Stem cells in the skin

Células-tronco na pele

ABSTRACT

This article assesses recent studies about stem cell research in dermatology. The interaction of stem cells in the maintenance and repair of the skin, as well as their participation in the hair follicle cycle and its pigmentation, are also discussed. Studying those mechanisms will increase understanding of the pathophysiology of diseases linked to dysfunctions in those processes, which will enable the development of therapeutic approaches to these situations.

Keywords: stem cell, skin, dermatology.

RESUMO

Este artigo tem por objetivo tratar de trabalhos recentes a respeito de pesquisas que vêm sendo realizadas em células-tronco, particularmente em dermatologia. O entendimento da interação das células-tronco na manutenção e reparo da pele, bem como, de sua participação no ciclo do folículo piloso e sua pigmentação, também é relatado. Através do estudo desses mecanismos, seremos capazes de entender a fisiopatologia de doenças relacionadas a disfunções nesses processos, além de, a partir daí, desenvolver abordagens terapêuticas para essas situações.

Palavras-chave: *célula-tronco, pele, dermatologia.*

INTRODUCTION

The study of stem cells and their therapeutic applications is currently one of the most promising areas in medicine. Research on this topic has allowed advances in understanding how to use those cells to treat degenerative diseases and has expanded knowledge in the areas of oncology and regenerative medicine. The publication of an article on human embryonic stem cells and their characteristics [1] not only aroused interest but also ethical and religious controversy.

This article will discuss the various options that those new technologies introduce for the treatment of dermatoses – such as androgenetic alopecia – as well as the possibility of using skin biopsies to supply material for studies on the pathophysiology of systemic diseases and the *extra vivo* experimental use of drugs in specific cell types.

STEM CELLS: DEFINITION

Stem cells are primitive cells that have the ability to divide themselves for long periods without differentiating. This self-renewal characteristic has an inherent great potential to differentiate into various cell types.

Continuing Medical Education

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Stem cells are classified into two major groups based on their origin: embryonic and somatic. Embryonic stem cells are derived from the very early stages of embryo formation – after fertilization and before implantation. They are totipotent cells, which means they are able to go through several cellular divisions *in vitro* without differentiating. [1] They can originate any embryonic or extra-embryonic tissue (placenta and umbilical cord, for instance), and thus have the ability to create a person.

Somatic stem cells are present in virtually all body tissues. They are the basis for homeostasis and tissue repair throughout life. They have the capacity to renew themselves indefinitely and generate daughter cells, which differentiate into one or more types of tissue. In the skin, stem cells are found in the epidermis, dermis, and subcutaneous tissue, as discussed below.

THE NICHE CONCEPT

A niche is a protected, isolated, and private environment. Populations of stem cells are located in specific anatomical locations – or niches – which ensure their preservation and the cellular interactions that are necessary for those cells to divide, take part in homeostasis, and engage in specific tissular repair. [2] A niche is therefore a specific anatomical location that constitutes a basic physiological tissular unit capable of maintaining the integrity of the organ through the biochemical interactions and signaling between cells. An example of the interaction between a niche's cells is the interaction between melanocytic stem cells and keratinocytes present in the follicular bulge (or hair follicle bulge). Molecular signals sent by the keratinocyte's precursors trigger the migration of melanocytes responsible for the pigmentation of forming hairs during the beginning of the anagen phase. [3,4] The niche concept is important when the objective is to use the stem cells' potential for therapeutic measures.

STEM CELLS IN THE SKIN

Epidermis and Hair Follicle

The epidermis is the outermost layer of the skin. Sweat glands and hair follicles are located in the epidermis; the latter is associated with sebaceous glands and the piloerector muscle. Those diverse components are in a constant turnover, replacing dead and injured cells. Currently it is known that a population of different types of stem cells that reside in the epidermis, hair and nails makes such a turnover possible.[3,4]

Stem cells randomly distributed in the basal layer of the epidermis divide themselves in order to repopulate the interfollicular epidermis, forming epidermal proliferation units. This division occurs asymmetrically. [3] One epidermal stem cell divides into two daughter cells, one of which differentiates and rises to more superficial layers of the epidermis, while the other remains in the basal layer and retains its differentiation capacity.

