Future Horizons in Hair Restoration

Bryan T. Marshall, PhD[a], Chris A. Ingraham, PhD[a], Xunwei Wu, PhD[a], Ken Washenik, MD, PhD[a,b,c,*]

KEYWORDS

• Cell therapy • Trichogenicity • Regenerative medicine • Dermal papilla • Hair follicle • Induced pluripotent stem cells (iPS) • Hair transplantation

KEY POINTS

- Hair follicles can be regenerated from cultured cells.
- Culture conditions impact the trichogenic property of cells.
- The delivery method impacts the potential for a cell-based therapy to produce follicle outgrowth.
- Advances in cell biology provide the possibility of follicle regeneration from additional cell sources.

INTRODUCTION

The most common form of hair loss is androgenetic alopecia (AGA). Those affected by AGA display an increased sensitivity to androgens, which leads to reduced follicular diameter. Orientreich[1] was the first to show that transplanted hair follicles retain the characteristics of their original location (namely androgen resistance when placed into an androgen-sensitive area). This concept is termed donor dominance. The growth pattern dominance of the follicular origin over recipient site placement has enabled surgical hair transplantation to be one of the most effective treatments to date. Despite the effectiveness of modern hair transplantation, there are challenges associated with this method such as the limitation of donor hair follicles. Currently, medical treatments attempting to bypass the need for additional donor follicles include minoxidil, a potassium channel agonist, and finasteride, an inhibitor of 5 alpha- reductase.[2] These drug therapies require continual use and can be associated several adverse effects. More recently, hair loss therapies based on the cellular components of hair follicles and the growth factors that drive the behavior of those cells have become foci of research efforts. Autologous cell-based therapies offer a unique solution requiring the potential of single treatment and the possibility of no significant systemic adverse effects. Several advances have been made in the fields of stem cell biology and regenerative medicine in the last decade. These advances have laid the foundation to develop new strategies to treat hair loss. The possibility now exists to harvest a small number of hair follicles from the occipital area of the patient, expand the trichogenic, or hair follicle growth-inducing, cell population from this tissue, and transfer these cells back to the patient as a regenerative treatment. Aderans Research Institute Incorporated (ARI, Marietta, GA) and Replicel Life Sciences Incorporated (Vancouver, Canada) are currently conducting separate clinical trials with cell-based solutions for alopecia. Similar clinical trials have also been undertaken by Intercytex, Incorporated. Additionally, Histogen Incorporated (San Diego, CA) and Follica Incorporated (Cambridge, MA) are both conducting phase 1 clinical trials exploring the use of

Disclosures: The authors have a royalty agreement with the Aderans Research Institute should future revenue result from the sale of this technology.

[a] Aderans Research Institute, 2211 Newmarket Parkway, Suite 142, Marietta, GA 30067, USA; [b] Bosley, 9100 Wilshire Boulevard, East Tower Penthouse, Beverly Hills, CA 90212, USA; [c] Department of Dermatology, New York University School of Medicine, 550 First Avenue, New York, NY 10016, USA

* Corresponding author. Bosley, 9100 Wilshire Boulevard, East Tower Penthouse, Beverly Hills, CA 90212.
E-mail address: washenik@bosley.com

Facial Plast Surg Clin N Am 21 (2013) 521–528
http://dx.doi.org/10.1016/j.fsc.2013.05.005
1064-7406/13/$ – see front matter

molecular growth factors aimed at the reinvigoration of dormant follicles. These small molecules are known agonists of follicular formation and growth pathways (eg, Wingless-related integration site [WNT], Sonic hedgehog [SHH], and fibroblast growth factors [FGF]).

Unlike most organs, hair follicles do not reach homeostasis once they mature. Instead there is a continuous cycle of growth, regression, shedding, and regeneration throughout life.[3] This inherent ability of hair follicle cycling lends credence to the idea of regenerative cell populations existing in the hair follicle itself. Several groups have demonstrated regeneration of hair follicles using cells dissected from the dermal papilla and dermal sheath of the hair follicle,[4–10] as well as follicular epidermal cells to form all lineages of the hair follicle[11,12] in animal models. This article addresses the history of hair follicle regeneration from follicular fragments and dissociated cells. The challenges of trichogenic in vitro culture and subsequent delivery into the patient are discussed, as well as cosmetic acceptance, recent achievements on regeneration of human hair follicles, and new potential cell sources (skin derived precursor cells [SKPs], Induced pluripotent stem cells [iPS]) for hair regeneration.

REGENERATION OF THE HAIR FOLLICLE FROM DISSECTED FRAGMENTS

One solution to increase the number of possible donor follicles is to divide up the hair follicle into dissected fragments in the hope that upon transplantation each fragment would develop into a complete follicle. While horizontal division of the hair follicles[13] has resulted in a complete hair follicle from the upper two-thirds, the lower one-third was not able to produce a follicle. A second study using transverse division[14] produced hair follicles from only one of the upper implants. The studies of these approaches were limited in size.

Another approach, using microdissected follicular dermal papillae (DP) or connective tissue sheaths (CTS),[4–10] was able to regenerate follicles upon insertion into afollicular skin. In people, the transplantation of male scalp dermal sheath (DS) fragments into female forearm skin resulted in follicular growth with male dermal lineage.[15]

The major caveat to these methods is the poor efficiency of regeneration (ie, they did not result in increase in the resultant number of hairs compared with the number of follicles used). The numbers of hairs were not increased, because at least 1 DP, DS, or CTS is required to form a new hair follicle. Hence, the major contribution of this research was the realization that cells within dissected follicular fragments are able to reorganize and induce new hair follicles or follicular growth. These experiments prompted additional research investigating the cells derived from these follicular fragments and the development of in vitro culture methods directed at trichogenic cell proliferation and maintenance of their inductive capabilities.

REGENERATION OF THE HAIR FOLLICLE FROM DISSOCIATED CELLS

A second approach, designed to create more hair follicles from the same number of donor follicles, consists of dissociated cell culture. Regeneration using dissociated cells has been tested in various models, mostly involving embryonic and neonatal mouse cells. The chamber assay[16,17] uses dissociated mouse neonatal dermal (MND) and mouse neonatal epidermal (MNE) cells combined (to a total of 10 million cells) and delivered into a silicon chamber already grafted onto the back of an immunocompromised (nu/nu) mouse. After 1 week, the chamber is removed to ultimately yield tufts of mouse hair on the back of the host mouse after 1 month, thereby indicating the trichogenic potential of the cells (**Fig. 1**). Zheng and colleagues[18] reported on the patch assay in 2005, which consists of a mixture of MND and MNE injected into the dermis of nu/nu mouse dorsal skin to generate hair after 10 to 14 days. Upwards of 10 samples were injected into a single mouse, with each injection using only 2 million total cells. Variations included placement of the cells into a kidney capsule or into a trachea.[12,19,20] In 2008, Qiao and colleagues[21] used a flap assay (a modification of the chamber assay) involving the use of a skin flap.

Recently, Lee and colleagues[22] combined aspects of the chamber assay and trichogenic patch assay to create a reconstituted hair assay in a nu/nu mouse model. Hair was formed using

Fig. 1. Chamber assay. Mouse neonatal epidermal and dermal cells were isolated and delivered (at a concentration of 10×10^6) into a silicon chamber implanted in the dorsal region of a nu/nu mouse to generate a tuft of hair (1 week = chamber removed, 4 weeks = assay completed). (*Courtesy of* Aderans Research Institute Inc., Marietta, GA; with permission.)