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Review

Reprint of: Extracellular matrix as a biological scaffold material: Structure and function

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ABSTRACT

Biological scaffold materials derived from the extracellular matrix (ECM) of intact mammalian tissues have been successfully used in a variety of tissue engineering/regenerative medicine applications both in preclinical studies and in clinical applications. Although it is recognized that the materials have constructive remodeling properties, the mechanisms by which functional tissue restoration is achieved are not well understood. There is evidence to support essential roles for both the structural and functional characteristics of the biological scaffold materials. This paper provides an overview of the composition and structure of selected ECM scaffold materials, the effects of manufacturing methods upon the structural properties and resulting mechanical behavior of the scaffold materials, and the in vivo degradation and remodeling of ECM scaffolds with an emphasis on tissue function.

1. Introduction

Biological scaffold materials composed of extracellular matrix (ECM) have been shown to facilitate the constructive remodeling of many different tissues in both preclinical animal studies and in human clinical applications. The ECM from which these scaffold materials are derived from a variety of tissues, including heart valves [1–7], blood vessels [8–11], skin [12], nerves [13,14], skeletal muscle [15], tendons [16], ligaments [17], small intestinal submucosa (SIS) [18–20], urinary bladder [21–23] and liver [24]. The mechanisms by which biological scaffold materials promote site appropriate tissue reconstruction are not well understood and there is legitimate controversy concerning the relevant importance of the composition vs. structure of these materials. The composition of ECM scaffolds consists of a complex mixture of molecules that mediate structural and/or biological properties. These molecules are arranged in unique three-dimensional (3-D) patterns that are ideally suited to the tissue from which the ECM is harvested. Typically, such scaffold materials are biodegradable unless processed in such a manner that irreversible cross-links are created between the resident molecules. The composite structure of these ECM molecules, as well as their in vivo degradability, has marked effects upon the host response and the remodeling events that determine the eventual clinical outcome. A partial list of commercially available products composed of extracellular matrix is provided in Table 1 as a testament to the clinical relevance of these concepts.

Although well-designed and informative studies have been conducted on a variety of ECM scaffold material, the most comprehensive studies regarding mechanical and structural properties, macro- and ultrastructure and biological activity have been reported for urinary bladder matrix (UBM) and SIS.

The objective of this paper is to provide an overview of structure/function relationships within these two biological scaffold materials, and to extend these relationships to other biological scaffold materials when possible. In the context of this overview, the term "function" is used in the broadest sense including biomechanical and physiologic effects.

2. Composition of biological scaffold materials

ECM scaffolds consist of the structural and functional molecules secreted by the resident cells of each tissue and organ from which they are prepared. Therefore, the specific composition and distribution of the ECM constituents will vary depending on the tissue source. The ECM scaffold derived from porcine small intestinal submucosa (SIS–ECM) is the biological scaffold material that has been most extensively characterized, and therefore will be used as a prototypical ECM scaffold. By dry weight, SIS–ECM scaffold is composed of greater than 90% collagen. The large majority of

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Table 1
Commercially available biological scaffold materials

Product	Company	Material	Processing	Form
AlloDerm	Lifecell	Human skin	Natural	Dry sheet
AlloPatch®	Musculoskeletal Transplant Foundation	Human fascia lata	Natural	Dry sheet
Axis™ dermis	Mentor	Human dermis	Natural	Dry sheet
Bard® Dermal Allograft	Bard	Cadaveric human dermis	Natural	Dry sheet
CuffPatch™	Arthrotek	Porcine small intestinal submucosa (SIS)	Cross-linked	Hydrated sheet
DurADAPT™	Pegasus Biologicals	Horse pericardium	Cross-linked	Dry sheet
Dura-Guard®	Synovis Surgical	Bovine pericardium	Cross-linked	Hydrated sheet
Durasis®	Cook SIS	Porcine small intestinal submucosa (SIS)	Natural	Dry sheet
Durepair®	TEI Biosciences	Fetal bovine skin	Natural	Dry sheet
FasLata®	Bard	Cadaveric fascia lata	Natural	Dry sheet
Graft Jacket®	Wright Medical Tech	Human skin	Natural	Dry sheet
Oasis®	Healthpoint	Porcine small intestinal submucosa (SIS)	Natural	Dry sheet
OrthADAPT™	Pegasus Biologicals	Horse pericardium	Cross-linked	Dry sheet
Pelvicol®	Bard	Porcine dermis	Cross-linked	Hydrated sheet
Peri-Guard®	Synovis Surgical	Bovine pericardium	Cross-linked	Dry sheet
Permacol™	Tissue Science Laboratories	Porcine skin	Cross-linked	Hydrated sheet
PriMatrix™	TEI Biosciences	Fetal bovine skin	Natural	Dry sheet
Restore™	DePuy	Porcine small intestinal submucosa (SIS)	Natural	Dry sheet
Stratasis®	Cook SIS	Porcine small intestinal submucosa (SIS)	Natural	Dry sheet
SurgiMend™	TEI Biosciences	Fetal bovine skin	Natural	Dry sheet
Surgisis®	Cook SIS	Porcine small intestinal submucosa (SIS)	Natural	Dry sheet
Suspend™	Mentor	Human fascia lata	Natural	Dry sheet
TissueMend®	TEI Biosciences	Fetal bovine skin	Natural	Dry sheet
Vascu-Guard®	Synovis Surgical	Bovine pericardium	Cross-linked	Dry sheet
Veritas®	Synovis Surgical	Bovine pericardium	Cross-linked	Hydrated sheet
Xelma™	Molnlycke	ECM protein, PGA, water		Gel
Xenform™	TEI Biosciences	Fetal bovine skin	Natural	Dry sheet
Zimmer Collagen Patch®	Tissue Science Laboratories	Porcine dermis	Cross-linked	Hydrated sheet

