



Point of View

The potential role of regenerative trichology in hair transplantation

Gulhima Arora¹, Venkataram Mysore²

¹Department of Dermatology, Mehektagul Dermaclinic, New Delhi, ²Department of Dermatology, The Venkat Centre for Skin, ENT and Plastic Surgery, Bengaluru, Karnataka, India.

***Corresponding author:**

Gulhima Arora,
Department of Dermatology,
Mehektagul Dermaclinic,
New Delhi, India.

gulhima@gmail.com

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ABSTRACT

Hair transplantation is an established surgical modality for alopecia but has its potential limitations of donor availability and the procedure not addressing the underlying mechanism of action of hair loss. A successful surgical outcome is synchronized with the long-term benefits by ensuring the maintenance of the health of transplanted hair follicles and their niche, adequately dealing with epigenetic factors, lifestyle components, and senescence. Combining regenerative modalities with hair transplantation increases the benefit of surgery by addressing these concerns to a promising extent. These modalities can be used before, during, or after the surgery to ensure the longevity of transplanted hair while maintaining the health of the scalp and existing hair. The regenerative therapies and treatments that can be harnessed are medical devices, stem cells, regenerative compounds, cell-based treatments, and biomaterials. Although the use and exact mechanisms of action of how these modalities work are still in the nascent stage and need standardization, several of them have been reported to enhance surgical outcomes. The article mentions the limitations and challenges faced with the use of these modalities and is presented to discuss the current and future potential role of these treatments with hair transplantation. It is put forth as a practice viewpoint for hair transplantation surgeons.

Keywords: Regenerative medicine, Regenerative trichology, Hair transplantation, Regenerative modalities, Platelet rich plasma

INTRODUCTION

Hair transplantation, which is an established treatment modality for alopecia, has ensured patients enjoy decades of transplanted hair post-surgery; however, it is imperative to maintain the health and longevity of this hair as well as of the existing hair for long-term benefits. The long-term success of this procedure is dependent upon conditions not only stemming from the surgery itself but also other factors, such as a healthy follicle microenvironment, epigenetic factors including lifestyle components and chronological aging, which affect not just the normal scalp hair, but also the transplanted hair. The recipient site influences may also affect the overall longevity of the transplanted hairs.¹ A good uptake of the new donor grafts is another factor that improves the overall clinical outcome of hair transplantation surgery.² Hair transplantation may also be a challenging surgery in terms of success rates in scarring alopecias where graft survival in scar tissue is unpredictable because of the underlying disease process.³

Regenerative modalities used with hair transplant surgery for improving the overall clinical outcomes have been suggested as potential options to deal with many of the above issues.⁴ They can be used pre-, intra-, or post-operatively to improve the clinical outcomes of surgery. These

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treatments have been viewed with great interest, partly because drug therapy has not made significant advances beyond minoxidil and antiandrogens and partly because surgery has potential limitations in donor availability, cost of surgery, and the progressive nature of the underlying hair loss process. This article reviews the topic in light of recent developments in regenerative trichology and discusses the current and future potential role of these treatments along with hair transplantation. It is clarified that with many of these therapies, evidence is still lacking; there is no standard protocol for the use of these treatments at present, and future developments will determine their precise utility and role. The cost of treatment due to additional intervention will also increase, although to improve the outcome of the surgery.

However, a hair transplant surgeon needs to be aware of the developments and their role in improving the outcomes of surgery.

REGENERATIVE TRICHOLOGY

Regenerative trichology involves three arms of the regenerative healing triad [Figure 1]. Either or all three of these arms can be harnessed to provide regenerative potential to the hair follicles. Hair transplant itself may be considered as a regenerative modality on account of it being an organ transplant. The different mechanisms of action by which regenerative modalities work which can be utilized with hair transplant are mentioned in Table 1. They present anti-inflammatory effects and anti-fibrotic effects, have an anti-apoptotic potential, are angiogenic, and support tissue remodeling.

PATHOPHYSIOLOGICAL BASIS FOR USING REGENERATIVE MODALITIES WITH HAIR TRANSPLANTATION

There may be several scenarios in hair transplant surgery wherein regenerative interventions may have a role and may involve both the donor, as well as the recipient sites.

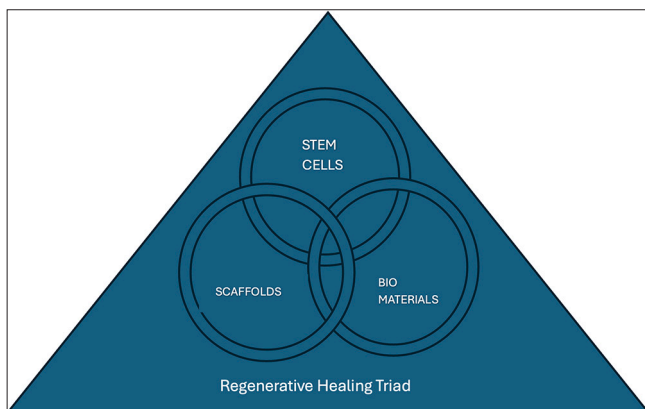


Figure 1: The three arms of the regenerative healing triad either or all of them may be used as potential regenerative modality.

