Review Article

Stem Cell Therapy and Hair Loss: Present Evidence and Future Perspectives

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Abstract

Stem cells may have potential as a treatment for regenerating hair. Initially, methods to obtain stem cells have concentrated on isolating the primary cells from the tissue of interest through biopsy and growing these cells outside the body to be transplanted into the patient. Stem cell treatment of nonautoimmune hair loss like androgenetic alopecia is promising. Although an autologous transplant is viewed as the standard, its use is limited because of a lack of data and the diminished viability of cells that are made available using this method. Adipose-derived stem cells are a promising alternative because of their limited immunogenicity. They are easy to obtain, are multipotent, and can differentiate into different cell lines. They also have significant potential for angiogenesis. More studies are needed to establish the efficacy of the various types of stem cell-based treatments for people with hair loss.

Keywords: Hair, hair follicles, hair growth, hair loss, stem cell treatment, stem cells

Introduction

Alopecia is a common hair loss disorder that may be due to hereditary factors, medical conditions, hormonal imbalances, autoimmune disorders, nutritional problems, environmental factors, psychological stress, and aging. All these damaging factors affect the hair cycle and reduce stem cell activity and the regeneration of hair follicles.[1] Alopecia is not painful or life-threatening; however, there can be skin irritation and physical problems brought about by the loss of hair, not only on the scalp but also in the eyelashes and eyebrows.[2] Alopecia that is due to chemotherapy, though having a different etiology, can also bring about anxiety and identity issues.[3]

Alopecia may have a few physically damaging effects; however, it may lead to psychological outcomes, such as anxiety and depression. Medical treatment for this disorder is not very much effective, and this inability to discover the right treatment can leave patients very distressed.[3]

Hair follicles have mature epithelial and melanocyte stem cells, also known as hair follicular stem cells (HFSCs), contained in a bulge in the attachment area of arrector pili muscles. In addition, HFSCs are likewise located inside the outer root sheath inside the area of the proximal end of the isthmus. HFSCs are involved in the regeneration of epidermal cells and the structure of hair follicles and sebaceous glands.[4] In the scalp of those with hair loss, the numbers of hair follicle stem cells remain unaltered, although there is a decrease in actively proliferating progenitor cells.[5] Thus, hair stem cell treatments are promising new treatments for hair loss. Hair stem cell treatments include the advancement of new autologous advances to include hair regrowth *in vitro* and *in vivo* through regeneration and stimulation.

Stem cells may have potential as a treatment for regenerating hair. Initially, methods have concentrated on isolating the primary cells from the tissue of interest through biopsy and growing these cells outside the body to be transplanted back into the patient.[5] Stem cells are a promising approach for the treatment of nonautoimmune hair loss like androgenetic alopecia. First, hair follicles are easily accessible and observable. Next, the anatomy and physiology of hair follicles are well studied. In addition, hair follicles and its derived cells have been cultured *in vivo* and autologous transplantation of

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hair follicles is widely done. The hair follicle is a self-renewing miniorgan with numerous stem cells at the bulge area and dermal sheath. Due to this, pluripotent, multipotent, and adipose-derived stem cells (ADSCs) have potential as cell-based treatments for hair loss.[6]

The regeneration of hair follicles relies upon well-organized interactions between epithelial receptors and mesenchymal parts. In the past, various epithelial and mesenchymal parts were consolidated and grafted *in vivo* to enhance interactions between them. Hypothetically, hair follicle stem cells could effectively yield hair follicles in typical assays. Thus, hair follicle stem cells were demonstrated to be beneficial materials for the regeneration of hair follicles.[6] This article aims to review the use and potential of hair follicle stem cell treatment in alopecia.

Methods

A systematic search for literature was done using PubMed. The keywords "stem cell hair loss" and "hair stem cells" were used. The studies were limited to those published in English, but the study location can be worldwide. Studies were included if they were the application of stem cells in hair loss. Only free full-text articles were included. The author narratively described the major findings and conclusions from individual studies. Out of the 849 studies reviewed, only 24 studies fit the criteria.

