

Chapter 2

Stem Cells in Oculofacial Plastic Surgery

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Abstract In the field of oculofacial plastic surgery, stem cells are beginning to be used in reconstructive and aesthetic applications. Adult mesenchymal stem cells, specifically adipose-derived stem cells (ADSCs), with their abundant supply, ease of harvest, and ability to differentiate into fat, bone, cartilage, muscle, and blood vessels appear to be excellent progenitor cells for use in facial reconstruction. ADSCs secrete cytokines which can enhance their own survival and engraftment. In addition, ADSCs have been utilized clinically for tissue engineering of facial structures including bone, cartilage, and fat and have the potential for engineering other mesenchymal structures the tarsus. Stem cells may augment wound healing, especially in the case of chronic wounds, free grafts, and flaps and theoretically could improve surgical outcomes, especially in high-risk settings. Lastly, the paracrine effect of adult mesenchymal stem cells has the potential to mitigate, and in some instances reverse, the process of age and oxidative skin damage. Well-designed, prospective, quantitative human trials need to be conducted to bring stem cell technology into standard oculofacial plastic surgical practice.

Introduction

With the potential to regenerate any kind of tissue, stem cell technology offers possibilities in all areas of medicine. In the field of oculofacial plastic surgery, stem cells are beginning to be used in reconstructive and aesthetic applications.

Embryonic stem cells (ESCs) are pluripotent and thus able to generate any cell type. However, since they are derived from fertilized embryos, ESCs present ethical

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challenges in their clinical application, as well as the possibility of rejection by the host immune system. Adult mesenchymal stem cells (MSCs), or stromal stem cells as they are sometimes called, have been isolated from the stromal compartments of several mesodermal tissues including bone marrow, muscle, perichondrium, and adipose tissue [1–5]. MSCs demonstrate vast proliferative capacity and multilineage potential including the ability to differentiate into bone, muscle, cartilage, and fat as well as certain non-mesodermal structures such as neurons and Schwann cells [6–10]. For plastic and reconstructive surgery, MSCs have obvious advantages over ESCs as they do not present any ethical issues, are autologously obtained thus eliminating the concerns about rejection, and can easily be harvested in large supply.

MSCs have been shown to migrate to the areas of injured, ischemic, or inflamed tissue, increase tissue angiogenesis, and help the repair of injured tissues through growth factor secretion (such as vascular endothelial growth factor and hepatocyte growth factor) and matrix remodeling [11–13]. While bone marrow-derived MSCs have been the primary source for therapeutic applications for the past 20 years, recent studies have demonstrated that MSCs can be harvested from adipose tissue via *ex vivo* expansion through serial passaging [6]. The abundant supply of adipose, often a by-product of common procedures such as liposuction, fat transfer, and blepharoplasty; the potential to differentiate into bone, muscle, cartilage, and possibly tarsus; and the functional characteristics of its MSCs make adipose-derived stem cells (ADSCs) attractive to the field of aesthetic and reconstructive oculofacial plastic surgery.

Adipose-Derived Stem Cells

Although Robdell first isolated a population of progenitor cells from rat adipose tissue in 1964, a third of a century would pass before ADSCs would be found to reside in lipoaspirate, a disposable by-product of liposuction, and recognized for their similarities to bone marrow-derived MSCs [6, 14]. In the process of liposuction, after a tumescent anesthetic solution is injected under the skin, a blunt cannula inserted through a small skin incision is used to aspirate the fat and tumescent solution. To harvest ADSCs, this lipoaspirate then undergoes collagenase digestion and centrifugation to isolate the stromal vascular fraction (SVF) pellet containing the ADSCs [11]. These ADSCs have been shown to easily differentiate into mesenchymal cells such as bone, fat, cartilage, and muscle and have the ability to undergo self-renewal [15, 16].