the collagen is type I, with minor amounts of collagen types (Col) III, IV, V and VI also present [25]. Urinary bladder matrix (UBM–ECM) also contains the same collagen types as SIS–ECM, with greater amounts of Col III being present, as well as Col VII. Col VII is an important component of the epithelial basement membrane that distinguishes this particular ECM scaffold from most other ECM scaffold materials [26]. SIS–ECM contains a variety of glycosaminoglycans (GAGs), including heparin, heparan sulfate, chondroitin sulfate and hyaluronic acid [27]. The amount of GAGs remaining in a tissue after decellularization depends greatly on the method of decellularization. For example, ionic detergents are often used in the decellularization process and such detergents can remove GAGs from the ECM [28]. SIS–ECM has been shown to contain adhesion molecules such as fibronectin and laminin [26,29], the proteoglycan decorin and the glycoproteins biglycan and entactin (unpublished data). Various growth factors are also present in SIS–ECM, including transforming growth factor-β [30,31], basic fibroblast growth factor (b-FGF) [31,32] and vascular endothelial growth factor (VEGF) [33]. Several of these growth factors have been shown to retain their bioactivity even after terminal sterilization and long-term storage [30,32]. In summary, biological scaffolds composed of extracellular matrix have a complex composition with a variety of diverse molecules that are perfectly suited to support the cellular processes necessary for optimal function of the tissue and organ from which they are harvested. The ability of an ECM harvested from one tissue to function as a biological scaffold material for the same or different tissue may vary.

3. Structure of ECM biological scaffold materials

The ultrastructure and 3-D architecture of ECM scaffolds can be largely preserved throughout processing steps required for decellularization of the tissue if care is taken to avoid harsh chaotropic agents [26,34]. There is morphological evidence that scaffolds composed of ECM from specific organs retain defining structures, such as the basement membrane of the urinary bladder in UBM and the stratum compactum of the small intestine [26]. Microscopic and ultrastructural features of the matrix play important roles in modulating the behavior of cells that contact the scaffold by controlling the cells' ability to migrate into the scaffold [26] or by influencing tissue specific cell phenotype [35,36]. For example, an intact basement membrane can largely prevent in vitro cell penetration into the underlying matrix and foster the formation of confluent cell populations that cover the surface [26]. Alternatively, an irregular fibrous surface architecture can facilitate penetration of selected cell types into the midsubstance of the ECM scaffold [26]. The ECM can dramatically affect the differentiation pathway of human embryonic stem cells and selected progenitor cell populations [35,37,38].

The collagen fiber architecture of an ECM scaffold plays a critical role in determining its biomechanical behavior. The alignment and organization of collagen fibers are dependent on the function of the source tissue from which the ECM is derived. For example, the collagen fibers within a ligament or tendon are highly aligned along the long axis of the tissue to provide the greatest resistance to strain in a load-bearing application. Thus, the use of ECM derived from tendons and ligaments is a logical choice for repair of structures, such as the anterior cruciate ligament [17,39,40]. The small intestinal submucosa also has a characteristic collagen fiber organization that is related to its native in vivo function. SIS–ECM has a preferred alignment along the native longitudinal axis of the small intestine, and it appears that this preference is a composite of two populations of collagen fibers with their centroids shifted ~30° from the longitudinal axis of the intestine [34]. This spiral arrangement of collagen fibers with their adjacent smooth muscle cell layer allows the small intestine to constrict in a manner that promotes the efficient transport of a bolus of biomass (i.e. peristalsis). When the SIS–ECM is subjected to biaxial mechanical testing, this preferred fiber orientation leads to an anisotropic biomechanical behavior, with greater strength and tangent modulus along the preferred fiber direction [34].

The degree of alignment of the collagen fibers within an ECM scaffold changes as the scaffold is loaded (Fig. 1). Not only do the collagen fibers straighten from their typical crimp pattern, but