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Leading Opinion

The extracellular matrix as a biologic scaffold material ☆

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Abstract

Biologic scaffolds composed of naturally occurring extracellular matrix (ECM) have received significant attention for their potential therapeutic applications. The full potential of the ability of ECM scaffolds to promote constructive remodeling will not be realized, however, until an understanding of the biology and the external influences that affect biology, are better achieved. The factors that appear important for the constructive remodeling of ECM biologic scaffolds are its ability to be rapidly and completely degraded with the generation of downstream bioactive molecules, the bioinductive properties of the functional molecules that compose native ECM material and the ability to engineer its mechanical properties at the time of implantation through an understanding of its collagen fiber microstructure.

Keywords: Extracellular matrix; Biologic scaffolds; SIS; Biomaterial

1. The extracellular matrix as a biologic scaffold material

The extracellular matrix (ECM) is by definition nature's ideal biologic scaffold material. The ECM is custom designed and manufactured by the resident cells of each tissue and organ and is in a state of dynamic equilibrium with its surrounding microenvironment [1]. The structural and functional molecules of the ECM provide the means by which adjacent cells communicate with each other and with the external environment [2–4]. The ECM is obviously biocompatible since host cells produce their own matrix. The ECM also provides a supportive medium or conduit for blood vessels, nerves and lymphatics and for the diffusion of nutrients from the blood to the surrounding cells. In other words, the ECM possesses all of the characteristics of the ideal tissue engineered scaffold or biomaterial.

The complex three-dimensional organization of the structural and functional molecules of which the ECM is composed has not been fully characterized; therefore, synthesis of this biomaterial in the laboratory is not possible. Individual components of the ECM such as collagen, laminin, fibronectin and hyaluronic acid can be isolated and used both *in vitro* and *in vivo* to facilitate cell growth and differentiation. Various forms of intact ECM have been used as biologic scaffolds to promote the constructive remodeling of tissues and organs [5–12]. These ECM scaffolds have been harvested from the small intestine, skin, liver, pancreas, and urinary bladder among other tissues. Many of these ECM materials have been commercialized for a variety of therapeutic applications. Table 1 identifies a partial list of biologic scaffold materials currently available for clinical use. One of the most widely studied of the ECM scaffolds is that derived from the small intestinal submucosa (SIS) [13–27]. The composition, macrostructure and microstructure, biomechanical properties, *in vivo* degradation rate, cell:matrix interactions, and ability to support constructive remodeling in a variety of

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Table 1
Partial list of commercially available devices composed of extracellular matrix

Product	Company	Material	Chemical modification	Form	Use
Acellular					
Oasis®	Healthpoint	Porcine small intestinal submucosa (SIS)	Natural	Dry sheet	Partial & full thickness wounds; superficial and second degree burns
Xelma™	Molnlycke	ECM protein, PGA, water		Gel	Venous leg ulcers
AlloDerm	Lifecell	Human skin	Cross-linked	Dry sheet	Abdominal wall, breast, ENT/head & neck reconstruction, grafting
CuffPatch™	Arthrotek	Porcine small intestinal submucosa (SIS)	Cross-linked	Hydrated sheet	Reinforcement of soft tissues
TissueMend®	TEI Biosciences	Fetal bovine skin	Natural	Dry sheet	Surgical repair and reinforcement of soft tissue in rotator cuff
Durepair®	TEI Biosciences	Fetal bovine skin	Natural	Dry sheet	Repair of cranial or spinal dura
Xenform™	TEI Biosciences	Fetal bovine skin	Natural	Dry sheet	Repair of colon, rectal, urethral, and vaginal prolapse, pelvic reconstruction, urethral sling
SurgiMend™	TEI Biosciences	Fetal bovine skin	Natural	Dry sheet	Surgical repair of damaged or ruptured soft tissue membranes
PriMatrix™	TEI Biosciences	Fetal bovine skin	Natural	Dry sheet	Wound management
Permacol™	Tissue Science Laboratories	Porcine skin	Cross-linked	Hydrated sheet	Soft connective tissue repair
Graft Jacket®	Wright Medical Tech	Human skin	Cross-linked	Dry sheet	Foot ulcers
Surgisis®	Cook SIS	Porcine small intestinal submucosa (SIS)	Natural	Dry sheet	Soft tissue repair and reinforcement
Durasis®	Cook SIS	Porcine small intestinal submucosa (SIS)	Natural	Dry sheet	Repair dura matter
Stratasis®	Cook SIS	Porcine small intestinal submucosa (SIS)	Natural	Dry sheet	Treatment of urinary incontinence
OrthADAPT™	Pegasus Biologicals	Horse pericardium	Cross-linked		Reinforcement, repair and reconstruction of soft tissue in orthopedics
DurADAPT™	Pegasus Biologicals	Horse pericardium	Cross-linked		Repair dura matter after craniotomy
Axis™ dermis	Mentor	Human dermis	Natural	Dry sheet	Pelvic organ prolapse
Suspend™	Mentor	Human fascia lata	Natural	Dry sheet	Urethral sling
Restore™	DePuy	Porcine small intestinal submucosa (SIS)	Natural	Sheet	Reinforcement of soft tissues
Veritas®	Synovis Surgical	Bovine pericardium		Hydrated sheet	Soft tissue repair
Dura-Guard®	Synovis Surgical	Bovine pericardium		Hydrated sheet	Spinal and cranial repair
Vascu-Guard®	Synovis Surgical	Bovine pericardium			Reconstruction of blood vessels in neck, legs, and arms
Peri-Guard®	Synovis Surgical	Bovine pericardium			Pericardial and soft tissue repair

