REGENERATIVE MEDICINE

Stem cell-derived cardiomyocytes heal a broken heart

Ischaemic heart disease is a major cause of death worldwide, yet few drugs to treat heart failure exist and novel treatment approaches are needed. In a new paper in *Nature Biotechnology*, Liu et al. report on repairing cardiac injury in a non-human primate (NHP) using human embryonic stem cell (hESC)-derived cardiomyocytes.

In a previous study in the NHP *Macaca nemestrina*, the authors demonstrated that transplanted hESC-derived cardiomyocytes remuscularized the heart following myocardial infarction, although the muscle grafts caused transient arrhythmias. Expanding on these findings, the authors sought to address whether transplantation improved the mechanical function of the heart and to identify the underlying cause of these arrhythmias.

Liu et al. first induced a large infarction in macaques by coronary occlusion, which resulted in a substantial reduction in the left ventricular ejection fraction (LVEF) (from a ~69% baseline to ~40% 2 weeks after infarction). Then, 2 weeks after infarction, treated animals received hESC-derived cardiomyocytes, whereas control animals received vehicle (culture medium). Remarkably, 1 month after transplantation, treated animals showed a substantial improvement in LVEF of ~10% versus 2.5% in the control animals. Furthermore, 3 months after transplantation, LVEF had improved

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in treated animals by a further 10% to ~62% — which is essentially within the normal range — but declined by ~3% in control animals.

The authors then examined the grafts using immunostaining with antibodies to cardiomyocyte markers and confirmed that ~90% of graft cells at 1 month post-injection and ~99% at 3 months post-injection were ventricular cardiomyocytes. Moreover, histomorphometry suggested that the transplanted cardiomyocytes were proliferating, as their abundance increased between 1 month and 3 months after injection. Importantly, the grafted cells showed electromechanical integration, including adherens junctions and gap junctions, with host cardiomyocytes. Additionally, vascularization of the grafts by the host circulation increased between 1 month and 3 months post-injection, whereas vascularization decreased in surrounding areas of infarction. Therefore, the grafts had integrated into the host myocardium and provided substantial improvement in cardiac function.

Finally, Liu et al. examined the arrhythmias in treated macaques using electrocardiogram telemetry and catheter-based mapping and were surprised to find that, instead of grafts generating a patch of slowly conducting tissue that produced arrhythmias by a re-entry mechanism, the grafts seemed to produce arrhythmias by behaving as ectopic pacemakers.

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The authors hope that delivering cells by an injection catheter instead of surgically and reducing the arrhythmias that occur after transplantation will improve the engraftment process. For clinical trials, the authors expect that their regenerative approach will synergize with current standard-of-care treatments, including revascularization and treatment with β -blockers and angiotensin-converting enzyme inhibitors.

Grant Otto

ORIGINAL ARTICLE Liu, Y.-W. et al. Human embryonic stem cell-derived cardiomyocytes restore function in infarcted hearts of non-human primates. *Nat. Biotechnol.* **36**, 597–605 (2018)

FURTHER READING Cahill, T. J., Choudhury, R. P. & Riley, P. R. Heart regeneration and repair after myocardial infarction: translational opportunities for novel therapeutics. *Nat. Rev. Drug Discov.* **16**, 699–717 (2017)