



Commentary

Fat for fostering: Regenerating injured heart using local adipose tissue



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In this issue of *EBioMedicine*, Bayes-Genis and colleagues (Bayes-Genis et al., 2016) reported the first clinical study investigating safety and efficacy of the adipose graft transposition procedure (AGTP) in patients with chronic myocardial infarction undergoing coronary artery bypass graft (CABG) surgery. This innovative approach takes advantage of the local existing tissue to repair damaged myocardium, simplifying the surgical procedure and potentially avoiding the risks of using non-autologous cells or stem cells that have been manipulated in petri dish.

Myocardial infarction (MI) is a devastating disease condition, and is one of the leading causes of morbidity and mortality in western countries. In the past decade, significant advance has been made to develop novel therapeutic approaches to regenerate infarcted myocardium, including the stem cell therapy and the most recent reprogramming approaches. Stem cell therapy currently faces the challenges of poor cell survival, limited cell–cell interaction and functional integration of engrafted cells, as well as unclear mechanisms of some beneficial effects observed in animal model. Clinical studies of using stem cell or stem cell-derived cardiomyocytes have a mixed result (Mummery et al., 2010). The newly emerged reprogramming approach converting endogenous fibroblasts into cardiomyocytes could potentially overcome some of these challenges (Qian and Srivastava, 2013); however, this approach is currently at its fledgling stage and has been primarily tested on small rodents for effectiveness and safety. In clinic, revascularization strategies, including fibrinolysis, percutaneous coronary intervention (PCI), and CABG, have greatly improved myocardial salvage and prognosis in patients suffering from acute myocardial infarction. However, patients who miss the narrow optimal time window for reperfusion therapy or those who experience detrimental ischemia reperfusion injury during revascularization, will develop myocardial scar over time, which ultimately contributes to cardiac dysfunction, malignant arrhythmia, sudden cardiac death and other major cardiovascular events (Klem et al.,

2012). Unfortunately, current treatment is unable to replace the chronically formed scar to restore functionality of the damaged myocardium.

In the current study, Antoni Bayes-Genis et al. conducted the first in-man trial that integrates cardiac adipose tissue derived cell therapy into tissue engineering for repairing damaged myocardium (Bayes-Genis et al., 2016). The innovative procedure involves dissection of a vascularized flap of autologous pericardial adipose tissue to cover the scar area. Adipose tissue, generally considered as a source of systemic inflammation and risk for cardiovascular diseases, has drawn extensive attention as an alternative source of multipotent stem cells for healing infarcted myocardium (Telukuntla et al., 2013; Zuk et al., 2002). Cardiac adipose tissue is primarily comprised of specially deposited visceral fat cells around heart supported with local vasculature system. The same group has discovered a progenitor cell population existing in human cardiac adipose tissue that has potential to be differentiated into cardiomyocytes and endothelial cells. Introduction of these cells ameliorated physical and pathological adverse changes in murine infarcted hearts (Bayes-Genis et al., 2010). Importantly the results from APOLLO, ADVANCE, MyStromalCell, and PRECISE trials proved the safety of adipose tissue-derived stem cell therapy through intracoronary or intramyocardial delivery (Telukuntla et al., 2013). However, AGTP procedure using pericardial adipose tissue flap is different in several ways that makes it necessary and important to evaluate the safety. For example, the flap used in AGTP contains more heterogeneous cell types and the cardiac adipose tissue is also shown as a risk factor for atherosclerosis, atrial fibrillation, and ventricular arrhythmia (Iacobellis and Bianco, 2011). As a step further, preclinical studies using large animals indicated that AGTP indeed exerted beneficial effects on infarct size, primarily through promoting angiogenesis in swine models of both acute and chronic myocardial infarction (Galvez-Monton et al., 2011; Galvez-Monton et al., 2013).

These promising laboratory findings and preclinical results inspired the current prospective, randomized, phase I/II clinical trial (NCT01473433, AdiFLAP Trial) designed to evaluate the safety and efficacy of AGTP in patients with chronic myocardial infarction undergoing CABG. Patients were enrolled if they were CABG candidates and also with an established chronic myocardial infarction lesion which wasn't the territory supplied with CABG target vessel(s). The patients were assessed with late gadolinium enhancement (LGE) MRI to identify chronic non-revascularization area to guide adipose graft transposition. The main safety events were defined as arrhythmia, hospital admission and death during 12-month follow-up. The feasibility endpoints included

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E-mail address: li_qian@med.unc.edu (L. Qian).<http://dx.doi.org/10.1016/j.ebiom.2016.03.024>2352-3964/© 2016 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

the change in cardiac geometry and function as determined by cardiac MRI, biomarkers of cardiac injuries (e.g., troponinI, and NTproBNP), NYHA class and Framingham derived clinical score.

The AdiFLAP trial included 10 eligible patients who were randomly divided at 1:1 ratio to receive CABG (control group) or CABG plus AGTP. One patient in control group was dropped out due to MRI claustrophobia. The AGTP procedures were well tolerated, including 4 inferior and 1 anterior grafts, and did not result in any surgery related complications. During the 12-month follow-up, none death or hospitalization due to cardiovascular events was reported in AGTP-treated group. The incidence of arrhythmias was comparable between control and AGTP-treated groups. Future studies to further investigate safety on a larger population and to closely monitor the adverse cardiovascular events in long term will be needed. In spite of the limited sample size and gender bias, findings in the current studies suggest that AGTP might be a safe procedure.