Epigenetic factors

Transplanted hair is resistant to the effect of dihydrotestosterone (DHT)⁵ and may not miniaturize. However, other epigenetic factors and pathological causes may affect even transplanted hair. It is thus important to make sure that the functional viability of the transplanted hair follicles is maintained adequately. Transplanted hair, just like native hair follicles, may be prone to the effects of environmental factors such as pollution,⁶ poor diet, smoking, stress, sleep disturbance, excessive alcohol consumption, oxidative stress, and the effects of medications.

Senile alopecia

Chronological aging leads to the depletion of the stem cell pool of the hair follicles and may lead to a disrupted hair growth cycle, hair loss of transplanted hair, or weak and thin hair.^{1,7}

Miscellaneous

Other causes of hair thinning and weathering, such as hair products, styling, and heat treatments, may also affect the transplanted hair shaft.

The above etiopathological factors may lead to brittle and dull hair, abnormalities in the hair growth cycle, or hair loss. This renders a good surgery clinically ineffective and may lead to psychological distress in a patient.⁸

COMBINING REGENERATIVE MODALITIES WITH HAIR TRANSPLANTATION SURGERY

The indications in hair transplantation surgery for which regenerative treatments may be used are outlined in Table 2.

Preoperatively

The microenvironment of both, the donor as well as the transplanted areas can be enriched for better quality of and uptake of grafts, respectively. Natural biomaterials such as platelet rich plasma (PRP),⁹ injectable platelet rich fibrin (iPRF),¹⁰ cell-based therapies (CBTs) such as autologous micrograft transplant,¹¹ nanofat or stromal vascular fraction (SVF),^{12,13}

Table 1: Mechanisms of action of regenerative modalities in hair transplantation.

- They can improve hair density and counts (evidence is lacking, but they may improve)
- Improve trophic signaling
- Regenerate follicles or cause neofolliculogenesis
- Make the follicle niche conducive for hair growth
- Maintain anagen
- Modulate immunity

Table 2: The indications in hair transplantation surgery for which regenerative treatments may be used

Indication	Regenerative modality	Mechanism of action
1. Oxidative stress due to lifestyle and epigenetic factors	Regenerative compounds Medical devices Cell-based therapies Biomaterials Exosomes	Immunomodulation Trophic effects in the microenvironment
2. Scarring alopecias (hair transplantation is conducted only selected cases)	Stem cell transplant Cell-based therapies Biomaterials Exosomes Gene editing Tissue engineering	Anti-inflammatory, Replenishment of progenitor cells
3. Hair Senescence of transplanted hair	Stem cell transplant Bio cell transplant Regenerative compounds Medical devices Cell-based therapies Biomaterials Exosomes	Trophic effects in the microenvironment Replenishment of progenitor cells Stimulating hair growth cycle via signaling pathways
4. Donor area scarring	Medical devices such as carboxytherapy Cell-based therapies Biomaterials Exosomes	Anti-inflammatory
5. Maintaining existing hair in the recipient area	Stem cell transplant Bio cell transplant Regenerative compounds Medical devices Cell-based therapies Biomaterials Exosomes	Trophic effects in the microenvironment Replenishment of progenitor cells Stimulating hair growth cycle via signaling pathways
6. Strengthening transplanted hair	Regenerative compounds Medical devices Cell-based therapies Biomaterials Exosomes	Trophic effects in the microenvironment Stimulating hair growth cycle via signaling pathways
7. Maintaining donor hair area	Regenerative compounds Medical devices Cell-based therapies Biomaterials Exosomes	Trophic effects in the microenvironment Replenishment of progenitor cells
8. Donor area scarring	Exosomes Biomaterials Regenerative compounds	Improve the healing
9. Donor hair effluvium	Exosomes Biomaterials Regenerative Compounds	Maintain and initiate anagen Improve follicle niche
10. Maintaining the existing DHT-dependent follicles	Combining Hair transplant with hair cloning	Prolong the time for miniaturization as the cultured DP cells migrate to the base of the hair follicles and replenish the lost DP cells

