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Commentary: Awakening the hibernating myocardium: The pristine business of mesenchymal stem cells

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CENTRAL MESSAGE

Mesenchymal stem cells restore the functional activity of hibernating myocardium by upregulating the mitochondrial proteomic profile.

Hibernation is a natural phenomenon adopted by many warm-blooded animals to survive adverse environmental situations (especially extreme winter) by minimizing their metabolic demands. The process of hibernation sustains the survival of those animals to restart their active life after surviving the period of adversity. Likewise, myocardial tissue undergoes a so-called clinical hibernation due to chronic ischemia following reduced coronary blood flow. Hibernating myocardium (HM) displays increased

regenerative capacity, decreased tissue mortality, and low risk of future failure suggesting the increased survival capacity of myocardial tissue following a coronary artery bypass graft (CABG) procedure.¹ The term *hibernating myocardium* was coined by renowned cardiologist Shahbuddin H. Rahimtoola in 1984 at the National Heart, Lung, and Blood Institute Workshop on the Treatment of Coronary Artery Disease.² Since then, HM has gained clinical attention in therapeutic and regenerative cardiology. Because HM is critically associated with myocardial energetics, the mitochondrial adaptations in HM tissue provoked research interests across the globe and led to several outstanding discoveries.

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Failure stories of CABG reflect the fact that mitochondrial dysfunction is the prime reason for inadequate cardiac function. The restoration of mitochondrial function presents an ideal therapeutic approach for improving functional cardiac outcomes following CABG procedures.¹ The compromised mitochondrial function in HM is primarily due to the dysregulation of mitochondrial proteome resulting in decreased myocardial oxygen consumption, whereas maintaining viability suggests an adaptive mechanism.³ Also, depressed state 3 mitochondrial respiration rate has been prevalent in HM; however, HM tissue presents improved antioxidant responses that sustain the viability of myocardial tissue despite the chronic ischemia.⁴ Although surgical revascularization by CABG aids in the recovery of HM, the impairment of the bioenergetic components continues to prevent the achievement of maximal electron transport and cardiac function.¹ Thus there is a necessity of adjuvant/alternative strategies to achieve complete cardiac recovery and prevent future failure episodes.

Stone and colleagues⁵ delineate a promising strategy to target HM employing their previously established swine model.⁶ The authors focus on the utilization of mesenchymal stem cells (MSCs) loaded into an epicardial patch to upregulate the mitochondrial proteomic profile and improve cardiac outcomes following CABG procedures. The article is conceptually unique in translational cardiology because the authors succeeded in upregulating protein peroxisome proliferator-activated receptor gamma coactivator-1 alpha signaling by allogeneic MSCs to restore the

mitochondrial proteome and activity via implantation of a pre-engineered epicardial patch immediately after CABG. The choice of the absorbable and compatible biomaterial polyglactin as the template for the fabrication of the epicardial patch is another potential merit of the study. The authors provide a strong message to translate their approach as an adjuvant strategy along with CABG to improve cardiac outcomes and to facilitate the functional recovery of HM. The overall schema of the study is displayed in Figure 1.

However, the underlying mechanisms for the effect of MSCs on the mitochondrial biology of HM tissue have not been delineated in this study. Also, the juvenile swine model used by Stone and colleagues⁵ raises critical concerns regarding the similarities with human clinical situations and the simulation of pathophysiology. What are the contents and influence of secretome from MSCs in HM? How do the cells communicate and migrate at the HM-implant interface? Moreover, limited information has been provided regarding the physiochemical and biological characterization of the patch implant. In addition, the mild inflammation associated with patch implantation may trigger tissue regeneration.⁷ Despite the wealth of scientific data on biomaterials and stem cells for cardiac regeneration,^{8,9} the interface biology of the implant and HM in the vicinity of epicardium warrants thorough histological and immunological investigation. The introduction of stimuli-responsive and/or smart/intelligent biomaterials for designing the epicardial patch could be an added merit. These concerns need to be considered from a cardiologist/

FIGURE 1. The overall schema for the recovery of hibernating myocardium using a mesenchymal stem cells-laden epicardial patch implant to facilitate the upregulation of mitochondrial proteome.

clinician perspective to translate the findings to the therapeutic arena.

Nonetheless, the findings by Stone and colleagues⁵ in their swine HM model demonstrate improvement in cardiac dysfunction due to chronic ischemic episodes by the implantation of an MSC-laden epicardial patch. The findings are promising but warrant consideration of confounding factors such as age, hyperlipidemia and inflammatory status as well as comorbidities including diabetes and other metabolic disorders in large animal models to closely simulate human pathology. Addressing such issues paves the ways for human clinical trials.

Accelerating mitochondrial activity by replenishing MSCs using appropriate biomaterials to salvage ischemic myocardium opens new interdisciplinary opportunities for improving the HM. The field of translational cardiology welcomes such outstanding discoveries that provide a pleasant hope for millions of people with cardiovascular diseases across the planet.

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