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Timing underpins the benefits associated with injectable collagen biomaterial therapy for the treatment of myocardial infarction

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ABSTRACT

Injectable hydrogel biomaterials are promising therapies to promote repair and regeneration post-myocardial infarction (MI). However, the timing of delivery and the mechanisms through which biomaterial treatments confer their benefits are translational issues that remain to be addressed. We assessed the efficacy of an injectable collagen matrix at 3 different delivery time points post-MI. Infarcted mice received the matrix or control (saline) treatment at 3 h, 1 week or 2 weeks after MI. The earlier treatment delivery better prevented negative ventricular remodeling and long-term deterioration of cardiac function (up to 3 months), whereas waiting longer to administer the matrix (1 and 2 weeks post-MI) reduced the therapeutic effects. Collagen matrix delivery did not stimulate an inflammatory response acutely and favorably modulated inflammation in the myocardium long-term. We found that the matrix interacts with the host tissue to alter the myocardial cytokine profile, promote angiogenesis, and reduce fibrosis and cell death. This work highlights that the timing of delivery can significantly affect the ability of an injectable hydrogel to protect the post-MI environment, which will be an important consideration in the clinical translation of cardiac biomaterial therapy.

1. Introduction

Heart failure is a burgeoning disease and ischemic cardiomyopathies such as myocardial infarction (MI) are a major cause of this complex clinical syndrome [1]. Despite prompt intervention to restore perfusion post-MI, the loss of viable myocardium and adverse ventricular remodeling leads to dilated and functionally incompetent myocardium in many patients [1–4]. The remodeling is at first compensatory, but as it progresses, it results in deformed geometry, increased wall tension and impaired contractility [5]. Today, no therapies exist to reverse ventricular remodeling or heart failure. Cell therapy has yet to demonstrate clinically meaningful regeneration; therefore, alternative or concomitant therapies are being explored [6]. It is plausible that functionally stabilizing the heart by targeting early post-infarction processes may limit or circumvent the need for regenerative therapies in many patients.

Acellular biomaterials, many based on natural extracellular matrix (ECM) components, are emerging as new treatments for MI. These have evolved rapidly into increasingly complex therapies being tested in clinically relevant models of MI and heart failure [7,8]. Several materials have been shown to improve or preserve cardiac function in rodent and swine MI models, as assessed by left ventricular ejection fraction (LVEF), and improved ventricular geometry such as end-diastolic (ED) or end-systolic (ES) diameters [7,8]. Injectable hydrogels are particularly attractive for cardiac applications owing to their ease of use and the possibility of minimally-invasive delivery to the infarcted myocardium. Despite their promise, the optimal timing for delivery and the mechanisms through which biomaterial treatments confer their benefits for the treatment of MI remain unknown.

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As MI involves distinct necrotic, inflammatory, proliferative and maturation phases, prior delineation of the ideal time of delivery is important to ensure optimal efficacy of the biomaterial therapy [7]. For example, early application should not prevent the acute inflammatory process, since early inflammatory cell cytokine signaling is required to initiate the healing process [9,10]. If therapy is applied too late, then major tissue damage and fibrosis have occurred, and there may be little myocardium to preserve and/or salvage. Given that a biomaterial's properties and the components from which it is made can differentially target and regulate cell and tissue functions [11], the ideal timing of delivery is likely to differ for different biomaterial therapies. These issues should be addressed in order to avoid shortcomings similar to those experienced with the clinical translation of stem cell therapies [12,13]. For example, the optimal time to deliver cells post-MI has only recently been investigated in the clinic, such as the TIME and SWISS-AMI trials [14,15]. Clinical translation of biomaterial therapies should, at a minimum, involve evaluation of these parameters in animal MI models prior to moving forward with patient trials. To our knowledge, the only study to consider the impact of time of delivery for a natural material was performed by Landa et al. using an alginate-based injectable hydrogel [16]; however, the study did not include an early time point (7 vs. 60 days post-MI were evaluated), and the mechanisms of action underlying the benefits were not elucidated.

We have previously reported that therapy using an injectable collagen-based matrix could mediate apoptosis, vascularization, and regeneration to confer functional recovery in models of ischemia, necrosis and/or infarction [17–19]. In this study, we sought: 1) to determine whether timing of administration affects the ability of our collagen matrix to preserve or improve cardiac function post-MI; and 2) to examine the mechanisms by which the matrix treatment mediates cardiac repair. We demonstrate that the collagen matrix can mediate multiple repair processes and prevent progressive cardiac decompensation post-MI, and that the magnitude of the therapeutic benefit achieved is dependent on the timing of treatment delivery.