Results

Background

The dermal papilla lying at the base of the hair follicle is rich in multipotent stem cells and gives out signals that influence the growth and actions of young cells. After birth, the hair follicles undergo cyclical growth. During catagen, the epithelial cells at the base of the follicle undergo death, but the dermal papilla remains intact and is pulled upward, until it is placed next to the stem cells located in the hair follicle bulge. This continues on during telogen. During anagen, the cells at the base of the follicle begin to grow and multiply, further resulting to the downward growth of the follicle into the dermal papilla [Figure 1]. If β-catenin signaling in the dermal papilla is interrupted, there is reduced proliferation of cells at the follicle's base, further inducing the catagen stage while further preventing the start of anagen. This causes alopecia.[7]

Types of stem cells for hair renegeneration

Stem cells are classified according to their plasticity. The classes into which they fall include: the multipotent stem cells, pluripotent stem cells, totipotent stem cells, and the adult stem cells which are a certain type of multipotent stem cell [Figure 2]. Studies on hair regeneration as of present have dwelt more on the use of pluripotent and multipotent stem cells and adipose tissue-derived stem cells.[8]

Autologous stem cells

Cellular therapy is being studied for alopecia in the form of autologous dermal papillae (DP) cells to induce hair follicular

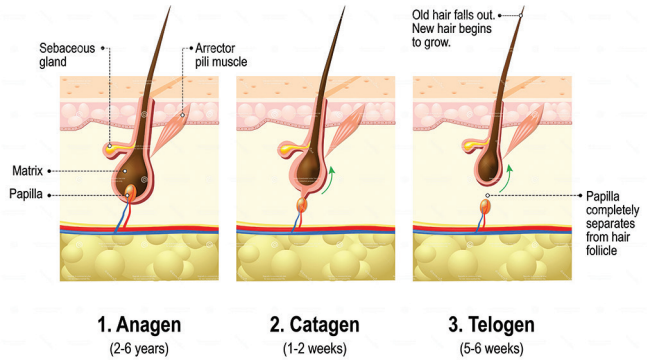

Figure 1: The hair growth cycle. In the anagen phase, the cells at the hair follicle base are actively growing, and the follicle grows into the dermal papilla. During catagen, the dermal papilla is still intact and is pulled upward until it is next to the stem cells in the budge. Alopecia is due to the decreased growth of cells during anagen. Source: Driskell RR, Clavel C, Rendl M, Watt FM. Hair follicle dermal papilla cells at a glance. J Cell Sci 2011;124:1179-1182

regeneration. Pluripotent stem cells may be coaxed into hair follicle lineages to promote hair growth.[9,10] Although an autologous transplant is viewed as the standard, its use is limited because of a lack of data and the diminished viability of cells that are made available using this method. As of now, techniques are being improved which improve the viability of autologous stem cells of the hair follicle.[1]

Cells can retain phenotypes and the ability to create hair follicles even after passing through bioreactors. Furthermore, the efficacy is five times higher than static cultures. This shows promise in the treatment of alopecia.[11] Cells that were obtained from the hair bulge can enhance hair thickness in patients with androgenic alopecia. In this method, cells were isolated without culturing. Increased hair thickness was seen in 11 men aged 38–61-year-old with androgenic alopecia. Following 23 weeks of treatment, the number of hairs and their thicknesses expanded by 29% ± 5% than the baseline in the treated area.[12]

The potential for regeneration of cultured dermal papilla to encourage the growth of a hair follicle was studied in the skin of mice. At first, dermal papilla cells (DPCs) were seen to grow with the expression of CD200, and these fusiform cells formed colonies in three to 5 days. After 2 weeks, they gained a passaging capability and formed an extracellular matrix after the third passaging. Histopathological examination in rodents showed that structures changed into hair follicles at the areas of infusion in the dermis.[13]

Autologous bone marrow mononuclear cells and stem cells were used to treat refractory patchy alopecia and androgenic alopecia. Cells were given in a solitary application, and 1 ml in a density of 100,000 cell/ml was infused with a needle per centimeter square of the treated site. There was significant improvement in the treated sites. Stem cell effects were similar, though they were from different sources.[14]

