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EDITORIAL COMMENT

Injectable Biomaterials and Myocardial Infarction

Gaining a Toehold in an Unstable Matrix*

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While significant advancements have been made in terms of reperfusion therapy for acute coronary syndromes, myocardial injury culminating in a myocardial infarction (MI) occurs, leading to left ventricular (LV) remodeling and reduced ejection performance and ultimately to what is now defined as heart failure with reduced ejection fraction (HFrEF). The current standard of care for HFrEF is the use of systemic pharmacotherapies that predominantly cause blockade of neurohormonal pathways and provide favorable effects to attenuate the trajectory of the HFrEF process. Thus, it could be argued that current combinatorial pharmacotherapy for HFrEF is palliative because the underlying cause of the disease process, in this case continuous remodeling of the MI region, can proceed unabated. Post-MI remodeling is heralded by changes in local stress-strain patterns, activation of local inflammatory cascades, and induction of proteases, all of which culminate as an unstable extracellular matrix (ECM) within the MI. The unstable ECM in and of itself then promulgates increased regional stress on the MI region and ultimately thinning and expansion, which is most commonly measured as an increase in LV volumes (dilation) and eventually reduced EF. This process has been generically termed adverse post-MI remodeling and remains an important therapeutic target.

Because adverse post-MI remodeling is fundamentally a regional event, specifically targeting the MI region through direct or indirect delivery of biomaterials, bioactive molecules, stem/progenitor cell constructs, or a combination of these approaches continues to gain momentum from a translational research perspective. The study by Diaz et al. (1) in this issue of *JACC: Basic to Translational Science* reports on the effects of using a decellularized partially digested porcine ECM injected into the MI region of rats. This group has used this injectable ECM hydrogel formulation in a number of previous animal studies and, as indicated in this report, has advanced to first-in-human studies. The authors identified some important new findings in this rat post-MI model in that the ECM hydrogel injections were performed at 8 weeks after MI, a significant and translationally relevant time point. Specifically, the preponderance of previous studies performed localized injections of different hydrogel/small molecule/cell formulations at the time of the index event (MI induction) or shortly thereafter. It remains unclear whether and to what degree localized injections of a hydrogel formulation would effect late post-MI remodeling, when presumably the acute inflammatory phase of ischemic injury has subsided. Diaz et al. (1) identified, through the use of cardiac magnetic resonance imaging (MRI), that targeted injection of the decellularized ECM hydrogel altered the trajectory of adverse post-MI remodeling defined as a relative reduction in LV dilation and regional MI wall thickness when measured 4 weeks after injection. In a separate set of studies using a gene array, injection of this ECM hydrogel formulation reduced the expression profiles primarily contained within the

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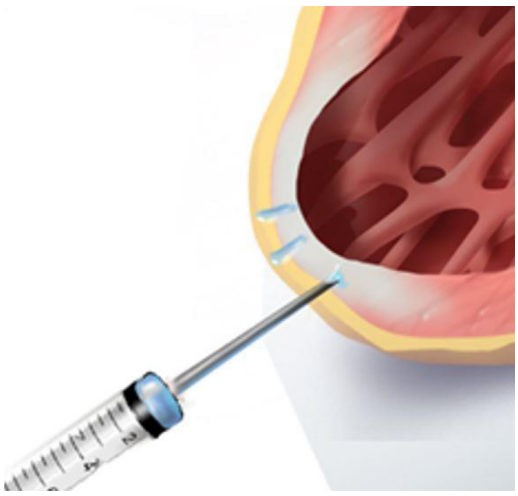
FIGURE 1 Targeting the MI Region With Injectable Biomaterials



The use of extracellular matrix–based injectable hydrogels not only can mitigate post-myocardial infarction (MI) remodeling, but also may serve as a platform for drug delivery and cell-based constructs.

inflammatory and proteolytic domains. The take-away message from this study is that even several months after MI, the MI region remains modifiable and is not an inert nonresponsive tissue. Thus, targeting the MI region at both early and late time points holds potential therapeutic value and expands the scope of potential patients that may benefit from localized delivery of hydrogel type constructs.