Adipose tissue contains up to 1 % ADSCs which is in stark contrast to the 0.001 % stem cell fraction found in bone marrow [17]. However, studies have demonstrated that not all fat depots are equal in terms of quality of associated ADSCs. ADSCs harvested from the superficial abdominal depot above Scarpa's layer have been shown to be more resistant to apoptosis than other subcutaneous depots including the arm, hip, and thigh regions [18, 19]. In addition, younger patients appear to have increased induction of their ADSCs than older patients [18]. Once harvested and isolated, ADSCs can be expanded in a monolayer tissue culture

to be used in clinical experiments and applications or cryopreserved for up to 6 months after harvest [15, 20].

Although there is great interest in the clinical applications of ADSCs, this field is still in its infancy. With the ability to be easily and safely obtained in large quantities from lipoaspirate, ADSCs are beginning to be of clinical interest to the oculofacial plastic surgeon in the areas of wound healing, tissue engineering, autologous fat grafting, and skin rejuvenation.

Orbital Stem Cells

While most adipose tissue in the human body is derived from mesenchyme, orbital fat and the fat surrounding the paratracheal region is uniquely of neural crest origin [21]. In 2009, Korn and colleagues isolated and characterized adult stem cells from human orbital fat excised during routine blepharoplasty [22]. Korn found that stem cells derived from orbital fat carried neuronal cell surface markers and could be induced to express neuronal and glial antigens in tissue culture. The authors postulate that these neural crest origin stem cells could have potential therapeutic uses in the treatment of retinal dystrophies, trabecular meshwork reconstruction, ganglion cell replacement, and ocular surface reconstruction.

Kang and colleagues reported using fat excised during cosmetic blepharoplasty to isolate stem cells with neural crest origin characteristics in order to treat diabetes. After harvest, these stem cells were cultured with nicotinamide, activin, and GLP-1 to allow for differentiation into insulin secreting cells. These cells were then transplanted into streptozotocin-treated immunocompetent type I diabetic mice. Kang found that in 50 % of the mice, hyperglycemia normalized and only human, not murine, insulin and c-peptide was found in the blood of the mice. At 2 months, these cells continued to function and there was no sign of rejection [23]. The authors suggest that the success of this xenogeneic transplant may be due to low levels of HLA class I and the absence of HLA-DR, HLA-DM, CD80, and CD86 molecules expressed on the surface of these stem cells. This technology holds promise as a possible cure for type I diabetes in humans.

Clinical Applications

Tissue Engineering and Grafting

In reconstructive plastic surgery, the principle of “replace like with like” is well respected and practiced whenever feasible. However, in periocular reconstruction, tissues the tarsus and conjunctiva are often in too limited a supply to be successfully used for grafting purposes without creating significant donor site morbidity. Autologous ear cartilage and hard palate have been used as substitutes for tarsus, and

buccal mucous membrane for conjunctiva. However, donor site morbidity and increased surgical time related to graft harvesting have led surgeons to search for alternative materials. Many surgeons have embraced human acellular dermis (Alloderm, Lifecell, Branchburg, NJ), or bioengineered materials cross-linked porcine dermal collagen (ENDURAGen, Stryker CMF, Newnan, GA) and synthetics such as tarSys (IOP Ophthalmics, Costa Mesa, CA) to substitute for tarsus [24–26]. Similarly, banked amniotic membrane is now often used instead of conjunctiva or buccal mucous membrane for socket reconstructions [27, 28]. However, each substitute has its limitations. The prospect of growing abundant, autogenous, adult stem cell-derived tissues such as tarsus, conjunctiva, bone, adipose, and skin to be used for reconstruction is extremely attractive to the oculofacial plastic surgery community.

In 1993, Langer and Vacanti outlined the three fundamental strategies of tissue engineering: isolated cells or cell substitutes, tissue-inducing substances, and cells placed on or within a matrix [29]. While these “pillars” remain today, scientists are beginning to realize the critical role that the interaction between each of these pillars plays in the bioengineering of larger tissues and organs.

