and the recruitment of progenitor cells. If these early response criteria are met, then an ordered repair sequence culminating in matrix synthesis and deposition may proceed. However, successful tissue formation during the repair phase does not alone guarantee long-term functional regeneration. The retention of newly-formed repair tissue and its integration with surrounding tissues depends on the subsequent remodeling response. For example, bone contains an intricate cellular communication network of osteocytes and is subject to local remodeling by bone-resorbing osteoclasts and bone-forming osteoblasts, serving under normal conditions to maintain skeletal structural integrity. In the absence of adequate mechanical stimuli, however, bone remodeling will also rapidly remove bone mass. This outcome is illustrated by a common model to test for bone-induction properties involving subcutaneous or intramuscular implantation of constructs into athymic rats and other animal species. Constructs that recruit local undifferentiated cells, induce differentiation along an

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osteogenic pathway, and subsequently mineralize are considered osteoinductive. The duration of these experiments is typically limited to approximately four weeks, however, because beyond that time a remodeling response begins to resorb the newly-formed bone.

We have recently studied the influence of the in vivo mechanical environment on the formation and retention of bone within tissue-engineered constructs implanted into hydraulic bone chambers. The bone chamber model is a hollow threaded implant that closely resembles the titanium cages currently being used clinically to fuse spines. A unique aspect of this model is the ability to apply a controlled cyclic mechanical stimulus to tissue developing within the chamber. In bilaterally implanted chambers, we tested the hypothesis that tissue-engineered constructs under dynamic loading would promote bone repair in vivo. Tissue was allowed to form within the constructs without mechanical stimulation for four weeks followed by four weeks of loading on one side only. Relative to the baseline bone formation response at four weeks, mechanical loading increased the amount of mineralized matrix present at eight weeks by 125%. In contrast, the amount of mineralized matrix present in the no-load control chambers had decreased by 75% from four to eight weeks.

Mechanical factors can have both positive and negative effects on the biological response to construct implants. Repeated disruption of vascular invasion at the construct interface with native tissues can result in nonunion. For example, the optimal porosity or pore size for bone regeneration scaffolds remains an open question the answer to which may depend on mechanical and vascular factors at the defect site. The optimal pore size for bone ingrowth has often been reported to be in the range of 150–600 microns. However, Whang and coworkers demonstrated substantial bone formation in non-load-bearing defects filled with polymer scaffolds possessing a median pore size less than 50 microns and porosity greater than 90%. The investigators proposed that high-porosity scaffolds with small pore sizes provided greater hematoma stabilization in the earliest phases of bone regeneration. The reason for uncertainty regarding optimal pore size may relate to variable interactions between the scaffold mechanical properties and the functional loading environment. The spatial requirement for vascularization and invasion of osteoprogenitor cells should be less than 20 microns based on the dimensions of blood vessels and bone cells. However, relative micromotion between the scaffold boundaries and surrounding tissue may disrupt vascular ingrowth into such small pores. Larger pores, although perhaps not optimal for hematoma stabilization or cell attachment, may allow vascular ingrowth to occur despite the presence of interface micromotion.

For load-bearing clinical applications, the implanted construct must therefore possess mechanical properties that provide adequate initial stability at the defect site and gradual transfer of physiological mechanical stimuli under functional loading to newly formed tissue. Constructs possessing insufficient strength and fatigue resistance properties are at risk for plastic deformation or brittle failure under functional loads, leading to collapse of the internal porosity and subsidence of the implant. Martin and coworkers, for example, found that a collagen sponge scaffold loaded with BMP effectively induced spine fusion in rabbits, but that the same scaffold failed as a delivery vehicle in a non-human primate spine fusion model due to mechanical collapse.

Although the influence of the local in vivo mechanical environment on repair and remodeling is well recognized in numerous tissue types, this potentially critical fac-
tor has not been well studied in the context of tissue-engineered constructs. An understanding of how mechanical signals affect construct integration and regeneration of function may provide microstructural design objectives for 3-D scaffold architectures and may have an impact on the selection of scaffold material, cell type or seeding density, and other construct parameters. Furthermore, it may be possible to exploit the adaptive potential of tissues by mechanically preconditioning constructs or cells prior to implantation. Many in vitro and in vivo test beds for reparative methods of mechanically functional tissues are non-load-bearing. Calvarial critical sized defects for bone repair and non-load-bearing articular cartilage defects for cartilage repair are two examples. Model systems that account for the three-dimensional, load-bearing functional requirements of tissues represent more rigorous test beds for these technologies and may ultimately prove to be more predictive of human clinical results.

REFERENCES