Follicular Bulge (Bulge Area)

The bulge area, or follicular bulge region, is the portion of the hair follicle that is located adjacent to the piloerector muscle's insertion. It contains the best-characterized population of stem cells in the epidermis. [5,6] Those stem cells originate the structures of the hair follicles and sebaceous glands, and participate in the repair of injured skin (following burns, for instance).

There is an additional population of stem cells located in a more superficial portion of the outer root sheath of the hair follicle (isthmus), above the bulge area. Those cells can originate all epidermal structures (interfollicular epidermis, hair follicles, and sebaceous glands). Those cells were only marked and characterized recently, when Snippert and colleagues demonstrated that the Lgr6 protein is expressed in that cellular group.[7] Likewise, today it is also known that there are stem cells exclusively responsible for regenerating sebaceous glands. [8]

The hair follicle is considered a unique structure due to the fact that it presents the growth cycle (anagen phase) interspersed with periods of apoptosis in its lower portion (catagen phase) and resting periods (telogen phase). At the beginning of the anagen phase, the stem cells located in the bulge area are responsible for recovering the lower portion of the follicle. Those cells migrate to the follicle's base and differentiate to originate the outer root sheath, the follicle's inner layers, and the hair shaft. In order to start the anagen phase, the keratinocyte's precursors (located in the bulge) receive signals from mesenchymal cells and the precursors of adipocytes (both are present in that area, the latter having only been recently identified in that region). [9,10] Similarly, it has only recently been shown that –through signals sent by keratinocytes' precursors in that area – bulge stem cell melanocyte precursors differentiate [9] and migrate [11] up to the hair follicle's base, which triggers the pigmentation of the forming hair.

The interaction between niche cells in the bulge of the hair follicle is critical for maintaining the skin's integrity. [3] As described in the following sections, disrupting this balance may initiate certain pathological processes.

Dermis and Subcutaneous/Adipose Tissue

The dermis contains a stem cell subtype that resembles mesenchymal cells, which are present in bone marrow. [12] This subtype is found in various tissues and can generate osteogenic, chondrogenic, and muscle cell lineages. This cell type is also found in adipose tissue, and is referred to as adipose-derived stem cells (ADSC). [13]

Those cells currently attract great interest, especially in plastic surgery. Many studies suggest that using stem cells derived from ADSC to enrich fat grafts can significantly improve the viability of the grafts. Furthermore, patients who have received fat grafts enriched with ADSC require fewer sessions to achieve satisfactory results compared to the traditional graft technique. Finally, fat grafts enriched with ADSC seem to be more efficient than traditional grafts in the reconstruction of areas with soft tissue, in difficult cases – such as post-radiation therapy – or in patients with Perry-Romberg syndrome. [13,14] In spite of the enthusiasm for this new possibility, there is still controversy about its safety. Given that those cells are highly proliferative and have a great capacity to produce cytokines, there is speculation that the use of ADSC could increase the risk of recurrence in patients with a history of cancer, for instance. One

example is the discussion about the safety of enriched grafts in patients who had a mastectomy due to breast carcinomas and are candidates for reconstruction. [15]

STEM CELLS AND ALOPECIA

Alopecia may be cicatricial or non-cicatricial. Understanding the physiology and location of stem cells in the skin, particularly in the hair follicle, provides a new perspective on the pathogenesis of this condition.