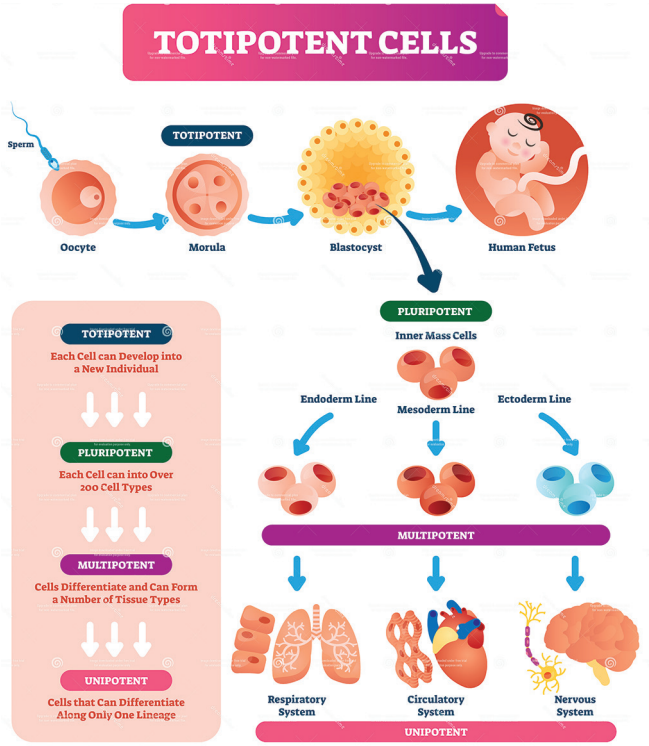

Figure 2: During natural embryo development, cells undergo proliferation and specialization from the fertilized egg, to the blastocyst during natural embryo development. Pluripotent, embryonic stem cells are derived from the inner cell mass of the blastocyst. Multipotent stem cells are found in the developing embryo or derived from pluripotent stem cells and are restricted to give rise to only cells of their respective germ layer. Source: Biehl JK, Russell B. Introduction to stem cell therapy. J Cardiovasc Nurs 2009;24:98-105

Autologous-induced pluripotent stem cells (iPSCs) are engineered stem cells that have been created from mature body cells by way of transduction of four reprogramming transcription factors which are mostly found in embryonic stem cells (ESCs). These factors are cMYC, SOX2, OCT4, and KLF4. iPSCs have certain growth characteristics and can differentiate in a manner that is similar to those of ESCs. These stem cells can be genetically modified to treat hair loss and are able to provide an unlimited source of specific cells for hair regeneration.[8]

Human iPSC-derived Ectodermal presursors (hiPSC-EPCs) can interact better with human DPCs than the WD39 and WDT2 cell lines when cultured together; these cells were able to contribute to hair morphogenesis *in vivo*. When converted to EPCs and brought in contact with human DPCs, 201B7 activated all follicular keratinocyte genes and biomarkers in the dermal papilla examined. Wingless-related integration site (WNT) and Sonic hedgehog signaling pathway (SHH) signaling are essential in hair follicle development. 201B7 hiPSC-EPCs when in a WNT-activated state may achieve greater hair follicle regeneration.[15]

Adipose-derived stem cells

ADSCs appear as an ideal cell population in regenerative medicine because there may be minimal immunogenic properties. They are also easy to obtain, are multipotent, and can easily differentiate into different cell lines. They also have significant potential for angiogenesis. These cells have appeared to be from mural cells situated in the perivascular areas, vascular smooth muscle cells, and pericytes. These cells are involved in the development of blood vessels and are receptive to vesicular endothelial growth factor (VEGF).[16]

As of present, there are no known tissue regeneration protocols for hair transplantation using ADSCs. Zanzottera *et al*. analyzed the capabilities of autologous cell suspensions in the Rigenera System which were from the mechanical fragmentation of subcutaneous and fat tissue from the occipital area. The cell suspension was placed in the hair transplant area, thus increasing growth factors. There was observed faster healing of microdamage and the faster growth of transplanted hair even 2 months after the procedure, with a shorter telogen phase.[17]

In a retrospective, observational study of outcomes in 27 patients with female pattern hair loss (FPHL) treated with ADSC-conditioned medium (CM), ADSC-CM was effective in treating FPHL after 12 weeks of therapy. There was increase in hair density from 105.4 to 122.7 hairs/cm in patients. There was also increase in hair thickness from 57.5 µm to 64.0 µm. There were no severe adverse reactions reported. The application of ADSC-CM is a potential treatment option for FPHL.[18]

In another study by Fukuoka and Suga, changes in hair numbers were measured using trichograms and the efficacy of ADSC-CM on hair growth was evaluated. ADSC-CM was given to 22 alopecia patients (11 men and 11 women) intradermally. Treatment was given every 3–5 weeks for a total of 6 sessions. Trichograms were taken before and after treatment to count hair numbers. Hair numbers were increased significantly after treatment in both male and female patients. Treatment using ADSC-CM appears highly effective for alopecia and may represent a new therapy for hair regeneration.[19] Won *et al*. likewise demonstrated that the use of ADSC-CM encouraged the growth of human DPCs by up to 130%.[20]

