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Biomaterials for tissue engineering applications

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ABSTRACT

With advancements in biological and engineering sciences, the definition of an ideal biomaterial has evolved over the past 50 years from a substance that is inert to one that has select bioinductive properties and integrates well with adjacent host tissue. Biomaterials are a fundamental component of tissue engineering, which aims to replace diseased, damaged, or missing tissue with reconstructed functional tissue. Most biomaterials are less than satisfactory for pediatric patients because the scaffold must adapt to the growth and development of the surrounding tissues and organs over time. The pediatric community, therefore, provides a distinct challenge for the tissue engineering community.

Introduction

Scaffold materials for tissue engineering/regenerative medicine can be broadly classified as either synthetic or naturally occurring in origin. Regardless of their origin, such scaffold materials are intended to support the attachment, maintenance, proliferation, and on occasion the differentiation of selected cell populations. In addition, the scaffold must provide adequate form and structural support for the intended anatomic site. These requirements are non-trivial and to make matters even more challenging, the host response to the presence of the material within the mammalian body must be one that allows for functional replacement of the injured or missing tissue over the life of the patient. This is particularly important in pediatric patients in whom the scaffold must adapt to the growth and development of the surrounding tissues and organs.

It can be argued that the most important measure of a scaffold material is not its composition, shape, mechanical properties, porosity, or ability to support cell growth, but rather the host response to the scaffold material. Regardless of how ideal the material looks and feels at the time of implantation, the true measure of success is how the material looks and feels 1, 5, and 10 years after implantation. There are pros and cons for each material and the optimal scaffold material for each clinical application will vary. Stated differently, one size does not fit all. The present article provides a brief overview of common strategies for scaffold design and development in the field of tissue engineering/regenerative medicine, with emphasis on the pediatric population.

Biomaterials for tissue engineering

Tissue engineering (TE) combines the principles of engineering and biology and generally involves the use of some combination of the following: biomaterials, cells, and bioactive molecules.[1] The appropriate contribution of each factor depends upon the application in question, the strategy for tissue replacement, and patient variables such as age, co-morbidities, and other factors. TE strategies can include both in vitro and in vivo approaches, and the optimal approach for each clinical application will continue to evolve as advances in stem cell biology, biomaterial science, and bioreactor technology occur. An additional obstacle to TE in the pediatric community, since patients are still growing, is the requirement for the engineered tissue to grow and adapt with surrounding tissue.

Biomaterials play an important, in fact indispensible, role in the field of TE. Biomaterials have been used for centuries for applications such as intraocular lens replacement and dental fillings, but advancements in cell and molecular biology, chemistry, materials science, and engineering have provided much broader opportunities for clinical use.

The definition of the ideal biomaterial has changed considerably during the past 50 years and, in fact, will vary between given applications.[2] In early biomaterial design, the goal was to match

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mechanical and material properties and to achieve a level of functional outcome that adequately matched the native tissue without invoking tissue damage or a deleterious host response. For example, bone cement, stainless steel, and Dacron were used extensively in early biomaterials because they were considered to be relatively inert and incited a predictable but tolerable foreign body response. Furthermore, these materials had favorable mechanical properties. Second-generation biomaterials included materials such as titanium, bioglass, PLGA, and collagen. These materials were engineered for biologic use and have bioactive properties that include osseointegration (titanium and hydroxyapatite), tissue integration (Bioglass), and biodegradation (PLGA and collagen). Many of the aforementioned materials maintain clinical relevance, but the field of TE is rapidly moving toward the use of biomaterials that integrate with adjacent tissue and are bioinductive, that is, materials that enhance the regenerative or reconstructive capacity of a given tissue or organ. Stated differently, these materials are polar opposite to the "inert" biomaterials of 50 years ago.

The basic role of a biomaterial in tissue regeneration is to provide support and scaffolding for cell growth. Nature's template for biomaterial is the extracellular matrix (ECM); the material secreted by resident cells that supports tissue and organs. The ECM provides not only physical support and spatial organization, but also a bioactive microenvironment that supports and promotes cellular functions. The ECM consists of structural proteins (e.g., collagen and elastin), cell adhesion proteins (e.g., fibronectin and laminin), and glycans [e.g., glycosaminoglycans (GAGs) and proteoglycans]. Glycans, molecules that swell in the aqueous spaces between protein fibrils allowing the diffusion of nutrients, provide a reservoir for signaling molecules and growth factors.[3]