preclinical studies have been exhaustively investigated for SIS [14,28–34]. Perhaps most importantly, the SIS–ECM has been used in more than one million human patients to reconstruct a variety of tissues including the integument [35–37], body wall [29,32,38], urinary bladder [14,31,39], rotator cuff [40–42], intestine [28,43], urethra [15,30,44–46], ureter [47–49], and diaphragm [50,51]. The outcome of these clinical studies has been very positive but there are selected applications where the results have been mixed. For example, SIS has been reported to have excellent remodeling properties in the surgical treatment of Peyronie's disease in some studies [45,52] and have no beneficial effect in others [53]. Similarly, the use of SIS–ECM for rotator cuff repair has shown very positive results in some studies [54] and to be ineffective in others [42,55]. The reasons for these disparate results are unknown but likely relate to patient selection, surgical technique and/or lack of our understanding regarding optimal use of an inductive scaffold for reconstruction of certain tissues.

The constructive remodeling induced by ECM scaffold materials and their widespread use across many clinical applications are a consequence of their bio-inductive properties, mechanical and material properties, the host tissue response to naturally occurring ECM, and the degradation properties of the material. These properties will be briefly discussed below.

Xenogeneic, porcine derived SIS will be used as a prototype ECM scaffold material but the large majority of comments and principles likely apply to all ECM materials

that are thoroughly decellularized, sterilized, and not modified by chemical crosslinking agents or other processing methods that produce unnatural protein crosslinks.

2. The bioinductive properties of ECM bioscaffolds

The mechanisms by which scaffolds composed of naturally occurring ECM facilitate the constructive remodeling of tissues are not completely understood. It is clear, however, that the bioinductive properties of these scaffolds play a very important role in tissue remodeling. The viscoelastic behavior, biomechanical properties, and ability to support host cell attachment through collagen, fibronectin and laminin ligands are insufficient alone to explain the constructive remodeling events that are observed following *in vivo* implantation of ECM scaffolds.

