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Review Article

Stem Cells and Their Potential Applications in Dermatology

Emma Bhattarai*, Yaser Mansoor Almutawa, Nishant Gautam and Jingjun Zhao

Department of Dermatology and Venerology, Tongji Hospital, School of Medicine, Tongji University, Shanghai, China

Abstract

In recent years, huge advances have been made in the field of cell repair and regeneration, among which usage of Stem Cells (SCs) and its activators are at the foremost. Various studies have been conducted in the field of regenerative medicine using SCs in clinical applications. These studies have shown potential of SCs in the management of those disease where satisfactory outcome is still not available. Huge appeal in SCs is mainly due to their ability for self-renewal, capacity to differentiate into their tissue of origin and their potential to differentiate into completely new cell type. Experiments conducted with regards to dermatological problems have shown positive results in many cases. This review aims to summarize stem cells biology and types, and their potential use in many dermatological conditions. This article also summarizes about the stem cells present in the skin, their usage and identification.

Keywords: Dermatology; Embryonic; Epidermal stem cells; Mesenchymal; Stem cells; Stem cell therapy

Introduction

Stem cells technology and its potential usage is a novel idea in the field of in cellular repair and regeneration. Stem cells are basically precursor cells for all cell types. Basically for a cell to be stem cells, it must have capacity for self-renewal and the potency to differentiate into similar and new cell type [1]. Self-renewal is the ability of SCs to undergo asymmetric mitotic division so as to retain same number of original undifferentiated cells and produce one progenitor cell which further divides to form required cell type. This ability of self-renewal should allow the stem cells to produce 40-60 doubling of population before the cell dies [2]. Plasticity is another ability of stem cells which allows formation of a new cell type different to its original tissue type [3,4].

***Corresponding author:** Emma Bhattarai, Department of Dermatology and Venerology, Tongji Hospital, School of Medicine, Tongji University, Shanghai 200092, China, E-mail: bhattaraiemma@gmail.com

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Types of Stem Cells

SCs are mainly categorized into embryonic and adult type. An example of embryonic stem cell is blastocyst [3]. Embryonic SCs has the capability to divide into the three germ layers: ectoderm, mesoderm and endoderm; and thus it can differentiate into any cell type. Due to this ability, embryonic SCs can lead to teratoma formation and may cause graft rejection [5-7]. Adult stem cells are of hematopoietic and mesenchymal type. They can be obtained from bone marrow, umbilical cord, liver, skin, adipose tissues, etc. unlike embryonic SCs teratoma formation and graft rejection is rare with adult SCs [8].

A new concept of induced Pluripotent Stem Cells (iPSCs) has evolved where few genes (3-4) obtained from stem cells are transfected into the receiving cells thus allowing the receiving cells to develop similar characteristics like that of donor stem cells [9]. This concept of converting the mesenchymal stem cells to iPSCs has given new ideas for treatment of incurable conditions as well as inherited skin diseases as iPSCs can act like embryonic stem cells i.e. it can give rise to any cell type and lineage, thus correcting genetic abnormality of the disease by homologous recombination. This concept can further revolutionize the future of stem cells and its use [10] (figure 1).

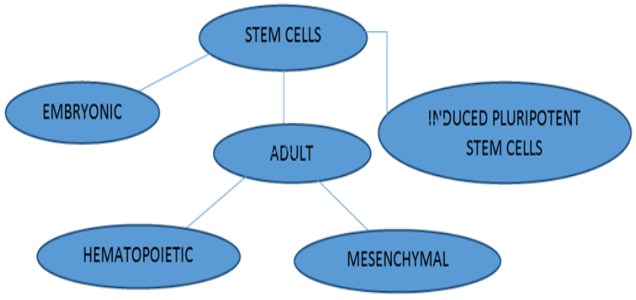

Figure 1: Stem cells classification.