As discussed earlier, ethical concerns limit the use of embryonic stem cells. However, adult mesenchymal stem cells, specifically ADSCs, with their abundant supply, ease of harvest, and ability to differentiate into fat, bone, cartilage, muscle, and blood vessels appear to be excellent progenitor cells for use in facial reconstruction. ADSCs, however, require highly regulated and critically timed signals, in the form of biomolecules and growth factors, to allow for differentiation into specific surgically useful tissues. For instance, fibroblast growth factor-2 (FGF-2) promotes cartilage differentiation but inhibits bone differentiation [30]. Culturing ADSCs in low-oxygen-tension conditions may enhance proliferation, differentiation, and growth factor proliferation [31]. In addition, the ADSCs themselves are able to secrete angiogenic biomolecules such as hepatocyte growth factor, vascular endothelial growth factor (VEGF), stromal-derived factor-1 alpha, and granulocyte/macrophage colony-stimulating factor which are likely critical for survival and engraftment of stem cell-derived tissues [15].

Scaffolds or matrixes create an extracellular environment for the ADSCs, providing biologic structural cues, protection and a means by which the primed ADSCs can be introduced into the body of the recipient [32]. Several scaffold matrix materials with various chemical compositions, three-dimensional structures and degrees of mechanical stability have shown promise in supporting ADSCs. These include hyaluronic acid and collagen sponges, placental decellular matrix (PDM), silk fibroin-chitosan scaffold, and injectable collagen microbeads and poly (lactic-co-glycolic acid) spheres [15].

Although stem cell-oriented tissue engineering is in its infancy in terms of clinical applications, a small number of cases have been reported describing reconstructions utilizing cell culture and stem cell technology that could be applied to periocular reconstruction.

Cartilage

Yanaga and colleagues reported using cultured autologous auricular chondrocytes for nasal augmentation in 75 patients [33]. In this study, harvested chondrocytes from the auricular concha were cultured on a gelatinous chondroid matrix and then injected into the subcutaneous nasal dorsum. The matrix changed from a soft gel to rigid neocartilage within 2–3 weeks of implantation and produced good long-term results [33]. Yanaga also reported using a 2-stage technique for the treatment of microtia in 4 children [34]. Chondrocytes were harvested from the auricular remnant and cultured in a multilayered fashion as in the prior study. This chondroid matrix was then injected subcutaneously into the abdomen to allow for growth into a large block of cartilage with a neoperichondrium. At 6 months, the graft was harvested from the abdomen, sculpted into the shape of auricular cartilage, and implanted subcutaneously in the area of the microtia to create the form of a new ear. At 2–5 years follow-up, the graft retained good shape without evidence of reabsorption. This technique allowed for minimal donor site morbidity and the generation of enough graft material to create a complete auricular cartilage structure.

Bone

In 2001, Quarto and colleagues reported the first clinical application of autologous adult stem cells in treating large long bone defects in 3 patients [35]. Stem cells were isolated from bone marrow, expanded *ex vivo*, placed on hydroxyapatite scaffolds tailored to fit the size of the specific bony defect, and implanted. External fixation was removed at 6–13 months and at 15–27 months there were no issues with the implants and all patients recovered limb function. This technique greatly reduced recovery time and morbidity compared with traditional noncellular implants. Warnke and colleagues later reported applying stem cell technology to reconstruct a 7 cm mandible defect after subtotal mandibulectomy [36]. For this technique, three-dimensional computed tomography was used to design a titanium mesh cage that would be a virtual replacement for the missing bone. The cage was then filled with bone mineral blocks and injected with human bone morphogenic protein 7 (BMP7) and the patient's non-processed bone marrow. This combination of scaffold, tissue-inducing substance, and stem cells was then implanted in a pocket created in the patient's latissimus dorsi muscle and transplanted as a free bone-muscle flap into the mandibular defect 7 weeks later. The patient had improved mastication and subjective aesthetic appearance following the procedure [36].

