Review Paper: Application of Hair Follicle Bulge Stem Cells in Wound Healing

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ABSTRACT

Despite the significant advances in regenerative medicine, wound healing has remained a challenging clinical problem. Skin is the largest human organ with many vital functions; therefore, any damage to its normal structure should be treated as soon as possible. Easy access to skin stem cells has created a lot of excitement in therapeutic applications. “Cell therapy” is considered a novel method in regenerative medicine, especially when conventional treatments fail. Candidate cell populations for therapeutic applications include embryonic, induced pluripotent, adult mesenchymal, and hair follicle stem cells. It is possible to differentiate stem cells separated from the bulge area of hair follicle into neurons, melanocytes, keratinocytes, glia and smooth muscle cells that are negative for the keratinocyte marker kr15.

This review discusses the plasticity of skin stem cells, especially stem cells located in the hair follicle and their involvement in wound healing, gene expression profile in wound healing, hair follicle stem cells, and their surrounding epidermis. Moreover, the ability of hair follicle stem cells for treating wounds and regenerative medicine is going to be discussed. Eventually we suggest the hair follicle as an ideal source of stem cells for cell therapy and regenerative medicine because they are abundant with easy access and great differentiation ability.

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1. Introduction

This study reviews the latest advances in the field of stem cells and their potential uses in cell therapy with special focus on wound healing. Despite the advances in regenerative medicine, wound healing has remained a challenging medical problem, mainly following operation and severe damage of the skin that increases the risk of infections, postoperative hospitalizations [1, 2], early and late complications, and eventually morbidity and mortality rate [3].

Skin is the largest human organ with many important functions including thermoregulation, sweat production, and protection against pathogens; thus, any damage to its normal structure should be cured as soon as possible [4]. The skin structure comprised two layers (dermis and epidermis) that are distinct functionally, anatomically, and developmentally [5].

The term "wound" can be defined as any disruption in the normal structure of the skin resulting in loss of its normal function [6]. Current therapies including surgery, wound bandage, common negative pressure, and substitutes of skin are not sufficient in all conditions and new methods should be introduced in the field of wound healing as soon as possible [3, 7, 8]. Wound healing process included three phases (inflammation, proliferation, maturation or remodeling) which overlap in the time and space [9]. Common wound curing is a complex mechanism, required coordinated interactions between different biological and immunological systems at many different levels such as molecular mediators, cells, and structural elements [10, 11].

Conventional treatments of wounds is not effective in all conditions so modern approaches should be developed. In this regard, growth factors and cell therapy have been widely used [12]. Based on the reports, the pluripotent nestin-positive, keratin (K15)-negative stem cells in the hair follicle of mouse can differentiate into glia, neurons, keratinocytes, melanocytes and smooth muscle cells. Nestin-expressing cells differentiate into neuronal and glial cells following transplantation to the damaged spinal cord and help in repairing injury and recovery of locomotor system. The nestin-expressing pluripotent stem cells from the dermal papilla are called Skin-derived Precursor (SKP) cells. These outcomes propose that stem cells of hair-follicle in bulge-area can be considered as an autologous and accessible source for multipotent stem cells to treat wounds.

Table 1. Cytokines and growth factors that accelerate keratinocyte proliferation and differentiation

Cytokines/Growth Factors	Key References
Epidermal growth factor	[13-15]
Insulin-like growth factor	[15, 16]
Epiregulin	[17]
Fibroblast growth factor	[18]
Transforming growth factor	[19]
Keratinocyte growth factor	[20]
Stem cell factor	[21]
Bone morphogenetic protein	[22]
Angiopoietin-related growth factor	[23]
Growth differentiation factor-5	[24]
Granulocyte/macrophage colony-stimulating factor	[25]
Tumor necrosis factor-a	[26]
Interleukin-1	[27]
Thymocyte-activating factor	[28]
Nerve growth factor	[29]

2. Growth Factors and Cytokines Involved in Wound Healing

Many studies demonstrated that keratinocyte proliferation and differentiation play a major role in wound healing. Many growth factors and cytokines are involved in this process. Here we have summarized the results in Table 1.

3. Cell Therapy and Regenerative Medicine

Growth factors, on their own are not effective in wound treatment [12]. Nowadays, researchers have focused on the application of cell therapy for treating several pathologies such as wound healing [30, 31]. Cell therapy is considered as a new method in regenerative medicine, especially when conventional treatments fail. Cell therapy involves applying live stem cells to repair or restore the function of a damaged tissue [32, 33]. Therefore, the application of stem cells in cell therapy are investigated in numerous fields of regenerative treatment.

