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Review article

Decellularized matrices in regenerative medicine

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ABSTRACT

Of all biologic matrices, decellularized extracellular matrix (dECM) has emerged as a promising tool used either alone or when combined with other biologics in the fields of tissue engineering or regenerative medicine – both preclinically and clinically. dECM provides a native cellular environment that combines its unique composition and architecture. It can be widely obtained from native organs of different species after being decellularized and is entitled to provide necessary cues to cells homing. In this review, the superiority of the macro- and micro-architecture of dECM is described as are methods by which these unique characteristics are being harnessed to aid in the repair and regeneration of organs and tissues. Finally, an overview of the state of research regarding the clinical use of different matrices and the common challenges faced in using dECM are provided, with possible solutions to help translate naturally derived dECM matrices into more robust clinical use.

Statement of Significance

Ideal scaffolds mimic nature and provide an environment recognized by cells as proper. Biologically derived matrices can provide biological cues, such as sites for cell adhesion, in addition to the mechanical support provided by synthetic matrices. Decellularized extracellular matrix is the closest scaffold to nature, combining unique micro- and macro-architectural characteristics with an equally unique complex composition. The decellularization process preserves structural integrity, ensuring an intact vasculature. As this multifunctional structure can also induce cell differentiation and maturation, it could become the gold standard for scaffolds.

Contents

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1. Introduction

Naturally derived biomaterials have proven to be superior to synthetic polymers as regenerative medicine matrix scaffolds, in that they can retain the hierarchical complexity of native tissues. In fact, these materials can be used to build matrices of increased complexity: from microtissues (comprised of a combination of single proteins) to organ scaffolds produced by decellularization of whole tissues. Decellularized extracellular matrices (dECM) derived from organs/tissues encompass the characteristics of an ideal tissue scaffold: complex composition, vascular networks, and unique tissue-specific architecture. Consequently, their use has propagated throughout regenerative medicine both in vitro and in vivo. Developmentally, extracellular matrices (ECM) provide a tissue framework that imparts micro- and macro-architecture, a niche for cells and tissue mechanics that help drive cell fate. A better understanding of these matrices should eventually increase their use both in vitro and in vivo, should lead to more robust tools for bioengineering applications, and could provide the missing piece for regenerative medicine strategies such as cell therapy.

Over the past two decades, regenerative medicine has emerged with an aim of directly repairing/regenerating injured or diseased tissue rather than treating disease symptoms. Stem cells represent a major tool in the regenerative medicine armamentarium due to their capacity both to self-renew and to generate differentiated progeny; they are delivered either systemically or locally to mediate injury repair [1]. In humans, stem cells are found in virtually every tissue, as well as in blood and, most notably, bone marrow. Yet despite dramatic increases in stem cell research, translational applications at least for cardiac repair have been disappointing. Instead, the delivery, retention, and appropriate differentiation of stem cells in vivo face therapeutic hurdles [2].

A major characteristic of stem cells is their ability to respond to environmental cues and differentiate accordingly; yet, in the context of cell therapy-based organ and tissue repair, the local cell environment is often ignored. Instead, cells are often delivered into damaged areas (e.g., infarcted heart or cirrhotic liver) that lack the 3-dimensional (3D) complexity, fiber orientation, vascularity, and biochemistry of native tissue; and repair-associated changes often occur at the scar border, where tissue architecture, composition, and mechanical properties are more “normal.”

By using biologic matrices that recapitulate native tissue to varying degrees, it is possible to augment the biochemical, mechanical, and vascular milieu of damaged tissues potentially both to increase cell retention or survival and to recapitulate native cues for cell behavior, enhancing the effectiveness of cell-based repair [3] (Fig. 1). Not only can matrix be used to deliver or retain cells in vivo, it can also serve as a framework for cells when engineering complex 3D tissues in vitro. Finally, biologic scaffolds can be used in the absence of cells to facilitate delivery of other biologics such as small molecules or genes, that either obviate the need for cells or provide new exciting natural niches for recruited or delivered cells.

This review includes a discussion of dECM from tissues and organs scaffold and discusses how dECM scaffolds may augment the use of cells or genes in regenerative medicine strategies. Dis-

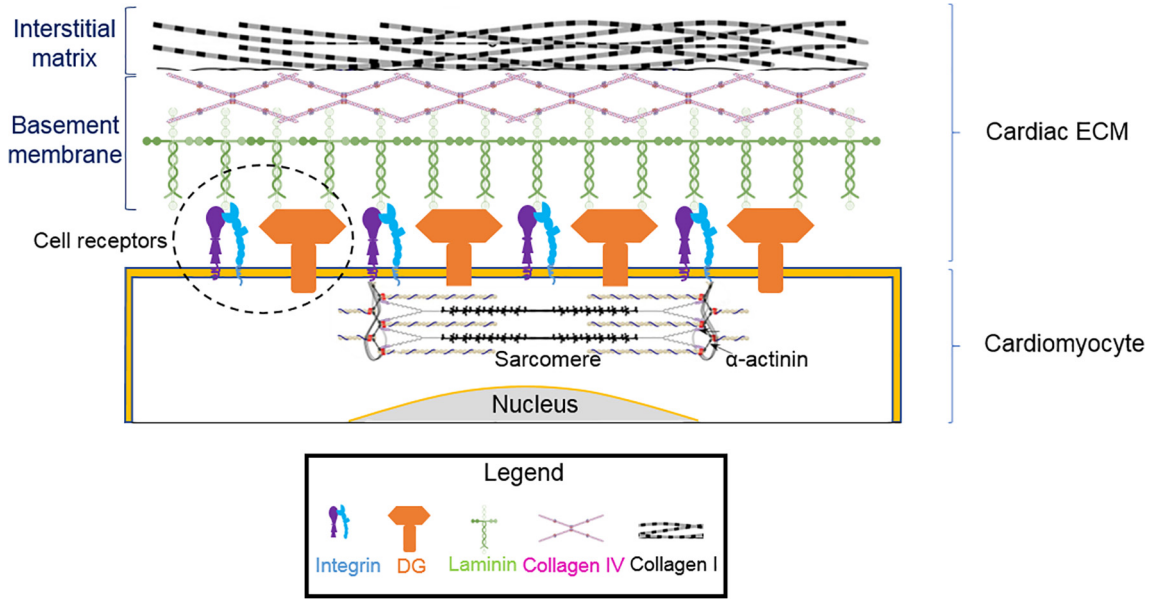

Fig. 1. Schematic representation of cardiac ECM-cardiomyocyte interactions. ECM is represented as two compartments: interstitial matrix – mainly composed by collagen type I; and basement membrane – mainly formed by laminin and collagen type IV. The cell-matrix interactions are mediated by cell receptors – integrin and dystroglycan (DG) present in the plasma membrane. (Simple microtissue comprised of these combinations of naturally occurring matrices is under development in our group.) In other organs, the composition of the two compartments and the specific cell receptor subunits may differ but the schema is the same. Adapted from [251].

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