2. Materials and methods

2.1. Study design

2.1.1. Rationale

The objective of the study was to determine the ideal time-point for the delivery of an ECM-based hydrogel biomaterial to improve cardiac function in the infarcted mouse heart. A chronic LAD permanent occlusion MI model was used. Three different delivery time-points were tested: 3 h, 7 d and 14 d post-MI (Fig. 1A). The primary end-point was the effect of treatment on cardiac function (%LVEF) at 4 wk post-treatment. Following this determination, mechanisms underlying the observed therapeutic benefits were investigated through histology, immunohistochemistry and molecular analyses. Further follow-up analysis of the 14d treatment cohort was not pursued due to lack of efficacy.

2.1.2. Randomization & blinding

All surgeries were performed by the same animal technician blinded to treatment allocation. Mice were assigned a code number associated with the study protocol but not treatment. The treatment delivered to each mouse was recorded

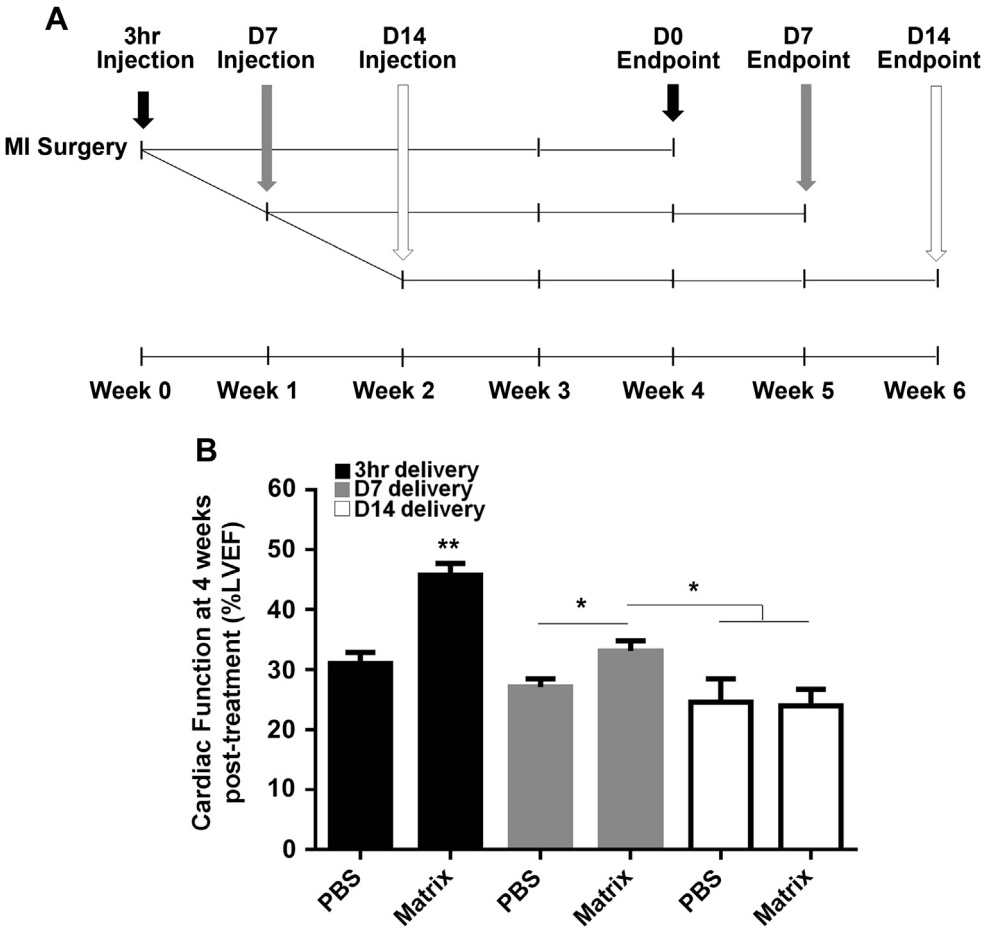

Fig. 1. Collagen-based matrix confers superior functional benefits when delivered earlier post-MI. (A) Schematic of experimental design. Chronic MI was induced and mice were subsequently randomized to both treatment (PBS or Matrix) and treatment timing (3 h, 7 days, or 14 days post-MI) and followed for 4 weeks post-treatment. (B) Cardiac function, assessed as % LVEF at 4 wk post-treatment. $^{**}p < 0.0001$ vs. all (one-way ANOVA); $^{*}p < 0.05$ (Fisher's least significant differences test); $n = 15$: PBS D0, $n = 16$: Matrix D0, $n = 14$: PBS D7, $n = 20$: Matrix D7, $n = 8$: PBS D14, $n = 5$: Matrix D14. (PBS, phosphate buffered saline; LVEF, left ventricular ejection fraction).