Stem Cells in terms of cell differentiation fall under 4 types; Totipotent, pluripotent, unipotent and multipotent SCs where potency is the ability of a cell to differentiate into specialized cell types. Totipotent SCs have the ability to replicate into placental cells as well as any other type of cells, has the capacity to form an entire organism and are found exclusively in embryonic developmental stage. Pluripotent SCs can develop into any other cell type but placenta. They have the capacity to form tissues from all three germ layers. Unipotent SCs only has the ability to form single specific type of cell whereas Multipotent SCs can develop into different cell type but of similar tissue of origin [11] (Table 1).

Adult stem cells can be of hematological and mesenchymal in origin. The mesenchymal stem cells are found in a niche of special surrounding needed for their control. Mesenchymal stem cells can be

found in various organs and tissues of body where there is large cell turnover such as skin, liver, intestinal mucosa, periosteum, cornea, dental pulp, adipose tissue [8,12,13].

Types	Examples
Totipotent	Morula, zygote
Pluripotent	Embryonic stem cells, induced pluripotent stem cells
Unipotent	Hepatoblast, osteoblast,
Multipotent	Hematopoietic stem cells, mesenchymal stem cells

Table 1: Classification of stem cells in terms of potency.

Mesenchymal Stem Cells

Mesenchymal Stem Cells (MSCs) originate from stroma and can be obtained from any tissues. According to The International Society for Cellular Therapy position statement there are three criteria to define MSC [14]:

1. Adherence to plastic
2. Specific surface antigen (Ag) expression
3. Multipotent differentiation potential

Mesenchymal Stem Cells (MSCs) are identified on basis of above three points.

1. Adherence to plastic

Plasticity is a term that defines the ability of cells to differentiate into a completely new cell type than its original cells.

2. Specific surface antigen (Ag) expression

Presence and absence of specific surface antigen expression helps in identification of mesenchymal stem cells. CD105, CD73, CD90 should be present on the cell surface while CD45, CD34, CD14 or CD11b, CD79a or CD19 and HLA class II must be lacking.

3. Multipotent differentiation potential

The cells under standard in vitro differentiating conditions must have the capacity to differentiate into osteoblasts, adipocytes and chondroblasts [14].

Skin Stem Cells

In both epidermal and dermal layer of skin, stem cells are present in specific areas so named 'niche', where the microenvironment allows the stem cells to hold on to their defined properties without any modifications. This niche also defends stem cells from signals that leads to apoptosis causing them to be less likely for any oncogenic changes leading to cellular DNA damage [15].

Epidermal stem cells are found evenly distributed along basal layer of epidermis and bear a resemblance to somatic stem cells. Its main function is to repair and maintain the integrity of the tissues they reside on. Epidermal stem cell helps repair injuries as well as maintain skin homeostasis and helps in hair regeneration [15,16]. Identifying markers are p63, $\beta1^{high}$/MCSP+(melanoma chondroitin sulfate proteoglycan+), $CD71^{dim}$ [17-19].

Melanocyte stem cells are found on the bulge region of outer root sheath of the hair follicle and functions in survival, growth, multiplication and differentiation of melanocyte cells [20,21]. The identifying cell markers for melanocyte stem cells are Dct, Pax3 and Sox10 [22,23].

Follicular stem cells are also found in the bulge region of hair follicles in the outer root sheath and helps in regeneration and repair of hair follicle including the outer, inner root sheath and the hair shaft [24]. The identifying cell marker for follicular stem cells are K15, CD34, Lgr5, Sox9, Lhx2, NFATC1, NFIB, PHLDA1, CD200, K19 [25].

Sebaceous gland stem cells are found sebaceous gland and the infundibulum. The stem cells in sebaceous gland itself gives rise to and sustain the mature sebocytes. The stem cells in the bulge region goes towards gland region and helps maintain the gland [26,27]. The identifying cell marker is Blimp1 [28].

Mesenchymal stem cells are located in dermis and at the root of hair follicle. It helps in formation of some neural cell types as well as into other cells of mesenchymal derivatives [29,30]. The identifying cell marker are CD105, CD73, and CD90 and exclude expression of CD45, CD34, CD14 or CD11b, CD79a (Table 2).

