Advances in Cosmetic Surgery 4 (2021) 59–70
ADVANCES IN COSMETIC SURGERY

# Stem Cells and Exosomes in Aesthetic Medicine

**Nina Semsarzadeh, MD, Wyatt Andrasik, MD, Shilpi Khetarpal, MD***
Department of Dermatology, Cleveland Clinic Foundation, Cleveland, OH 9500 Euclid Avenue, A61, Cleveland, OH 44195, USA

**KEYWORDS**
• Stem cells • Exosomes • Extracellular vesicles • Hair loss • Androgenetic alopecia • Skin rejuvenation

**KEY POINTS**
- Stem cell and exosome therapy represent new, prospective minimally invasive tools in aesthetic medicine.
- Early clinical studies have demonstrated efficacy of stem cells and stem cell conditioned medium for use in androgenetic hair loss and skin rejuvenation.
- Early in vitro and in vivo studies support the use of exosome therapy for hair loss and skin rejuvenation although translational work in humans is still lacking.
- Lack of standardized preparations and large, randomized controlled trials serve as barriers to the use of stem cells and exosomes in aesthetics.

## INTRODUCTION

### Stem Cells

Stem cells (SCs) have the unique ability to self-renew and differentiate into various cell types. These regenerative capabilities have garnered the interest of many medical disciplines [1]. In recent times, SCs have been adapted for use in the aesthetic arena.

Embryonic SCs (ESCs) represent a source of pluripotent SCs: SCs that can differentiate into any embryonic cell type. Ethical considerations surrounding the derivation of ESCs, which often requires the disruption of an early embryo, has led to the exploration of other SC sources [1].

Induced pluripotent SCs (iPSCs) represent another source of pluripotent SCs that are derived from somatic cells, obviating the ethical controversies [2]. These mature cells are "reprogrammed" to behave as an immature cell akin to an ESC via ectopic expression of certain ESC genes [2].

More recently, adult SCs have gained popularity given their presence in numerous somatic tissue types where they play a role in tissue maintenance injury repair. These cells demonstrate multipotency: propagation into a more limited subset of cells usually confined to single germ layer. The list of adult SC sources is expanding and include adipose tissue, bone marrow, blood, umbilical cord, amniotic fluid, dental pulp, and skin.

Adipose-derived stem cells (ASCs) represent the most commonly used adult SCs in aesthetics given their abundance, ease of harvesting, and uncontroversial nature [1,3]. Autologous ASCs are commonly isolated after liposuction; the resultant lipoaspirate is centrifuged to separate the mature adipocytes from the pelleted stromal vascular fraction (SVF). The SVF contains ASCs, in addition to a myriad of other cell types including preadipocytes, pericytes, hematopoietic progenitor cells, fibroblasts, endothelial cells, smooth muscle cells, monocytes, macrophages, and lymphocytes [4]. Although ASCs can be further isolated from the SVF via filtration techniques and expansion in vitro, the SVF is often used in whole to conserve time, cost, and labor [5].

*Corresponding author, *E-mail address:* khetars@ccf.org

https://doi.org/10.1016/j.yacs.2021.01.003
2542-4327/21/ 

### Mechanism of action

SCs immediately gained popularity in medical research for their regenerative capabilities. Implanted ASCs have been shown to differentiate into adipogenic, chondrogenic, myogenic, and osteogenic cells in the presence of lineage-specific induction factors [6,7]. Autologous and allogeneic SC implantation can also stimulate and recruit endogenous SCs.

That being said, the function of SCs is complex and goes far beyond their, albeit remarkable, regenerative capacity. SCs are now known to secrete numerous cytokines and growth factors, collectively referred to as the secretome, which have downstream effects in immunomodulation, angiogenesis, wound healing, and tissue regeneration [8].

## Exosomes

Extracellular vesicles (EVs) are cell-derived, membranous structures that are released by nearly all human cells and can be broadly categorized into exosomes, microvesicles and apoptotic bodies [9]. Initially, they were thought to function as a means to release cellular waste products [9]. More recently, their role in intercellular communication and ability to regulate functions such as angiogenesis, immune modulation, proliferation, migration, and rejuvenation has become increasingly recognized [10].

Exosomes are nano-sized EVs with important roles in skin homeostasis and skin disease. Investigations regarding their role in cutaneous immunity, as biomarkers for melanoma and Merkel cell carcinoma, psoriasis, and skin repair and regeneration are under way [11]. Recently, studies have focused on exploiting their functions for aesthetic purposes.

Exosomes are composed of a lipid bilayer that surrounds a biologically active core composed of proteins such as ligands, receptors and transcription factors, lipids, and a diverse collection of nucleic acids including messenger RNAs, microRNAs, and DNA, among others [11,12]. Exosomes are generated inside multivesicular bodies, which are formed by internal budding of endosomes and are secreted to the extracellular space on fusion with the plasma membrane [10,12]. Exosomes can then be internalized through several different uptake processes [11]. Their downstream functions vary greatly based on the composition of their cargo provided by the paternal cell [10,11]. They have been shown to play a major role in the paracrine effects of the stem cell secretome, discussed previously, and thus are viewed as a promising new, "cell-free" therapy, safe from the undesired complications of traditional stem cell therapy such as tumorigenicity and immune rejection [10,13].

