Commentary: What’s on the inside counts

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Therapeutic options for patients with incompletely revascularized and non-revascularizable coronary artery disease and residual chronic myocardial ischemia are limited. Chronic ischemia generates inflammation, which contributes to the development of heart failure through maladaptive remodeling processes of the left ventricle. Thus, targeting the underlying inflammatory process provides a promising therapeutic approach for this patient population.

Extracellular vesicles (EVs) are lipid-bound particles and are heterogeneous in size, composition, cellular origin, and function. The effect of EVs is attributed to their delivery of bioactive molecules (including a variety of DNAs, RNAs, proteins, and lipids) to target cells. This leads to changes in signaling cascades, epigenetic modulation, and phenotypic alteration. Myocardial repair via EVs has gained interest as a treatment for cardiovascular diseases. In fact, stem cell–derived EVs have been reported to induce angiogenesis, promote myocyte proliferation, decrease cell death, and reduce fibrosis in myocardial ischemia. In addition, modulating the inflammatory response in myocardial ischemia to reduce maladaptive remodeling is an important concept that has proven effective with EVs in acute ischemic disease.

In this issue of the Journal, Sabe and colleagues study the modulatory effects of human bone marrow mesenchymal stem cell (HBMSC)-derived EV therapy on inflammation in chronic myocardial ischemia as a potential mechanism underlying their previously reported benefits of EV therapy. The authors use a clinically relevant porcine model of ischemia coupled with metabolic syndrome. The authors conclude that HBMSC-EVs decrease proinflammatory protein expression and increase anti-inflammatory protein expression. Specifically, they report a reduction in the nuclear factor-kB signaling cascade, a main mediator of inflammatory response, although these changes appear to be independent of Toll-like receptor 4 and nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha. This mirrors previous reports on the key role the nuclear factor-kB signaling cascade plays in the inflammation seen in chronically ischemic myocardium. This finding is supported by the increased expression of anti-inflammatory markers, specifically interleukin (IL)-10. The injection of IL-10–expressing cells into the myocardium after acute ischemic injury has been shown to improve myocardial function in an IL-10–dependent manner, and the protective effect has been attributed to reduced T-cell recruitment. The current work shows absolute inflammatory cell count remained unchanged with EV treatment. It is also noteworthy that while some inflammatory markers were altered, other key players remained unchanged. It remains undetermined if this observation is attributable to a lack of power in this study or the innate characteristics of the EV cargo used.

This study is encouraging, but it will be important to specifically correlate EV composition (and variations in that composition) to previously demonstrated functional benefits of EV administration in chronically ischemic myocardium. Further EV therapeutic content characterization...
and standardization are necessary and potentially formidable challenges to the clinical applicability of this new treatment strategy. What’s on the inside counts, and we look forward to Professor Selke’s characterization of EV cargo via transcriptomic studies, bringing this treatment approach one step closer to clinical translation.

References