Angiogenesis, abundant host cell infiltration, mitogenesis, and deposition and organization of new host ECM are common events during the remodeling of ECM scaffolds such as SIS. Component growth factors such as vascular endothelial cell growth factor (VEGF), basic fibroblast growth factor (bFGF), and transforming growth factor beta (TGF-β) are released during scaffold degradation and exert their biologic effects as they are dissociated from their binding proteins and activated [27,56–60]. These growth factors survive tissue processing and terminal sterilization [59,61] and promote angiogenesis, mitogenesis and cellular differentiation during the remodeling process. The rapid degradation of the native ECM scaffold material is mediated by enzymatic and cellular processes and may be considered as a mechanism for controlled release of the ECM constituent molecules. The process of scaffold degradation and growth factor release continue until the scaffold is completely degraded. Perhaps more importantly, degradation products of the parent molecules that constitute the ECM appear to mediate a subsequent series of remodeling events. Cryptic peptides released by the degradation process initiate and sustain the recruitment of circulating, bone-marrow-derived cells that actively participate in long-term tissue remodeling [62,63]. At least some of the recruited cell populations represent undifferentiated progenitor cells that express genes such as MSX-1, Pref-1 and TBX-5 [64]. The specific role of these cell populations in the constructive remodeling events associated with ECM scaffolds has not been determined. Antimicrobial peptides are generated that protect the remodeling site from potential pathogens [21,65–68]. Peptides that modulate angiogenesis and the recruitment of endothelial cells facilitate the development of a rich blood supply to the remodeling tissue for as long as 6–8 weeks [69]. Therefore, sustained bioinductive properties are a hallmark of ECM scaffolds that are susceptible to *in vivo* degradation; i.e. not chemically crosslinked. The concept of cryptic peptides released from parent ECM molecules is not new, but has not been previously considered in the context of ECM use as a biologic scaffold material. Table 2 provides examples of peptide derivatives of parent ECM molecules.

In contrast, ECM scaffolds that resist or retard the degradation process elicit a chronic inflammatory response and host fibrous connective tissue deposition [12]. Stated differently, maintenance of the bioinductive properties of ECM scaffolds and the host response to such bioscaffolds can be critically dependent upon methods used to process these materials.

3. Biomechanical properties of ECM

The mechanical properties of the ECM are largely a consequence of its collagen fiber architecture and kinematics. With the exception of ECM derived from the small intestine (SIS) and urinary bladder, there has been almost no systematic examination of the biomechanical properties of ECM scaffold materials, especially with respect to the effect of processing methods (e.g., sterilization) upon such properties.

SIS has been shown to have a global preferred fiber alignment along the longitudinal axis of the small intestine [70–72]. This alignment is the composite result of two distinct populations of fibers with preferred alignment roughly 30° from the longitudinal axis of the small intestine [72]. It is likely that this spiral arrangement of SIS fibers facilitates dilation and retraction of the small intestine during bolus transport of intraluminal contents. More broadly considered, the tissue from which an ECM scaffold is harvested will define its structural characteristics and mechanical properties. The global preferred fiber alignment of SIS leads to orthotropic mechanical behavior of the scaffold, with the preferred fiber direction showing greater stiffness and strength than the cross-preferred fiber direction [72]. The collagen fiber alignment of the urinary bladder submucosa and tunica propria, alternative tissue

Table 2
Examples of "cryptic" peptides that are fragments of parent molecules within naturally occurring ECM

- Endostatin—a derivative of collagen XVIII that inhibits angiogenesis
- Angiostatin—a derivative of the plasminogen molecule that inhibits angiogenesis
- Anastellin Fragment III1C—a peptide derivative of the first type III repeat in fibronectin that inhibits angiogenesis
- Canstatin—a 24 kDa fragment of the á1 chain of Type IV collagen that induces apoptosis and inhibits endothelial cell migration and proliferation
- A 4 kDa fragment of α1, Antitrypsin, that shows chemoattractant activity for neutrophils
- Restin—the c-terminal fragment of the alpha-1 chain of collagen XV that specifically inhibits endothelial cell-migration
- Tumstatin—the NC1 domain of the α-3 chain of collagen IV has both anti-angiogenesis activity *in vitro* and anti-tumor activity *in vivo*
- ABT-510—fragment of second type-1 repeat of thrombospondin-1 (TSP-1) that possesses antiangiogenic activity

sources of ECM scaffolds, show a much more isotropic fiber alignment than SIS. An understanding of the collagen fiber alignment of ECM derived from each organ is obviously important for the design of tissue scaffolds if the intent is to closely match the scaffold mechanical properties to those of the target organ of its intended use.