4. History of Stem Cells Therapies for Wound Healing

The term "stem cells" was first defined at the end of the 19th century as a theoretical assumption for self-renewing ability of the certain tissues (skin, blood, etc.) for the lifetime of an organism while they are made of short-lived cells. Many years later and following advancements in isolation of stem cell candidates, along with their potential testing after transplantation in vivo models, stem cells were identified as distinct cellular population. In 1966, Friedenstein et al. first isolated bone marrow-derived Mesenchymal Stem Cells (MSCs) [34], from humans by aspiration from the iliac crest. Later, the cells were extended in culture and topically applied to wounds to improve repairing tissue.

5. Stem Cells and Regenerative Medicine

By definition, stem cell are specific cell types that are self-healing and can proliferate and differentiate into other cell lines [35]. So far, the suitable source of stem cells has remained a major challenge, because their underlying mechanism is not completely understood [36]. Stem cells are able not only to produce cell types of their own tissue, but also cell types presenting in other tissues [37]. Cell therapy employs embryonic [38] or adult stem cells [39] to reconstruct injured tissues. Applications of embryonic stem cells has risen ethical concerns. The differentiation ability of adult stem cells has provided a chance for researchers to apply them in regenerative medicine [36]. Obtaining adult stem cells is possible from numerous organs of the body [40]. More studies are needed to focus on the function of stem cells in wound treatment to improve their efficacy (Table 3) [9].

Stem cells are undifferentiated cell populations which have capacity to differentiate into progenitor, or precursor cells of other cell types [37]. Adult stem cells are frequently used in therapeutic applications; some characteristics of adult stem cells have been mentioned in some research studies. It is simple to experiment on and culture them in vitro and it does not create moral concerns. Such stem cells as embryonic cells with high proliferative ability and differentiation potential can be collected from almost any tissue [41]. Table 2 lists some stem cells found in the hair follicle and surrounding skin.

6. Stem Cell Populations for Cutaneous Repair

Numerous sources of stem cells have been tested in preclinical and clinical settings for their potential to improve wound treatment. They have shown positive clinical outcomes and demonstrated autologous stem cell therapy to be safely tolerated. For example, Lee et al. showed that application of adipose tissue-derived stem cell implanting in a patient suffering from critical limb ischemia, could decrease the frequency of minor limb amputation, pain rating scales, and significantly improve claudication walking distance [58, 65].

Therapeutic capacity of the most stem cell populations including Embryonic Stem Cells (ESCs), induced Pluripotent Stem Cells (iPSCs), hair follicle bulge stem cells and adult MSCs, for wound healing have already been tested [61, 66].

7. Clinical Applications of Embryonic and Induced Pluripotent Stem Cells

Embryonic stem cells are pluripotent cells. They result from the internal cell mass corresponding to the blastocyst and have capacity to form a complete organism [67]. In an effort to use ESCs for repairing cutaneous tissue, they were differentiated by Guenou et al. into functional keratinocytes and applied for regeneration of the epidermis [61]. However, current clinical application of ESCs because of the possibility of immunogenicity, tumorigenicity, and ethical controversy is not promising [68].

Induced Pluripotent Stem Cell (iPSC) is a novel source of stem cells that possibly has the benefits of ESCs. These cells were generated by Takahashi and Yamanaka by reprogramming of adult fibroblasts into pluripotent immature state [66]. The iPSC technology allows to create populations of autologous pluripotent stem cell from adult differentiated cells. iPSCs are autologous and non-immunogenic, so spare the ethical issues associated with human ESCs. In vitro, 3-D

Table 2. Stem cells in the hair follicle and surrounding skin

Stem Cells	Location	Derivative Cell Types	References
Stem cells of dermal-sheath	Hair follicle dermal sheath	Dermal papilla cells and wound treating fibroblasts	[42, 43]
Stem cells of epidermis	Basal layer of the epidermis	Transient intensifying cells and terminal-differentiated epidermal cells	[44]
Stem cells of endothelium	Dermis	Endothelial cells	[45]
Stem cells of follicle multipotent	Bulge region of hair follicle	Hair follicle epithelium (containing external root sheath, inside root sheath, hair shaft, etc.), sebaceous gland cells and epidermal cells	[46-48]
Stem cells of hematopoietic tissue	Dermal papillae of hair follicle	All erythroid and myeloid lineages	[49, 50]
Stem cells of neural-crest	Dermal papillae of hair follicle	All neural cell types and a number of mesodermal derivatives	[51]
Stem cells of melanocyte	Bulge region of hair follicle	Melanocytes	[52]
Mesenchymal stem-cell-like cells	Dermis	Mesodermal derivatives and several neural cell types	[53]