Recent studies on the pathogenesis of cicatricial alopecia suggest that the inflammation process' target seen in *lichen planopilaris*, for instance, is bulge stem cells with CD8 lymphocytes' inflammatory infiltrate, which results in the depletion of those cells early in the course of the disease. [16]

Likewise, in alopecia areata (AA), the focus of the inflammatory process is the dermal papilla region, and the preservation of the bulge – which may explain the regrowth in AA areas many years after the beginning of disease. [16]

A recent study found evidence that the androgen action in androgenetic alopecia (ANA) is responsible for inhibiting the signalling of mesenchymal cells in the differentiation of the bulge cells. [17] That knowledge has stimulated the search for treatment options for ANA. In a clinical study, ANA patients received a single injected intradermal dose in the affected area of the scalp of a combination of factors known to stimulate bulge stem cells. Study participants presented improvement in all parameters evaluated up to one year after the procedure. [18]

HOW CAN SKIN CELLS HELP IN OTHER AREAS OF MEDICINE?

INDUCED PLURIPOTENT CELLS (IPSC)

Due to the ethical issues involving the use of human embryonic stem cells for research purposes, a technique of genetically reprogramming adult somatic cells has been developed. In 2006, Takahashi and colleagues were able to genetically reprogram differentiated cells from adults into pluripotent cells with characteristics similar to those of embryonic cells. [19]

The cells were transformed by introducing four transcription factors, [1] which induced a behavior similar to that of pluripotent embryonic cells. The resulting cells presented normal karyotypes and telomerase activity, and expressed the markers and genes that characterize embryonic cells. They also have the potential to differentiate into cells of the three germ layers.

The cells resulting from that genetic reprogramming process were named induced pluripotent stem cells (iPSC). The ease with which adult somatic cells can be obtained (from peripheral blood or skin, for instance), and transformed into iPSC, constitutes excellent tools for studying disease mechanisms, testing drugs, and treating various diseases. For example, adult patients' fibroblasts (obtained through skin biopsy) can be reprogrammed to obtain undifferentiated cells that can then be differentiated into the type of cell required for research or therapeutic purposes. [20]

More recently, a research group used fibroblasts obtained from two patients with recessive epidermolysis bullosa in order to obtain iPSCs and, from these cells, to obtain keratinocytes.[21] The resulting cells presented all characteristics of keratinocytes except for the production of type VII collagen, due to the mutation responsible for the disease. This study 20 demonstrates the possibility of using iPSCs technology to obtain models of diseases in vitro that can be used to study therapeutic measures.

IPSCS DERIVED FROM SKIN CELLS AND THEIR APPLICATION IN OTHER AREAS OF MEDICINE

Based on skin biopsies from patients with Timothy syndrome (a disease associated with neurodevelopmental delay and autism), fibroblasts were obtained and reprogrammed into iPSCs and subsequently into neurons. Given that those cells retain the patient's genetic background, the mutation responsible for the syndrome might be more easily studied at the cellular level, contributing considerably to the understanding of the disease's pathogenesis. [22] Similar studies were performed in patients with schizophrenia. These advances will allow unprecedented studies of neurological and psychiatric diseases, which previously could only be studied through biopsies of cerebral tissue. [23]

An in vitro study carried out using fibroblasts from mice has shown that it is possible to reprogram those cells by turning them into iPSCs and subsequently inducing their differentiation into heart muscle cells. [24] A further step would involve the *in situ* reprogramming of the effected cells, in order to induce the fibrotic tissue to differentiate back into healthy tissue. This approach could revitalize an infarcted heart, for instance.

CONCLUSION

Currently there are two ongoing FDA-approved clinical studies using embryonic stem cells. While one focuses on spinal cord lesion treatment, the other focuses on macular degeneration of the retina. Other clinical trials using iPSCs are underway.

Many advances have been achieved in this area. In dermatology and plastic surgery, given their greater ability to correct defects and their capacity to improve the appearance of the skin adjacent to implants, the enrichment of fat grafts with stem cells is seen as a promising alternative to traditional grafts. These effects have been reported as rejuvenating. Likewise, obtaining and reprogramming skin cells in order to yield cells of other tissues may be important tools in research and therapy in the near future.