# CLINICAL RESULTS IN THE LITERATURE

## Stem Cells

### Hair loss

Androgenetic alopecia (AGA) remains the most common cause of hair loss among men and women. Minoxidil and finasteride are the only 2 treatments approved by the Food and Drug Administration (FDA), and their use and efficacy are often compromised by noncompliance and adverse effects. Hair restoration surgery presents another more permanent solution, but the cost and invasive nature of surgery is prohibitive for many.

The hair follicle contains stem cell niches, including hair follicle SCs (HFSCs) present in the bulge and dermal papilla cells [14]. These stem cell sources are imperative to the cycling between the growing (anagen), regression (catagen), and quiescent (telogen) phases of hair growth and regeneration. Given the current subpar treatments for AGA, SCs have become an enticing remedy (Table 1) [14–24].

Many clinical studies investigating SCs in aesthetics use ASC-conditioned medium (ASC-CM), which is available commercially as a lyophilized form of proteins secreted from cultured ASCs collected from healthy adults. ASC-CM is rich in growth factors, including vascular endothelial growth factor, hepatocyte growth factor, platelet-derived growth factor, keratinocyte growth factor, and insulinlike growth factor 1 [25]. ASC-CM was found to enhance the survival and proliferation of dermal papilla cells [26]. In a mouse model, injections and topical application of AS-CSM resulted in earlier telogen to anagen transition and accelerated hair growth, respectively [26].

With repeated intradermal injections into half the scalp of patients with AGA, ASC-CM led to subjective improvement in the visual analog scale (VAS) scores, as well as objective improvement in the number of hairs on trichogram images when compared with baseline and control half [15,16]. Improvement was also noted when ASC-CM was applied with a microneedle roller once weekly with significant increases in hair density and hair thickness noted after 12 weeks of treatment [17].

Autologous ASCs have also been studied in AGA. In a pilot study, autologous fat and SVF, obtained by liposuction, was combined with Lactated Ringer solution and injected into the scalp of patients with AGA. The 6 patients available for evaluation at 6 months demonstrated a significant increase in hair count [18].

**TABLE 1**
**Summary of Select Studies Exploring the Use of SCs in AGA**

| Study, Year | n | Study Type | Treatment Protocol | Clinical Outcome |
|---|---|---|---|---|
| Fukuoka et al, [15] 2012 | 25 | Prospective case series | ASC-CM scalp injections<br>Every 3–5 wk for 4–6 treatments<br>Follow-up: at least 1 y after final treatment | Significant improvements in physician and patient visual analog scale (VAS) scores compared with baseline after the fourth treatment |
| Fukuoka & Suga [16], 2015 | 32 | Prospective, partially half-head study | ASC-CM injections into the whole scalp for 22 patients<br>ASC-CM injections into the left scalp and saline injections into the right scalp for 10 patients<br>Every 3–5 wk for 6 treatments<br>Follow-up: 1 and 3 mo after final treatment | Significant increase in mean hairs compared with baseline ($29 \pm 4.1$ in men and $15.6 \pm 4.2$ in women in 95 $mm^2$ area)<br>Significant increase in mean hairs compared with placebo |
| Shin et al, [17] 2015 | 27 | Retrospective case series | ASC-CM applied to the scalp with microneedle roller<br>Once weekly for 12 treatments<br>Follow-up: at time of final treatment | Significant increase in hair density (17.3 hairs/$cm^2$, $P<.001$) compared with baseline<br>Significant increase in hair thickness (6.5 um, $P<.001$) compared with baseline |
| Perez-Meza et al, [18] 2017 | 9 | Prospective case series | Autologous SVF + fat graft + LR (harvested by liposuction) injected into the scalp<br>One treatment<br>Follow-up: 6 mo after treatment | Significant increase in hair count (31.2 hairs/$cm^2$, $P = .017$) compared with baseline |
| Gentile et al, [19] 2017 | 11 | Prospective, randomized, half-head study | Autologous HFSCs injected into one area of hair loss, saline injections in another area of hair loss involving the scalp<br>Every 60 d for 2 treatments<br>Follow-up: 23 wk after final treatment | Significant increase in hair density compared with placebo ($29\% \pm 5\%$ vs 1%)<br>Significant increase in mean hair count and hair density compared with baseline |
| Elmaadawi et al, [20] 2018 | 20 | Prospective, randomized, unblinded study | Randomized to receive scalp injections of either autologous BMMC or HFSCs | Significant increase in mean percentage of improvement in both BMMC ($52\% \pm 28\%$) |

(*continued on next page*)

TABLE 1
(*continued*)