DHT: Dihydrotestosterone, DP: Dermal papilla

regenerative devices such as erbium lasers,¹⁴ carboxytherapy¹⁵ or microneedling,¹⁶ and regenerative compounds such as peptides or exosomes¹⁷ can all be used. Pharmacotherapy with the use of vitamins, minerals, and micronutrients also helps with strengthening the microenvironment and making it more conducive for hair growth.¹⁸

Postoperatively

The potential remaining donor area of the scalp (for future sessions of transplant if needed), the used donor, and transplanted areas can be enriched with the above-mentioned regenerative therapies to tackle epigenetic factors that may adversely affect any area.¹⁹ Prescriptions of inorganic pharmacotherapeutic agents prevent adenosine tri phosphate (ATP) depletion for better graft survival.¹⁸

Intraoperatively

The harvested grafts can be placed in a growth-factor-rich medium or conditioned media as a holding solution for better survival.^{9,20}

EXPLORING REGENERATIVE THERAPIES FOR HAIR TRANSPLANT

Stem cell transplant

The hair follicle stem cells (HFSC) or the dermal papilla (DP) cells would be an ideal situation to restore the senescent stem cell pool or maintain the recipient or donor area. However, isolation is difficult, and culture is not only difficult but also prohibited from being performed without a good manufacturing procedure (GMP) certified facility and without being a part of a clinical trial.^{21,22} However, suspensions of a cocktail of progenitor cells sourced from hair follicles, epidermis, and dermis can be used instead.^{23,24}

Secretomes and conditioned media

Secretomes and conditioned media, which contain a number of growth factors, cytokines, progenitor cells, extracellular matrix proteins, shed receptors and other trophic molecules, can also be used.

Regenerative compounds

Regenerative compounds, which can be natural or engineered, are used to enhance the regenerative capacity of the hair follicle progenitor cells as well as nurture the microenvironment. These are mostly biomaterials, which are substances that have been designed to integrate with biological systems for medical purposes. Some natural and bioinert scaffolds prepared by tissue engineering may also act as regenerative compounds. Autologous blood-derived compounds such as PRP, iPRF,

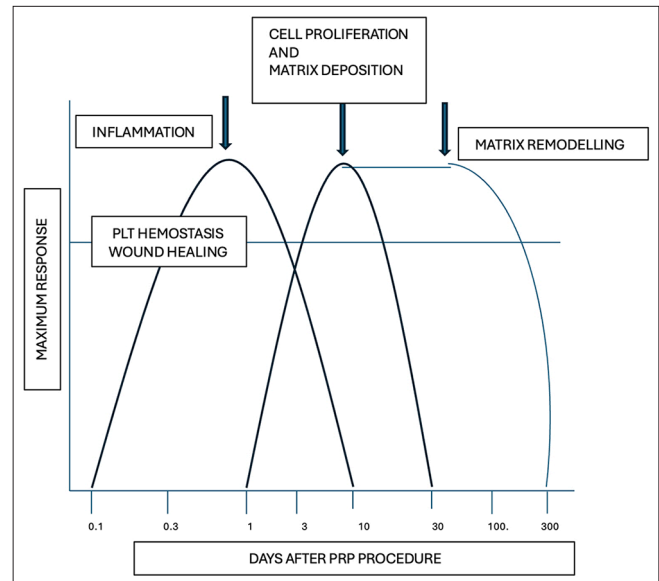


Figure 2: Platelet rich plasma - mechanism of action. PRP: Platelet rich plasma, PLT: Platelet

and growth factor concentrate are biomaterials and natural compounds. There are several studies to support the beneficial role of PRP as an adjunct to hair transplantation surgery. Reduced post-surgical erythema, crusting, and discomfort have been seen with the use of PRP as an adjunct.²⁵ Increased size of the follicular units and hastened hair growth have also been seen along with the use of vascular endothelial growth factor.²⁶ The use of PRP has even led to an increase in the yield of follicular units by 15.1%, with an increase of 480 hairs per cm².²⁷ Botulinum toxin is a synthetic regenerative compound which increases the scalp perfusion.²⁸ Peptides and engineered growth factors can be delivered to the scalp to improve hair follicle growth and make its niche more conducive for it.

Extracellular matrix scaffolds

Either alone or with biomaterials may also aid in regeneration, thus utilizing two arms of the regenerative triad.²⁹

Medical devices

That aid in regeneration include lasers such as erbium glass 1550 nm and erbium yttrium aluminum garnet (YAG) 2490 nm. Both have been shown to push the follicles into the anagen phase by stimulating the wnt/ β catenin pathways.³⁰ Other newer devices that use skin patting with acoustic waves along with controlled microdissection and infusion of growth factors through electroporation and the use of photothermal energy to stimulate platelets to release more growth factors and to produce autologous exosomes are now being used. Carboxytherapy, ionizing therapy, and smooth threads, although they have not yet been used in hair transplantation, can also be used to

increase the perfusion of the hair follicle and improve the microenvironment.^{31,32}

