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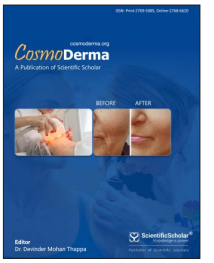

Review Article

Regenerative medicine in aesthetics

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Received : 13 April 2022
Accepted : 16 May 2022
Published : 01 June 2022

DOI
10.25259/CSDM_46_2022

Quick Response Code:

ABSTRACT

Regenerative medicine refers to the restoration of the form and function of damaged and diseased tissues by upregulation of natural regenerative processes present in the human body. Applications of regenerative medicine in dermatology are numerous, ranging from the acceleration of wound healing, hair restoration, mesenchymal stem cell augmented fat transfer, skin rejuvenation, enhancing results, and reducing downtime postprocedure and postlaser, etc. In modern aesthetic practice, the most prominent among current regenerative treatments are platelet-rich plasma (PRP), stem cells, growth factors, and most recently, exosomes. Most of the modalities available at present lack high-quality evidence supporting their use and good quality clinical trials are required for the optimization of cellular source, dose, and administration intervals before these modalities are deemed acceptable for use at a wider scale.

Keywords: Aesthetics, Regenerative, Stem cells, Platelet-rich plasma, Exosomes

REGENERATIVE MEDICINE IN AESTHETICS

Regenerative medicine can be defined as "an interdisciplinary field of research and clinical applications focused on the repair, replacement or regeneration of cells, tissues or organs to restore impaired function resulting from any cause, including congenital defects, disease, trauma, and aging." The idea behind regenerative medicine is to restore form and function to damaged and diseased tissues through biological approaches. Modern regenerative treatments work at the cellular level to upregulate natural regenerative processes present in the human body. Applications of regenerative medicine in dermatology are numerous, ranging from the acceleration of wound healing with platelet-rich fibrin (PRF), hair restoration, skin rejuvenation, mesenchymal stem cell augmented fat transfer, enhancing results, and reducing downtime postprocedure and postlaser, etc.

Regenerative medicine aims at understanding the cell to cell interactions and what drives them, in order to harness them for therapeutic use without causing injury. Procedures such as radiofrequency ablation and carboxytherapy employ natural healing mechanisms of the skin and may be considered a form of regenerative therapy. In modern aesthetic practice, the most prominent among current regenerative treatments are platelet-rich plasma (PRP), stem cells, growth factors, and most recently, exosomes. The idea is to develop safe and effective therapies which produce desired results either alone or in combination with existing therapies. Regenerative medicine is among the most rapidly growing branches of science, and knowledge regarding the basic principles of regenerative aesthetics is imperative among dermatologists and aesthetic practitioners.

STEM CELLS

The cardinal properties of stem cells, that is, self-renewal and plasticity have been utilized in the field of regenerative medicine. According to their differentiation potential, they may be categorized into totipotent, pluripotent, multipotent, and unipotent stem cells.[1] Totipotent and pluripotent stem cells are only found in the embryo and can differentiate into cell lines of all three germ layers. Derivation of embryonic stem cells (ESCs) requires disruption of the early embryo and is hence associated with several ethical concerns. Somatic cells from adults may be reprogrammed by activation of certain transcription factors to generate induced pluripotent stem cells.[2] Adult stem cells include multipotent and unipotent stem cells which have gained popularity in recent times due to their role in tissue maintenance and injury repair.

Umbilical cord blood is a source of multipotent stem cells that does not require surgical intervention for retrieval as it is obtained after clamping of the umbilical cord.[3] Sources of autologous stem cells include adipose-derived stem cells (ADSCs), hair follicle stem cells (HFSCs), dermal fibroblast-derived stem cells, and melanocyte stem cells.[4] ADSCs represent the most popular stem cells utilized in aesthetics due to their abundance, safety, and ease of harvesting.[5] A stromal vascular fraction (SVF) is obtained by centrifugation of aspirate obtained via liposuction.[6] In addition to adipocyte stem cells, SVF consists of preadipocytes, pericytes, hematopoietic progenitor cells, fibroblasts, myocytes, monocytes, endothelial cells, macrophages, and lymphocytes. ADSCs may be isolated from SVF or the SVF may be used directly for aesthetic procedures.

