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Clinical Applications of Mesenchymal Stem Cells in Soft Tissue Augmentation

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Abstract

Based on a variety of preclinical studies showing that mesenchymal stem cells (MSC) play a significant role in tissue repair and homeostasis, MSC have rapidly moved into a phase of clinical trials investigating their efficacy as a cell-based therapeutic modality for a diverse group of applications. An emerging body of evidence shows that in addition to being a progenitor cell population with self-renewing and multipotent differentiation capabilities, MSC have unique immunomodulatory properties, making them even more attractive for regenerative medicine. Emerging discoveries in stem cell biology have revealed a multitude of mechanisms through which MSC could potentially augment the current techniques in aesthetic surgery. In this article, the authors review the clinical advances in cell-based therapies relevant to aesthetic surgery, including tissue augmentation, rejuvenation, and regeneration.

Keywords

mesenchymal stem cells; fat grafting; cosmetic augmentation; immune modulation

Cell-based therapy, which involves the transplantation of stem/progenitor or (less frequently) terminally differentiated cells to patients through local delivery or systemic infusion, is now being widely adopted as a novel therapeutic modality for a variety of diseases. Based on recent advances in regenerative medicine, it is thought that cell therapy could affect underlying pathophysiology through multiple pathways, providing an advantage

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over current treatments.[1] Although a wide range of cells could be chosen for tissue regeneration, stem cells have an advantage in that they can differentiate along multiple tissue lineages as well as proliferate over time, thereby providing a continuous source of new cells to replace those present tissues or pathologies with high cellular turnover. Of particular interest are multipotent mesenchymal stem cells (MSC), originally isolated from bone marrow more than three decades ago.[2-4]

During the last decade, MSC have rapidly moved from being investigated through in vitro and animal studies to clinical trials, where their efficacy is being studied as a therapeutic modality potentially applicable to a wide range of disorders.[5-7] Recent studies show that MSC can be isolated from most adult tissues, including fat, by ex vivo expansion through serial passaging, a method similar to the derivation of bone marrow MSC.[8,9] Interestingly, these adipose-derived precursor cells were first identified in the stromal vascular fraction of adipose tissue more than three decades ago around the same time that bone marrow isolation was taking place,[10] although at that time they were not characterized as MSC. We now know that MSC isolated from different tissue sources have the capability of differentiating into different mesenchymal tissue lineages[11,12] and have similar immunomodulatory properties.[13,14] However, evidence suggests that these cells, based on their tissue source, are not phenotypically or genotypically completely identical.[15] Although the differentiation potential of MSC into other nonmesenchymal lineages (such as neural or cardiac tissues) has been shown in vitro by some investigators, the degree of contribution of such trans-differentiation capabilities to their in vivo tissue regeneration remains a matter of debate.[16]

Despite the controversy about the magnitude of MSC differentiation potential, several functional characteristics have been identified that make these cells attractive for regenerative medicine applications. There is ample evidence that MSC migrate to the site of injured tissue or inflammation, support proliferation and differentiation of resident progenitor cells to replace lost cells, increase tissue angiogenesis,[17] and promote recovery of injured tissues through growth factor secretion and matrix remodeling.[13,14,18-20] Moreover, MSC have been shown to modulate the activation and proliferation of immune cells such as T- and B-lymphocytes, natural killer cells, dendritic cells, and macrophages.[21-24] Such properties have been the basis of placing allogeneic MSC without human leukocyte antigen (HLA) matching in a variety of clinical applications, such as graft versus host disease.[7] Furthermore, allogeneic MSC are currently being investigated for their potential efficacy for treatment of disorders such as myocardial infarction, newly-diagnosed diabetes mellitus, Crohn’s disease, chronic obstructive pulmonary disease, and amyotrophic lateral sclerosis. Although it is not clear for which of these disorders MSC will provide a therapeutic advantage, it is expected that the applications for tissue-derived MSC and other novel cell therapies will only expand in regenerative medicine and tissue engineering.

PHYSIOLOGIC BASIS FOR RENEWED INTEREST IN FAT GRAFTING

Adipose tissue is widely distributed throughout the human body and serves as the primary site of fat metabolism and energy storage for triglycerols. The growth of adipose tissue is the result of a combination of increased adipocyte number and increased adipocyte size or lipid accumulation.[25] It is now well established that a variety of cytokines and growth factors

found in adipose tissue regulate endocrine and metabolic homeostasis, as well as precursor differentiation, throughout one's lifetime.[25] Plastic surgeons have been applying fat as a soft tissue filler for more than a century and since then, the techniques for harvest and administration have been modified to address the viability of cells within the lipoaspirate and (more importantly) the stromal vascular fraction (SVF).[26-28] Although the primary cell type found in the SVF is rich in MSC, populations of vascular endothelial cells, pericytes, and monocytes have been identified as good sources as well.[29,30] However, it is assumed that the MSC present in the SVF, rather than mature adipocytes, are of considerable significance in the viability and outcome of autologous fat grafts.

