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EDITORIAL COMMENT

Myocardial Matrix Hydrogels for Cardiac Repair

The Devil Is in the Details*

Marika Fava, PhD, Antonio Cannata, MD, Javier Barallobre-Barreiro, PhD

Right heart failure (RHF) encompasses signs and symptoms of HF resulting from a dysfunction of the right ventricle (RV). Cardiomyopathies, ischemic damage, and abnormal loading conditions, such as severe valve disease, chronic lung disease, or pulmonary hypertension, may be the cause of RV dysfunction. RHF usually follows left ventricular HF,[1] as the RV and left ventricle (LV) are integrated anatomically and physiologically. More than one-third of patients with new-onset HF present with coexisting RV dysfunction, often normalizing under guideline medical treatment.[1,2] Patients with HF with reduced ejection fraction are more likely to have RV dysfunction in comparison to those with preserved ejection fraction. Patients with biventricular failure have a higher rate of hospitalization and a decreased survival compared to patients with LV dysfunction alone.[2] Yet, current pharmacologic therapies for RHF are not RV-specific, and highly invasive nonpharmacologic strategies, including atrial septostomy and lung transplantation, are reserved for severe cases of RV dysfunction.[1] This highlights the clinical need for targeted strategies to ameliorate RV maladaptive remodeling.[1]

Extracellular matrix (ECM) hydrogels can be used as a targeted approach for the treatment of cardiac pathologies. These bioscaffolds consist of hydrated polymers that maintain structural integrity by physical and chemical crosslinks between polymer chains. When derived from decellularized tissues, critical ECM components remain within the hydrogel, retaining important traits of the native ECM. Several injectable hydrogels have US Food and Drug Administration approval and have been used in patients for the treatment of various diseases. ECM hydrogels derived from decellularized myocardial matrix (MM) have been shown to be safe and efficacious in large and small animal models of myocardial infarction (MI).[3] Their safety and feasibility have also been confirmed in patients with MI and LV dysfunction in a phase I clinical trial.[4]

In this issue of *JACC: Basic to Translational Science*, Hunter et al[5] evaluate for the first time the effectiveness of injectable MM hydrogels to mitigate negative RV remodeling. The investigators used a rat model of RHF, where RV dysfunction was achieved using pulmonary artery banding. MM hydrogels, derived from decellularized porcine myocardium and obtained separately from each ventricle, were injected in the RV of rats 2 weeks after banding. The efficacy of the treatment in recovering RV function was assessed by echocardiography using tricuspid annular plane systolic excursion. RV systolic function was improved on MM hydrogel injection, and this improvement was marginally better for LV-derived MM hydrogels, consistent with their cardiac magnetic resonance imaging findings. Using bulk RNA-sequencing, gene expression profiles were explored 1 week after injection in the RV of rats treated with LV- or RV-derived MM hydrogels compared to saline. A more proinflammatory and profibrotic profile was detected in response to RV-derived MM hydrogels, but no differences emerged in macrophage and myofibroblast content using immunofluorescence.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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Notably, the transcriptional profile does not account for the potential retention of soluble factors within the MM, which might contribute to differences in inflammatory responses. Thus, assessments at the protein level are important to characterize tissue remodeling on treatment, possibly not only after 1 week, but on more prolonged time periods post administration. In this regard, a suitable technique is mass spectrometry, which can also discriminate ECM proteins from different species, because the exogenous MM hydrogels can persist in the tissue for up to 2-3 weeks.[3] Likewise, a promising observation involved a reduction in fibrosis and cardiomyocyte hypertrophy 1 month after treatment with MM hydrogels of both LV or RV origin, suggesting that the gene expression differences obtained after 1 week might be less relevant on more prolonged periods, at least for these parameters.

A notable advantage of an experimental design including RV- and LV-derived MM hydrogels is that the differences in their performance offer an opportunity to shed light on the ECM components that are essential for the beneficial effects of this approach. For this, thorough characterizations of these injectable products are required. In a previous study using proteomics, the same group demonstrated a reduced presence of residual intracellular proteins after decellularization, and acknowledged the diversity of ECM proteins that constitute MM hydrogels beyond collagens. For example, after characterization of RV and LV-derived MM hydrogels using heavy labeled internal standards, the authors found that LV MM hydrogels contained a greater amount of several basement membrane proteins, including agrin.[6] Interestingly, agrin has been shown to promote cardiac regeneration in mice after MI.[7] Thus, specific ECM compositions characterize different cardiac regions,[6,8,9] but the individual ECM proteins that are directly responsible for the differences in performance of RV- and LV-derived MM hydrogels are yet to be pinpointed. Post-translational modifications, mostly glycosylation, also determine ECM properties, including immunogenicity and its ability to act as an appropriate scaffold for cardiac cells. Noteworthy, glycosaminoglycan binding was one of the most enriched pathways affected in the hearts of rats treated with MM hydrogels of either origin. Moreover, whereas total sulphated glycosaminoglycan content was similar in the ECM of RV and LV,[6] glycosylation patterns were not explored in more detail. Using MI models, Kong et al[10] have recently shown that the addition of a synthesized glycopeptide to porcine MM hydrogels improves cardiac repair by restoring the native ECM structure of the myocardium and offering binding ligands for host cell homing, adhesion, and infiltration. A characterization of ECM glycosylation patterns[8] in different cardiac regions could help to understand the properties of MM hydrogels derived from LV and RV. Thus, to elucidate the mechanisms behind the benefits of MM hydrogels, ECM composition should be at the center of the discussion table before this promising approach can be used as a viable and fully informed therapeutic alternative.

In the model presented here, RV dysfunction was achieved using pulmonary artery banding, resembling a cor pulmonale. This neglects the contribution of LV dysfunction to RHF, and therefore, it only represents a fraction of the clinical scenarios. The encouraging observations in the present study using a simplified, small animal model should be reproduced in larger models. In addition, experimental conditions should recapitulate more closely the clinical reality where other factors come into place. These include the etiology of RHF, the use of standard medications, and the time at which this therapy can be realistically delivered during disease progression. For example, we demonstrated that the use of beta-blockers in patients with ischemic HF is associated with a diminished synthesis of ECM components, most notably proteoglycans,[9] suggesting that part of the benefits of MM hydrogel-based therapies for RHF (ie, a reduction in fibrosis) could overlap with those already obtained with standard medication. Likewise, in patients with dilated cardiomyopathy, pathogenic mutations determine myocardial properties and composition. Any future clinical trials for the use of MM hydrogels in the setting of RHF should consider comorbidities, medications and genetics, and the efficacy of this strategy should be evaluated on prolonged times, after which the effect of these factors can be fully assessed. Lastly, the positive findings of the present study might not be directly relevant to the pediatric population. In these patients, RV dysfunction presents not only a different etiology and pathophysiology, but it is also accompanied by a myocardial configuration characteristic of early stages, including ECM composition. Therefore, the efficacy of MM hydrogel-based strategies could be reduced in this group of patients.

In summary, the promising results obtained by Hunter et al[5] using injectable MM hydrogels in a rat model are important because they provide the foundation for more targeted therapeutic avenues aimed to ameliorate RV dysfunction. Further research should address the specific molecular mechanisms leading to the beneficial effects of this therapy and explore the realms of its applicability in the often-complex clinical setting.

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