Stem cells in hair restoration

Stem cells are present in hair follicle bulge and dermal *papilla* and are essential for the normal hair cycle. Exogenous stem cells are an exciting approach to the management of androgenetic alopecia (AGA) due to their potential role in hair growth and regeneration. Several studies have utilized ADSCs as a remedy for AGA. A pilot case series of nine patients utilizing SVF-enhanced autologous fat transfer reported a 23% increase in hair density after 24 weeks.[7] A large study of 71 AGA patients (STYLE trial) compared two doses of ADSCs with autologous fat transfer and saline.[8] Low dose ADSCs were found to significantly improve hair density in the subgroup with early hair loss in this study. Topically applied ADSCs have also shown promise as a therapy for AGA.[9]

Other studies have utilized an ADSC-conditioned medium, which comprises a lyophilized form of protein secreted from cultured ADSCs amassed from healthy adults. This medium is rich in growth factors that enhance the longevity and multiplication of dermal papilla cells.[10] A significant increase in hair density on trichogram was noted after 3 monthly injections of this protein extract and noticeable improvements were seen clinically after 4–5 months.[11]

Other stem cell sources that have been used for AGA include HFSCs and bone marrow-derived mononuclear cells. HFSCs have been obtained by splitting and centrifugation of scalp biopsies, and a significant increase in hair count and density was observed as compared to placebo in split-scalp studies after three injections administered 45 days apart.[12] No significant difference in stem cell count and hair density was noted in a study that compared autologous HFSCs and bone marrow-derived mononuclear cells as stem cell sources.[13]

Stem cells in skin rejuvenation

ADSCs have been demonstrated to have a whitening effect, anti-oxidant action, and stimulate fibroblast proliferation in preclinical studies, suggesting their possible role in the treatment of skin aging.[14-17] This has been translated to clinical improvement in several studies, most of which combined stem cells with microneedling.[18] Zhou *et al.* compared the combination of ADSCs and fractional carbon dioxide laser with fractional carbon dioxide laser alone in a split-face trial of 13 patients with acne scars and nine patients with skin rejuvenation needs.[19] A higher improvement in patient satisfaction, skin elasticity, and hydration was noted in the combination group. Recently, nano fat emulsions have been utilized for facial rejuvenation.[20] These are obtained by mechanical emulsification of liposuction aspirate to yield a liquid solution. Other stem cells that have been utilized for facial rejuvenation include ESCs and amniotic membrane stem cells.[21,22]

Stem cells in wound healing

Stem cells possess the ability to induce cellular differentiation, regeneration, ability to release of growth factors, and immunomodulation. These properties may be useful in the management of chronic nonhealing ulcers. Among various cutaneous stem cell sources, SVF from adipose tissue has been used widely, due to its ability to differentiate into different components that may expedite wound healing, such as hematopoietic stem cells, fibroblasts, pericytes, endothelial cells, and preadipocytes. Garg *et al.* described the successful use of a combination of erbium YAG laser, PRP, and autologous fat transplantation in a patient with a recurrent trophic ulcer.[23]

Other dermatologic disorders in which stem cell therapy has been utilized include pemphigus, systemic sclerosis, systemic lupus erythematosus, psoriasis, vitiligo, and epidermolysis bullosa.[24] It must be noted that stem cell therapies are still in their nascent stages. Potential adverse effects such as rejection, malignant potential, uncontrolled

proliferation, cross-contamination with other cell lineages, and hyperimmune response cannot be ignored. No standard protocols are available for obtaining autologous stem cells, and as a result standardization and quality remain an issue. Large-scale studies and randomized controlled trials are necessary, along with strict regulatory oversight. Stem cells are currently not approved for commercial use in India and their use outside the purview of clinical trials is prohibited. Among dermatological disorders, the use of Hematopoetic Stem Cell Transplantation (HSCT) is permitted for children (but not adults) with systemic sclerosis.[24]

GROWTH FACTORS

Growth factors are chemical messengers that act by modifying the cellular microenvironment to enhance cell growth, differentiation, and tissue repair. PRP is a platelet concentrate derived from whole blood. It is rich in growth factors that modulate biological activities, including stimulation of stem cell proliferation and differentiation, angiogenesis, and collagen production. The growth factors secreted from PRP include (but are not limited to) transforming growth factor-β, platelet-derived growth factor, insulin-like growth factor-1 (IGF-1), hepatocyte growth factor (HGF), keratinocyte growth factor (KGF), epidermal growth factor and vascular endothelial growth factor. The biological characteristics of PRP depend upon the concentration of platelets and the method of preparation. Platelet concentration up to five times is generally considered adequate for its biological action, with higher concentration not necessarily producing better results.[25] No standard guidelines have been formulated for the preparation of PRP. On the basis of composition, PRP has been classified into pure PRP, leukocyte and PRP, pure PRF, and leukocyte and PRF.[26] PRP is currently being used in aesthetics for skin rejuvenation, hair restoration, and scar repair, usually combined with other procedures such as microneedling.