Fat grafting for cosmetic soft tissue augmentation has received much attention over the past few decades. However, the safety and efficacy of autologous fat transfer continue to be debated. Recently, because of the renewed interest in fat grafting, the American Society of Plastic Surgeons commissioned a task force to evaluate the limited literature regarding such procedures and potentially develop evidence-based practice recommendations.[31] However, there is a paucity of clinical studies documenting the long-term safety and efficacy of autologous fat grafts.[32] Although the fate of grafted fat has not been fully elucidated, there has been no concrete evidence to suggest that it is less safe than biomaterial alternatives. With regard to autologous fat breast augmentation or reconstruction, a primary concern is the inflammatory response that can lead to fat necrosis, microcalcifications, and cyst formation, all of which may potentially interfere with breast physical examination or cancer detection as well as cosmetic outcome and satisfaction regardless of treatment site.[26] Additionally, techniques of tissue harvest, processing or preparation, and injection are not standardized, which further limits the reliability of data to formulate clinical recommendations. Nevertheless, much attention has been focused on enhancing the results of autologous fat grafting through the potential utilization of adipose-derived stem cells to improve graft survival.

CELL-ASSISTED LIPOTRANSFER FOR SOFT TISSUE AUGMENTATION

Since the amount of fat transferred as a graft has a variable survival rate, only about 25% to 60% of the volume of transferred fat remains after a few months. In an effort to improve the "graft take" and therefore the predictability and efficacy of autologous fat grafting, Matsumoto and colleagues[29] developed a novel method of concurrent transfer of lipoaspirated fat with adipose derived stem cells, termed cell-assisted lipotransfer (CAL). In this technique, a portion of the lipoaspirated fat is processed to isolate the heterogeneous mixture of cells of the SVF; the remaining lipoaspirate is processed for fat grafting, serving as a biological scaffold for the SVF cells. The foundation of this technology is that the additional cells will improve graft survival and reduce postoperative atrophy or resorption through enhanced angiogenesis and cell self-renewal.

Yoshiumura et al[33] described the outcomes of this technique for cosmetic breast enhancement in 40 healthy patients treated with CAL. The mean volume of injected fat was around 270 mL per breast (268.1 ± 47.6 mL left; 277.3 ± 39.1 mL right). The authors noted some resorption of the adipose tissue within the first two months; however, the final breast volume was augmented by 100 to 200 mL. Unfortunately, the authors did not offer any

control patients who had fat grafts placed without CAL, so it is difficult to suggest that this technique offers a significant improvement in outcomes. Microcalcification was detected via mammography at 24 months in two patients, cyst formation was detected by magnetic resonance imaging in two patients (<12 mm), and fibrous breast tissue was observed by computed tomography at six months in two patients with physical findings of firmer breast tissue compared with other cases. A similar case series by this group described the successful employment of progenitor-rich fat transfer in 15 patients following breast implant removal secondary to capsular contracture or other complications. Although long-term results have yet to be established, these studies illustrate the safety and utility of combining adipose-derived cells with autologous fat grafts for cosmetic breast augmentation. Tissue processing was performed in 90 minutes during the operative procedure, although there was no indication as to how much time this added to the total surgical case.

CAL has also been utilized for other indications for fat grafting such as facial contouring.[34] In one study, a small group of patients with facial lipoatrophy from lupus erythematosus profundus or Parry-Romberg syndrome (idiopathic hemifacial lipoatrophy) were treated with fat injections, with or without additional cells or CAL (n = 3 per group). The average volume of lipoinjection was 100 mL and the cell-processing procedure took 90 minutes. The CAL treatment group showed a better clinical improvement score; however, this was not statistically significant given the small study size. One patient in the non-CAL group was treated for fat necrosis. Again, the data in this study help establish safety of the technique in soft tissue augmentation, although larger and more structured clinical trials would be necessary to draw further conclusions.

MESENCHYMAL STEM CELLS IN WOUND THERAPY

Currently, MSC derived from bone marrow and fat are being actively pursued as an alternative for soft tissue reconstruction or as an augmentation to standard treatment modalities. One major confounding factor in these trials is the lack of a standardized procedure for isolation and characterization of the cells selected; some studies have focused on bone marrow or fat aspirates, with the assumption that these tissues are rich in MSC, whereas others have considered highly enriched populations of MSC through culture expansion.

For example, applications of autologous bone marrow MSC have been reported in topical treatment of nonhealing wounds.[3] In these studies, cells were derived from autologous bone marrow and uses ranged from topical application of concentrated bone marrow aspirate[35-37] to direct injection of culture-expanded bone marrow MSC.[38] The outcomes were similarly varied among the reports; however, all patients showed improved healing (ie, skin graft take or closure) of wounds that had been previously refractory to standard treatments.

