Fat is not all bad: how to make good use of adipose tissue

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This editorial refers to 'Intracoronary administration of autologous adipose tissue-derived stem cells improves left ventricular function, perfusion, and remodelling after acute myocardial infarction' by C. Valina et al., on page 2667

Myocardial infarction (MI) continues to represent a major health problem. Improved healing and/or regeneration of infarcted myocardium by injection of progenitor cells has been proposed as a promising approach to prevent cardiac remodelling or even restore myocardial tissue. Several adult stem cell types have shown efficacy in the preclinical setting, including skeletal myoblasts, umbilical cord cells, bone marrow-derived mononuclear cells, and, more recently, adipose tissue-derived stem cells.1,2 Although the debate as to which cell type (or combinations thereof) is best suited for the treatment of acute MI continues, the mesenchymal stem cell (MSC)3 is particularly interesting. Thus, MSCs have been shown to be multipotent, to be capable of homing to infarcted myocardium, inducing angiogenesis and differentiating into myogenic cells, and, more recently, adipose tissue-derived stem cells.3–5 Although the opinion that stromal-derived factor 1 (required for recruitment of progenitor cells) is upregulated immediately following myocardial injury. Future studies should address the effect of timing of MSC injection on cell retention in

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Bone marrow-derived MSCs have already shown significant benefit in animal models of MI-induced left ventricular dysfunction.1 For example, in swine with MI produced by a 30 min coronary artery occlusion, allogenic bone marrow-derived MSCs injected into the coronary artery 3 days after reperfusion resulted in a reduction in infarct size and improvement of left ventricular function at 4 weeks follow-up.6 More recently, adipose tissue-derived MSCs have also shown potential in rodent studies. Thus, in models of permanent coronary artery ligation,7–9 MSC application (either as a grafted monolayer8 or via intramyocardial injection8,9), administered either immediately8 or 3–4 weeks after induction of MI,7,9 resulted in improved left ventricular geometry and function another 4–8 weeks later. Although these studies are encouraging, they differ significantly from the clinical setting in terms of animal model, the type of infarction, and route of cell administration. Valina et al.5 have compared the effects of intracoronary injections of adipose tissue-derived or bone marrow-derived autologousMSCs on left ventricular remodelling, function, and perfusion after an acute transmural MI produced by a 3 h coronary artery occlusion followed by reperfusion in swine. Their main conclusions are that both cell types reduced infarct size and improved global left ventricular function at 30 days follow-up. The study is important for several reasons. First, Valina et al.5 applied clinically relevant procedures in a large animal model, employing intracoronary cell injection following an ischaemia–reperfusion protocol that resulted in transmural infarction. This approach is clinically more relevant than the intramyocardial or systemic cell injections following permanent ligation, commonly used in rodents. Secondly, the authors performed a detailed analysis of global left ventricular geometry and function and regional perfusion, in conjunction with MSC cell tracking and phenotype analysis at 4 weeks follow-up. Although the results of this study, together with other preclinical studies on MSCs, warrant investigation of the clinical usefulness of MSC therapy, several questions remain to be addressed.

The optimal methodology of cell therapy remains insufficiently understood. For example, the optimal timing of cell administration in reperfused myocardium remains incompletely understood. There is evidence from clinical studies to suggest that injection at 5–10 days after reperfusion is optimal, at least in the case of injection of the mononuclear cell fraction of bone marrow.10 Somewhat disparate from current clinical practice, with regards to the bone marrow-derived mononuclear cell fraction, Valina et al.5 injected MSCs, expanded ex vivo for 13 ± 5 days, already after 15 min of reperfusion, which they based on the notion that stromal-derived factor 1 (required for recruitment of progenitor cells) is upregulated immediately following myocardial injury. Future studies should address the effect of timing of MSC injection on cell retention in
reperfusion of myocardium and left ventricular structural and functional recovery. This is particularly important because administration of autologous MSCs in patients with an MI within 15 min after reperfusion would require harvesting of MSCs in virtually the entire adult population >30 years of age (particularly since in ~30% of patients an MI is the first symptom of ischaemic heart disease), and stored for later use. Consequently, it is important to establish whether MSCs are still as effective when given 14 days after MI, thereby allowing sufficient time for ex vivo expansion prior to administration.