Adipose

Autologous adipose has been traditionally used for a number of aesthetic and reconstructive indications, including hemifacial atrophy; soft tissue defects following infection, trauma or radiation; facial augmentation and facial rejuvenation

[11, 37–39]. Unfortunately, autologous fat grafts have survival rates between 25 % and 60 % making their use clinically somewhat unpredictable; often multiple grafting sessions are required to achieve satisfactory results [13]. Cell-assisted lipotransfer (CAL) is a technique by which adipose-derived stem cells (ADSCs) are used to augment standard lipoinjection. Lipoaspirate, typically harvested from the abdomen, is divided in half. One half undergoes collagenase digestion and centrifugation to isolate the stromal vascular fraction (SVF) as described earlier. The SVF is then added back to remaining lipoaspirate to create ADSC-rich fat, which can then be injected in the manner of traditional lipotransfer. Compared with traditional lipotransfer, CAL has been shown to have 35 % improved graft survival with microvasculature detected more prominently in the outer layers [40].

Sterodimas and colleagues reported a prospective, randomized, non-blinded, interventional study of 20 patients with congenital or acquired facial tissue defects who were treated with either traditional lipotransfer or CAL [11]. In the traditional lipotransfer group, 30 % achieved aesthetically acceptable results after the initial treatment with the remaining 70 % requiring one or more additional treatments. In the CAL group, 100 % of the patients required only a single treatment. While those in the CAL group had higher initial patient satisfaction scores, at 18 months there was no difference between groups. There were no complications in either group.

In a separate report, the same authors describe a case of 19-year-old patient with Parry–Romberg syndrome and progressive hemifacial atrophy who was treated with 90 cc of cell-assisted lipotransfer. At 1 year, the patient was satisfied with the aesthetic result and did not require further treatment [15].

It is unclear the precise role ADSC plays in CAL. Preadipocytes and ADSCs are thought to be more resistant than mature adipocytes to the trauma of graft harvest and postimplantation ischemia [11, 41–43]. In fact, ADSCs have been demonstrated to increase proliferation in response to hypoxia [44]. In addition, ADSCs are known to secrete VEGF and hepatocyte growth factor both of which may contribute to neoangiogenesis following implantation [11]. ADSCs may also, themselves, act as vascular endothelial progenitor cells [45]. Hence, it follows logically that grafts with higher concentrations of ACSCs may have improved and less variable survival.

Wound Therapy

Normal wound healing occurs in four distinct but overlapping phases: hemostasis, inflammation, proliferation, and remodeling. In the abnormal, chronic wound, ischemia and bacterial overgrowth lead to a relentless cycle of inflammation and tissue injury. While the oculofacial plastic surgeon rarely encounters venous ulcers, pressure ulcers and diabetic ulcers which comprise the majority of non-healing wounds, poor wound healing can present in facial burns, advancement flaps and free grafts, especially in the setting of previously irradiated or scarred tissue, infection, smoking, and advanced age [16, 46].

As discussed earlier, mesenchymal stem cells have the ability to differentiate into multiple cell types and release pro-angiogenic cytokines which likely benefit tissues undergoing wound healing. In addition, the low oxygen tension of chronic wounds, flaps and free grafts may actually further stimulate mesenchymal stem cells to proliferate and release growth factors [15, 31].

Simman and colleagues, in a prospective, interventional murine experiment, found that “priming” the donor site of a skin flap with subcutaneously injected bone marrow-derived stem cells and angiogenic factors 1 week prior to flap elevation significantly improved flap survival compared to priming with only control medium, angiogenic factors alone, or stem cells alone. Interestingly, the authors found that the same introduction of angiogenic factors and stem cells did not significantly improve flap survival when injected at the time of flap elevation [47].

With the ease of harvest and abundant supply of adipose-derived stem cells (ADSCs), investigators have recently focused on the therapeutic uses of ADSCs for wound healing. Kim and colleagues found that ADSCs promote dermal fibroblast proliferation and significantly accelerate the rate of wound closure without the formation of hypertrophic scar [48]. In addition, Ebrahimian and colleagues determined that ADSCs can differentiate into keratinocytes and produce angiogenic growth factors in both normal and irradiated tissues [49]. Nambu showed that the negative effect of diabetes mellitus on wound healing could be counteracted by the introduction of ADSCs to the wound [50]. Furthermore, Altman found that human acellular dermal matrix seeded with ADSCs differentiated into vascular endothelial, fibroblastic, and epidermal epithelial cells after in vivo engraftment and significantly improved wound healing [51].