The study by Diaz et al. (1) used a decellularized/denatured ECM formulation (75 μl), which was injected directly into the mid-region of the MI in rats. As such, a significant amount of the MI region was infused with this ECM hydrogel, and MRI measurements identified that this caused significant thickening of the injected MI region compared with saline solution injections. While not directly measured in this study, this likely reduced regional LV stress within the injected MI region. Indeed, the use of MI patches or restraint devices have been shown to favorably move regional MI stress-strain relations (2,3). The study by Diaz et al. (1) continues to support the postulate that local injections of biomaterials stabilize the MI region, shift stress-strain patterns, and in turn break the futile cycle of ECM turnover. However, while this study demonstrated that targeted injections of an ECM hydrogel formulation mitigated indices of adverse post-MI remodeling, there remain a number of outstanding issues. First and foremost, this study was performed in a rodent MI model whereby the injection of the ECM hydrogel covered a relatively large amount of the MI. However, the relative mass of the ECM hydrogel formulation in relation to MI volume in this rodent model may not be readily translatable to larger animal models or humans. In a large-animal post-MI model, a discrete injection pattern of a hydrogel formulation attenuated adverse post-MI remodeling (4). Thus, the optimal relative volume and distribution of targeted hydrogel injections into the MI region in terms of interrupting the progression of post-MI remodeling remains to be established. The present study by Diaz et al. (1) used a denatured/decellularized ECM formulation that will undergo degradation and ultimately dissolution over time. This is true for a number of ECM-based hydrogel formulations. Despite this, the preponderance of past studies and the present study by Diaz et al. (1) demonstrate a significant attenuation of the post-MI remodeling process, presumably long after the hydrogel has been degraded. In some instances, ECM-based hydrogels, such as those using a hyaluronic acid–based construct, are "tunable" in terms of degradation kinetics (5). Thus, another important research direction is to determine whether and to what degree modifying the degradation kinetics of these injectable hydrogels influences the post-MI remodeling process.

Diaz et al. (1) used a decellularized porcine ECM formulation, which, as reported by the authors, contains a diversity of molecules, many of which may have bioactive signaling properties. Thus, the relative contribution of this ECM formulation with respect to the biophysical and/or biochemical determinants of post-MI remodeling is difficult to discern. Nevertheless, Diaz et al. (1), in a set of mRNA array studies, identified significant shifts in the relative expression profiles for inflammatory cascades, transforming growth factor signaling, and determinants of ECM proteolysis. It should be pointed out that these measurements were not temporally aligned with the LV functional studies whereby the mRNA measurements were made at 1 week after injection. Nevertheless, these observations are consistent with past studies targeting the MI region with injectable biomaterials (4,5). Importantly, the localized injection of these ECM-based biomaterials is not associated with an amplification of the inflammatory response, but rather attenuation of proinflammatory molecules and signaling pathways. This is a critical observation if these injectable hydrogel constructs are to be further advanced to clinical application.

The study by Diaz et al. (1) reported what is defined as a "trend" in fibrillar collagen content within the MI region with the ECM hydrogel injections. There are

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several considerations to be taken into account with this portion of the study. First, the use of a Trichrome histologic stain for assessment of fibrosis can be relatively insensitive and nonspecific for fibrillar collagen content. Second, the relative composition/structure of the ECM within the MI region with this histologic approach is problematic. Finally, whether and to what degree reducing fibrillar collagen content within the MI region holds long-term benefit regarding overall MI thickness and structural stability remain to be determined.

With the continuous development of improved imaging and minimally invasive approaches to access the MI region, using injectable therapeutics will continue to be an important area of exploration. What is most exciting is that the ECM-based hydrogels, such as that used by Diaz et al. (1), are amenable to injection approaches (**Figure 1**) and allow for precise targeting and control of delivery. This precision coupled with the fact that these injectable hydrogels do not evoke an inflammatory response also opens up an entirely new direction for translational research. Specifically, if indeed the injection of these ECM-based hydrogels are arguably safe and can provide at least a transient benefit after MI, then a larger research question arises: Can these ECM-based formulations be used as a platform for the localized delivery/release of small molecules and/or encapsulation of cell constructs within the MI region? Several proof-of-concept studies suggest that this indeed may be the case and makes studies such as this one by Diaz et al. (1) provocative in terms of what the future may hold for engineered injectable biomaterials and localized therapeutics in the treatment and potential reversal of an important cause of HFrEF.

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