Commentary on: Clinical Applications of Mesenchymal Stem Cells in Soft Tissue Augmentation

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The article by Drs. Hanson, Gutowski, and Hematti is timely, as the focus on regenerative medicine is increasing and cell therapy modalities are becoming more available in multidisciplinary clinics and hospitals around the world. Several of these therapies are potentially useful in aesthetic applications. Although the number of publications concerning fat grafting has increased exponentially in the past decade, most are based only on an expert’s clinical experience and opinions, for which the evidence-base is perhaps weaker than we would like. Surgeons need more data to be able to determine the appropriate therapy for each patient, as well as to determine the ideal source of multipotential stem cells—autologous bone marrow or adipose tissue–derived mesenchymal stromal stem cells (MSC) from liposuction aspirate.

The authors unfortunately focus on MSC, which are rare cells found in bone marrow aspirate and subsequently replicated extensively in tissue culture, resulting in a homogeneous, fibroblast-like population of cells.1 MSC clearly have a regenerative capacity and treatments are under development to investigate presumed immunomodulatory properties of MSC in the treatment of disorders such as Crohn disease and acute respiratory distress syndrome, as well as neuroinflammatory disorders such as multiple sclerosis. The results of clinical trials with MSC for medical indications have yielded mixed results and near-term or broad-based aesthetic applications are unlikely because of regulatory, cost, sourcing, and harvesting issues.

In contrast, cultured autologous fibroblasts, although not true stem cells, have been used extensively for dermal filling.2 Approximately 5000 patients have been treated and the clinical data have been promising in terms of safety and efficacy for the skin and dermis. However, Isolagen, the company that commercialized the technology, is no longer active in the field.

Lately, a century of fat grafting experience has begun to merge with more recent advances in stem cell therapy. Fat tissue is a particularly good source of stem cells3 and this tissue, harvested by any “friendly” means (ie, not fatal to fat cells), can be processed manually or automatically to remove the mature fat cells and yield a profoundly heterogeneous mixture of cells. Inside the resulting matrix of cells, fewer than 5% are true stem cells.4 Interestingly, the concentration of MSC in adipose tissue is 100-fold higher than the concentration in bone marrow. However, when cultured, these stem cells can be expanded into a homogeneous population that is similar to bone marrow MSC in its ability to differentiate into other cell types.5 In fact, adipose tissue–derived MSC may differentiate in vitro faster than bone marrow–derived MSC. These cultured cells are termed “adipose-derived stem cells,” or ADSC.

An increasing body of data suggest that the mix of cells obtained prior to cell culture (ie, the population consisting of 5% stem cells and 95% other regenerative cells, such as endothelial cells, smooth muscle cells, and blood cells) may be capable of providing benefit without the need for cell culture5-7 and that the mixture of cells interacting together may be more efficacious than the stem cells operating alone.5,9 Furthermore, primary cells—such as those present within ADSC—are fresh, normal or resting, and unmanipulated; therefore, they possess a substantially different potential and theoretical risk profile than cells that have been subject to serial passages in long-term cell cultures. For example, stem cell–mediated adipocyte turnover in the adult human is on the order of only 8% per year,10 whereas cultured ADSC have a turnover of 100% every 30 hours or so.11 For this reason, I would have encouraged Hanson et al to focus more attention on the cell mix, often called “adipose-derived regenerative cells,” or ADRC.

As the authors mention, ADRC have now been employed extensively around the world for a variety of aesthetic and medical indications, ranging from heart attack to breast augmentation and wrinkle fill. Applied alone, the cells may be useful for skin rejuvenation.12 However, as a cautionary note, since the ADRC are derived in part through

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enzymatic digestion of fat tissue, processing of the cells must involve an added step to remove an excess enzyme. This step helps prevent matrix degradation and skin necrosis. Once the residual enzyme is removed, these cells are known to produce collagen and other matrix components; in particular, they are also a source for cells and growth factors that facilitate additional blood supply. This effect on blood supply may be complementary in terms of skin rejuvenation. As a biological indicator of the cell mixture’s utility in the skin, Akita et al have shown dramatic healing of previously refractory, chronic wounds secondary to irradiation in extremely challenging clinical situations. It is not difficult to extrapolate these findings to rejuvenation patients, but more data are required.

Another application of ADRC is cotransplantation with autologous fat tissue, usually referred to as either cell-assisted lipotransfer or cell-enriched fat grafting. Preclinical data by Zhu et al and others showed a doubling of graft take when ADRC were added to fat grafts. The clinical data, as these authors note, are promising.

Over the past three years, I have treated 40 patients with the Celution system (Cytori Therapeutics, Inc, San Diego, California), which automatically forms a cell-enriched graft in just over an hour. Anecdotally, my results have been impressive. I have employed it primarily for fat grafting in hostile tissues such as irradiated and scarred regions, but also in breast augmentation, breast asymmetry, facial rebalancing, and either around silicone breast implants or in the pocket after having removed them. More recently, we have begun applying the same device, modified for intravascular treatment, to isolate ARDC for treatment conditions such as graft versus host disease and multiple sclerosis–related neurodegenerative disorders.

Whether there is a clear benefit to applying cell-enriched fat grafting as opposed to regular fat in normal recipient tissues is yet to be determined. To that end, several clinical trials and studies are underway with different modifications of the basic technology. Although the authors note that comparative studies have not been performed in aesthetic surgery, the design of these studies is problematic. As aesthetic surgeons, we are still in the process of perfecting our techniques for harvesting, processing, and grafting; as a result, a gold standard does not exist for this particular technique. Critical issues such as donor site, graft water content, oil content, presence of contaminating cells, liposuction technique, lidocaine and adrenalin additives, injection technique, patient smoking and body mass index, and many other specific factors can widely influence graft take. Reported graft take in the literature varies dramatically—between 20% and 80%, depending on technique. We must reach a consensus about these variables and establish a preferred method so that a control group can be established against which we can compare the results in a comparative study.

There is no more exciting new development in the world of medicine and plastic surgery than cell therapy, but there is much work to be done. The review by Hanson et al provides a short, but directed, road map for the future.

Disclosures
Dr. Schefflan is an unpaid investigator for Cytori Therapeutix.

REFERENCES