Cell-based therapy (CBT)

Involve the use of adult multipotent stem cells derived from the bone marrow, adipose tissue, or the skin. Since isolating and culture of HFSC is difficult, CBT is useful as it can be utilized after minimal manipulation and does not need GMP-certified facilities for their use.²² They are autologous and used in a single sitting along with the transplant. A stem cell cocktail, rather more of a progenitor cell cocktail with its niche in the form of micrografts, can be transplanted into the scalp to increase the hair follicle count and density. These autologous micrografts can be prepared manually using devices or filters and blades.^{23,33} Both micro-fragmented adipose tissue and SVF sourced from it can be used as trophic elixirs for hair follicles.^{12,22}

Exosomes

Exosomes are to regenerative cells what atoms are to molecules. They are the subsets of regenerative cells which bring about the actual action through immune modulation or paracrine signaling.³⁴ They carry cargos according to the parent cells they are sourced from. However, they can be engineered and loaded with specific cargos.³⁵ They have the advantage of being commercially available, topically delivered compounds, which have multiple benefits of being anti-inflammatory, immune-modulatory, and trophic for hair follicle growth.

Hair follicle cloning

The latest research in cloning of hair follicles holds a promising place in hair restoration. Cryopreserved hair follicles from DHT-resistant areas of the scalp are banked for future use. The DP cells from them are cloned (cultured) and injected into the dermis in the area of the scalp containing follicles which are actively miniaturizing but can be rejuvenated into forming terminal hair. This can be combined with hair transplantation surgery, which is done for areas where the cloned DP cells will not rejuvenate the existing hair follicles due to excessive loss of the existing DP cells (>2/3rd) in those follicles.³⁶

UNTOWARD EFFECTS OF USING REGENERATIVE MODALITIES

The use of regenerative therapies may be promising for better surgical outcomes; however, a cautious approach is advisable to prevent iatrogenic complications and be aware of existing limitations and challenges associated with some of them. There is excessive publicity of these products on social media

and hasty and aggressive promotion by commercial interests. Regulations and institutional clearances are still lacking for many of the products. Many of the products are still in the early phase of trials, and concrete evidence is lacking. Until greater evidence is sought and standard operating procedures are in place, hair transplant surgeons are advised to exercise caution while using such products³⁷⁻³⁹ and avoid medicolegal suits.

With the use of natural or engineered biomaterials such as PRP, one needs to be mindful of not performing the procedure before the inflammatory phase of the treatment subsides, as this may lead to an accumulation of pro-inflammatory cytokines released by the growth factors [Figure 2]. Care must ideally be taken not to exceed the red blood cell count in the preparation to over 1000/ μ mL, to avoid oxidative stress.⁴⁰ Repeated delivery at intervals shorter than 4 weeks with microneedling or injections can lead to potential scarring of the area.⁴¹

The exosomes used should have regulatory approvals for use and their source and purity verified. The cargo they carry is true to their parent cells, and their use does not always translate to positive downstream effects.⁴² It should be noted that there are currently no Food and Drug Administration-approved exosome products.⁴³ The use of cultured cells or adding a chemical or enzyme to progenitor cells is against regulations at point-of-care clinics. Only minimally manipulated adult multipotent cells which are washed, concentrated, or centrifuged can be used in translational medicine as progenitor cells, without being enrolled in a clinical trial.

The use of CBTs has several limitations, such as not knowing the dose of cells needed, methods of delivering them, ensuring their homing to the desired area, and developing better methods to culture them and their duration of action. Tumorigenesis is an undesired theoretical complication associated with the use of stem cells noted in animals. The pro-tumorigenic potential is due to the immunosuppression caused by them as well as providing chemoresistance to the cancer cells to thrive.⁴⁴

Limited evidence of the use of medical devices such as lasers, which help with regeneration, is present, but multiple sessions are needed, which may lead to non-compliance.³⁰

In view of the progressive nature of the underlying diseases, combination and rotational therapies may provide a solution.^{45,46}

CONCLUSION

Hair transplant is an established procedure for various types of alopecia. Standard practice guidelines need to be followed to ensure the safety and success rate of this surgery.

However, there are still many challenges to the short and long-term success of surgery. Maintaining the transplanted

hair, dealing with recipient site influences, preserving the donor's hair, and replenishing the progenitor cell pool to ensure the longevity and health of the transplanted hair are a few such challenges. Combining regenerative therapies with hair transplants bridges the gap between a well-performed surgery and its overall clinical outcome and success. A hair transplantation surgeon should be aware of the existing regenerative modalities and their potential role along with surgery to tackle its limitations. However, more research and studies are needed to advocate their substantial role.

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