ECM Science and Decellularization Article and Abstract Guide

1 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. 2008 Acta Materialia Inc. Published by Elsevier Ltd. All rights reserved.

2 Extracellular matrix structure

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ABSTRACT

Extracellular matrix (ECM) is a non-cellular three-dimensional macromolecular network composed of collagens, proteoglycans/ glycosaminoglycans, elastin, fibronectin, laminins, and several other glycoproteins. Matrix components bind each other as well as cell adhesion receptors forming a complex network into which cells reside in all tissues and organs. Cell surface receptors transduce signals into cells from ECM, which regulate diverse cellular functions, such as survival, growth, migration, and differentiation, and are vital for maintaining normal homeostasis. ECM is a highly dynamic structural network that continuously undergoes remodeling mediated by several matrix-degrading enzymes during normal and pathological conditions. Deregulation of ECM composition and structure is associated with the development and progression of several pathologic conditions. This article emphasizes in the complex ECM structure as to provide a better understanding of its dynamic structural and functional multipotency. Where relevant, the implication of the various families of ECM macromolecules in health and disease is also presented. © 2015 Elsevier B.V. All rights reserved.

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3 **Controlling stem cell behavior with decellularized extracellular matrix scaffolds**
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https://www.sciencedirect.com/science/article/abs/pii/S1359028616300043?via%3Dihub

ABSTRACT

Decellularized tissues have become a common regenerative medicine platform with multiple materials being researched in academic laboratories, tested in animal studies, and used clinically. Ideally, when a tissue is decellularized the native cell niche is maintained with many of the structural and biochemical cues that naturally interact with the cells of that particular tissue. This makes decellularized tissue materials an excellent platform for providing cells with the signals needed to initiate and maintain differentiation into tissue-specific lineages. The extracellular matrix (ECM) that remains after the decellularization process contains the components of a tissue specific microenvironment that is not possible to create synthetically. The ECM of each tissue has a different composition and structure and therefore has unique properties and potential for affecting cell behavior. This review describes the common methods for preparing decellularized tissue materials and the effects that decellularized materials from different tissues have on cell phenotype.

4 **The effect of cell debris within biologic scaffolds upon the macrophage response**
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ABSTRACT

All biomaterials, including biologic scaffolds composed of extracellular matrix (ECM), elicit a host immune response when implanted. The type and intensity of this response depends in part upon the thoroughness of decellularization and removal of cell debris from the source tissue. Proinflammatory responses have been associated with negative downstream remodeling events including scar tissue formation, encapsulation, and seroma formation. The relative effects of specific cellular components upon the inflammatory response are not known. The objective of the present study was to determine the effect of different cell remnants that may be present in ECM scaffold materials upon the host innate immune response, both in vitro and in vivo. Collagen scaffolds were supplemented with one of three different concentrations of DNA, mitochondria, or cell membranes. Murine macrophages were exposed to the various supplemented scaffolds and the effect upon macrophage phenotype was evaluated. In vivo studies were performed using an abdominal wall defect model in the rat to evaluate the effect of the scaffolds upon the macrophage response. Murine macrophages exposed in vitro to scaffolds supplemented with DNA, mitochondria, and cell membranes showed increased expression of pro-inflammatory M1 marker iNOS and no expression of the proremodeling M2 marker Fizz1 regardless of supplementation concentration. A dose-dependent response was observed in the rat model for collagen scaffolds supplemented with cell remnants. DNA, mitochondria, and cell membrane remnants in collagen scaffolds promote a proinflammatory M1 macrophage phenotype in vivo and in vitro. These results reinforce the importance of a thorough decellularization process for ECM biologic scaffold materials. VC 2017 Wiley Periodicals, Inc. J Biomed Mater Res Part A: 105A: 2109– 2118, 2017.