The ECM is said to be in a state of dynamic reciprocity with the resident cells, that is, the ECM provides signaling and biophysical cues that influence the cell morphology and phenotype. In turn, the cells modify their secreted ECM products in response to microenviromental signals, including mechanical stimuli, oxygen and nutrient concentration, and all factors that contribute to the microenvironmental niche.[4] During tissue regeneration, the ECM is subject to extensive remodeling. Proteolytic degradation of the matrix scaffold provides morphogenic cues in the form of cryptic peptides, which influence cell survival, proliferation, migration, polarization, and differentiation.[4–8] The constructive remodeling of a scaffold into a functional tissue requires scaffolding that will provide such structural and signaling support. Thus, biomaterial research has largely been aimed at mimicking the native structure and composition of ECM.

Owing to the complexity of composition and ultrastructure of native ECM, synthesis of an ECM mimic with any degree of fidelity is not yet feasible. For this reason, typical approaches of biomaterial design focus on a few of the mechanisms by which ECM influences cells and attempts to effectively present these cues for a given tissue. Synthetic biomaterials [e.g., poly(ethylene glycol), poly(lactic-co-glycolic acid), poly(ethylene terephthalate), polyglycolic acid] are attractive because they can be manufactured reproducibly with the ability to control strength, structure, and degradation rate. Naturally occurring materials include the naturally occurring polymers (e.g., silk and chitosan), purified ECM proteins (e.g., collagen and elastin), and ECM derived by decellularization of various tissues (e.g., small intestinal submucosa, dermis, and urinary bladder matrix). The naturally occurring materials have certain advantages such as favorable immune recognition by the recipient and the presence of embedded structural and functional molecules.

A number of biomaterials for TE are available for various clinical applications (Table 1). The use of biomaterials should be used in an application-specific nature, that is, a biomaterial that achieves success in one application should not necessarily be expected to perform well in an application that is very different. For pediatric patients, a biomaterial should degrade over time or have the capability change shape and size so the engineered tissue can grow with surrounding tissue. Further, if a scaffold is biodegradable the biomaterial must provide adequate mechanical support during the time of scaffold remodeling.[9]

Table 1
Clinically available biomaterials for tissue engineering applications.

Product	Description	Application	Company
Apligraf®	Allogeneic fibroblasts on a bovine collagen I matrix with upper keratinocyte cell layer	Skin	Organogenesis
Dermagraft®	Allogeneic fibroblasts on a vicryl mesh scaffold	Skin	Shire Regenerative Medicine, Inc.
TransCyte®	Allogeneic fibroblasts on a nylon mesh with upper silicone layer	Skin	Shire Regenerative Medicine, Inc.
Oasis® Wound Matrix	Decellularized porcine small intestinal submucosa	Skin	Cook Biotech
Integra® Bilayer Wound Matrix	Type I bovine collagen with chondroitin-6-sulfate and silicone	Skin	Integra Life Sciences
Epicel®	Autologous keratinocyte cell sheets	Skin	Genzyme
REGRANEX®	PDGF within a hydrogel	Skin	Healthpoint Biotherapeutics
Carticel®	Autologous chondrocytes	Cartilage	Genzyme
NeoCart®	Autologous chondrocytes on type I bovine collagen	Cartilage	Histogenics
VeriCart™	Type I bovine collagen	Cartilage	Histogenics
Osteocel® Plus	Allogeneic bone with mesenchymal stem cells	Bone	NuVasive
Pura-Matrix™	Hydrogel composed of a self-assembling peptide (RADA)	Bone	3DMatrix
OsteoScaf™	PLGA and calcium phosphate scaffold	Bone	Tissue Regeneration Therapeutics
INFUSE® Bone Graft	Recombinant human BMP-2 absorbed in a bovine type I collagen sponge	Bone	Medtronics
Lifeline™	Autologous fibroblast tubular cell sheet lined with autologous endothelial cells	Blood vessels	Cyotgraft Tissue Engineering
Omniflow® II	Polyester mesh with cross-linked ovine collagen	Blood vessels	Binova
Anginera™	Allogeneic fibroblasts on vicryl mesh	Cardiac	Theregen
CardioWrap®	Membrane composed of a copolymer of 70% L-lactide and 30% D,L-lactide	Cardiac	MAST Biosurgery, Inc.
CryoValve® SynerGraft Pulmonary Heart Valve	Decellularized allogeneic pulmonary valve	Cardiac	Cryolife
Encapsulated Cell Technology implant	Polysulfone capsule with PET scaffold containing immortalized retinal epithelial cells	Retinal	Neurotech Pharmaceuticals