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EDITORIAL COMMENT

Extracellular Matrix Biomaterial Therapy for Myocardial Infarction

New Delivery Route and Immunomodulatory Effects*

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New treatments for myocardial infarction (MI) and ischemic heart failure continue to be a pressing unmet clinical need. Although regenerative medicine approaches have historically focused on cellular therapy and more recently gene therapy, biomaterials are increasingly showing promise as a more cost-effective alternative that can promote endogenous tissue repair and regeneration. In particular, biomaterials derived from decellularized tissues, whereby the cells are removed leaving behind the extracellular matrix (ECM) scaffold, have been shown as pro-regenerative in multiple preclinical animal models as well as in patients where commercial products are available in sheets and micronized powders. In the case of treating the heart, decellularized ECM has been used as epicardial patches and as ECM hydrogels with preclinical success and initial feasibility demonstrated in a clinical pilot[1] and Phase 1 clinical trial,[2] respectively. In general, multiple preclinical studies have shown how decellularized ECM promotes a proremodeling immune response driven by Th2 T cells and M2 macrophages.

The study by Vasanthan et al[3] in this issue of *JACC: Basic to Translational Science* reports on the use of a micronized decellularized ECM derived from a commercially available porcine small intestine submucosa (SIS) delivered via intrapericardial injection in a mouse MI model. This group has previously evaluated sheets of SIS implanted on the epicardium via invasive surgery in MI models for cardiac repair as mentioned in this new article, showing the patch promotes vascularization and improves cardiac function. The studies by this group demonstrated immunomodulatory properties of the SIS patch via neutrophils and monocytes. In this new study, they test proof-of-concept for delivering SIS in a micronized form via intrapericardial injection. Injectable biomaterials for treating MI have typically been delivered via intramyocardial injection, either transepicardial via surgery, or transendocardial via minimally invasive catheter. Recently, intrapericardial delivery has emerged as a potential delivery route for injectable biomaterials whereby the material is injected in the pericardial cavity.[4] This route has the potential to be delivered in a less invasive manner compared with surgical implantation through a percutaneous procedure, which could open this up to application in a larger patient population compared with epicardial delivery because that is likely to be applicable mainly to patients who are already undergoing a cardiac surgical intervention. Vasanthan et al[3] showed intrapericardial injection of micronized SIS suspended in saline in a total occlusion C57BL/6 mouse MI model increased ejection fraction, stroke work and volume, and cardiac output as well as reduced ventricular stiffness as measured by pressure-volume loops at 28 days following delivery compared to saline. Via histologic assessment the authors show that the biomaterial led to increases in vascular density, predominantly capillaries, in the border zone; perfusion of fluorescent beads confirmed the vasculature was functional. These data show for the first time that an ECM biomaterial can be delivered via intrapericardial injection and affect

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cardiac remodeling and function, which opens up a new clinical delivery route. Interestingly, another recent study that evaluated a hydrogel form of decellularized myocardial ECM delivered intrapericardially did not show improvements in cardiac function,[4] although this similar hydrogel has been shown to be efficacious with intramyocardial injection. Vasanthan et al[3] postulate that the improvements they found may be a result of differences in growth factors inherent in the SIS material compared with the ECM hydrogel. Given that the processing of decellularized ECM hydrogels includes a digestion step, which has been shown to reduce growth factors, this may indeed be the case and suggests that materials delivered into the pericardial space need a diffusible therapeutic component to penetrate through the epicardium and into the infarct area and border zone myocardium. This may be an important design consideration for biomaterial-based therapeutics being delivered via intrapericardial injection and will need to be explored further as additional research groups begin to evaluate this alternative delivery route. Another study that would be interesting to explore would be whether a micronized myocardial specific ECM would have enhanced effects given some studies in the literature suggest tissue specificity enhances the regenerative response of decellularized ECM biomaterials.

As mentioned in this paper, decellularized ECM is known to be immunomodulatory with effects on both macrophages and T cells. To date, studies in the literature have focused on these 2 cell types, but it is known there is significant cross-talk across the many cell types of the immune system. One of the key findings by Vasanthan et al[3] is that the SIS material mediates an eosinophilic response in the pericardium and neighboring myocardium. In the mouse model they evaluated the immune response in the pericardial space showing an increase in eosinophils and major histocompatibility class II+ macrophages, but not other immune cells types compared with saline. In the infarcted myocardium, similar results were observed except that increased CD4+ T cells were also found, predominantly driven by increases in Gata3+ Th2 cells. An increase in the eosinophil chemokine, eotaxin, was also found. Using human pericardial fluid cells collected from patients undergoing cardiac surgery, micronized SIS was shown to stimulate eotaxin production, demonstrating that these cells are likely mediating the eosinophilic response. Back in the mouse MI model, multiplex cytokine analysis showed increased levels of vascular endothelial growth factor, hepatocyte growth factor, interleukin (IL)-4, and IL-5 specifically in the border zone. Eosinophils are known to produce vascular endothelial growth factor, and IL-4 and IL-5 are both eosinophil mediators, suggesting the cardiac repair response induced by implantation of micronized SIS was at least partially driven by eosinophils. When the material was tested in an infarcted Gata 1 knockout (KO) mouse model, which is an eosinophil knockout, it did not improve any measure of cardiac function compared with saline and some measures (dP/dt_{max}, dP/dt_{min}, and end-systolic pressure) worsened. Likewise, there were no improvements in border zone vessel density in the knockout mice, suggesting the micronized SIS promotes angiogenesis and cardiac repair through an eosinophil-mediated response. This corroborates similar findings in a corneal wound-healing model whereby the sheet form of SIS also up-regulated IL-4, and healing was not observed in GATA1 KO model.[5]

Although the study by Vasanthan et al[3] nicely shows proof-of-concept for intrapericardial delivery of micronized SIS in a mouse MI model, the mouse heart size and pericardium are very different than that of a human heart. In particular, rodent pericardium is very thin and, therefore, there may be differences when performing intrapericardial injections in larger animals and patients. Large animal studies will be a critical next step in the translational process, particularly those that use the same access route as intended in patients. In addition, injections in this study were performed immediately post-MI. Future studies should be performed at a more clinically applicable timepoint especially given the temporal nature of the immune response post-MI. It will be critical to assess whether the effects on eosinophils and improvements in cardiac function occur if the material is delivered at a later timepoint.

Overall, the paper by Vasanthan et al[3] highlights the need to explore how biomaterials affect other immune cells beyond macrophages and T cells to drive tissue repair and regeneration, and further supports the design of new biomaterial-based strategies that can modulate the immune system and endogenous repair for treating the heart post-MI. It also adds to recent studies showing that intrapericardial delivery may be a viable translational route for some injectable biomaterials, particularly those that have a growth factor component or a

diffusible therapeutic that could penetrate into the infarct area and border zone.

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