| Study, Year | n | Study Type | Treatment Protocol | Clinical Outcome |
|---|---|---|---|---|
| | | | One treatment<br>Follow-up: 6 mo after treatment | and HFSC (42% ± 27%) treatment groups compared with baseline<br>Significant increase in hair width and density in both BMMC and HFSC treatment groups compared with baseline |
| Gentile [21], 2019 | 35 | Retrospective, randomized, half-head study | Autologous HFSCs injected into half the scalp, saline injections into the other half of the scalp<br>Every 45 d for 3 treatments<br>Follow-up: 23 and 44 wk after final treatment | Significant increase in mean hair density at compared with baseline and placebo (33% ± 7.5% vs 1%) at 23 wk<br>Significant increase in mean hair density at compared with baseline and placebo (27% ± 3.5% vs 0.7%) at 44 wk |
| Gentile et al, [22] 2020 | 27 | Prospective, randomized, evaluator blinded, half-head study | Autologous HFSCs injected into one area of hair loss, saline injections in another area of hair loss involving the scalp<br>Every 45 d for 3 treatments<br>Follow-up: 58 wk after the final treatment | Significant increase in hair count compared with baseline and placebo (+18 vs + 1.1 hairs/0.65 $cm^2$, $P<.0001$)<br>Significant increase in hair density compared with baseline and placebo (23.3 hairs/$cm^2$ vs 0.7 hairs/$cm^2$, $P<.0001$) |
| Kuka et al, [23] 2020 | 71 | Prospective, randomized, multicenter, nonblinded study | Randomized to receive fat enriched with high dose ASCs ($1 \times 10^6/cm^2$), low-dose ASCs ($0.5 \times 10^6/cm^2$), fat alone, or saline injection in a 2:2:2:1 ratio<br>One treatment<br>Follow-up: 6, 24, and 52 wk after treatment | In Norwood-Hamilton III ad hoc subgroup, significant increase in terminal hair count in low-dose ASC group compared with baseline at week 6 (13.90 ± 16.68), week 12 (11.75 ± 19.42), and week 24 (16.56 ± 14.68); effect not maintained at 52 wk (2.78 ± 16.15).<br>In Norwood-Hamilton III ad hoc subgroup, significant increase in terminal hair count in low-dose ASC group compared with saline control at 24 wk ($P = .0318$) |

(*continued on next page*)

**TABLE 1 (*continued*)**

| Study, Year | n | Study Type | Treatment Protocol | Clinical Outcome |
|---|---|---|---|---|
| | | | | In the intention-to-treat group, significant increase in hair count for low-dose ASC group compared with baseline at 6 wk (13.65 ± 18.01)<br>No significant changes in total hair width |
| Tak et al, [24] 2020 | 38 | Prospective, randomized, double-blind, vehicle controlled study | Randomized to topical formulations of either ASCs obtained from healthy donors via liposuction or placebo<br>Twice daily for 16 wk.<br>Follow-up: 8 and 16 wk from start of treatment | Significant increase hair density at 8 wk compared with control (19.2%)<br>Significant increase in hair diameter at 16 wk compared with control (14.2% vs 6.3%)<br>No significant improvement in investigator or self-assessments using photographs |

*Abbreviations:* AGA, androgenetic alopecia; ASC, adipose-derived stem cell; ASC-CM, ASC-conditioned medium; BMMC, bone marrow–derived mononuclear cells; HFSC, hair follicle stem cell; LR, lactated ringer's solution; SC, stem cell; SVF, stromal vascular fraction.

Recently, trials boasting larger sample sizes have been published. The STYLE trial randomized participants to receive fat enriched with ASCs (in 2 different doses), fat alone, or a saline injection in a 2:2:2:1 ratio. The investigators found significant increases in hair counts in the low-dose ASC-enriched purified fat in men with early hair loss (Norwood-Hamilton 3). The improvement was not sustained at the 1-year follow-up, suggesting the need for repeat or combination treatment [23]. Another recent trial randomized patients to receive topical formulations of either ASCs or placebo, which was applied daily for 16 weeks. When compared with placebo, the treatment group was found to have a significant increase in hair density and thickness on trichoscopy; an improvement in investigator and self-assessments based on clinical photos failed to reach significance [24].

Aside from ASCs, few other sources of adult SCs have been tested for use in AGA. Gentile and colleagues [19] developed a method of isolating autologous HFSCs from mechanical centrifugation of scalp punch biopsy specimens. In their preliminary study, patients with AGA received both autologous HFSCs and saline injections into predetermined areas of hair loss in 2 sessions spaced 60 days apart. At the 23-week follow-up, the participants were found to have significant increases in hair count and density compared with baseline and placebo [19]. The group has since recreated these auspicious results in a refined process termed the "Gentile procedure" in which HFSCs are isolated via splitting and centrifugation of scalp punch biopsies yielding higher numbers of SCs [21]. In 2 subsequent half-head studies, autologous HFSCs and saline injections were performed in 3 sessions, 45 days apart with significant increase in hair count and hair density on trichograms compared with baseline and placebo. Of note, a significant increase in hair follicles was also appreciated histologically compared with baseline [21,22].

Last, intradermal injections of HFSCs were compared with bone marrow–derived mononuclear cells (BMMCs) with no significant difference in the SC sources. Six months after the treatment sessions, both groups were found to have significant increases in hair width and density, as well as an increase in stem cell immunostaining histologically when compared with baseline [20].

### *Skin rejuvenation*

The interest in minimally invasive skin rejuvenating procedures has grown tremendously, and early clinical studies support the use of SCs as a promising new

technique. Early in vitro studies suggested both lightning and antioxidant effects of ASC-CM [27,28]. In a subsequent study, ASCs and ASC-CM applied to photoaged human dermal fibroblasts were found to induce fibroblast proliferation, increase expression of type I collagen, and decrease expression of matrix metallopeptidase (MMP)-1 and p16 supporting additional antiaging effects [29]. In a mouse model, human ASCs were shown to improve UVB-induced wrinkles clinically, increase dermal thickness and collagen density histologically, and modulate collagen and MMP expression molecularly [30]. These promising data have been translated to human studies over the past decade (Table 2).

