Inject Me Once and Inject Me Twice.
Then Inject Me Once Again

Mark A. Sussman

Nature is far too subtle to repeat herself.

—Paul Muni

A though nature may be subtle, our interventional approaches to enhancing myocardial regeneration can be anything but. We genetically re-engineer cells to enhance their potential, reorder cells from one type to another, apply patches of cells like plaster on a wall, or inject unfathomable numbers of cells hopeful that a small fraction cling to the heart and to life long enough to make a difference. Clearly, the weight of the evidence supports the assertion that cell therapy can confer beneficial effects, but consensus opinion is that the degree of improvement generally falls markedly short of what is needed for full restoration of hemodynamic performance and that we need to do better. And in this next installment of approaches to tweak the Natural Order of things, Tokita et al lend a hand by offering Nature in this next installment of approaches to enhance myocardial regeneration can be anything but.

The premise is a breathtakingly simple one as put forth in the introductory remarks of the study: “Just as most pharmacological agents are ineffective when given once but can be highly effective when given repeatedly, so a cell product that appears to be ineffective or modestly effective when given as a single treatment may, in fact, turn out to be quite efficacious if given repeatedly.” In layman’s terms, if one injection of cells yields beneficial effects, then multiple injections of cells could build on one another to create cumulative gains greater than any derived from a single treatment as previously established. Thus, armed with this fairly straightforward premise, Tokita et al set about devising a strategy to perform multiple injections of c-kit<sup>POS</sup> cardiac progenitor cells (CPCs) in a rat myocardial infarction model. So if the idea is so appealingly simple, then why has it taken so long for the study to be performed? As it turns out, the challenge of repeated intramyocardial cell delivery spaced weeks apart required sophisticated technical tools and skill.

The rat myocardial infarction model was well established by the authors and previously shown to benefit from a single intracoronary cell infusion. Now, with 3 administrations of CPCs performed 35 days apart into a pathologically injured heart as 30 days postinfarction challenge, the authors considered the consequences of cell delivery in the rodent. Infusion of CPCs by intracoronary or intramyocardial routes in this rat experimental model requires an open chest procedure, and delivery of cells by an intravenous route was unable to achieve cell retention in the heart. Another way of delivering CPCs to the damaged region without risking mortality from repeated thoracotomies needed to be developed. The authors turned to percutaneous, closed chest, echo-guided intramyocardial injection with impressive results, losing 9 out of the starting cohort of 73 animals because of technical issues. As a proof of principle study for repeated cell therapy, the survival rate of 88% with a robust starting population number provided more than enough animals for analysis. Of course, this is not the first time echo-guided intramyocardial injection in rodents has been performed, but this would seem to represent the first time this technique has been successfully applied in the context of repeated cell therapy injections.

Findings from the study by Tokita et al conclude that a triple dose of CPCs in their experimental model resulted in greater cumulative beneficial effects for myocardial structure and function compared with a single dose of CPCs. Regional and global left ventricular function improved to a similar degree after each sequential CPC injection. Specifically, CPC infusion produced ejection fraction improvements in the single infusion group that were a modest 3.4% increase, whereas the triple infusion ultimately produced a 13% increase. Parameters of myocardial remodeling in the multiple injection group exhibited more viable tissue, less scarring, and greater myocyte density in the area at risk. When the authors turned their attention to mechanism, they concluded that paracrine effects must play a major part in the observed beneficial outcome. Particulars of the paracrine hypothesis are implied rather than demonstrated because the notably low persistence of long-term adoptively transferred cells leaves no other plausible explanation. However, as in prior reports from the same group, inferred activation and participation of endogenous repair is suggested to be primarily responsible for beneficial effects without delving into deeper molecular analyses that were clearly never intended as part of the study. In the end, we are left with the inescapable conclusion that more CPCs are better, but only when delivered in multiple doses over a period of time.

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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prolonged time course rather than as a single bolus injection. Just how many injections could be administered and when does the cumulative beneficial effect of repeating cell infusions lose its luster remain open unanswered questions. But as with so many aspects of cardiac stem cell research, these are just the tip of the proverbial iceberg leading to Rumsfeldian “things that we now know we don’t know.”

The field of cardiac stem cell research continues to evolve in new directions at a rapid pace. The study by Tokita et al represents a worthy contribution to the literature by establishing inherent value of repeated dosing of cells into a pathologically injured heart as a way to enhance the repair process. However, even in the current study, some might argue that a 13% increase, while laudable, still leaves a lot to be desired to get back to preinfarction performance that is the Holy Grail of myocardial regeneration. No single tweak to current therapeutic intervention is likely to be the panacea for restoration of myocardial function. Ever-expanding horizons of novel cell types, combinatorial cell therapy, genetic modification of cells, preconditioning/pretreatment of cells, concurrent pharmacological sensitizers, preemptive amelioration of the recipient host environment, and declining endogenous regenerative and reparative responses inescapable in the aging human heart are some of the multiple facets to be considered and coordinated. Leveraging increasing appreciation of the nuanced and complex processes of tissue regeneration against the notoriously underperforming response of the mammalian heart to acute injury will offer our best chance for overcoming current limitations that restrain full recovery of the heart. Cardiovascular researchers are inherently stubborn by necessity to persevere in this quest, and Tokita et al have provided initial evidence that forced repetition might be yet another useful adaptation to impose on Nature if she is too subtle to repeat herself in the mammalian heart the way she does so well in lower vertebrates. The title song of this editorial touts the beneficial effects of repetition in the next lyric verse: “Haven’t felt like this, my dear, since I can’t remember when. It’s been a long, long time.”

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None.

References


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