For clinical use, the mechanical behavior of a single layer of SIS–ECM is insufficient for most load bearing applications. The strength of an SIS scaffold can be custom engineered by creating multiple layers of the material that are bonded together by vacuum pressing which yields a dry, stiff construct. Rehydration of the construct restores the more pliable handling characteristics of the material. The desired mechanical behavior of these multilaminate scaffolds can be designed into the manufacturing process. For example, the Restore® device (DePuy, Warsaw, IN), a commercially available form of SIS for orthopedic soft tissue reconstruction consists of 10 layers of SIS oriented such that the final construct is isotropic. It is possible to take advantage of the knowledge of the collagen fiber architecture to design isotropic or orthotropic mechanical behavior in an ECM scaffold. Similarly by increasing the number of layers, the strength of an ECM scaffold can be increased. A study evaluating the ball-burst strength of multilaminate ECM scaffolds showed that by increasing the number of layers of SIS–ECM in a scaffold from two to four, there was an increase in strength of nearly 150% [73]. Since ECM scaffolds are typically degraded rapidly, it is important to remember that the mechanical properties of the scaffold material are only relevant for the time of surgical implantation. These properties will change immediately as a function of both the degradation rate and the remodeling that is facilitated by the bioinductive properties of the scaffold. The change in strength during remodeling of a multilaminate form of SIS showed a nadir at 10 days following implantation as a body wall scaffold and a subsequent increase in strength to a value that exceeded that of native tissue by approximately 45 days [19].

The methods used to process tissues to create an ECM scaffold can affect the mechanical and biologic properties. For example, the lyophilized form of SIS–ECM shows different fiber kinematics as compared to the hydrated form of SIS–ECM, especially in the cross-preferred direction [74,75]. The method of terminal sterilization can affect the strength and functionality of bioactive growth factors with an ECM scaffold. SIS treated with peracetic acid and sterilized by ethylene oxide showed a loss of only 8% of TGF-β activity compared to the non-processed SIS [59].

Alternative forms of ECM materials, such as powdered products or gels, will obviously have different mechanical and material properties compared to sheet forms of ECM scaffolds. The alternative forms provide properties that facilitate clinical use including the ability to inject the inductive ECM into a site of interest via minimally invasive procedures. Therefore, from a practical viewpoint the most important material properties would be viscosity of the gel or particle size of a suspension to allow injection through a small bore needle. Of greater importance is the retention of bioinductive properties during the processing steps required to manufacture a gel or particulate form of an ECM scaffold.

4. Host tissue response to xenogeneic SIS–ECM

The use of xenogeneic ECM as a biologic scaffold should logically raise questions regarding the host (recipient) immune response. Many ECM scaffolds are of porcine origin including SIS. However, bovine tissue (e.g., TissueMend®) and allogeneic human tissue (e.g., AlloDerm) are well represented among the group of ECM biomaterials. Non-autologous biologic materials have been used for many years in humans without evidence of adverse immunologic outcomes. For example, porcine heart valves for valve replacement, porcine skin for the temporary treatment of burn victims, and porcine and bovine insulin for the treatment of type I diabetes have widely been accepted as safe products for human use.

Few controlled studies have been reported that evaluate and characterize the host immune response to most non-autologous ECM scaffold materials. In contrast, a number of studies have been conducted to characterize the immune response to xenogeneic SIS–ECM. For example, it has been shown that SIS–ECM contains small amounts of the galactosyl 1,3 galactose epitope (i.e., gal-epitope) [76] but its presence does not result in complement activation or cell mediated rejection following implantation [77]. If concerns regarding the gal epitope in xenogeneic ECM scaffolds still exist, it is possible to harvest ECM from transgenic gal-knockout pigs that have been bred for this specific purpose, or to treat harvested ECM with galactosidase as part of scaffold processing. van Seventer evaluated the T-cell response to SIS and found that human helper T-cell activation and differentiation are suppressed when these cells are cultured *in vitro* in the presence of processed SIS material [78].

Tissue cytokine and the serum humoral response to SIS was shown to be consistent with a Th-2 type immune response (accommodation) in contrast to the expected Th-1 (cell mediated rejection) type of response [79]. Even repeat exposure to xenogeneic ECM failed to cause sensitization or a Th-1 type response in a mouse model. Recipients of SIS–ECM scaffolds recognize the material as "non-self" and produce antibodies, but these antibodies appear to be limited to the non-complement fixing Th-2 profile, a finding consistent with their ability to induce constructive remodeling and avoid a classic tissue rejection response. It is unknown whether the simple absence of the cellular component provides for this favorable immunologic response or whether there is a pro-active, immune modulatory component of the ECM that directs this response.

