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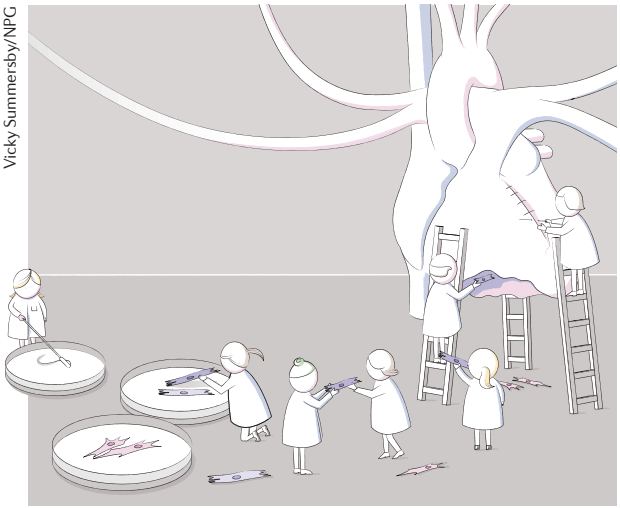
STEM CELLS

A step closer to cardiac repair therapies



Vicky Summersby/NPG

> grafted cardiomyocytes electrically coupled with the host heart … and improved cardiac contractility

Cardiomyocytes derived from induced pluripotent stem cells (iPSCs) show great promise for regenerating the damaged heart. The injection of cardiomyocytes differentiated from patient-specific iPSCs (autologous transplantation) would be an ideal strategy to avoid inducing an immune response. However, this approach faces important manufacturing challenges. An alternative is to use cardiomyocytes from donor-derived iPSCs (allogeneic transplantation), which can solve some of the practical issues of autologous transplantation, matching the major histocompatibility complex (MHC) between donor and host in order to avoid graft rejection. A new study published in *Nature* demonstrates that this strategy can provide long-term graft survival and can regenerate infarcted hearts of non-human primates.

"This study addresses a question that everyone in the field has been wondering for a while," remarks Christine Mummery, from Leiden University Medical Centre in the Netherlands, who was not involved in the study. "What would happen if you transplant pluripotent stem cell-derived cardiomyocytes with an MHC match (for example, from a universal donor) into a recipient with myocardial infarction while suppressing the immune system?"

Most studies in this field have been performed using xenogeneic (cross-species) transplantation models. "[Xenogeneic models] have critical limitations, especially in terms of interpretation of the immune response," explains Yuji Shiba, lead author of the paper. In this study, the researchers performed an allogeneic transplantation in cynomolgus monkeys, which have an MHC system very similar to that of humans.

iPSCs were derived from an MHC haplotype homozygous monkey and differentiated into cardiomyocytes. The investigators then induced myocardial infarction in monkeys, and after 2 weeks, transplanted the iPSC-derived cardiomyocytes by direct intra-myocardial injection. All the animals were treated with the immunosuppressive drugs methylprednisolone and tacrolimus.

When the investigators transplanted iPSC-derived cardiomyocytes into MHC-mismatched monkeys ($n = 2$), the grafts were rejected after 4 weeks. However, when the iPSC-derived cardiomyocytes were transplanted into five monkeys in which either of the MHC haplotypes was identical to that of the donor, the grafts survived for 12 weeks without major immune rejection. This result contrasts with findings from a previous study showing graft rejection after allogeneic transplantation of MHC-matched iPSC-derived cardiomyocytes in cynomolgus monkeys. Shiba and colleagues argue that the combination of the immunosuppresants might have been sufficient to prevent immune rejection of the transplanted allogeneic cardiomyocytes. "Nevertheless, further studies are required to establish the minimum amount of immunosuppression required to control immune rejection following cell transplantation," explain the investigators.

iPSC-derived cardiomyocytes not only survived for 12 weeks, but also integrated and partially remuscularized the infarcted hearts. In addition, the grafted cardiomyocytes electrically coupled with the host heart (as assessed by intravital fluorescence imaging of hearts perfused with a fluorescent calcium indicator) and improved cardiac contractility, as revealed by microCT and echocardiography at 4 and 12 weeks after transplantation. Importantly, at 12 weeks none of the animals had tumour formation. Shiba and colleagues observed, however, that transplantation of iPSC-derived cardiomyocytes also induced transient abnormal beating. The incidence of arrhythmias increased significantly after transplantation, peaking at day 14 in 4 of the 5 monkeys. "We don't know the mechanisms responsible for the post-transplant arrhythmia yet, and this is one of our current studies ", says Shiba. According to Mummery, future studies should include a longer follow-up and larger grafts, but she points out that these findings contribute to moving these therapies towards the clinic.

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ORIGINAL ARTICLE Shiba, Y. *et al.* Allogeneic transplantation of iPS cell-derived cardiomyocytes regenerates primate hearts. *Nature* http://dx.doi.org/10.1038/nature19815 (2016)
FURTHER READING Chen, I. Y. *et al.* Induced pluripotent stem cells: at the heart of cardiovascular precision medicine. *Nat. Rev. Cardiol.* **13**, 333–349 (2016) | Behfar, A. *et al.* Cell therapy for cardiac repair—lessons from clinical trials. *Nat. Rev. Cardiol.* **11**, 232–246 (2014)