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Synthetic MSC? Nothing Beats the Real Thing

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Bone marrow-derived mesenchymal stem cells (MSCs) are a widely used and promising stem cell type to treat ischemic heart disease. Ease of access for MSC isolation and relatively straightforward culture/expansion protocols led to numerous studies to explore therapeutic potential of MSCs. Direct injection of MSC into infarcted hearts showed fusion with resident cardiomyocytes[1], transdifferentiation into cardiomyocytes and coronary vessels[2], as well as improvement of ventricular function coupled with beneficial remodeling[3,4]. However, as is the case for multiple types of cardiac stem cell therapies, uncertainty and limitations also exist in adoptive transfer of MSCs. Major issues include poor intramyocardial engraftment, negligible long-term retention, marginal transdifferentiation capacity, and modest understanding of biologically relevant cytokines released following transplantation. MSCs are postulated to ameliorate heart disease through release of soluble factors that contribute to extracellular matrix remodeling, pro-survival and proliferative signaling, and also stimulate cell-cell communication and recruitment of endogenous cardiac stem cells through paracrine action[5]. To support the paracrine hypothesis of action, MSC secretome products have been suggested to serve as an alternative to MSC therapy. Concentrated MSC-conditioned medium enriched for cellular secretion significantly reduced infarct size and improved ventricular function following intramyocardial delivery[6]. However, the short half-life of released cytokines and inability to maintain cytokine production following delivery are limitations of cytokine/paracrine-based treatments. Exosomes derived from MSCs, bi-lipid membrane bound vesicles carrying secretory signaling molecules, exert cardioprotective actions but were less potent relative to conditioned medium[7]. Therefore, an important challenge remains as to how the secreted cocktail from MSCs can be most effectively delivered. A new study in this current issue of *Circulation Research* offers a simple and effective maneuver, using the MSC's own vessel to bag its own goodies.

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Disclosures

M.A. Sussman is a founder and co-owner of CardioCreate Inc. M. Monsanto and B. Wang report no conflicts.

The study by Luo *et al.*[8] in this issue of *Circulation Research* used fabricated synthetic MSCs (synMSCs), a cell-free therapeutic microparticle with cell membranes derived from MSCs that encapsulate concentrated MSC secretome. Briefly, poly(lactic-co-glycolic acid) (PLGA) was used to encapsulate enriched secretome harvested from MSC conditioned medium and the PGLA-secretome emulsion was coated with isolated MSC membrane, forming a sphere structure with a cell membrane on the surface and the full spectrum of cell secretome captured inside. These synMSCs share similar cell dimension and surface markers as human bone marrow-derived MSCs. Secretory molecules such as VEGF, SDF-1, IGF-1 can be continuously released from synMSCs for up to one week. When injected into infarcted hearts, synMSCs significantly reduced infarct size and maintained thicker ventricular wall at 14 days, to the same extent as intact MSC-based therapy. Therapeutic benefits of synMSCs were thereby explained by paracrine effects along with recruitment of endogenous c-Kit$^+$ cardiac progenitor cells and promotion of angiogenesis consistent with increased number of CD34$^+$ cells.

Immunomodulatory properties of synMSCs were also postulated to confer added benefits. MSCs have reduced expression of major histocompatibility complex (MHC) class I and co-stimulatory molecules such as CD40, CD80, and CD86[9]. This hypoimmune profile prompted Luo *et al.* to coat microparticles with MSC cell membranes. Unlike other non-cellular based therapies, such as exosomes or injection of soluble factors[5,10], the synMSC membranes may allow for increased duration prior to clearance due to their larger size and lowered immunogenicity. With the advantage of a native MSC surface profile, synMSCs interact with and stimulate cardiomyocyte contractility when co-cultured with neonatal rat cardiomyocytes *in vitro*. MSCs may also exert protective effects upon resident cardiac cells after ischemic damage via direct cell-to-cell interactions and small diameter nanotubes that facilitate intercellular communication including exchange of mitochondria[11,12]. Direct exchange of intracellular components and information is clearly a limitation of synMSCs that lack mitochondria, leading to diminished cellular communicative capacity. In addition to nanotubes and gap junctions[13], cell surface receptors and membrane bound proteins allow cells in close proximity to interact. The most likely reason why synMSCs show improved cardiomyocyte contractility and increased cardiomyocyte number relative to treatment with uncoated microparticles is the retention of MSC cell surface proteins on the synMSCs membrane. However, if administration of cell-free secretome is not significantly more efficacious than intact MSCs, then what makes synMSC more attractive than real MSC?

The simple answer is ease of synMSC cryopreservation and subsequent delivery to patient. Freeze-thawing presents a major hurdle for cell viability, as dynamic secretome composition can rapidly change by cryopreservation, storage, and subsequent cell recovery. Because synMSCs are not “real cells”, post-thaw synMSCs maintain surface marker expression, structure and size, and sustained release of VEGF. Impressively, when injected *in vivo*, the synMSCs show decreased activation of CD86$^+$ macrophage compared to cellular MSCs.

Despite the stable packaging of secretome afforded by synMSCs, the composition and sustainability of the MSC secretome once injected *in vivo* still remains unclear. Growth factors, cytokines, extracellular matrix components, hormones, are all present in a cell’s secretome. Characterization of the complete secretome profile would provide insight toward

which factors are present and presumptively contributing to the beneficial effects observed. Similar to injection of exosomes[7], naked DNA[14], or specific growth factors and cytokines[10], synMSCs are unable to sense their environment and adapt to secret cytokines relative to environmental cues. Degradation of synMSCs is inevitable, especially given the myocardial environmental changes that occur following ischemia and reperfusion. Combating these issues following transplantation remains a major issue to be further examined.

In spite of the innovative nature of the synMSCs, the predominant disconcerting outcome from the report of Luo *et al.* is that synMSCs exhibit equivalent efficacy compared to real MSCs without evidence of any functional advantage[8]. This may simply be a case of "two steps forward, three steps back", with the synthetic cell concept just beginning to be explored. Future possibilities could be envisioned wherein synthetic cells with artificially engineered customized membranes encapsulate cellular factors or microparticles[15]. This would streamline production by creating artificial membranes in days rather than growing up cells for weeks, saving both time and money. While cognizant of current overt limitations in functional superiority of synMSC over the tried-and-true cellular delivery of intact MSC, only time will tell if synMSC are the direction with which we should be marching.

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