The application of stem cell technology for wound healing was recently described in a cohort of human subjects. Rigotti and colleagues demonstrated significant improvements in radiation-induced wounds of the chest wall and supraclavicular region with the injection of ADSC-rich purified lipoaspirate. In this study 95 % of the 20 patients showed improvement of their wounds following one or more injections [52].

From these studies, it follows that stem cells have the potential to improve wound healing and could prove clinically useful, especially in high-risk settings. Further human studies need to be performed to determine the optimal methods and surgical timing for stem cell-assisted wound therapy.

Skin Rejuvenation

During normal aging the skin becomes less elastic, irregularly pigmented, and thinner. Both genetic predisposition and environmental factors such as smoking and ultraviolet light exposure have been shown to contribute to age-related skin damage. Mesenchymal stem cells are thought to counteract the appearance of skin aging not only via direct cell-to-cell interactions but also through paracrine effects of the various secreted growth factors and cytokines [53]. For example, ADSC culture medium (ADSC-CM) containing secreted cytokines and growth factors from

ADSCs has been shown to induce dermal fibroblast migration and enhance type I collagen secretion [48].

ADSCs may have a significant role in protecting skin from damage due to oxidative stress. In animal models of oxidative skin injury, ADSC-CM protected dermal fibroblasts against *t*-butyl hydroperoxide free radical damage and inhibited apoptotic cell death induced by reactive oxygen species [53]. In addition, ADSC-CM has been shown to inhibit melanoma B-16 cells by arresting them in the G1 phase, thus delaying the cancer progression [53].

Ultraviolet radiation is at least partly responsible for skin pigmentation and fine wrinkling. Kim and colleagues created a murine model of UV light-induced wrinkles and examined the effects of ADSCs. Wrinkling was significantly lessened while dermal thickness and collagen content in the dermis was increased after subcutaneous injection of ADSCs [53]. Furthermore, ADSC-CM increased the production of type I collagen and decreased the level of matrix metalloproteinase 1 (MMP 1) in fibroblasts which may contribute to the thickened dermis [54]. The paracrine effects of ADSCs also appear to alter pigmentation. ADSC-CM was found to inhibit melanin synthesis and tyrosinase in melanoma B16 cells and therefore may be useful to treat the dyspigmentation associated with photodamage [55].

Park and colleagues report a case of a human subject receiving injections of purified autologous lipoaspirate containing approximately 20–30 % ADSCs to treat photoaged periorbital skin [56]. The patient received two injections 2 weeks apart and at 2 months the texture of the patient's skin and fine wrinkles were subjectively improved. In addition, the dermal thickness over the area of treatment had increased by over 10 % (2.054 mm vs. 2.317 mm) after the treatment.

These studies suggest that stem cells and their paracrine effects may significantly improve age-related and oxidative skin damage by inducing fibroblast migration, increasing collagen production, protecting against free radical damage, inhibiting matrix metalloproteinases, and inhibiting dyspigmentation. Further human studies are necessary to bring this technology to clinical practice.

Conclusions

In the field of oculofacial plastic surgery, the application of stem cell technology has the potential to improve both aesthetic and reconstructive outcomes. Autologous adipose-derived stem cells have the potential to allow for tissue engineering of vital periocular structures, improve wound healing and the success of tissue grafts and flaps, and augment the ability to aesthetically treat the aging face. Additional well-designed, prospective, quantitative human trials need to be conducted to bring this technology into standard clinical practice.

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<http://www.springer.com/978-1-4614-5492-2>

Stem Cell Biology and Regenerative Medicine in
Ophthalmology

Tsang, S.H. (Ed.)

2013, XVI, 188 p., Hardcover

ISBN: 978-1-4614-5492-2

A product of Humana Press