In addition, LGE-MRI analysis revealed a -2.16% improvement in necrosis ratio in AGTP-treated group at 3 month, whereas $+1.80\%$ deterioration in control group, showing a trend towards attenuating chronic scar compared to the control group ($p = 0.06$). However, this trend did not result in a further improvement at 12 month. Similar trend was also observed in left ventricular end systolic volume (LVESV) and extracellular volume (ECV). Unfortunately, no statistically significant differences were identified in other cardiac function indices, biomarkers, NYHA class and Framingham-derived clinical score evaluation. Thus a more detailed segmental analysis is needed in the follow-up studies. It is worth mentioning that one patient responded unexpectedly well to the AGTP procedure, whose scar size reduced significantly in short term and long term at one-year follow-up accompanied with remarkably improved heart function. It is intriguing to explore the genetic and cellular bases of the differential responses from various individuals to AGTP treatment. Cellular reprogramming techniques coupled with high-throughput sequencing based omics studies on these patients' samples might provide clues to the underlying mechanisms and help to discover bio-markers to define the AGTP optimal responders for effective treatment.

Based on the previous animal studies, mechanistically AGTP may exert its functions through stimulating neovascularization, improving the local microcirculation and metabolism. Thus, evaluation of the local neo-angiogenesis and cardiomyocyte metabolism will be helpful to determine the efficacy of AGTP. The paracrine effects from adipose-derived progenitor/stem cells might contribute to improving the micro-environment at the scar site thus enhance the myocardium contractility. Furthermore, if and how AGTP treatment influences the local inflammatory responses as well as extracellular matrix degradation, tissue stiffness, cellularity of the scar area for cytokine/small molecule invasion are all interesting directions to follow up for detailed mechanistic studies. Despite the unclear mechanism and the non-significant differences between the control and treatment groups possibly due to its small number of enrollments, AGTP procedure holds promise as a novel therapy in the near future.

Taken together, the results from current study indicate that AGTP is a safe treatment option for patients with chronic myocardial infarction. A larger trial, enrolling patients with a wide arrange of necrotic areas and

including additional outcome endpoints, shall be performed to further evaluate the safety and efficacy of AGTP procedure. Nevertheless, utilizing local adipose tissue might minimize the complications resulted from introducing exogenous stem cells or stem cell-derived cardiomyocytes; neither does it introduce any ectopic gene expression or delivery vehicles such as viruses and DNA constructs used in gene therapy approaches. Thus local adipose tissue might serve as an important and perhaps advantageous source for tissue regeneration and disease treatment.

Author contributions

H.M. drafted the commentary, J.L. provided critical comments and revised the manuscript, L.Q. supervised the writing, revised and finalized the manuscript.

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Conflict of interest

None.

References

- Bayes-Genis, A., Gastelurrutia, P., Cámara, M.L., et al., 2016. First-in-man safety and efficacy of the adipose graft transposition procedure (AGTP) in patients with a myocardial scar. *EBioMedicine* 7, 248–254.
- Mummery, C.L., Davis, R.P., Krieger, J.E., 2010. Challenges in using stem cells for cardiac repair. *Sci. Translat. Med.* 2, 27 (ps17).
- Qian, L., Srivastava, D., 2013. Direct cardiac reprogramming: from developmental biology to cardiac regeneration. *Circ. Res.* 113, 915–921.
- Klem, I., Weinsaft, J.W., Bahnson, T.D., Hegland, D., Kim, H.W., Hayes, B., Parker, M.A., Judd, R.M., Kim, R.J., 2012. Assessment of myocardial scarring improves risk stratification in patients evaluated for cardiac defibrillator implantation. *J. Am. Coll. Cardiol.* 60, 408–420.
- Telukuntla, K.S., Suncion, V.Y., Schulman, I.H., Hare, J.M., 2013. The advancing field of cell-based therapy: insights and lessons from clinical trials. *J. Am. Heart Assoc.* 2, e000338.
- Zuk, P.A., Zhu, M., Ashjian, P., De Ugarte, D.A., Huang, J.L., Mizuno, H., Alfonso, Z.C., Fraser, J.K., Benhaim, P., Hedrick, M.H., 2002. Human adipose tissue is a source of multipotent stem cells. *Mol. Biol. Cell* 13, 4279–4295.
- Bayes-Genis, A., Soler-Botija, C., Farre, J., Sepulveda, P., Raya, A., Roura, S., Prat-Vidal, C., Galvez-Monton, C., Montero, J.A., Buscher, D., Izpisua Belmonte, J.C., 2010. Human progenitor cells derived from cardiac adipose tissue ameliorate myocardial infarction in rodents. *J. Mol. Cell. Cardiol.* 49, 771–780.
- Iacobellis, G., Bianco, A.C., 2011. Epicardial adipose tissue: emerging physiological, pathophysiological and clinical features. *Trends Endocrinol. Metab.* 22, 450–457.
- Galvez-Monton, C., Prat-Vidal, C., Roura, S., Farre, J., Soler-Botija, C., Llucia-Valldeperas, A., Diaz-Guemes, I., Sanchez-Margallo, F.M., Aris, A., Bayes-Genis, A., 2011. Transposition of a pericardial-derived vascular adipose flap for myocardial salvage after infarct. *Cardiovasc. Res.* 91, 659–667.
- Galvez-Monton, C., Prat-Vidal, C., Roura, S., Soler-Botija, C., Llucia-Valldeperas, A., Diaz-Guemes, I., Sanchez-Margallo, F.M., Bayes-Genis, A., 2013. Post-infarction scar coverage using a pericardial-derived vascular adipose flap. Pre-clinical results. *Int. J. Cardiol.* 166, 469–474.