5 Properties of the Amniotic Membrane for Potential Use in Tissue Engineering

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ABSTRACT

An important component of tissue engineering (TE) is the supporting matrix upon which cells and tissues grow, also known as the scaffold. Scaffolds must easily integrate with host tissue and provide an excellent environment for cell growth and differentiation. Most scaffold materials are naturally derived from mammalian tissues. The amniotic membrane (AM) is considered an important potential source for scaffolding material. The AM represents the innermost layer of the placenta and is composed of a single epithelial layer, a thick basement membrane and an avascular stroma. The special structure and biological viability of the AM allows it to be an ideal candidate for creating scaffolds used in TE. Epithelial cells derived from the AM have the advantages of stem cells, yet are a more suitable source of cells for TE than stem cells. The extracellular matrix components of the basement membrane of the AM create an almost native scaffold for cell seeding in TE. In addition, the AM has other biological properties important for TE, including anti-inflammatory, anti-microbial, anti-fibrosis, anti-scarring, as well as reasonable mechanical property and low immunogenicity. In this review, the various properties of the AM are discussed in light of their potential use for TE.

6 Methods of tissue decellularization used for preparation of biologic scaffolds and *in vivo* relevance

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ABSTRACT

Biologic scaffolds composed of extracellular matrix (ECM) are widely used in both preclinical animal studies and in many clinical applications to repair and reconstruct tissues. Recently, 3-dimensional ECM constructs have been investigated for use in whole organ engineering applications. ECM scaffolds are prepared by decellularization of mammalian tissues and the ECM provides natural biologic cues that facilitate the restoration of site appropriate and functional tissue. Preservation of the native ECM constituents (i.e., three-dimensional ultrastructure and biochemical composition) during the decellularization process would theoretically result in the ideal scaffold for tissue remodeling. However, all methods of decellularization invariably disrupt the ECM to some degree. Decellularization of tissues and organs for the production of ECM bioscaffolds requires a balance between maintaining native ECM structure and the removal of cellular materials such as DNA, mitochondria, membrane lipids, and cytosolic proteins. These remnant cellular components can elicit an adverse inflammatory response and inhibit constructive remodeling if not adequately removed. Many variables including cell density, matrix density, thickness, and morphology can affect the extent of tissue and organ decellularization and thus the integrity and physical properties of the resulting ECM scaffold. This review describes currently used decellularization techniques, and the effects of these techniques upon the host response to the material.

7 Consequences of ineffective decellularization of biologic scaffolds on the host response

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ABSTRACT

Biologic scaffold materials composed of extracellular matrix (ECM) are routinely used for a variety of clinical applications. Despite known variations in tissue remodeling outcomes, quantitative criteria by which decellularization can be assessed were only recently described and as a result, the amount of retained cellular material varies widely among commercial products. The objective of this study was to evaluate the consequences of ineffective decellularization on the host response. Three different methods of decellularization were used to decellularize porcine small intestinal ECM (SIS-ECM). The amount of cell remnants was quantified by the amount and fragmentation of DNA within the scaffold materials. The M1/M2 phenotypic polarization profile of macrophages, activated in response to these ECM scaffolds, was assessed in vitro and in vivo using a rodent model of body wall repair. The results show that, in vitro, more aggressive decellularization is associated with a shift in macrophage phenotype predominance from M1 to M2. While this shift was not quantitatively apparent in vivo, notable differences were found in the distribution of M1 vs. M2 macrophages within the various scaffolds. A clear association between macrophage phenotype and remodeling outcome exists and effective decellularization remains an important component in the processing of ECM-based scaffolds. © 2011 Published by Elsevier Ltd.

8 The promotion of a constructive macrophage phenotype by solubilized extracellular matrix

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ABSTRACT

The regenerative healing response of injured skeletal muscle is dependent upon a heterogeneous population of responding macrophages, which show a phenotypic transition from the pro-inflammatory M1 to the alternatively activated and constructive M2 phenotype. Biologic scaffolds derived from mammalian extracellular matrix (ECM) have been used for the repair and reconstruction of a variety of tissues, including skeletal muscle, and have been associated with an M2 phenotype and a constructive and functional tissue response. The mechanism(s) behind in-vivo macrophage phenotype transition in skeletal muscle and the enhanced M2:M1 ratio associated with ECM bioscaffold use in-vivo are only partially understood. The present study shows that degradation products from ECM bioscaffolds promote alternatively activated and constructive M2 macrophage polarization in-vitro, which in turn facilitates migration and myogenesis of skeletal muscle progenitor cells. © 2014 Elsevier Ltd. All rights reserved.