The ‘hearty’ fat: adipocytes as a source of functional cardiomyocytes

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Online publish-ahead-of-print 2 November 2009

This editorial refers to ‘Spontaneously beating cardiomyocytes derived from white mature adipocytes’ by M. Jumabay et al., pp. 17–27, this issue.

Repair of tissues or organs, characterized by a limited regenerative potential, is the major goal of cell therapy. Cardiac pathologies are among the leading causes of mortality and morbidity in industrialized countries, and current treatments are aimed at preserving the cardiac function compromised by the pathology rather than restoring the proper functions. The discovery of various stem/progenitor cells with different degrees of plasticity has opened the possibility to regenerate the lost myocardium and thus to improve cardiac function.

Stem cells can be classified as pluripotent or multipotent on the basis of their differentiation capacity. Although the ability of pluripotent stem cells to differentiate into cardiomyocytes is well established,1,2 their high teratogenic potential is one of the major limitations of their use in therapeutic interventions.3,4 Multipotent stem cells of mesodermal origin such as haematopoietic stem cells (HSCs), mesenchymal stem cells (MSCs), skeletal myoblasts, and cardiac stem cells (CSCs), might represent a more suitable source of cells for autologous interventions. Unfortunately, their ability to differentiate into cardiomyocytes is still being debated.5 Adipose tissue is composed of mature adipocytes and of adipose stromal cells (ASCs), and it has recently emerged as a possible source of progenitor cells.

In 2004, ASCs were shown for the first time to spontaneously differentiate into beating cardiomyocytes, although with a poor yield, when grown in a semisolid methylcellulose medium enriched with growth factors.6 A poor differentiation might result, as for bone marrow-derived stem cells, from the heterogeneity of the population composing ASCs.7 Mature adipocytes are instead a homogeneous cell population; Matsumoto et al.8 have recently shown that human mature adipocytes in culture lose lipid droplets, lose mature adipocyte markers (de-differentiate), and acquire a proliferative fibroblast-like morphology with an antigenic profile similar to MSCs. These adipocyte-derived, fibroblast-like cells, termed ‘dedifferentiated fat’ (DFAT) cells, can be then induced to differentiate into several mesenchymal (adipogenic, osteogenic, chondrogenic) lineages.

In this issue, Jumabay et al.9 have reported that mouse white adipocytes, isolated from subcutaneous fat, can be de-differentiated into a homogeneous population of DFAT cells, expressing the typical MSC markers Sca1, ckit, and CD90, which undergoes spontaneous differentiation into both autorhythmic and quiescent cardiac myocytes. Although pluripotent stem cells have been shown to spontaneously differentiate, both in vitro and in vivo, into functional cardiac myocytes,4,10,11 none of the adult stem cells studied thus far have been reported to spontaneously differentiate into cardiomyocytes in vitro and required either co-culture with isolated cardiomyocytes (HSCs and MSC) or treatment with agents such as methylation inhibitors and histone deacetylase inhibitors (MSCs, CSCs).12–14 Furthermore, these adult stem cells induced in vivo improvements of left ventricular function of infarcted heart, despite the poor myocardial regeneration observed.5 Interestingly, Jumabay et al. reported that 10–15% of DFAT cells spontaneously differentiate into sarcomeric actin/GATA4- or Troponin-I/GATA4-positive cardiac myocytes. These cells present some important functional and electrical features of cardiomyocytes such as triggered and spontaneous action potentials (whose frequency can be modulate by adrenergic agonists) and synchronous sarcoplasmic Ca2+ release; these data clearly indicate the presence of the molecular machinery needed for propagation of the electrical stimulus and excitation–contraction coupling.9

In view of a potential therapeutic application of adipocyte-derived DFAT cells, a possible drawback is their limited in vitro self-renewal capacity; indeed, after few passages, DFAT cells lose the ability to differentiate into cardiac myocytes. However, mature adipocytes do not represent a limited population in vivo and can indeed be isolated in great quantity directly from...
subcutaneous fat. For this reason, neither a high proliferative potential nor an extensive cellular amplification is necessary to ensure an adequate number of DFAT cells. Another important feature of DFAT cells is that they derive from a population of 99.9% pure adipocytes; the abundance, purity, and homogeneity of the starting cell population may be particularly important in order to avoid the chance that contaminating cell types overgrow and eventually differentiate towards undesired phenotypes. For example, this can be associated with the prolonged amplification in culture necessary to obtain an adequate number of adult stem cells which are scarcely represented in the tissue of origin.

An intriguing hypothesis arising from the work of Jumabay et al. is that adipocytes and cardiomyocytes may be developmentally close and that DFAT cells may represent a common precursor to both lineages. Indeed, along with the evidence of spontaneous cardiac differentiation, this is indicated by the result that the cardiac differentiation of DFAT cells is increased by inhibition of the BMP or the Wnt pathways, a mechanism already reported to be important during both heart development and cardiac differentiation of embryonic stem cells.16

Recently, DFAT cells have also been derived from GFP-transgenic rats by the same group.17 These cells can be induced to differentiate into cardiomyocytes in vitro by specific culture conditions (direct co-culture with neonatal cardiac myocytes or culture with neonatal cardiac myocytes-conditioned medium or culture in MethoCult) and in vivo by injection in the infarcted heart. In this case, beside surviving for several weeks, these rat DFAT cells also induced neangiogenesis. Unfortunately, no analysis has been made of functional/electrical properties of in vitro/in vivo DFAT-derived cardiomyocytes, nor has any improvement in cardiac function been demonstrated.

Because of their abundance, easy isolation procedure, little in vitro processing, and high yield of spontaneous differentiation, subcutaneous white adipocyte-derived DFAT cells appear more suitable to autologous cardiac regeneration than the most commonly used progenitor/stem cells. Nonetheless, further research is needed to better characterize this cellular substrate, and some caution is necessary until human DFAT cells can be shown to possess all the molecular and functional properties that will make them a selectable source of exogenous myocytes for heart repair.

Conflict of interest: none declared.

References