Purified lipoaspirate has also been studied in 20 patients for treatment of wounds resulting from radiation therapy to the chest wall or supraclavicular region.[39] In this study, lipoaspirate was centrifuged, the oil/liquid layer was discarded, and the remaining adipose tissue was injected into the wounded tissue. Patients received from one to six injections, based on the severity of their wound. Outcomes measurements included clinical healing,

symptom improvement, and recurrence. Only one patient of the 20 showed no sign of improvement.

Culture-expanded adipose-derived MSC have been applied in combination with a fibrin glue sealant to treat complex perianal fistula tracts.[40,41] These phase I and II clinical trials were the first to document the safety of culture-expanded MSC derived from lipoaspirate. Despite the data in these two reports being limited because of the small patient numbers, the approaches were novel and the results were promising. Although the underlying pathology associated with chronic cutaneous wounds is complex, these studies establish the foundation for similar safety and feasibility studies with culture-expanded, pure MSC populations derived from adipose tissue or lipoaspirate for other clinical indications.

Local Injection of Cells for Skin Rejuvenation

Much of the interest in adipose-derived stem cells in plastic surgery focuses on wound healing and replacement of tissue defects; however, the paracrine effects of these cells as described above (including stimulation of extracellular matrix deposition and resident cell recruitment) have recently been applied to skin rejuvenation. Conventional treatments for aging skin—such as topical retinoids or laser therapy—seek to induce fibroblast activation and collagen synthesis in a manner similar to adipose-derived stem cells, as documented by in vitro and preclinical studies. In one clinical case report, a high concentration of autologous, purified lipoaspirate cells in saline was injected directly into the photoaged periorbital dermis of one patient to test this theory.[42] The patient underwent two injections with a two-week interval between treatments. The report showed follow-up at two months after the last injection. Although there was subjective improvement in the periorbital skin demonstrated in the posttreatment photographs, the authors also noted an increase in dermal thickness measured by ultrasonography (2.054 mm pretreatment vs 2.3217 mm posttreatment). This finding, coupled with preclinical work showing a culture-expanded MSC increase in type I collagen and a variety of growth factors in normal skin, offers promise for the application adipose MSC in skin rejuvenation and sets the foundation for future clinical studies.

DISCUSSION

Despite the lack of well-designed controlled clinical trials, emerging clinical data on the safety of bone marrow- and adipose tissue-derived MSC in wound healing and a variety of inflammatory disorders warrant consideration of these cells in a wider range of applications, including aesthetics and reconstruction. There are several prospective roles in which MSC could participate in soft tissue augmentation, as indicated above. These multipotent progenitor cells will likely continue to be the cell of choice for tissue engineering strategies,[43,44] given the access to and ease of harvest of adipose tissues by plastic surgeons. Furthermore, there is evidence to suggest that MSC may be employed in conjunction with such methods to improve healing and allograft survival and to mediate the inflammatory response associated with composite tissue transfer.[6] A thorough understanding of the immunobiology of MSC is necessary to realize the complement of pathologies that could be affected by MSC-based therapy.

The long-term outcomes of the innovative methods outlined in this review are eagerly awaited. Although clinical recommendations cannot be drawn from these cases, they add to the variety of indications that may benefit from cell-based therapies. When considering MSC for such therapies, it is necessary to address engraftment and tumorogenicity. The exact fate of locally or systemically delivered MSC has not been clearly established, and one can imagine that this tissue will be subjected to the same limitations or concerns that are present with standard fat grafting techniques. Many preclinical and clinical studies show variations in engraftment of MSC in a variety of tissues,[17] potentially limiting the anti-inflammatory or regenerative effect. Moreover, it has been speculated that bone marrow-derived MSC are a source of tumor-associated stromal cells and, as such, can enhance tumor growth,[45,46] although this has not been shown to be of clinical concern with adipose-derived cell populations.

CONCLUSIONS

Although it is thought that MSC are recruited to sites of inflammation or injury through a variety of cytokines, it has yet to be established how the addition of autologous cells will affect normal, aged, or transplanted tissue. Such pre-clinical animal work is the interest of our group, as well as many others in regenerative medicine. In many of the studies reviewed, the exact phenotypes of cells utilized are not characterized or reported. Such lack of understanding of the cellular compositions in different studies makes the task of comparing these studies even more difficult. Nevertheless, the novel methods for MSC application as reviewed in this article are highly promising and bring us closer to the goal of identifying new therapeutic approaches to soft tissue augmentation and safely accelerating the transition of basic research findings into clinical advances in many areas of regenerative medicine and aesthetic surgery.

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