Stem cells	Location	Identifying markers
Epidermal stem cells	Basal layer of epidermis	p63, β1high/MCSP+(melanoma chondroitin sulfate proteoglycan+), CD71dim
Melanocyte stem cells	Follicular bulge region and hair germ	Dct, Pax3, and Sox10
Follicular stem cells	Follicular bulge region	K15, CD34, Lgr5,Sox9, Lhx2, NFATC1, NFIB, PHLDA1, CD200, K19
Sebaceous gland stem cells	Sebaceous glands and infundibulum	Blimp1
Mesenchymal stem cells	Dermis	CD105, CD73, and CD90 and negative for CD34,CD45, CD14 or CD11b, CD79a/CD19 & HLA-DR

Table 2: Skin stem cell type with identifying markers.

Potential Uses of Stem Cell Therapy in Dermatological Conditions

Cutaneous wound healing

The normal wound healing of human skin in not perfect even in best circumstances with the delayed healing, scar formation being a persistent eventuality. In the scenario of long term delayed wound healing, scarring mesenchymal stem cells have shown excellent promise. Migration, angiogenesis, epithelialization, and granulation tissue formation is encouraged by MSCs which expedites wound healing and further promotes regenerative wound healing leading to decrease scarring [31]. In both acute and chronic wounds, MSCs can be administered directly to the wounds by injecting, or even spraying (e.g., autologous MSCs using fibrin spray, lead to direct delivery of stem cells in acute and chronic wounds in mice and humans [32]) leading to acceleration of wound healing, angiogenesis, releasing of paracrine signalling molecules as well as enhanced reepithelialisation. Similarly, Studies have shown that hair follicle stem cells contributes to wound healing [33,34]. Stem cells from hair follicles and interfollicular epidermis move towards the wound area in response to injury.

In a study by Ito et al., [35] fate-mapping experiments have shown that, k15 positive hair follicle stem cells help in re-epithelialization of full-thickness wounds. After the injury to epidermis, the follicular epithelial cells migrate rapidly towards the center of wound in a radial pattern thereby forming transient cells which oversees acute wound repair.

Vitiligo

Vitiligo, a disorder caused by loss of melanocytes leads to formation of colourless patchy skin. Presence of melanocytes from the hair follicle unit, border of lesion and from unaffected melanocytes within the depigmented areas decides regimentation in vitiligo [36]. Tacrolimus, phototherapy and dermabrasion are commonly used therapy for vitiligo which does provide result in some patients. Progress in stem cells therapy has brought new hope in field of vitiligo management. In a study by Zhu et al., [37], the expression of PTEN (phosphatase and tensin homolog) in human vitiligo was found to be elevated with due inhibition of the AKT growth signalling pathway. This finding actually shows that PTEN has an important role in melanocytic growth and survival. In same study Zhu et al., found that MSCs can regulate the expression of PTEN protein in Melanocytes and can further decrease impairments due to overexpression of PTEN and H2O2 induced oxidative stress. Similarly, dermal MSCs can help in vitiligo by improving melanocyte transplantation efficacy as dermal MSCs inhibits CD8+ T cell proliferation, induce apoptosis of T cells and further regulate the cytokine and chemokines production [38].

Alopecia

Hair loss from single area or multiple areas forming bald patches is seen in alopecia. Autologous hair transplantation is considered gold standard but its use is limited due to limited amount of material as well as decreased viability of the material. In study by Nilforoushzadeh et al., [39] induction of new hair growth was seen after Injecting a combination of human cultured dermal papillary cells and hair epithelial cells with CD200+ and k15 identifying markers in nude mice. This does give emphasis on the subject that stem cell therapy does indeed lead to hair growth in alopecia patient. Recently a new method for hair regrowth in androgenic alopecia was suggested by Gentile et al., [40] which used a mixture of centrifuged hair follicle stem cells and dermal MSCs. The study showed hair growth and increased hair density in the sites where the mixture was injected. This study suggests that injection of HFSCs has good prognostic value on male pattern androgenic alopecia.