The integration of SCs into topical cosmeceutical products has been limited given the inability of hydrophilic molecules greater than 500 Da to penetrate the stratum corneum [38,39]. That being said, SCs have been combined with minimally invasive procedures by using mechanical and thermal active transport methods to enhance their penetration into the skin.

In a pilot study, each side of the face was randomized to receive either topical ASC-CM or control (fetal bovine serum [FBS]-free Dulbecco's modified Eagle's medium [DMEM]) after fractional carbon dioxide laser in 3 sessions at 4-week intervals. The experimental group was associated with significant improvements in patient satisfaction scores, melanin index, skin elasticity, transepidermal water loss (TEWL), skin hydration, and skin roughness compared with baseline and placebo. Histologic examination mirrored these clinical results with increases in dermal collagen and elastin [33].

SC conditioned mediums are more commonly combined with microneedling: a mechanical active transport method used for transdermal delivery of therapeutic agents. In an initial split-face study, each half of the face was randomized to saline or human ESC–derived endothelial precursor cells conditioned medium (hESC-EPC CM) in conjunction with microneedling with radiofrequency. After 3 treatments, significant improvements in patient satisfaction scores, investigator evaluation scores, and skin roughness were noted in the experimental half compared with the control half [31]. A similar split-face study combining hESC-EPC CM and microneedling demonstrated significant improvements in patient satisfaction, wrinkles, pigmentation, erythema, and pore size in the experimental half [32]. Since then, split-face studies investigating both amniotic membrane SC–conditioned media (AMSC-CM) and ASC-CM with microneedling showed similar improvements in clinical endpoints compared with placebo [36–38].

In addition to the use of SC conditioned mediums, autologous fat transfer has proven a successful minimally invasive skin rejuvenation technique. Autologous macrofat and microfat transfers were initially used for volume loss reversal. More recently, nanofat suspensions, achieved via liposuction with small, multiport cannula and subsequent mechanical emulsification and filtration to yield a liquid solution, are being used for skin rejuvenation due to the presence of SCs in these autologous fat grafts [38,40].

In a retrospective analysis of 67 patients, nanofat intradermal and subdermal injections were described for rejuvenation of perioral skin, glabellar skin, décolletage, and lower eyelid darkness. Molecular evaluation of a nanofat suspensions confirmed abundant ASCs and no viable mature adipocytes. The investigators noted clinical improvement in superficial rhytides and dark circles peaking 4 to 6 months after treatment with no adverse effects. The group has also described the delivery of their nanofat suspension via microneedling with similar reduction of rhytides, as well as improvement in texture and color of the facial skin [41]. Since then, numerous case reports and case series have asserted their positive results with similar fat and SVF suspensions, although larger, randomized controlled trials are lacking [34,42–44].

## Exosomes

### *Skin rejuvenation*

Exosomes derived from adult or mesenchymal SCs (MSCs) may offer a new, minimally invasive skin rejuvenating alternative to SC procedures that could theoretically be made available as an off-the-shelf product. Although still in its infancy, early in vitro and in vivo studies have demonstrated potential in photoaging.

Studies have demonstrated that MSC exosomes can promote wound healing and tissue regeneration by increasing fibroblast proliferation and migration, promoting angiogenesis and inducing endogenous stem cell recruitment [12]. Newer evidence shows exosomes from young mice could reverse the expression of aging associated molecules and telomerase related genes of old mice [13].

An in vitro study showed MSC exosomes from human umbilical cord increased production of collagens, fibronectin, and elastin in human dermal fibroblasts while decreasing production of matrix metallopeptidase 1, functions important to skin rejuvenation [45]. Another study showed MSC exosomes from bone marrow reduced UVB-induced inflammation and senescence expression by downregulating tumor necrosis factor-$\alpha$ and restored type 1 procollagen and inhibited

**TABLE 2**
**Summary of Select Studies Exploring the Use of SCs in Skin Rejuvenation**

| Study Year | N | Study Type | Treatment Protocol | Clinical Outcome |
|---|---|---|---|---|
| Seo et al, [31] 2013 | 15 | Prospective, randomized, double blinded, split-face study | Each half of the face randomized to receive microneedling with RF with either hESC-EPC CM or saline<br>Every 4 wk for 3 treatments<br>Follow-up: 4 wk after final treatment | Significant improvement of wrinkles and overall skin appearance in experimental half compared with control (2.20 ± 0.68 vs 2.06 ± 0.70, *P*<.05)<br>Significant increase in patient satisfaction scores in experimental half compared with control (2.35 ± 0.42 vs 2.00 ± 0.65, *P*<.05)<br>Significant reduction in skin roughness in experimental half compared with control |
| Lee et al, [32] 2014 | 25 | Prospective, randomized, double blinded, slit-face study | Each half of the face randomized to receive microneedling with RF with either hESC-EPC CM or saline<br>Every 2 wk for 5 treatments<br>Follow-up: 2 wk after final treatment | Significant increase in patient satisfaction scores in experimental half compared with control (3.25 ± 1.26 vs 2.72 ± 1.45, *P*<.05)<br>Significant improvement in pigmentation of experimental half compared with control (1.54 ± 0.57 vs 1.32 ± 0.62, *P*<.05)<br>Significant improvement of wrinkles in experimental half compared with control (1.92 ± 0.42 vs 1.49 ± 0.48, p < .05) |
| Zhou et al, [33] 2016 | 22 | Prospective, split-face study | Each half of the face randomized to receive either ADSC-CM or FBSE-free DMEM medium after fractional $CO_2$ laser resurfacing<br>Every 4 wk for 3 treatments<br>Follow-up: 4 wk after final treatment | Significant increase in subjective satisfaction scores in experimental half (2.56 ± 0.65) compared with control<br>Significant increase in clinical assessment scores in experimental half compared with control (2.78 ± 0.45 vs 2.00 ± 0.71)<br>Significant improvement in melanin index, elasticity, TEWL, hydration, skin roughness in experimental half compared with control |

