Regenerative Medicine in Cosmetic Dermatology

Sucharita Boddu, MD; Peter W. Hashim, MD, MHS; John K. Nia, MD; Rebecca Horowitz; Aaron Farberg, MD; Gary Goldenberg, MD

PRACTICE **POINTS**
- Multipotent stem cells derived from the bone marrow, umbilical cord, adipose tissue, dermis, and hair follicle bulge show promise in tissue regeneration for various dermatologic conditions and aesthetic applications.
- Induced pluripotent stem cells, progenitor cells that result from the dedifferentiation of specialized adult cells, have potential for collagen generation.

Stem cell therapies are at the forefront of regenerative aesthetic medicine. Multipotent stem cells and induced pluripotent stem cells (iPSCs), progenitor cells that result from the dedifferentiation of specialized adult cells, have demonstrated promise in tissue regeneration for a wide range of dermatologic conditions and aesthetic applications. Herein, we review the potential of stem cells as a new frontier in aesthetic dermatology.

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Regenerative medicine encompasses innovative therapies that allow the body to repair or regenerate aging cells, tissues, and organs. The skin is a particularly attractive organ for the application of novel regenerative therapies due to its easy accessibility. Among these therapies, stem cells and platelet-rich plasma (PRP) have garnered interest based on their therapeutic potential in scar reduction, antiaging effects, and treatment of alopecia.

Stem cells possess the cardinal features of self-renewal and plasticity. Self-renewal refers to symmetric cell division generating daughter cells identical to the parent cell.[1] Plasticity is the ability to generate cell types other than the germ line or tissue lineage from which stem cells derive.[2] Stem cells can be categorized according to their differentiation potential. Totipotent stem cells may develop into any primary germ cell layer (ectoderm, mesoderm, endoderm) of the embryo, as well as extraembryonic tissue such as the trophoblast, which gives rise to the placenta. Pluripotent stem cells such as embryonic stem cells have the capacity to differentiate into any derivative of the 3 germ cell layers but have lost their ability to differentiate into the trophoblast.[3] Adults lack totipotent or pluripotent cells; they have multipotent or unipotent cells. Multipotent stem cells are able to differentiate into multiple cell types from similar lineages; mesenchymal stem cells (MSCs), for example, can differentiate into adipogenic, osteogenic, chondrogenic, and myogenic cells.[4] Unipotent stem cells have the lowest differentiation potential and can only self-regenerate. Herein, we review stem cell sources and their therapeutic potential in aesthetic dermatology.

Multipotent Stem Cells

Multipotent stem cells derived from the bone marrow, umbilical cord, adipose tissue, dermis, or hair follicle bulge have various clinical applications in dermatology. Stem cells from these sources are primarily utilized in an autologous manner in which they are processed outside the body and reintroduced into the donor. Autologous multipotent hematopoietic bone marrow cells were first successfully used for the treatment of chronic wounds and show promise for the treatment of atrophic scars.[5,6] However, due to the invasive nature of extracting bone marrow stem cells and their declining number with age, other sources of multipotent stem cells have fallen into favor.

Umbilical cord blood is a source of multipotent hematopoietic stem cells for which surgical intervention is not necessary because they are retrieved after umbilical cord clamping.[7] Advantages of sourcing stem cells from umbilical cord blood includes high regenerative power compared to a newborn's skin and low immunogenicity given that the newborn is immunologically immature.[8]

Another popular source for autologous stem cells is adipose tissue due to its ease of accessibility and relative abundance. Given that adipose tissue–derived stem cells (ASCs) are capable of differentiating into adipocytes that help maintain volume over time, they are being used for midface contouring, lip augmentation, facial rejuvenation, facial scarring, lipodystrophy, penile girth enhancement, and vaginal augmentation. Adipose tissue–derived stem cells also are capable of differentiating into other types of tissue, including cartilage and bone. Thus, they have been successfully harnessed in the treatment of patients affected by systemic sclerosis and Parry-Romberg syndrome as well in the functional and aesthetic reconstruction of various military combat–related deformities.[9,10]

Adipose tissue–derived stem cells are commonly harvested from lipoaspirate of the abdomen and are combined with supportive mechanical scaffolds such as hydrogels. Lipoaspirate itself can serve as a scaffold for ASCs. Accordingly, ASCs also are being utilized as a scaffold for autologous fat transfer procedures in an effort to increase the viability of transplanted donor tissue, a process known as cell-assisted lipotransfer (CAL). In CAL, a fraction of the aspirated fat is processed for isolation of ASCs, which are then recombined with the remainder of the aspirated fat prior to grafting.[11] However, there is conflicting evidence as to whether CAL leads to improved graft success relative to conventional autologous fat transfer.[12,13]