A second methodological issue that remains to be addressed is the optimal number of cells to be injected. Unfortunately, Valina et al.5 did not assess the retention rate of the cells after injection, but several studies report a retention rate of injected (mononuclear or mesenchymal stem) cells of only ~6% at 14 days after injection.11,12 It will be important to determine whether a higher number of injected cells (or improved retention) will improve functional outcome, or if microvascular obstruction may, at least in part, offset some of the benefit of increasing cell numbers. For example, several groups of investigators reported microvascular obstruction and microinfarctions following injection of ~10 million13 or ~50 million11 MSCs or ~100 million umbilical cord-derived unrestricted somatic stem cells (USSSCs)14 in healthy myocardium, whereas freshly obtained mononuclear cells were devoid of such side effects.12 The discrepancy appears to be due to the increased cell size13,14 and/or increased adhesion molecule expression15 associated with the process of cell culturing. For this reason, Valina et al. first determined in pilot experiments the maximum number of MSCs that could be safely administered without causing vascular obstruction (~10 million cells) and elected to inject no more than 2 million cells per animal. Future studies are needed to determine whether increasing the number of injected cells to 10 million and/or improving cell retention will result in further benefit.

A third methodological issue is the optimal route of cell administration. Several procedures are currently available in the clinical setting, including epicardial injection during surgery, and catheter-based transendocardial, systemic (e.g. intravenous), and intracoronary injection of which the latter has become the standard route of administration of mononuclear cells. All these routes have been used to administer either bone marrow- or adipose tissue-derived MSCs and, since the large majority of studies have shown a beneficial effect on infarct size and/or left ventricular function, it could appear as if the route of administration is of less importance in the case of MSCs. However, two preclinical studies that directly compared routes of administration indicated that the degree and consistency of grafting differed markedly between the various routes.11,16 Although the functional effects of these routes were unfortunately not determined in the latter studies, they underscore the importance of (pre)clinical studies that directly compare different methodologies of cell therapy.

Finally, the mechanism by which MSC therapy reduces infarct size and/or improves left ventricular function remains elusive. Thus, at 4 weeks after implantation Valina et al.3 observed that enhanced green fluorescent protein (eGFP)-labelled MSCs had differentiated into endothelial cells (expression of von Willebrand factor) and vascular smooth muscle cells (expression of smooth muscle actin and desmin), but not into cardiomyocytes (no expression of troponin T). These findings confirm previous observations on bone marrow-derived1 and adipose tissue-derived2 MSCs, and suggest that modified infarct healing rather than true myocardial regeneration is probably involved in the infarct size reduction. True myocardial salvage is also unlikely in view of the 3 h coronary artery occlusion which, in a collateral-deficient species such as the pig, resulted in a large transmural infarction. Information on regional myocardial contractile function, which was unfortunately not presented, would have allowed better discrimination between active and passive regional left ventricular properties. In addition, an MSC-induced improvement in regional and global left ventricular function should be confirmed in future studies with a longer follow-up, to exclude the possibility of only a temporary effect, as suggested by the BOOST trial.17

In conclusion, the study by Valina et al.5 shows that MSCs obtained from either bone marrow or adipose tissue were effective in ameliorating the consequences of MI in a clinically highly relevant experimental set-up, which supports the ongoing clinical evaluation of MSC cell therapy. However, in a recent commentary, Nadal-Ginard and Fuster18 proposed that clinical studies be halted completely until preclinical research has resulted in a significant advancement of our understanding of several aspects of cell therapy, in particular: (i) the best cell type; (ii) the optimal methodology for cell administration; and (iii) the mechanism of efficacy of cell therapy. Although a lack of solid understanding of the mechanism of therapy may not be sufficient reason to refrain from entering clinical efficacy trials once cell therapy has been shown to be safe,19 there is clearly a need for large-scale long-term preclinical studies to investigate in a highly systematic manner (and preferably in a multicentre setting) the optimal cell type (including isolation procedure) and number, route, and timing of cell administration after MI. Such an approach will be mandatory in order to establish the full potential of cell therapy for patients suffering from an acute MI. The study of Valina et al. strongly supports the inclusion of adipose tissue-derived MSCs in such studies.

Conflict of interest: none declared.

References

A 41-year-old female patient with no previous history of cardiovascular disease nor cardiovascular risk factors was admitted to the emergency department for typical chest pain associated with diffuse non-specific ST-segment changes and an increase in CK-MB and troponin T. Two-dimensional echocardiography showed normal dimensions and function of the left ventricle (LV). The patient was therefore submitted to coronary angiography which showed normal coronary arteries, whereas LV angiography showed the presence of a small localized aneurysm in the posterobasal segment of the LV and a larger aneurysm with a cylinder shape and multiple lateral prickles resembling the aspect of the saw of a sawfish (Panels A–C). Ergonovine provocation test failed to induce coronary spasm of both left and right coronary arteries. Multiple endomyocardial biopsies obtained in the regions close to the apical aneurysm showed the presence of active lymphocytic myocarditis (Panel D). No viral genome was detected by PCR on frozen myocardial samples.

Acute myocarditis may mimic an acute coronary syndrome and may cause localized LV aneurysms often associated with ventricular arrhythmias. As small ventricular aneurysms may not be recognized at two-dimensional echocardiography, LV angiography should be performed in patients presenting with chest pain and/or ventricular arrhythmias and normal coronary arteries, in order to better address further clinical investigation.