(*continued on next page*)

**TABLE 2 (*continued*)**

| Study Year | N | Study Type | Treatment Protocol | Clinical Outcome |
|---|---|---|---|---|
| Amirkhani et al, [34] 2016 | 16 | Prospective case series | Autologous injection of SVF harvested after liposuction into the nasolabial groove<br>One treatment<br>Follow-up: 6 mo after treatment | No phenotypic or pigmentations change compared with baseline<br>Significant improvement in water evaporation from skin surface, skin elasticity, and dermal thickness and density compared with baseline |
| Wang et al, [35] 2018 | 30 | Prospective, randomized, double blinded, slit-face study | Each half of the face randomized to receive microneedling with either ASC-CM or ultrapure water<br>Every 2 wk for 6 treatments<br>Follow-up: 2 wk after final treatment | Significant improvement in melanin index, skin color, skin radiance, elasticity, periorbital skin relief in the experimental half compared with control<br>No significant difference in skin surface topography of the cheek between experimental and control groups |
| Prakoeswa et al, [36] 2019 | 48 | Prospective, randomized study | Randomized to receive microneedling followed by either AMSC-CM or normal saline<br>Every 2 wk for 3 treatments<br>Follow-up: 4 wk after final treatment | Significant improvement in pore, wrinkle, spot polarized and spot UV parameters in experimental group compared with control<br>No significant improvement in skin tone in either group |
| El-Domyati et al, [37] 2020 | 10 | Prospective, blinded, split-face study | AMSC-CM applied to right half of the face after full-face microneedling with dermaroller<br>Every 2 wk for 5 treatments<br>Follow-up: 4 wk after final treatment | Significant improvement in physician assessment in experimental half compared with control ($60.6 \pm 9.77$ vs $33.2 \pm 8.95$, $P<.001$) |

*Abbreviations:* ADSC-CM, adipose-derived stem cells conditioned medium; AMSC-CM, amniotic membrane SC–conditioned media; ASC-CM, ASC-conditioned medium; DMEM, Dulbecco's modified Eagle's medium; FBS, fetal bovine serum; hESC-EPC CM, human epidermal SC–derived endothelial precursor cells conditioned medium; RF, radiofrequency; SC, stem cell; SVF, stromal vascular fraction; TEWL, transepidermal water loss.

matrix metalloproteinase 1 by activating transforming growth factor-β [46]. An in vivo study on photoaged mice showed MSC exosomes from human umbilical cord can repair UV damage via proliferation of human dermal fibroblasts and reduction in proportion of senescent cells. In addition, MSC exosomes reversed the downregulation of dermal collagen I, elastin, and fibronectin and suppressed the upregulation of fibroblast matrix metallopeptidase 1 [12].

### Hair loss

Biomolecules carried by exosomes are involved in controlling the hair follicle cycle, thus targeted exosome therapy could play a role in hair disease. Although

few studies have focused on exosomes for hair growth, initial findings are promising [9].

Dermal papilla (DP) cells secrete growth factors, activate Wnt signaling, and promote differentiation of HFSCs; therefore, MSC exosomes from DP cells are hypothesized to promote hair growth [13]. Early studies showed that MSC EVs induced hair follicle conversion from telogen to anagen [47]. More recent studies demonstrate injecting MSC exosomes from human DP cells increase the anagen-to-catagen ratio in mice by delaying the transition from anagen to catagen via enhanced β-catenin expression [48]. Another study showed MSC exosomes from human DP cells increased the percentage of Ki67-positive cells in cultured hair follicles and induced hair follicles in mice by activating Wnt and bone morphogenic protein signaling [49].

### Other applications

Exosomes may have applications in other cosmetic domains such as fat grafting and pigmentary disorders.

MSC exosomes from adipocytes have been used in fat grafting to promote neovascularization and enhance survival of fat grafts [50]. A study involving exosomes from keratinocytes showed that tyrosinase, microphthalmia-associated transcription factor, and Rab27, which all play important roles in the pigmentation process, were increased in melanocytes in the presence of exosomes, thus enhance melanin synthesis by increasing both expression and activity of melanosomal proteins [51].

## POTENTIAL COMPLICATIONS AND LEGAL CONSIDERATIONS

The clinical studies outlined previously were carried out with minimal adverse effects, supporting the use of SCs and exosomes as a safe, minimally invasive tool gaining popularity in aesthetics. That being said, there remains a degree of uncertainty and controversy.