The skin also serves as an easily accessible and abundant autologous source of stem cells. A subtype of dermal fibroblasts has been proven to have multipotent potential.[14,15] These dermal fibroblasts are harvested from one area of the skin using punch biopsy and are processed and reinjected into another desired area of the skin.[16] Autologous human fibroblasts have proven to be effective for the treatment of wrinkles, rhytides, and acne scars.[17] In June 2011, the US Food and Drug Administration approved azficel-T, an autologous cellular product created by harvesting fibroblasts from a patient's own postauricular skin, culture-expanding them in vitro for 3 months, and reinjecting the cells into the desired area of dermis in a series of treatments. This product was the first personalized cell therapy approved by the US Food and Drug Administration for aesthetic uses, specifically for the improvement of nasolabial fold wrinkles.[18]

In adults, hair follicles contain an area known as the bulge, which is a site rich in epithelial and melanocytic stem cells. Bulge stem cells have the ability to reproduce the interfollicular epidermis, hair follicle structures, and sebaceous glands, and they have been used to construct entirely new hair follicles in an artificial in vivo system.[19] Sugiyama-Nakagiri et al[20] demonstrated that an entire hair follicle epithelium and interfollicular epidermis can be regenerated using cultured bulge stem cells. The cultured bulge stem cells were mixed with dermal papilla cells from neonatal rat vibrissae and engrafted into a silicone chamber implanted on the backs of severe combined immune deficient (SCID) mice. The grafts exhibited tufts of hair as well as a complete interfollicular epidermis at 4 weeks after transplantation.[20] Thus, these bulge stem cells have the potential to treat male androgenic alopecia and female pattern hair loss. Bulge stem cells also have been shown to accelerate wound healing.[21] Additionally, autologous melanocytic stem cells located at the hair follicle bulge are effective for treating vitiligo and are being investigated for the treatment of hair graying.[22]

Induced Pluripotent Stem Cells

Given the ethical concerns that surround the procurement and use of embryonic stem cells, efforts have been made to retrieve pluripotent stem cells from adults. A major breakthrough occurred in 2006 when researchers altered the genes of specialized adult mouse cells to cause dedifferentiation and the return to an embryoniclike stem cell state.[23] Mouse somatic cells were reprogrammed through the activation of a combination of transcription factors. The resulting cells were termed *induced pluripotent stem cells* (iPSCs) and have since been recreated in human cell lines. The discovery of iPSCs precipitated a translational science revolution. Physician-scientists sought ways to apply the reprogrammed cells to the pathophysiology of obscure diseases, examination of drug targets, and regeneration of human tissue.[24] Tissue regeneration via induced naïve somatic cells has shown promise as a future method to treat neurologic, cardiovascular, and ophthalmologic diseases.[25]

As the technology of cultivating and identifying optimal sources of iPSCs continues to advance, stem cell–based treatments have evolved as leading prospects in the field of biogerontology.[26-29] Although much of the research in antiaging medicine has utilized iPSCs to reprogram cell senescence, the altering of iPSCs at a cellular level also allows for the stimulation of collagen synthesis. This potential for collagen generation may have direct applicability in dermatologic practice, particularly for aesthetic treatments.

Much of the research into iPSC-derived collagen has focused on genodermatoses. Itoh et al[30] examined the creation of collagen through iPSCs to identify possible treatments for recessive dystrophic epidermolysis bullosa (DEB). Recessive DEB is characterized by mutations in the *COL7A1* gene, which encodes type VII collagen, a basement membrane protein and component of the anchoring fibrils essential for skin integrity.[31] Itoh et al[30] began with source cells obtained from a skin biopsy. The cells were dedifferentiated to iPSCs and then induced into dermal fibroblasts according to the methods established in prior studies of embryonic stem cells, namely with the use of ascorbic acid and transforming growth factor β. The newly formed fibroblasts were determined to be functional based on their ability to synthesize mature type VII collagen.[30] Once the viability of the iPSC-derived fibroblasts was confirmed in vitro, the cells were further tested through combination with human keratinocytes on SCID mice. The human keratinocytes grew together with the iPSC-derived fibroblasts, producing type VII collagen

in the basement membrane zone and creating an epidermis with the normal markers.[30] Similarly, Robbins et al[32] utilized SCID mice to successfully demonstrate that the transfection of keratinocytes from patients with junctional epidermolysis bullosa into SCID mice produced phenotypically normal skin.