Growth factors in hair restoration

AGA is characterized by premature termination of the anagen phase of the hair cycle due to dysregulation of the β-catenin/WNT pathway. Growth factors in PRP are individually known to play important roles in the regulation of the hair cycle.[27–29] They act either by regulating of β-catenin/WNT pathway or by providing a permissive microenvironment for hair growth. The therapeutic efficacy of PRP in patients with AGA has been demonstrated in several clinical trials. A quantitative meta-analysis included 17 trials of PRP therapy in AGA, including both male and female AGA, monotherapy, and combination therapy. A significant increase in hair density was noted, from 141.9 ± 108.2 hairs/cm^2 at baseline to 177.5 ± 129.7 hairs/cm^2 at the end of the treatment period (P = 0.0004).[30] A significant positive correlation was observed between the number of treatment sessions per month and hair regrowth (r = 0.5, P = 0.03), while mean age was negatively correlated with the percentage change in hair density (r = -0.56, P = 0.016).[30] Most studies that recruited both men and women indicate that PRP treatment may be more effective in male AGA. Several randomized controlled trials have demonstrated synergistic effects of the combination of PRP with oral finasteride and topical minoxidil.[31-34] Overall, the evidence suggests that PRP is a safe and effective treatment for hair loss due to AGA.

Growth factors in skin rejuvenation

Tissue regeneration properties of PRP have been utilized for facial rejuvenation, both topically and as intradermal injections. Most of the clinical benefits have been reported by uncontrolled studies such as case reports and case series, many of which have failed to describe the method of PRP preparation and activation and lacked clearly defined endpoints. Efficacy in controlled studies with a high level of evidence has been less promising. A recent split-face study of 19 women compared the efficacy of lyophilized PRP with saline injection.[35] A higher increase in dermal thickness was observed with saline solution, with no difference in collagen synthesis among the two arms. The synergistic effect of PRP with hyaluronic acid was reported by another large trial, and significant improvement in skin elasticity and facial appearance was noted with the combination as compared to either therapy alone.[36] Increased concentration of growth factors has been observed to improve efficacy, although not in direct proportion to the concentration.[37] Microneedling with PRP and PRP injection can be combined, as the former improves skin texture while the latter improves volume by stimulating collagen production.

Growth factors in acne scars

Several studies have utilized PRP as an adjunctive treatment to microneedling and fractional carbon dioxide laser in acne scarring. A systematic review analyzing the utility of PRP in acne scarring concluded that two to three consecutive monthly sessions of PRP in combination with fractional carbon dioxide laser may improve the results and reduce postlaser downtime.[38] The evidence in support of microneedling and PRP combination is however scarce. Although some studies have reported improved results with a combination,[39–41] others have shown no added benefits.[42,43] It is notable that patients subjectively report higher satisfaction rates with a combination of PRP and microneedling owing to the reduction in post-procedure erythema and edema. Objective evidence regarding improvement of acne scarring with the combination is lacking.

Considered one of the safest aesthetic procedures and cures for all, the future of PRP is quite promising. The major limitation in the evaluation of therapeutic efficacy of PRP is the lack of standardized protocol for PRP preparation and

activation. Little is known about the biological action and tissue interactions of PRP. The need for repeated injections and lack of long-term safety and efficacy data are other limitations to PRP therapy.

EXOSOMES

Exosomes are cell-originated vesicular structures with a lipid bilayer membrane containing proteins, nucleic acids, and lipids secreted by various cells. They have been demonstrated to play an important role in cell-to-cell communication and modulation of cellular replication, differentiation, and apoptosis. Endogenic exosomes in the skin have been implicated in various chronic inflammatory skin diseases.[44] Exosomes derived from stem cells may have a potential therapeutic role in hair restoration by regulation of hair cycle, in skin pigmentation by modulation of melanin synthesis, in skin rejuvenation and scar repair by alteration of collagen synthesis.