The multipotent nature of SCs has raised concerns about their possible effects on tumorigenesis with discordant results in the literature. Adult stem cells, including ASCs, have revealed tumorigenic properties in in vitro studies using breast and endometrial cancer cell lines [52–55]. These studies raised concerns that SCs may support malignant growth and metastasis through tumor tropism, enhancement of cell proliferation, and promotion of neovascularization. Interestingly, there are studies showing antitumor effects of SCs in in vitro and animal hematopoietic, breast, and pancreatic cancer models [56–59].

In addition, regulatory red tape continues to surround SC research and use. In the United States, the FDA regulates the use of SCs, which are considered human cells, tissues, and cellular and tissue-based products (HCT/Ps). The 361 registration is for homologous-use tissue, which refers to the repair, reconstruction, replacement, or supplementation of a recipient's cells that perform the same basic function in the recipient as in the donor. These products must be minimally manipulated, not combined with other agents, and collected and delivered at the same surgical setting. This is in contrast to the 351 drug pathway, which is for cellular or tissue products that do not meet the description of minimal manipulation. These products are typically cultured in a laboratory and processed in a way that alters its original form. Unlike the 361 registration, these products are required by the FDA to apply for an investigational new drug (IND), which can be costly and time-consuming. Physicians who choose to use these products before FDA approval must be part of the IND, and patient consent is required to participate in the experimental drug clinical trial, which is governed by an institutional review board.

Unfortunately, companies have been marketing SC and exosome products without approval by the US FDA. A company's SC product was found to contain no living SCs, but did contain *Escherichia coli* bacteria that caused sepsis in more than a dozen patients [60]. After similar issues from various companies, the FDA issued a warning in December 2019 alerting the public to be cautious of any claims, because there are no FDA-approved SC or exosome products, even under the 351 drug pathway. Over the next decade, a surge in exosome and SC products is inevitable, but it is imperative clinicians be abreast of the status of FDA approval to best promote patient safety.

## SUMMARY

SCs and exosomes are undoubtedly gaining momentum in aesthetics. Despite promising preclinical and clinical data, their role in cosmetics is still not fully understood. Large, randomized controlled trials are lacking Moreover, an enormous amount of heterogeneity exists in the studies with differences in purity and molecular phenotype of the stem cell and exosome sources. This heterogeneity makes it difficult to assess the actual efficacy of these products, which is one of thousands of cells in the experimental products. Moreover, their effects are often altered by the microenvironment, which is difficult to control. Nevertheless, the current preclinical and preliminary clinical studies will undoubtedly pave the way

for more advanced clinical trials to seal the fate of SCs and exosomes in the aesthetics arena.

## CLINICS CARE POINTS

- Early clinical studies have demonstrated stem cell therapy to be efficacious in the androgenetic alopecia and skin rejuvenation.
- In vitro and in vivo studies support the use of exosomes as a possible, novel treatment option for hair loss and skin rejuvenation.
- Lack of standardized protocols and randomized controlled trials serve as barriers to the use of stem cells and exosomes in aesthetics.

## DISCLOSURE

Shilpi Khetarpal MD is a consultant for Eclipse aesthetics and has received research equipment and honorarium. Khetarpal is also a speaker and trainer for Galderma and Allergan.

