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Injectable extracellular matrix derived hydrogel provides a platform for enhanced retention and delivery of a heparin-binding growth factor

Sonya B. Seif-Naraghi, Dinah Horn, Pamela J. Schup-Magoffin, Karen L. Christman *

University of California, San Diego, La Jolla, CA, USA

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ABSTRACT

Injectable hydrogels derived from the extracellular matrix (ECM) of decellularized tissues have recently emerged as scaffolds for tissue-engineering applications. Here, we introduce the potential for using a decellularized ECM-derived hydrogel for the improved delivery of heparin-binding growth factors. Immobilization of growth factors on a scaffold has been shown to increase their stability and activity. This can be done via chemical crosslinking, covalent bonding, or by incorporating natural or synthetic growth factor-binding domains similar to those found in vivo in sulfated glycosaminoglycans (GAGs). Many decellularized ECM-derived hydrogels retain native sulfated GAGs, and these materials may therefore provide an excellent delivery platform for heparin-binding growth factors. In this study, the sulfated GAG content of an ECM hydrogel derived from decellularized pericardial ECM was confirmed by Fourier transform infrared spectroscopy and its ability to bind basic fibroblast growth factor (bFGF) was established. Delivery in the pericardial matrix hydrogel increased retention of bFGF both in vitro and in vivo in ischemic myocardium compared to delivery in collagen. In a rodent infarct model, intramyocardial injection of bFGF in pericardial matrix enhanced neovascularization by approximately 112% compared to delivery in collagen. Importantly, the newly formed vasculature was anastomosed with existing vasculature. Thus, the sulfated GAG content of the decellularized ECM hydrogel provides a platform for incorporation of heparin-binding growth factors for prolonged retention and delivery.

1. Introduction

In many disease states—myocardial and peripheral ischemia, diabetic ulcers, retinal diseases, chronic wounds, etc.—the pathology is caused by a reduced blood supply [1]. This causes cell death in the downstream tissue, followed by degradation of the associated extracellular matrix. Tissue-engineering approaches, designed to mitigate the damage and promote healing or regeneration, focus on eliciting angiogenesis and remodeling of the damaged region. This remodeling can be achieved by encouraging endogenous cell infiltration into an acellular biomaterial or by delivering exogenous cells; in both cases, the goal is to encourage repair and contribute to the function of the organ. In order to do this, many tissue-engineering strategies have attempted to design materials to mimic the structure and composition of the native extracellular matrix (ECM) [2–5]. More recently, scaffolds derived from the native ECM of decellularized tissues have been developed and used in tissue-engineering applications [6–9]. These materials can be used intact as three-dimensional implantable scaffolds, as well as processed into injectable hydrogels that self-assemble in situ. When implanted or injected in vivo, previous work has demonstrated that these materials provide a template for cell infiltration and neovascularization [10–12]. In the case of cardiac repair, injectable ECM-derived hydrogels from decellularized small intestinal submucosa and the myocardium have been explored [7,13,14]. Injected alone into an infarct in small animals, these materials promote cell infiltration and have also been shown to preserve cardiac function post-myocardial infarction (MI) [13,14]. While the mechanisms behind their effectiveness in vivo have yet to be fully elucidated, it is clear that ECM-derived hydrogels provide porous, fibrous scaffolds that allow for cellular infiltration and neovascularization in ischemic regions.

In addition to their use as biomaterial-only therapies and cellular delivery platforms, tissue-engineered scaffolds can also be used to deliver bioactive moieties such as growth factors. Therapeutic angiogenesis via administration of angiogenic factors, such as vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF), has specifically been investigated in a variety of disease models including myocardial and peripheral ischemia [15–20] and wound repair [21–26]; a number of good reviews have been written on the topic [1,27–29]. Restoring blood supply has been demonstrated to have positive effects; for example, using growth factors for cardiac repair has demonstrated that inducing

* Corresponding author. Tel.: +1 858 822 7863; fax: +1 858 534 2722.
E-mail address: christman@eng.ucsd.edu (K.L. Christman).

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