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skin equivalents were generated by Itoh et al. [63] which composed mainly of human iPSC-derived keratinocytes and fibroblasts. Differentiation of iPSCs into folliculogenic human epithelial stem cells was demonstrated by Yang et al. [69] that restored all parts of the hair follicle. These results could improve the iPSC-based generation corresponding to full cutaneous equivalents, including epidermal appendages for wound healing.

iPSCs show the hybrid benefits of the ESCs and MSCs. Though, there are still many risks, including their tumorigenicity in an undifferentiated state, which must be solved prior to extensive clinical application. In spite of advantages of iPSC-based therapies in wound healing, it is essential to raise their safety ethics and improve the current approaches for their differentiating into keratinocytes, fibroblasts, and related cells in the wound bed with a focus on its cost-effectiveness and efficiency [70].

8. Clinical Applications of Mesenchymal Stem Cells (MSCs) in Wound Healing

The clinical usefulness of MSCs in wound treatment has already been published in several studies. The most used source of adult stem cells is Bone Marrow (BM). Several studies demonstrated that cells collected from the BM contribute in regenerating or repairing numerous tissues, comprising the bone, myocardium, cartilage, tendons, and skin [71].

BM contains a variety of heterogeneous cell populations, such as adipocytes, fibroblasts [72], Mesenchymal Stem Cells (MSCs), and Hematopoietic Stem Cells (HSCs). Both

Table 3. Summary of cells applied in wound healing

Cell Type	References
BM-MNC* BM-MSC	[31, 54-57]
ASC	[12, 58-60]
ESCs	[61]
iPSC	[62-64]

* BM-MNC: Bone Marrow Mononuclear Cells

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MSCs and HSCs have a great potential of plasticity, and can contribute into hematopoietic and non-hematopoietic tissues [73]. Both MSCs and HSCs mobilize from the BM to the wound site, once a wound occurs. In the wound place, they control proliferation and migration of cells in the inflammation phase [74]. MSCs produce several growth factors which induce dermal fibroblast proliferation, angiogenesis and also collagen deposition [75]. Recent studies demonstrated that BM stem cells play an important role in skin regeneration and vascularization [60]. Furthermore, MSCs have antimicrobial activity [76].

Clinical uses of BM derived MSCs (BM-MSCs) in wound treatment have been documented. Badivas et al. demonstrated that injecting BM directly into the wound edges followed by using cultured MSCs, lead to full closure of the wound and tissue reconstruction in 3 patients with chronic ulcers where traditional treatment regimens had failed [54]. In 2009, Dash et al. showed the effect of intramuscular application of autologous BM-MSCs at the edges of the wound in 24 subjects with wounds in the lower edges because of vasculitis or diabetes. The results demonstrated that implanting autologous BM-MSCs in non-treating wounds improves clinical parameters and accelerates the healing process significantly [57]. In systemic administration of MSCs carried out by Lu et al. on diabetic subjects suffering from lower limb ischemia, the pain relief and increase in treatment rate of the wound was significant [77]. Remarkable improvement in the regeneration of the dermis has been achieved through transplanting BM-MSCs. In fact, application of these cells with stem cell properties might be helpful in wound healing and reducing scar formation [78].

During the repair process, cells extracted from BM can be an important source of endothelial progenitor cells and inflammatory cells to repair cutaneous wounds [79], moreover, the contribution of BM-MSCs derived fibroblasts and endothelial cells in wound healing has been documented. In these cases, circulating fibrocytes (contributing to the myofibroblast population) have an important role in wound closure [80]. There is a wealth of evidence supporting the existence of BM-derived epithelial cells in the tissues of skin 71; BM cells can form epidermal keratinocytes [81, 82]. These outcomes also confirm the application of BM-derived cells in epidermal healing and repair. Further study suggests that BM-derived cells are able to constitute the functional skin cells and restore cutaneous tissue [71, 82].

9. Medical Applications of Adipose-Tissue-Derived MSCs (ASCs) in Wound Treatment

As mentioned before, it is possible to obtain MSCs from diverse tissues but harvesting them is invasive and painful [83]; thus, Zuk and associates characterized and defined adipose tissue derived MSCs (ASCs) from lipoaspirates, in 2001 [84].