## REFERENCES

[1] Blau HM, Daley GQ. Stem cells in the treatment of disease. N Engl J Med 2019;380(18):1748–60.
[2] Takahashi K, Yamanaka S. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. Cell 2006;126(4):663–76.
[3] Wang JV, Schoenberg E, Rohrer T, et al. Stem cells in aesthetic dermatology: bioethical and professional obligations. Arch Dermatol Res 2019;311(10):833–5.
[4] Gimble JM, Katz AJ, Bunnell BA. Adipose-derived stem cells for regenerative medicine. Circ Res 2007;100:1249–60.
[5] Kapur SK, Dos-Anjos Vilaboa S, Llull R, et al. Adipose tissue and stem/progenitor cells: discovery and development. Clin Plast Surg 2015;42:155–67.
[6] Zuk PA, Zhu M, Ashjian P, et al. Human adipose tissue is a source of multipotent stem cells. Mol Biol Cell 2002; 13:4279–95.
[7] Zuk PA, Zhu M, Mizuno H, et al. Multilineage cells from human adipose tissue: implications for cell-based therapies. Tissue Eng 2001;7:211–28.
[8] Kapur SK, Katz AJ. Review of the adipose derived stem cell secretome. Biochimie 2013;95(12):2222–8.
[9] Carrasco E, Soto-Heredero G, Mittelbrunn M. The role of extracellular vesicles in cutaneous remodeling and hair follicle dynamics. Int J Mol Sci 2019;20(11):2758.
[10] Ferreira ADF, Gomes DA. Stem cell extracellular vesicles in skin repair. Bioengineering (Basel) 2018;6(1):4.
[11] McBride JD, Rodriguez-Menocal L, Badiavas EV. Extracellular vesicles as biomarkers and therapeutics in dermatology: a focus on exosomes. J Invest Dermatol 2017;137(8):1622–9.
[12] Zhang K, Yu L, Li FR, et al. Topical application of exosomes derived from human umbilical cord mesenchymal stem cells in combination with sponge spicules for treatment of photoaging. Int J Nanomedicine 2020;15: 2859–72.
[13] Ha DH, Kim HK, Lee J, et al. Mesenchymal stem/stromal cell-derived exosomes for immunomodulatory therapeutics and skin regeneration. Cells 2020;9(5):1157.
[14] Gentile P, Garcovich S. Advances in regenerative stem cell therapy in androgenic alopecia and hair loss: wnt pathway, growth-factor, and mesenchymal stem cell signaling impact analysis on cell growth and hair follicle development. Cells 2019;8(5):466.
[15] Fukuoka H, Suga H, Narita K, et al. The latest advance in hair regeneration therapy using proteins secreted by adipose-derived stem cells. Am J Cosmet Surg 2012; 29(4):273–82.
[16] Fukuoka H, Suga H. Hair regeneration treatment using adipose-derived stem cell conditioned medium: follow-up with trichograms. Eplasty 2015;15:e10.
[17] Shin H, Ryu HH, Kwon O, et al. Clinical use of conditioned media of adipose tissue-derived stem cells in female pattern hair loss: a retrospective case series study. Int J Dermatol 2015;54(6):730–5.
[18] Perez-Meza D, Ziering C, Sforza M, et al. Hair follicle growth by stromal vascular fraction-enhanced adipose transplantation in baldness. Stem Cells Cloning 2017; 10:1–10.
[19] Gentile P, Scioli MG, Bielli A, et al. Stem cells from human hair follicles: first mechanical isolation for immediate autologous clinical use in androgenetic alopecia and hair loss. Stem Cell Investig 2017;4:58.
[20] Elmaadawi IH, Mohamed BM, Ibrahim ZAS, et al. Stem cell therapy as a novel therapeutic intervention for resistant cases of alopecia areata and androgenetic alopecia. J Dermatolog Treat 2018;29(5):431–40.
[21] Gentile P. Autologous cellular method using micrografts of human adipose tissue derived follicle stem cells in androgenic alopecia. Int J Mol Sci 2019; 20(14):3446.
[22] Gentile P, Scioli MG, Cervelli V, et al. Autologous micrografts from scalp tissue: trichoscopic and long-term clinical evaluation in male and female androgenetic alopecia. Biomed Res Int 2020;2020: 7397162.
[23] Kuka G, Epstein J, Aronowitz J, et al. Cell enriched autologous fat grafts to follicular niche improves hair regrowth in early androgenetic alopecia. Aesthet Surg J 2020;40(6):NP328–39.
[24] Tak YJ, Lee SY, Cho AR, et al. A randomized, double-blind, vehicle-controlled clinical study of hair regeneration using adipose-derived stem cell constituent extract in androgenetic alopecia. Stem Cells Transl Med 2020; 9(8):839–49.