There is a great need for a better understanding of the relationship between the classic indicators of inflammation, such as cellular infiltration, angiogenesis, hyperemia, and tissue swelling and the same processes that are involved in constructive remodeling of tissue. In fact, the clinical evaluation of SIS induced tissue remodeling, especially in cases of musculotendinous soft tissue reconstruction, has occasionally been confused with inflammation. Necessary and critical components of ECM scaffold remodeling include cellular infiltration, deposition of new ECM in response to mechanical stimuli, self-assembly of various cell populations and re-establishment of an interface between remodeling tissue and adjacent normal tissue. If biologic scaffold materials, such as SIS, are intended to modify the default mechanisms and patterns of wound healing toward more constructive tissue remodeling, then a re-examination of the spatial and temporal events that characterize similarities and differences between these two processes is warranted.

Recently, the role of mononuclear macrophages in the host response to implanted biologic scaffold materials has been investigated (unpublished data). These studies suggest that macrophages differentiate toward a phenotype that is associated with either cytotoxic inflammation or constructive remodeling [80,81]. The factors that influence the pro-inflammatory (M1) versus anti-inflammatory (M2) polarization profile of a mononuclear macrophage population are largely unknown. It appears, however, that ECM scaffold materials that are resistant to degradation elicit a pro-inflammatory (M1) type of response whereas the anti-inflammatory (M2) macrophage phenotype predominates with native ECM scaffold materials that are readily degraded.

5. Degradation of SIS–ECM

Perhaps the most important characteristic of SIS–ECM is its ability to be rapidly and completely degraded [20,82,83]. Quantitative studies of ^{14}C-labeled SIS used in both augmentation cytoplasty procedures and Achilles tendon reconstruction show that greater than 50% of the ECM scaffold is degraded and removed from the implantation site by 28 days and virtually all of the SIS is replaced by 60 days. The fate of 95% of the SIS degradation products is urinary excretion and it appears that there is no recycling of the biologic products to other tissues [20,84].

The rapid replacement of the degraded SIS with functional host tissue in both the urinary bladder location and the load bearing Achilles tendon location occurred without loss of function, that is, without bladder or tendon rupture. These findings suggest a very rapid infiltration and/or proliferation of functional host cells at the remodeling site and the deposition and assembly of new replacement matrix.

The factors that influence the rate and pattern of remodeling, especially the biomechanical factors, have not been studied in a systematic and comprehensive fashion. In the two animal models described above that quantitatively evaluate the degradation of SIS, the urinary bladder and Achilles tendon dog models, the influence of biomechanical factors upon the remodeling process is dramatic. In the augmentation cystoplasty model, constructive remodeling is virtually abolished if a Foley catheter is left in the urinary bladder preventing filling and emptying of the bladder on a regular basis. Instead of a mixture of well-organized smooth muscle cells, loose connective tissue and abundant vasculature, scar tissue replaces the scaffold material when the catheter is left in place. Similarly, if a non-weight bearing cast is placed on the lower limb following placement of an SIS scaffold as an interpositional Achilles tendon graft, the scaffold degrades leaving loose connective tissue that cannot withstand load and that ruptures immediately following subsequent attempts at weight bearing. Alternatively, if partial and progressive weight bearing is allowed beginning immediately after the surgical procedure, a well-organized tendon-like collagenous connective tissue forms at the site of remodeling. Our ability to utilize biologic scaffolds such as SIS is critically dependent upon our understanding of the factors that modulate the remodeling response.

6. Summary

Biologic scaffolds composed of naturally occurring ECM such as SIS have received significant attention for their potential therapeutic applications. The full potential of the ability of ECM scaffolds to promote constructive remodeling will not be realized, however, until an understanding of the biology and the external influences that affect biology, are better achieved. The factors that appear important for the constructive remodeling of SIS are its ability to be rapidly and completely degraded with the generation of downstream bioactive molecules, the bioinductive properties of the functional molecules that compose the native SIS material and the ability to engineer its mechanical properties at the time of implantation through an understanding of its collagen fiber microstructure.

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