ASCs secrete different cytokines and growth factors similar to those released by BM-derived MSCs [85]. These properties make ASCs a common source for cell treatment, and currently they are applied in diverse clinical treatment, such as wound healing [12, 41, 86, 87]. In 2012, Lee et al. reported the result of intramuscular use of ASC in 15 patients with critical limb ischemia. In their findings, decrease in the pain rating scale and improve in claudication walking distance was significant. This study concluded that ASC application may be a safe method to attain healing angiogenesis in subjects suffering from critical limb ischemia where other treatment modalities failed58.

10. Plasticity of Skin Stem Cells

Plasticity is a concept to define the multipotency characteristic of adult cell populations. This means that adult cells have the capacity to transdifferentiate and or be reprogramed and fuse, or persist corresponding to multipotential stem cells of adult tissues and organs [88, 89].

Skin cell plasticity has many therapeutic advantages. There are some multipotent stem cells in skin; epidermal stem cells in the epidermis basal layer, mesenchymal stem cell like cells and skin-derived progenitor cells in the dermis [53], and Hair Follicle Stem Cells (HFSCs). These cells like BM-MSCs are able to differentiate into mesodermal derivatives and neural cell types; therefore, they could be a source for fibroblasts that are essential in wound treatment events [78, 90].

Epidermal stem cells of adult human, in both the hair follicle and the epidermis have a high expansion capacity, and can form colonies in vitro: studies reported the successful transplantation of cultured epithelia for large and deep burn wounds, especially if this method was mixed with fibrin matrices to ease the application corresponding to epidermal stem cells [91].

11. Stem Cells Located in Hair Follicle

Recent developments have been made in locating and detecting diverse adult stem cell progenies in the skin and hair follicle, for example, epidermal stem cells located in the basal layer of epidermis. They are unipotent and provide regeneration of the epidermis in adult skin 44. These unipotent stem cells arise from multipotent stem cells, located in the bulge of hair follicles. Researches

show that bulge of hair follicle is an important place for multipotent stem cells [47, 92].

Subgroups of these multipotent stem cells are able to migrate out of the hair follicles to repair the damaged epithelium in the wounded site; but they little participate in the intact epidermal layer. Moreover, these hair-follicle-derived stem cells are able to participate in the follicles reconstruction (comprising the external root-sheath, internal root-sheath and hair shaft) and also the sebaceous gland. Furthermore, melanocyte stem cells are also present in the hair follicle bulge region [52].

Hair follicle dermal cells also contain hematopoietic cell population, which are CD 45-positive, and mesenchymal stem cell population [50, 93]. Follicle dermal cells have capacity to generate hematopoietic cells and could reconstitute the hematopoietic system in lethally irradiated mice [49]. The human scalp hair follicle dermal sheath can induce the formation of hair follicles, form new dermal papilla, and when transplanted onto the skin, can produce hair shafts [94]. In the case of implanting the follicle dermal cells into skin wounds, they have the ability to reconstitute the fresh dermis like skin wound-healing fibroblasts [43].

According to the available evidence, HFSCs are a source for dermal and epidermal cell populations [95]. In allograft transplantation of dermal sheath cells from one individual to another, they generate follicles that result in normal growth of hair with no rejection [94]; thus the immune privilege of such stem cells make them universal donors in cell-based therapy applications and also suitable targets [96]. Skin cells are largely available, especially hair follicles. They can be exploited as unique populations, a perfect source of autologous or allogeneic applications. The hair follicle displays immune privilege consequence of a unique immunological profile: having no expression for MHC class I and low amount of hair follicle immune cells [96].

12. Hair Follicle Bulge Stem Cells

The accessibility of stem cell sources in therapeutics approaches is a key point. Skin stem cells ease of access created much excitement in therapeutic applications. Skin stem cells provide hope to induce adult wound healing like embryonic ones, with fast regeneration, no scarring, and full reconstitution of hair and glands [79]. Moreover stem cells of skin have the therapeutic potential for treating wounds and diseases in other tissues [95].

Stem cells of the hair follicle bulge of adults is one of the candidate sources for regenerative drugs [97]. The hair follicle reconstructs itself via the cycle comprising three phases of anagen (growing phase), catagen (regression phase), and telogen (resting phase), all proposing the existence of its own stem cells [43, 92]. Some of HFSCs are located in the bulge region, which is between the arrector pili muscle insertion and the sebaceous gland duct [98].

13. Bulge Stem Cells and Wound Healing

Recent studies show that cell therapy with endogenous stem cell populations placed in the bulge region of hair follicle is a suitable method in coetaneous wound treatment [99].