Exosomes in scar repair

Exosome-mediated intercellular communication among macrophages, fibrocytes, and fibroblasts/myofibroblasts are essential for scar formation.[45,46] Blockade of exosome generation by M2 macrophages has been successfully used to suppress hypertrophic scar formation.[45] Hu *et al.* demonstrated the wound healing potential of adipose mesenchymal stem cells (ASC) derived exosomes in a mouse model.[47] ASCs-derived exosomes were internalized by fibroblasts and optimized their migration and replicative capabilities along with collagen and elastin production. Further exploration of the role of ASCs-derived exosomes revealed their role in extracellular matrix remodeling and scarless wound repair, by regulation of collagen type III to type I ratio, transforming growth factor (TGF)—β3 to TGF-β1 ratio, and matrix metalloproteinase-3 to tissue inhibitor of metalloproteinase-1 ratio, and by modulation of fibroblast differentiation.[48] Exosomes derived from other types of mesenchymal stem cells (MSCs), such as induced pleuripotent stem cells,[49] human menstrual blood-MSCs,[50] human umbilical cord MSCs,[51] human umbilical cord plasma cells[52] have also been demonstrated to modulate scar repair in mouse models.

Exosomes in hair restoration

Hair follicle stem cells and dermal papilla cells (DPCs) are essential for hair growth and maintenance of the normal hair cycle. Exosomes derived from DPCs have been observed to accelerate the onset of the anagen phase and delay catagen in mouse model.[53] Stimulation of β-catenin and the sonic hedgehog was observed, with enhanced stimulation and migration of outer root sheath cells. Increased hair shaft elongation was noted in another study, with increased expression of growth factors such as HGF, IGF-1, and KGF in DPCs.[54] DPC-derived exosomes may be a promising agent for the prevention and treatment of hair loss. Suspension mediums such as cryogel wound dressings[55] and hyaluronic acid patches [56] have been utilized to increase the efficiency and prolong the action of exosome injections in promoting hair regrowth.

Exosomes in skin rejuvenation

Regulation of the properties of human dermal fibroblasts (HDF) via exosomes may potentially have a role as an anti-aging therapy. Exosomes derived from HDF spheroids led to increased production of procollagen type I and decreased expression of matrix metalloproteinase-1 in a nude mice photoaging model, via upregulation of TGF-β and down-regulation of tumor necrosis factor-α.[57] Human-induced pleuripotent cell-derived exosomes amended changes of photoaging in HDFs by increasing collagen I production, reduction of expression of MMP-1/3, and downregulation of senescence-associated β-galactosidase production.[58] Embryonic stem cell-derived exosomes have exhibited amelioration of senescence via modulation of the TGF-β receptor 2 pathway in HDFs.[59]

Exosomes in skin pigmentation

Exosomes derived from keratinocytes have an important role in pigment production by melanocytes.[60] Keratinocyte derived exosomes had a high concentration of miR-330–5p which led to an increased expression of miR-330–5p in melanocytes, with the end result of decreased melanin production and tyrosinase gene expression.[60] Phototype-dependence and UV-B mediated modulation of miRNA profile of keratinocyte-derived exosomes was reported by Cicero *et al.*[61] Kim *et al.* reported stimulation of melanin production by inhibition of MITF expression by miR-675 from keratinocyte-derived exosomes.[62] Further studies on exosome-mediated interaction between keratinocytes and melanocytes present an exciting prospect for the regulation of pigment production in healthy and diseased states.

The promising field of exosomes is however not devoid of limitations. Lack of standardization in isolation, production, yield, and identification compromises the qualitative analysis of exosomes. Complete isolation of exosomes from the source is difficult, improvement in isolation techniques is desirable to improve yield and purity. The existing literature only pertains to preclinical studies and hence may not be predictive of human skin. The mechanism of exosomes and the biological information transmitted by them is quite complex and not entirely understood at present. As demonstrated by the pre-clinical data, exosomes derived from different sources may

have similar actions, which type of exosome produces higher clinical efficacy with fewer side effects remains to be explored.

CONCLUSION

The rapidly expanding realm of regenerative medicine is undoubtedly going to play an important role in the field of aesthetics. There is an increasing demand from patients as well as physicians for effective aesthetic procedures that are safe and harness the natural regenerative mechanisms of the human body. Most of the modalities available at present lack high-quality evidence supporting their use and good quality clinical trials are required for the optimization of cellular source, dose, and administration intervals before these modalities are deemed acceptable for use at a wider scale. We offer key insights into this exciting branch of science that may be the future of aesthetics in the coming decades.

Declaration of patient consent

Patient consent not required as there are no patients in this study.

Financial support and sponsorship

Nil.

Conflict of interest

Author Sunil Dogra is the Deputy Editor of the journal.

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How to cite this article: Mehta H, Bishnoi A, Dogra S. Regenerative medicine in aesthetics. CosmoDerma 2022;2:41.