Commentary: “Shear” patience for post–myocardial infarction regenerative therapy

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Christopher T. Ryan, MD (left), and Ravi K. Ghanta, MD (right).

Central Message

The sequence of changes in microenvironment after myocardial infarction may have critical implications for the timing of regenerative therapy.

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Adverse ventricular remodeling remains a significant threat to long-term cardiac function after myocardial infarction (MI), even with timely coronary revascularization. The sequence of changes that follow ischemic insult has been well characterized. The initial stage of cardiomyocyte loss and acute inflammation is followed by a complex interplay of cellular, paracrine, and neurohormonal factors that result in chronic fibrosis with maladaptive changes in ventricular geometry.¹ A variety of innovative strategies to halt, or even reverse, these changes are under investigation. Shear-thinning hydrogels (STGs) exhibit fluidlike properties that allow potential catheter delivery and in situ self-assembly to prevent infarct expansion and mechanically stabilize injured myocardium.² Extracellular vesicles (EVs) secreted by endothelial progenitor cells play a role in endogenous tissue response to hypoxia, suggesting a potential therapeutic application. EVs are promising because they can be maintained more easily in a clinical environment than cellular therapy and have been demonstrated to induce neovascularization in ischemic tissue.³ The combination of STG stabilization with regenerative therapy, such as EVs, is a rational evolution of this therapeutic strategy and has shown promising preliminary success.

In this issue of the *Journal*, Chung and colleagues⁴ rigorously evaluate the efficacy of combined STG-EV therapy and optimize therapy timing in a preclinical model, a step that is essential in light of critical oversights that plagued clinical trials for angiogenic therapy and stem cell implantation.^{4,5} First, Chung and colleagues⁴ establish that cells exposed long term to hypoxia in vitro exhibit greater uptake of STG-EVs than those exposed to only a short period of acute hypoxia. These cells also formed significantly more vascular meshes, an established in vitro assay for angiogenesis.⁶ This in vitro study establishes a potential rationale for ischemia duration and therapeutic efficacy. Chung and colleagues⁴ then used a rat MI model to compare the in vivo

efficacy of STG-EVs administered at different time points after induced MI. Time points were selected to represent the inflammatory (3 hours postinfarct), proliferative (4 days postinfarct), and fibrotic (2 weeks postinfarct) phases described after MI.⁷ The most favorable outcomes with respect to systolic and diastolic function, infarct thickness, and ventricular geometry were seen with STG-EV administration during the proliferative phase at 4 days postinfarct. Given the dense inflammatory cell infiltrate during this phase, it is hypothesized that STG-EVs may confer benefit through an immune-modulating effect that truncates the maladaptive paracrine cascade. Alternatively, structural stabilization and unloading of the weakened left ventricular wall may be attributable to the STG delivery vehicle. This latter explanation is partly supported by the observation that some benefit is observed with injection of STG without the EV component, albeit less than that seen with STG-EV injection. This finding is consistent with previously reported benefits of myocardial STG injection immediately after MI in sheep models.² This benefit may be more pronounced during the proliferative phase, because the myocardium is structurally at its weakest as a result of the action of matrix metalloproteases from activated inflammatory cells.

Although these studies are preliminary, Chung and colleagues⁴ demonstrate the promise of a potential acellular transcatheter therapy that may be more feasible in a clinical environment than other regenerative strategies. On the basis

of the results of this study, other angiogenic therapies may be optimized by appropriate timing. It remains to be seen whether the proliferative phase represents the optimal timing for other strategies addressing postinfarct fibrosis and remodeling, such as small molecules, gene therapy, or alternative biomaterials. Investigators of these preclinical therapies would be wise to emulate the methodical approach of Chung and colleagues.⁴

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