A clinical series by Perez-Meza *et al*. showed that enhancing fat tissue with a stromal vesicular part bolsters adipocyte viability and yields better results for a hair transplant when they are available in grafts. In this study, lipoaspirate from abdominal fat was given to the scalp at 1.0 ml/cm^2. Hair increased by 23% after 6 months.[21]

Embryonic stem cells

Human ESCs (hESCs) were activated to first create neural cells and then into hair-inducing DP-like cells in culture. hESC-derived DP-like cells express markers typically found in adult human DP cells and are able to encourage the growth of hair follicles when transplanted under the skin of mice. These hESC-derived dermal papilla-like cells were placed into the dermal papilla of newly formed hair follicles, and appropriate markers were expressed. Prior to the study, the knowledge

that DP cells were proposed as the cell-based treatment for hair loss diseases initially struck the researchers; however, they are not suitable for this purpose because they cannot be obtained in needed amounts, and they can rapidly lose their ability to induce hair follicle formation when they are cultured. Functional hESC-DP cells are capable of inducing greater hair growth for the treatment of alopecia.[22]

Cord blood stem cells

Wharton's jelly is a gel-like substance that is present inside the umbilical cord and in the vitreous humor. It has become a good source of stem cells because it is widely available from many donors, it is noninvasive and painless and offers no risk to the donor. There are also no ethical considerations, has a weak immunogenic potential, and can grow and differentiate easily. Furthermore, it carries a minimal risk for infections.[23]

In 2013, two studies exhibited that it is possible to get cells with cytokeratin 19 (CK19) expression and hair-like structures from WJMSC *in vitro*. CK19 is a marker of bulge stem cells which reflects the regeneration capability of altered skin.[24,25]

Yoo *et al*. analyzed the impact of human Wharton's jelly stem cell (hWJSC) on faster wound healing and the growth of hair follicles. Enriched hWJSC cells were able to create new hair follicles. Growth factors may be added to the culture medium, such as hepatocyte growth factor which enhances hair follicle growth, basic fibroblast growth factor (bFGF) which enhances DPC growth, and VEGF which also enhances hair follicle growth.[26]

In addition, the effects of bone marrow and umbilical cord stem cells to dermal papilla-like tissue growth were examined. Cells of the outer sheath of the hair were utilized for incubation and infused into the skin of mice. The mice were then studied after 6 weeks. Accordingly, hair follicle development was observed.[27]

Wu *et al*. showed that the potential for hMSC from human embryos to DPCs in hMSC cultures utilizing DPCs acquired from patients. Versican, CD133, stem cell factor, endothelin-1, and fibroblast growth factor expressions were seen during differentiation.[28]

Li *et al*. in 2015 have previously described a new type of stem cell from human umbilical cord blood which is known as cord blood-derived multipotent stem cell (CB-SC). CB-SCs are different from other types of stem cells functionally and genetically such as monocyte-derived stem cells hematopoietic stem cells, endothelial progenitor cells (EPCs), and mesenchymal stem cells (MSCs). According to the authors, clinical data have demonstrated that a single treatment was able to provide balanced immune responses that allowed the regeneration of hair cells. Their study focused on the therapeutic potential of Stem Cell Educator therapy in alopecia areata patients.[29] The authors created a Stem Cell Educator therapy, wherein patient's blood is circulated through a closed-loop system that could separate mononuclear cells from whole blood further allowing cells to briefly interact with human CB-SCs and to return the "educated" cells to the patient's blood circulation. The results showed that patients with severe alopecia areata achieved improved hair regrowth and quality of life after they received Stem Cell Educator therapy. Immunohistochemistry revealed the formation of a "ring of transforming growth factor-beta 1" around hair follicles, leading to the restoration of immune balance in the hair follicles and the protection of newly created hair follicles against destruction by the body's own cells.[29]

Conclusion

The hair follicle is an interesting organ. The application of stem cells in hair regeneration is promising because these stem cells can lead to follicle regeneration. Stem cell regeneration for the treatment of nonautoimmune hair loss such as androgenetic alopecia or FPHL is very feasible for various reasons. Although an autologous transplant is viewed as the standard, its use is limited because of a lack of data and the diminished viability of cells that are made available using this method. ADSCs are easy to obtain, are multipotent, and can easily differentiate into different cell lines, along with their significant potential for angiogenesis. More studies are needed to establish the efficacy of the various types of stem cell-based treatments for people with hair loss.

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Conflicts of interest

There are no conflicts of interest.

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