

Adipose-Derived Stem and Regenerative Cells: An Overview

The concept that adipose tissue contains cells with broad potential for regenerative medicine had its beginnings in a paper in the journal *Tissue Engineering* published in 2001¹. In this work the authors placed cells obtained from human adipose tissue in culture and showed that the cultured cell population possesses a key characteristic of stem cells; it can differentiate into cells of multiple lineages. This study is the most cited paper in the history of *Tissue Engineering* having been cited over 900 times; it is still amongst the journal's most frequently downloaded papers. The following year the same research team published a follow-up study that proved that the property of multilineage differentiation was possessed by single cells within the cell population thus proving that there are stem cells in human adipose tissue². The cultured cell population is usually described in the literature as Adipose-Derived Stem Cells (ADSC). ADSC have many properties in common with a related cell type cultured out of bone marrow that is generally referred to as Mesenchymal Stem Cells or Marrow Stromal Cells (MSC)³. For example, both cell types can differentiate along osteogenic, adipogenic, chondrogenic, and myogenic lineages²⁻⁴ and express similar, though not identical, cell surface markers⁵.

As research into adipose stem cells continued it became apparent that the cell population used to start the cultures has properties that could be valuable in the clinic. First, it contains stem cells that can be grown up in

culture to generate ADSC. In fact, adipose tissue is the richest known source of adult stem cells which usually comprise around 1-2% (and as much as 5%) of the starting population obtained from adipose tissue^{6,7}. This compares very favorably with age-matched marrow in which MSC usually comprise only 0.0004% of cells⁸. Second, the cell population used to start ADSC cultures also contains other cells that have potentially useful properties including endothelial progenitor cells, leukocytes, endothelial cells, and smooth muscle cells. For this reason we refer to this non-cultured cell population as Adipose-Derived Stem and Regenerative Cells (ADRC).

Adipose-Derived Stem and Regenerative Cells (ADRC) are a population of cells that can be extracted from adipose tissue by a process of washing, enzymatic digestion, and filtration.

ADRCs are similar to the cell population referred to as the stromal vascular fraction or processed lipoaspirate.

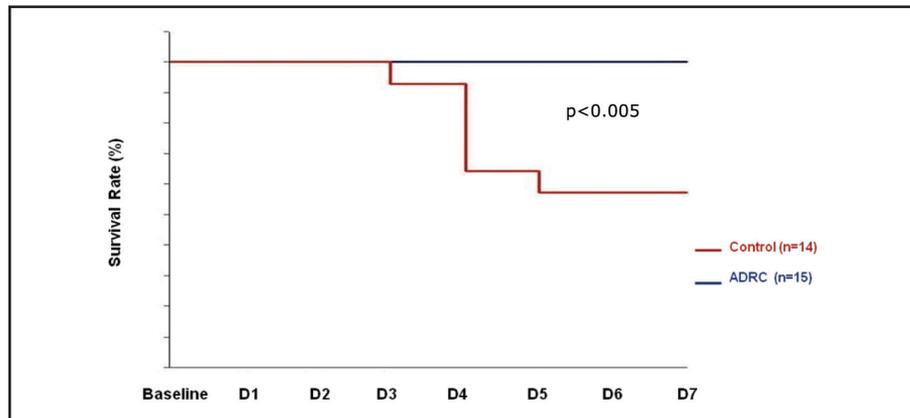
PRE-CLINICAL AND CLINICAL STUDIES WITH ADRC

ADRCs have been shown to possess the ability to improve function following injury in a number of preclinical animal models. For example, Nambu *et al* showed improved wound healing in db/db diabetic mice treated with ADRC loaded onto a collagen-based scaffold⁹. The results showed a doubling in

granulation tissue thickness at two weeks and a 50% increase in the rate of epithelialization at 1 and 2 weeks in ADRC-treated animals. These cells have also shown to provide significant improvements in cardiac function following acute myocardial infarction (AMI) in both small and large animal studies. Thus, one group has shown improved cardiac output and left ventricular end diastolic volume at 12 weeks following severe AMI in a rat model¹⁰. A second group delivered the ADRC directly into the coronary artery following induction of an AMI in a swine injury model. In this study cell-treated animals showed significantly reduced perfusion defect and improved left ventricular ejection fraction (43±7% compared to 35±3% in control animals) eight weeks after treatment¹¹. ADRC-treated animals also showed improved ventricular wall thickness and increased capillary density in the border zone around the infarct. Miranville *et al* have shown similar improvements in a rodent surgical model of peripheral vascular disease¹². More recently, it has been shown that intra-arterial administration of ADRCs significantly improves renal function and survival in a rat model of acute renal ischemia¹³. Thus, whereas survival of control animals at day 7 was only 56%, survival of animals treated with ADRC was 100% (Figure 1).

In the first published clinical study with ADRC Lendeckel *et al* used ADRC in combination with other agents to heal a large calvarial bone defect in a young girl¹⁴. Later Alvarez *et*

Figure 1: Acute Renal Ischemia Model: Kaplan-Meier Survival Data



al used ADRC to treat a tracheomediastinal fistula arising secondarily to radiotherapy for lymphoma¹⁵. Complete closure of the fistula within a short period was observed.

ADRCs have also been used in two areas within the field of Plastic and Reconstructive Surgery. Initial preclinical research in a rodent model has shown that supplementing an autologous fat graft with ADRCs results in a doubling of graft retention¹⁶. Kitamura et al have extended this observation in clinical studies using ADRC to enhance engraftment of autologous fat grafts in the breast following partial mastectomy¹⁷. In this study the authors

demonstrated excellent long term retention of the grafts and a correspondingly improved cosmetic outcome. In other published research, Park *et al* have followed preclinical studies using cultured ADSC¹⁸ with a case report showing reduction in periorbital wrinkles and increased skin thickness in a patient treated with ADRCs¹⁹.

There is also a recent report using ADRCs in the treatment of multiple sclerosis. The rationale for this study was based on both the immunomodulatory properties of cultured ADSC²⁰ and the ability of ADSC to differentiate into cells with properties

of Schwann cells^{21,22}. However, in these studies, as in the preclinical and other clinical studies listed above, the ability of cultured ADSC to express multiple growth factors^{23,24} suggests that many of the effects of ADSC and ADRC are mediated by growth factors released from the cells in response to their microenvironment. Human clinical trials with ADRC are currently underway in several disease indications including Liver Cirrhosis (Clinicaltrials.gov Study Identifier NCT00913289), Acute Myocardial Ischemia with ST segment elevation (Study Identifier NCT00442806), Non-Revascularizable Myocardial Ischemia (Study Identifier NCT00426868), and Breast Reconstruction following partial mastectomy (Study Identifier NCT00616135)

SUMMARY

The description of stem cells within adipose tissue initiated a new and very promising area of regenerative medicine. These cells are already being used in clinics today. Meanwhile preclinical studies being performed at centers around the world are demonstrating promise in many different medical specialties.

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