Hair Follicle bulge Stem Cells (HFSCs) are appropriate source for pluripotent adult stem cells used in regenerative medicine because these cells are available, can be cultured easily, and unlike embryonic and fetal stem cells, are not associated with ethical issues. Also they prevent additional surgery complications [46, 100, 101].

Recent research demonstrated that population of stem cell in bulge region has positive expression of nestin, neural stem cell marker, and could differentiate into keratinocytes, neurons, glia, melanocytes, smooth muscle cells, and blood vessels [102-105]. These stem cells may be an accessible, autologous source and have high therapeutic value in regenerative medicine. Also their application does not raise any immunological problems or ethical concerns [106].

14. Wound Healing and Hair Follicle Gene Expression

Following full-thickness wounds, cells from the Interfollicular Epidermis (IFE) and the hair follicles migrate into the damaged area [48, 107]. Studies demonstrate that delayed wound healing occurs in mice lacking hair follicles [108]. That means that few hair follicle derived cells are involved in the re-epithelialization of epidermis in full-thickness wounds. Lineage detecting of Lrig1+ cells top of the bulge and Gli1+ cells in the junctional area indicate that hair follicle fate is able to persist for longer time [109, 110] but following repair, these hair follicles offspring are mainly substituted with epidermal progeny [111]. Thus, Interfollicular Epidermis (IFE) plays a major role in wound re-epithelialization rather compared to hair follicles. Overall, the source of new hair follicle placodes in repaired skin are not Keratin 15+ bulge stem cells from normal periwound hair follicles [112], but other populations of hair follicles stem cells which are Lrig+ and Lgr6+ stem cells [113].

Gene expression in hair follicle stem cells and its surrounding epidermis Skin epithelia display distinct populations of stem cell in hair follicles and epidermis. Epithelial

Table 4. Distribution of different genes in Hair follicle stem cell

Marker	Location	References
CD34+	Bulge	[116]
CD200+	Bulge	[117, 118]
K15+	Bulge	[119]
Sox9+	Bulge	[115]
Lhx2+	Bulge	[115]
Tcf3	Bulge	[115]
Nfatc1	Bulge	[115]
Lgr1+	Isthmus	[120]
Plet1+	Isthmus	[115]
Gil1+	Isthmus	[115]
Lgr6+	Isthmus	[121]
Blimp1+	SG	[122]
Sca1+	Infundibulum	[123]
Lrig1+	Junctional zone	[115]
CD200+	Secondary hair germ	[115]
K15+	Secondary hair germ	[115]
Gil1+	Secondary hair germ	[115]
Lgr5+	Secondary hair germ	[115]

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stem cells have diverse lineage capacity in different locations [114]. Physiologically, stem cells in the follicular infundibulum and interfollicular epidermis are limited to the fate of epidermal cells.

Stem cells of interfollicular epidermal can be offered as slow-cycling populations in label retaining research, but specific indicators are unknown. Hair follicles have several specific epithelial cell populations in the isthmus and junctional area that are Lrig1+ (yellow), Lgr6+, and Gli1+stem cells (green), which preserve the isthmus and contribute to infundibulum, sebaceous gland, and to interfollicular epidermis. Progenitors of sebaceous gland are unipotent and identified by Blimp [1] (orange). The stem cells of bulge (blue) normally reconstitute all lineages of hair follicle and can be detected with the expression of CD34, Krt15, Sox9, CD200, Lhx2, Lgr5, Nfatc1, and Tcf3. The telogen hair follicles secondary germ (purple) express CD200, Gli1 and Lgr5 (Table 4) [115].

15. Conclusion

Any damage to the normal anatomical structure of the skin resulting disrupts its normal function and can be defined as wound. Despite the advances in regenerative medicine, wound healing has still remained a challenging clinical problem. A new field of medicine is cell therapy which applies embryonic or adult stem cells to reconstruct injured tissues. Numerous sources of stem cells are being studied in clinical treatment for their potential to improve wound treatment and autologous stem cell therapy to be safely tolerated. The easy access of stem cell sources is a key point in therapeutics approaches.

While the wound healing with stem cells has shown promising results, identifying the cells that have the most beneficial effect will be an effective approach. For this purpose, the hair follicle stem cells especially in bulge area are a suitable source, because they can differentiate into different lineages with no expression of MHC class I. Therefore, the

immune privilege of these stem cells make them universal donors in cell-based therapy. Given that in normal mode, stem cells of hair follicle are involved in wound treatment, the similar studies about the bulge area of hair follicle and wound healing may lead to novel techniques for application of stem cells in clinical treatment of wound healing.

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Compliance with ethical guidelines

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Conflict of interest

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