Extracellular matrix as an inductive scaffold for functional tissue reconstruction

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The extracellular matrix (ECM) is a meshwork of both structural and functional proteins assembled in unique tissue-specific architectures. The ECM both provides the mechanical framework for each tissue and organ and is a substrate for cell signaling. The ECM is highly dynamic, and cells both receive signals from the ECM and contribute to its content and organization. This process of "dynamic reciprocity" is key to tissue development and for homeostasis. Based upon these important functions, ECM-based materials have been used in a wide variety of tissue engineering and regenerative medicine approaches to tissue reconstruction. It has been demonstrated that ECM-based materials, when appropriately prepared, can act as inductive templates for constructive remodeling. Specifically, such materials act as templates for the induction of *de novo* functional, site-appropriate, tissue formation. Herein, the diverse structural and functional roles of the ECM are reviewed to provide a rationale for the use of ECM scaffolds in regenerative medicine. Translational examples of ECM scaffolds in regenerative are provided, and the potential mechanisms by which ECM scaffolds elicit constructive remodeling are discussed. A better understanding of the ability of ECM scaffold materials to define the microenvironment of the injury site will lead to improved clinical outcomes associated with their use. (Translational Research 2014;163:268–285)

Abbreviations: ADAMTS = metalloproteinase with thrombospondin motif families; CO_2 = carbon dioxide; DNA = deoxyribonucleic acid; ECM = extracellular matrix; EMR = endomucosal resection; HGD = high grade dysplasia; MMP = matrix metalloproteinase; SIS = small intestinal mucosa; TMJ = temporomandibular joint; TMJD = Temporomandibular joint disorder; UBM = urinary bladder matrix; VEGF = vascular endothelial growth factor

The extracellular matrix (ECM) is a composite of the secreted products of resident cells in every tissue and organ. The matrix molecules represent a diverse mixture of structural and functional proteins, glycoproteins, and glycosaminoglycans among other molecules that are arranged in an ultrastructure that is unique to each anatomic location. The ECM exists in a state of dynamic reciprocity with the resident cells. That is, the matrix composition and organization change as a function of the metabolic adaptations of the cells in response to shifts in the mechanical properties, pH, oxygen concentration, and other variables in the microenvironment.[1] This constantly adapting structure-function relationship, therefore, represents the ideal scaffold for the resident cell population.

Although the ECM is a known repository for a variety of growth factors, it also represents a source of bioactive cryptic peptides.[2-4] Fragments of parent molecules such as collagen and fibronectin have been shown to

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Table I. Partial list of commercially available scaffold materials composed of ECM

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

Abbreviations: ECM, extracellular matrix; ENT, ear nose throat; SIS, small intestinal submucosa.

have a diverse array of biologic activities including angiogenesis,[5] anti-angiogenesis,[6] antimicrobial effects, and chemotactic effects, among others. These growth factors and bioactive peptides play important roles in defining the microenvironmental niche within which cells function in both normal homeostasis and in response to injury. The matrix has also been shown to be important in fetal development[7] and also plays a critical role in determination of stem/progenitor cell differentiation fate.[8,9]

The tremendous complexity of the composition and ultrastructure of the ECM is only partially understood. Therefore, it is hardly possible to design and engineer a mimic of this complex structure. However, the