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Review Article

Stem cell therapy on skin: Mechanisms, recent advances and drug reviewing issues

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ABSTRACT

Stem cell products and its clinical applications have been widely discussed in recent years, particularly when the Japanese "induced pluripotent stem cells" founder Dr. Yamanaka was awarded as Nobel Prize laureate in 2013. For decades, major progresses have been achieved in the stem cell biology field, and more and more evidence showed that skin stem cells are involved in the process of skin repair. Stem/progenitor cells of the epidermis are recognized to play the most essential role in the tissue regeneration of skin. In this review, we first illustrated basic stem cell characteristics and various stem cell subtypes resided in the skin. Second, we provided several literatures to elucidate how stem/progenitor cells collaborate in the process of skin repair with the evidence from animal model studies and *in vitro* experiments. Third, we also introduced several examples of skin cell products on the pharmaceutic market and the ongoing clinical trials aiming for unmet medical difficulties of skin. Last but not least, we summarized general reviewing concerns and some disputatious issues on dermatological cell products. With this concise review, we hope to provide further beneficial suggestions for the development of more effective and safer dermatological stem/progenitor cell products in the future.

1. Skin stem cells and the mechanism of skin repair

Stem cells generally have two major characteristics that they can give rise to specialized cell lineages or cells and are capable of self-renewing for long periods [1,2]. Traditionally, stem cells can be categorized into two different groups, embryonic stem cells and somatic stem cells. Embryonic stem cells are obtained from the inner cell mass of blastocyst in mammalian embryos. Embryonic stem cells are pluripotent; therefore, they have the potential to derive progeny cells

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belonged to all three germ layers including ectoderm, endoderm and mesoderm [3]. Unlike embryonic stem cells, somatic stem cells are typically found in mature organs or tissues. Some somatic stem cells might be multipotent but majority of them are lineage limited, i.e. hematopoietic stem cells can only give rise to mature blood cells [4], whereas neural stem cells can only divide into neuronal and glial cells [5]. With the huge success of Professor Yamanaka's lab in Kyoto, differentiated, adult somatic cells can be reprogrammed to generate induced pluripotent stem cells (iPSCs), and now iPSCs become a new emerging group of stem cells. The reprograming is achieved by exogenous addition of four transcription factors (Oct-3/4, Sox2, c-Myc, and Klf4) using retroviral transduction. IPSCs have been shown to be pluripotent and can give rise to a wide range of mature cell types [6].

Skin stem cells as well fall into the classification as somatic stem cells, however, due to the cellular heterogeneity of skin, various types of skin stem cells were found in past decades [7]. Recently, significant advances have been made in identifying different types of skin stem cells with the aid of molecular tools. Subgroups of skin stem cells are listed as below.

1.1. *Epidermal stem cells*

Most resided in the basal layer of epidermis, can derive into transient amplifying cells and terminal-differentiated epidermal cells. Specified cell markers are p63, $\beta1^{high}$/melanoma chondroitin sulfate proteoglycan + (MCSP+), $\alpha6^{high}$/$CD71^{dim}$ [8–10].

1.2. *Follicular stem cells*

Located at the follicle bulge region, can derive into hair follicle epithelium, including outer root sheath, inner root sheath, and hair shaft. Specified cell markers are K15, CD34, Lgr5, Sox9, Lhx2, NFATC1, NFIB, K15, PHLDA1, CD200, K19, etc. [11–17].

1.3. *Melanocyte stem cells*

Located at the follicle bulge region and hair germ. Specified cell markers are Dct, Sox, and Pax3 [18–21].

1.4. *Sebaceous gland stem cells*

Resided around sebaceous glands and infundibulum. The unique cell marker is Blimp1 [22].

1.5. *Mesenchymal stem-cell-like cells*

Located at dermis, might divide into Mesodermal derivatives and some neural cell types. Specified cell markers are CD70, CD90, and CD105 whereas negative for CD34 [23].

1.6. *Neural progenitor cells*

Located at the follicle dermal papillae, might divide into neural and glial lineages, shared similar cell markers as counterparts in other organs or tissues.

1.7. *Hematopoietic stem cells*

Located at the follicle dermal papillae, might divide into erythroid and myeloid lineages, shared similar cell markers as counterparts in other organs or tissues.

Among all these distinct skin stem cell subgroups, epidermal stem cells are the most deeply correlated to tissue repair and skin regeneration. Scientific reports supported that stem cells of epidermis are rare, infrequently dividing, and generate short-lived, rapidly dividing cells that carry out the regeneration of the epidermis. The same infrequently dividing stem cells of epidermis are assumed to be the major epidermal cell population responsible for repairing skin injury. Most epidermal stem cells reside in the basal layer of epidermis, some might also be found in the bulge region of the hair follicle and the base of the sebaceous glands [24,25]. Throughout its whole life cycle, epidermal stem cells are circulated between two different cell phases. Under the slow cell phase, epidermal stem cells are quiescent. While entering transit amplifying cell phase, they are quickly divided and the number of skin cells is amplified for the replenishment of skin tissue. Finally, they undergo numerous cell divisions before becoming terminally differentiated to accomplish skin regeneration.

Toward skin injury, both epidermal stem cells and follicular stem cells contribute to the re-epithelialization of wounds [26–28]. In the full-thickness wound, epidermal stem cells and progenitor cells from the hair follicle initially migrate toward the wound site. Epidermal stem cells have been reported to be reactivated in response to skin injury and contribute to skin regeneration on the cellular level [29]. Further clinical evidence also suggested that epidermal stem cells and follicular stem cells participate in the re-epithelialization of wounds by evaluating the potential healing capacity of autologous scalp follicle grafts transplanted into chronic leg ulcerations. This pilot study reported that the size of ulcer areas reduced (27.1% vs. 6.5%, compared to the control group) by the end of eighteen weeks' engraftment in totally ten patients [30]. Epithelialization, neovascularization, and dermal reorganization were also enhanced within these wound areas. One interesting finding to note is that hair follicular progenitor cells were largely replaced by epidermal progeny following repair in a long-term follow-up. This accidental finding might indicate that nevertheless epidermal stem cells and hair follicular stem cells collaborate in the early phase of skin healing, however, the hair follicular stem cells might not be essential for the long-term maintenance after skin repair.

With the major advances of molecular biology, the role of small molecules involved in skin repairing has been well documented, ex. the miRNAs. MiRNAs are central regulators of gene expressions and are capable of tuning genes with either upregulations or downregulations. Therefore, miRNAs play key roles in various biological processes including cell survival, homeostasis, and differentiation. Several miRNAs were identified to be expressed exclusively in epidermal stem cells in animal models compared with other skin cells, including miR-200, miR-141, miR-429, miR-19 and miR-20 [31,32]. Upregulation of several miRNAs was also reported

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