Commentary: The stem cell bridge: Forging a path above cold storage

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Heart transplantation remains the gold standard of treatment for patients with end-stage heart failure, with a median survival of 13 years. However, owing to the scarce and stagnant supply of donor organs in the United States over the past 3 decades, patients continue to experience significant mortality on the waiting list. Although one of the significant limitations is supply, the other is inherent to the current standard of donor organ preservation—cold static storage—which poses temporal and geographic challenges to facilitating safe, equitable organ allocation. The risk of primary graft failure and death correlates with increasing duration of ischemia.

Mesenchymal stem cell (MSC) therapy has held promise for regenerative cardiac therapies for decades. In tandem with small clinical trials demonstrating the safety and limited efficacy of MSCs in improving cardiac function after ischemic injury or cardiac surgery, the mechanisms behind these cellular therapies are beginning to be explored. More so than cell engraftment and growth from exogenous cells, paracrine pathways and the release of extracellular nanoparticles have recently been highlighted as important mechanisms of action of MSCs. The translational potential of this finding is currently under active investigation across various domains.

It is at this opportune moment that Wang and colleagues share their insights on the role of MSC-derived therapy in reducing injury from prolonged cold ischemia in an ex vivo mouse heterotopic transplantation model. MSC conditioned medium (CM), designed to include a comprehensive MSC “secretome,” was delivered as an adjunct to standard preservation solution and demonstrably improved donor heart recovery after 6 hours of ischemic cold, static storage. These observations were consistent across hemodynamic and histological analyses and were partially reversed by concomitant use of an exosome-release inhibitor. Hearts in the intervention arms also returned to spontaneous contractility more readily on reperfusion.

The study by Wang and colleagues is significant in that it is one of the first studies to highlight this therapy in a cold ischemia model. Although intuitively, this may follow previous work surrounding ischemia-reperfusion injury and ischemic cardiomyopathies, the authors are to be commended for helping to bring MSC therapy into the conversation surrounding donor organ preservation and transplantation. The authors postulate exosomal transfer of microRNA from MSCs to donor heart as a possible mechanism, which has significant implications, as exosomes are highly conducive to clinical applications and can be relatively easily prepared, stored, and used for therapy.

References
2. Mitroupolos FA, Odim J, Marelli D, Karandikar K, Gertsen D, Ardehali A, et al. Outcome of hearts with cold ischemic time greater...
Commentary: The dilemma of donor heart cold storage: Are stem cell extracellular vesicles the answer?

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Many donor-specific variables affect the feasibility and outcomes of heart transplantation. The ability of a donor heart to tolerate only a short period of cold ischemia has direct implications on when, where, and how donor hearts are procured. Strategies to extend the period of cold storage have been proposed, with focus on mitigating ischemic damage to the donor heart. These include modifying the conditions of cold storage by adding protective agents to the storage solution.

Wang and colleagues describe a novel way to extend the period of cold storage in an experimental model of heart transplantation. The additives to the storage solution are extracellular vesicles (EVs). EVs are carriers of bioactive proteins and nucleic acids that are involved in intercellular communication. The 3 main types of EVs, apoptotic bodies, microvesicles, and exosomes, are differentiated based on size, contents, and surface markers.

Wang and colleagues use cultured mesenchymal stem cells (MSCs) as the cell source for EVs in their model. The secretory products of the MSCs are released into the medium in which they are cultured, creating conditioned medium. They use a purification process to isolate predominantly exosomes; however, their methodology allows for contamination with microvesicles. The purified EVs (mixture of exosomes and microvesicles) are a cell-free preparation; when considering how one might translate this experimental work clinically, this is an important feature because issues related to immunogenicity or tumor formation from exogenous stem cells is avoided.

MSCs are of significant interest in regenerative medicine due to their plasticity (i.e., ability to differentiate into numerous cell types depending on the microenvironment) and paracrine effects. In experimental models of