Companies are already using genetically engineered cells as dermal substitutes, and even in cosmetic dermatology. While promising, these practices require attention and well-defined protocols in order to ensure their effectiveness and safety. Thus the professional dermatological community should be vigilant. ●

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Questions for continuing medical education (CME)

1) It is correct to state that

a) somatic stem cells are found exclusively in the skin, bone marrow, and adipose tissue
b) the renewal capacity of stem cells is linked to the process of differentiation into other types of cells
c) the interaction between different types of cells that are present in the niches is responsible for the differentiation of stem cells
d) iPSCs are obtained from embryonic stem cells
e) the epidermis is renovated with cells originally from the sweat glands

2) Which of the following is false?

a) Transcription factors (TF) are proteins involved in gene transcription
b) The binding of transcription factors to DNA sequences may block the activation of genes
c) Genes that are transcribed based on the interaction of TFs may regulate cell division
d) TFs have been introduced into adult cells, transforming them into embryonic cells
e) The use of iPSCs allows the in vitro study of drugs and diseases

3) About stem cells derived from adipose tissue, it is false to state that

a) they are similar to bone marrow mesenchymal cells
b) they can generate osseous and cartilage tissues
c) they increase the recurrence of breast cancers due to the effect of cytokines
d) they are used to enrich fat grafts
e) enriched fat grafts can be used in reconstructions after radiation therapy

4) The bulge region has stem cells

a) that are responsible for reconstructing the lower portion of the hair follicle in the anagen phase
b) that are precursors of melanocytes
c) that are responsible for regenerating the sebaceous gland
d) none of the above
e) a, b, and c

5) In the epidermis, there are stem cells in the basal layer that

a) migrate to the more superficial layers of the skin without differentiating
b) form units of epidermal proliferation
c) divide into identical daughter cells, which repopulate the affected epidermis
d) exclusively repopulate the epidermis
e) divide asymmetrically in the hair follicle bulge

6) The onset of the anagen phase is characterized by

a) the bulge region's cells signalling for that phase's characteristic migration and differentiation
b) the asymmetric division of basal layer cells
c) the migration of the bulge's melanocytes to the basal layer of the epidermis
d) the differentiation of melanocyte precursors in the base of hair follicles due to the stimulation of adipocytes
e) the regeneration of sebaceous and sweat glands

7) Regarding alopecia,

a) the androgenic action is responsible for inhibiting the signalling that leads to differentiation in the bulge cells
b) factors that stimulate the differentiation of bulge cells can be used to treat lichen planopilaris alopecia, given its pathogenesis
c) inflammatory infiltrate in the bulge explains the regrowth in alopecia areata
d) CD8 lymphocytes must be targeted in the treatment of non-cicatricial alopecia
e) the niche cells in the bulge area are not affected

8) Reprogramming somatic cells can be useful, except for

a) obtaining cell types for studying drugs
b) treating spinal cord lesions with embryonic cells
c) in areas of medicine in which it is difficult to obtain biopsies, as in psychiatry
d) in understanding the pathogenesis of various diseases
e) in regenerating injured tissues due to various pathological processes

9) In the anagen phase,

a) there is apoptosis in the lower portion of the follicle
b) there is a migration of melanocytes from the basal layer to the hair pigmentation
c) the bulge mesenchymal cells release cytokines that act on the precursors of keratinocytes in this region
d) the keratinocytes receive signals from mesenchymal cells and enter into a resting state until the next anagen phase
e) the hair pigmentation precedes the bulge keratinocytes' signalling about the precursors of melanocytes

10) Skin stem cells are

a) embryonic
b) responsible for differentiating into various tissues
c) reprogrammed by transcription factors
d) easily characterized
e) arranged in niches

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1d 2a 3a 4b 5e 6a 7c 8b 9e 10b

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