[25] Fukuoka H, Narita K, Suga H. Hair regeneration therapy: application of adipose-derived stem cells. Curr Stem Cell Res Ther 2017;12(7):531–4.
[26] Wong CH, Yoo HG, Kwon OS, et al. Hair growth promoting effects of adipose tissue-derived stem cells. J Dermatol Sci 2010;57(2):134–7.
[27] Kim WS, Park SH, Ahn SJ, et al. Whitening effect of adipose-derived stem cells: a critical role of TGF-beta 1. Biol Pharm Bull 2008;31(4):606–10.
[28] Kim WS, Park BS, Kim HK, et al. Evidence supporting antioxidant action of adipose-derived stem cells: protection of human dermal fibroblasts from oxidative stress. J Dermatol Sci 2008;49(2):133–42.
[29] Song SY, Jung JE, Jeon YR, et al. Determination of adipose-derived stem cell application on photo-aged fibroblasts, based on paracrine function. Cytotherapy 2011;13(3):378–84.
[30] Jeong JH, Fan Y, You GY, et al. Improvement of photoaged skin wrinkles with cultured human fibroblasts and adipose-derived stem cells: a comparative study. J Plast Reconstr Aesthet Surg 2015;68(3):372–81.
[31] Seo KY, Kim DH, Lee SE, et al. Skin rejuvenation by microneedle fractional radiofrequency and a human stem cell conditioned medium in Asian skin: a randomized controlled investigator blinded split-face study. J Cosmet Laser Ther 2013;15:25–33.
[32] Lee HJ, Lee EG, Kang S, et al. Efficacy of microneedling plus human stem cell conditioned medium for skin rejuvenation: a randomized, controlled, blinded split-face study. Ann Dermatol 2014;26(5):584–91.
[33] Zhou BR, Zhang T, Bin Jameel AA, et al. The efficacy of conditioned media of adipose-derived stem cells combined with ablative carbon dioxide fractional resurfacing for atrophic acne scars and skin rejuvenation. J Cosmet Laser Ther 2016;18(3):138–48.
[34] Amirkhani MA, Shoae-Hassani A, Soleimani M, et al. Rejuvenation of facial skin and improvement in the dermal architecture by transplantation of autologous stromal vascular fraction: a clinical study. Bioimpacts 2016;6(3):149–54.
[35] Wang X, Shu X, Huo W, et al. Efficacy of protein extracts from medium of adipose-derived stem cells via microneedles on Asian skin. J Cosmet Laser Ther 2018;20(4):237–44.
[36] Prakoeswa CRS, Pratiwi FD, Herwanto N, et al. The effects of amniotic membrane stem cell-conditioned medium on photoaging. J Dermatolog Treat 2019;30(5):478–82.
[37] El-Domyati M, Moftah NH, Nasif GA, et al. Facial rejuvenation using stem cell conditioned media combined with skin needling: a split-face comparative study. J Cosmet Dermatol 2020. https://doi.org/10.1111/jocd.13594.
[38] Pourang A, Rockwell H, Karimi K. New frontiers in skin rejuvenation, including stem cells and autologous therapies. Facial Plast Surg Clin North Am 2020;28(1):101–17.
[39] Fabi S, Sundaram H. The potential of topical and injectable growth factors and cytokines for skin rejuvenation. Facial Plast Surg 2014;30(2):157–71.
[40] Tonnard P, Verpaele A, Peeters G, et al. Nanofat grafting: basic research and clinical applications. Plast Reconstr Surg 2013;132(4):1017–26.
[41] Verpaele A, Tonnard P, Jeganathan C, et al. Nanofat needling: a novel method for uniform delivery of adipose-derived stromal vascular fraction into the skin. Plast Reconstr Surg 2019;143(4):1062–5.
[42] Marten TJ, Elyassnia D. Fat grafting in facial rejuvenation. Clin Plast Surg 2015;42(2):219–52.
[43] Bernardini FP, Gennai A, Izzo L, et al. Superficial enhanced fluid fat injection (SEFFI) to correct volume defects and skin aging of the face and periocular region. Aesthet Surg J 2015;35(5):504–15.
[44] Gennai A, Zambelli A, Repaci E, et al. Skin rejuvenation and volume enhancement with the micro superficial enhanced fluid fat injection (M-SEFFI) for skin aging of the periocular and perioral regions. Aesthet Surg J 2017;37(1):14–23.
[45] Kim YJ, Yoo SM, Park HH, et al. Exosomes derived from human umbilical cord blood mesenchymal stem cells stimulates rejuvenation of human skin. Biochem Biophys Res Commun 2017;493(2):1102–8.
[46] Hu S, Li Z, Cores J, et al. Needle-free injection of exosomes derived from human dermal fibroblast spheroids ameliorates skin photoaging. ACS Nano 2019;13(10):11273–82.
[47] Rajendran RL, Gangadaran P, Bak SS, et al. Extracellular vesicles derived from MSCs activates dermal papilla cell in vitro and promotes hair follicle conversion from telogen to anagen in mice. Sci Rep 2017;7(1):15560.
[48] Zhou L, Wang H, Jing J, et al. Regulation of hair follicle development by exosomes derived from dermal papilla cells. Biochem Biophys Res Commun 2018;500(2):325–32.
[49] Kwack MH, Seo CH, Gangadaran P, et al. Exosomes derived from human dermal papilla cells promote hair growth in cultured human hair follicles and augment the hair-inductive capacity of cultured dermal papilla spheres. Exp Dermatol 2019;28(7):854–7.
[50] Xiong M, Zhang Q, Hu W, et al. Exosomes from adipose-derived stem cells: the emerging roles and applications in tissue regeneration of plastic and cosmetic surgery. Front Cell Dev Biol 2020;8:574223.
[51] Lo Cicero A, Delevoye C, Gilles-Marsens F, et al. Exosomes released by keratinocytes modulate melanocyte pigmentation. Nat Commun 2015;6:7506.
[52] Zimmerlin L, Donnenberg AD, Rubin JP, et al. Regenerative therapy and cancer: in vitro and in vivo studies of the interaction between adipose-derived stem cells and breast cancer cells from clinical isolates. Tissue Eng A 2011;17(1–2):93–106.

[53] Zhang Y, Daquinag A, Traktuev DO, et al. White adipose tissue cells are recruited by experimental tumors and promote cancer progression in mouse models. Cancer Res 2009;69(12):5259–66.

[54] Linkov F, Kokai L, Edwards R, et al. The role of adipose-derived stem cells in endometrial cancer proliferation. Scand J Clin Lab Invest Suppl 2014;244:54–8.

[55] Kuhbier JW, Bucan V, Reimers K, et al. Observed changes in the morphology and phenotype of breast cancer cells in direct co-culture with adipose-derived stem cells. Plast Reconstr Surg 2014;134(3):414–23.

[56] Zhu Y, Sun Z, Han Q, et al. Human mesenchymal stem cells inhibit cancer cell proliferation by secreting DKK-1. Leukemia 2009;23(5):925–33.

[57] Qiao L, Xu ZL, Zhao TJ, et al. Dkk-1 secreted by mesenchymal stem cells inhibits growth of breast cancer cells via depression of Wnt signalling. Cancer Lett 2008;269(1):67–77.

[58] Sun B, Roh KH, Park JR, et al. Therapeutic potential of mesenchymal stromal cells in a mouse breast cancer metastasis model. Cytotherapy 2009;11(3):289–98.

[59] Cousin B, Ravet E, Poglio S, et al. Adult stromal cells derived from human adipose tissue provoke pancreatic cancer cell death both in vitro and in vivo. PLoS One 2009;4(7):e6278.

[60] Wan W, McGinley L. 'Miraculous' stem cell therapy has sickened people in five states. Washington, DC: The Washington Post; 2019. Available at: https://www.washingtonpost.com/national/health-science/miraculous-stem-cell-therapy-has-sickened-people-in-five-states/2019/02/26/c04b23a4-3539-11e9-854a-7a14d7fec96a_story.html. Accessed March 24, 2020.