Stem cell therapy has thus come forward for alopecia as it helps to regenerate hair by altering pathological reasons of hair loss, helps to regenerate complete hair follicles and helps form new hair follicles.

Melanoma

Melanoma in past was thought to be due to cancer cells arising from melanocyte cells but these days it has been studies that it may also occur due to cellular changes in melanocytes, melanocytic stem cells or both [41,42]. Studies have shown MSCs can reach both the primary and metastatic tumor site with help of various chemokines and cytokinesemitted from the tumor [43,44]. Pessina et al., [45] demonstrated that MSCs, when loaded in vitro with an anti-cancer drug (e.g. Paclitaxel(Dr-MCsPTX)) becomes drug releasing mesenchymal cells which inhibits the growth of cancer cells strongly. MSCs in melanoma act not just as vector to in improving the delivery of targeted agents (adipose derived mesenchymal stem cells expressing TRAIL, interferon-α/γ, pigment epithelium-derived factor and cytosine deaminase) but also express a distinct set of biologically functional chemokines and tumor supressing agents. MSCs can also be genetically modified with tumor suppressive genes to stop the pathways that cause progression and metastasis of melanoma [46-48].

Anti-aging therapies

Aging is natural phase of life and every organ of our body goes through it. Reduced function is one of the main changes seen due to aging. Physical changes seen in skin just highlight this phase. Usually the cell in our body wears out and gets replaced continuously with the help of stem cells. Decrease in ability of the stem cells to regenerate and repair is the main causation of aging. Xu et al., [49] , compared adipose stem cell and placental stem cell in secretion characteristics and facial anti-aging. The study shows that the protein secreted from adipose stem cells were more versed towards cell adhesion and migration, and were more helpful in would healing and tissue repair. Also the improvement of melanin index was more pronounced with the injection of the adipose stem cell conditioned medium. Similarly, the proteins from placental stem cells were found to be defter towards angiogenesis, cell proliferation and differentiation, cell survival, degradation of collagen and in immunomodulation. Both of these conditioned medium helped improve the facial index.

Improvement in this ability of regeneration and repair can be made by using stem cell therapy which helps delay the process of aging and help manage aged diseases [50].

Conclusion

In any new discipline of study, there will always be intricate relationship between knowledge and hypothesis of the intrinsic mechanism with development of new clinical plans. Many studies have shown that stem cells have the capability to transform itself into any mature cell type. This feature of stem cells has led many researchers to conduct studies on certain dermatological conditions, such as, treating chronic wound repair with MSCs and epidermal stem cell. Studies have also been conducted in conditions like alopecia and vitiligo where use of epidermal and dermal stem cells has shown great benefits. Similarly, in condition like melanoma, stem cells have been used along with other agents like anticancer drugs with MSCs acting as vector thereby improving the delivery of targeted agents. Studies in antiaging with stem cells have shown great promise in improving the body's ability to increase the repair and regeneration of aged cells and as such delaying aging.

Despite these positive results with stem cell therapy, the need for further study will always be there. Till date our knowledge regarding the complex signaling cascades, environmental influence on the stem cells or its epigenetic modulation is still limited and much work is still needed. Stem cells also show some adverse events particularly when it comes to characterize graft versus host stem cell immune interactions, tumorigenesis, metastasis and potential drug resistance, which too needs to be addressed.

In the field of dermatology, due to readily accessible topical approach towards the epidermal and dermal stem cells, it seems easier to obtain the samples of stem cells from cutis and subcutis. Also the dermatological conditions are easily reachable without using any

interventions, for example, using stem cell laden fibrin spray in chronic wound so as to modulate rapid wound healing without scarring.

Though the studies till date show mostly promising results, however the subjects and controls are usually too small to allow for proper assessment of the efficacy of the therapies. Therefore, further research and large, controlled clinical trials are required to obtain necessary data regarding the outcome, safety and efficacy of the stem cell therapies. Despite these limitations, there is still hope that safe and efficient approach is forthcoming and there will be safe and sophisticated treatment modalities with stem cells.

Conflicts of Interest

The authors declare no conflicts of interest.

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