Sebastiano et al[33] combined the concepts of iPSCs and genome editing in another study of recessive DEB. The investigators first cultured iPSCs from biopsies of affected patients. After deriving iPSCs and correcting their mutation via adenovirus-associated viral gene editing, the *COL7A1* mutation-free cells were differentiated into keratinocytes. These iPSC-derived keratinocytes were subsequently grafted onto mice, which led to the production of wild-type collagen VII and a stratified epidermis. Despite this successful outcome, the grafts of iPSC-derived epidermis did not survive longer than 1 month.[33]

One of the many obstacles facing the practical use of stem cells is their successful incorporation into human tissue. A possible solution was uncovered by Zhang et al[34] who examined iPSC-derived MSCs. Mesenchymal stem cells communicate via paracrine mechanisms, whereby exosomes containing RNA and proteins are released to potentiate a regenerative effect.[35] Zhang et al[34] found that injecting exosomes from human iPSC-derived MSCs into the wound sites of rats stimulated the production of type I collagen, type III collagen, and elastin. The wound sites demonstrated accelerated closure, narrower scar widths, and increased collagen maturity.

Understanding the role that local environment plays in stem cell differentiation, Xu et al[36] aimed to create an extracellular scaffold to induce fibroblast behavior from iPSCs. The authors engineered a framework similar to the normal extracellular membrane using proteoglycans, glycosaminoglycans, fibrinogen, and connective tissue growth factor. The iPSCs were then applied to the scaffolding, which led to successful fibroblast differentiation and type I collagen synthesis.[36] This use of local biosignaling cues holds important ramifications for controlling the fate of stem cells that have been introduced into a new environment.

Although the application of iPSCs in clinical dermatology has yet to be achieved, progress in the field is moving at a rapid pace. Several logistical elements require further mastery before therapeutics can be delivered. These areas include the optimal environment for iPSC differentiation, methods for maximization of graft survival, and different modes of transplanting iPSC-derived cells into patients. In cosmetic practice, success will depend on intradermal injections of collagen-producing iPSC-derived cells that possess long-term proliferative potential. Current research in mice models has demonstrated viability up to 16 weeks after intradermal injection of such cells.[37]

Plant Stem Cells
In discussing the dermatologic applications of stem cell technology, clinicians should be aware of the plant stem cell products that have become a popular cosmeceutical trend. Companies advertise plant cells as a natural source of regenerative cells that can induce rejuvenation in human skin; however, there are no significant data to indicate that plant stem cells encourage or activate cellular growth in humans. Indeed, for stem cells to differentiate and produce viable components, the cells must first be incorporated as living components in the host tissue. Because plant stem cells do not survive in human tissue and plant cell cytokines fail to interact with the receptors on human cells, their current value in cosmeceuticals may be overstated.

Platelet-Rich Plasma
Platelet-rich plasma also is commonly associated with stem cell therapy, as PRP is known to potentiate stem cell proliferation, migration, and differentiation. However, PRP does not contain stem cells and is instead autologous plasma concentrated with platelets. In fact, platelets cannot even be classified as cells given that they lack a nucleus; platelets are considered cell fragments. The regenerative potential of PRP can be attributed to the growth factors released from platelets, which play an important role in tissue regeneration and repair. Platelet-rich plasma currently is being used in dermatology for skin rejuvenation (reduction of wrinkles and furrows) and treatment of acne scars.[38] There also is evidence supporting the effectiveness of PRP for alopecia and wound therapy, as growth factors play a vital role in hair growth and wound healing.[38] Apart from the use of PRP on its own, it can be used as a supplement to enhance the effects of antiaging procedures such as microneedling.[39]

Future Directions
Multipotent stem cells and iPSCs discussed herein provide much promise in the field of regenerative dermatology. They are increasingly accessible and circumvent the use of ethically questionable embryonic stem cells. Although there is a general consensus on the great potential of stem cells for treating aesthetic skin conditions, high-quality randomized controlled trials remain scarce within the literature. Recognizing and optimizing these opportunities remains the next step in the future delivery of evidence-based care in regenerative dermatology.

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