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Sweat gland regeneration after burn injury: is stem cell therapy a new hope?

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Abstract

Stem cells are the seeds of tissue repair and regeneration and a promising source for novel therapies. The skin of patients with an extensive deep burn injury is repaired by a hypertrophic scar without regeneration of sweat glands and therefore loses the function of perspiration. Stem cell therapy provides the possibility of sweat gland regeneration. In particular, recent studies have reported the reprogramming of mesenchymal stromal cells into sweat gland–like (SGL) cells. We present an overview of recent researches into sweat gland regeneration with stem cells. Difficulties of sweat gland regeneration after deep burns have been elaborated. The advantage and disadvantage of several stem cell types in sweat gland regeneration have been discussed. Additionally, the possible mechanisms for reprogramming stem cells to SGL cells are summarized. A brief discussion on clinical application of stem cell–derived SGL cells is also presented. This review may possibly provide some implications for sweat gland regeneration.

Key Words: *burn injury, regenerative medicine, reprogramming, stem cells, sweat glands*

Introduction

The key points of regenerative medicine are repair, replacement or regeneration of cells, tissues or organs, and therefore recovery of the disrupted functions resulting from any reason including congenital defects, disease, trauma and aging. The most valuable cells in regenerative medicine are stem cells, a kind of special cell with capabilities of self-renewal and differentiation into specific types of functional cells. In recent years, stem cells and regenerative medicine have comprised a new prospective field of biomedicine and exhibit a great potential for clinical application [1,2]. Recently, the regeneration of cutaneous appendages during the repair of damaged skin has become an important direction in the field of stem cells and regenerative medicine [3].

As an important appendage of the skin, which is the largest organ of the body, sweat glands perform several functions including secretion of sweat, excretion of wastes, maintenance of body temperature and inhibition of bacterial growth by secretion of lactate. In patients with deep burns, the injury can reach the muscle tissues and damage sweat glands. Although the current success rate of burn treatments is higher and higher, the skin of almost all treated patients with large-area burns is repaired by hypertrophic scarring without regeneration of sweat glands. Because of the loss of perspiration, burn survivors have severe pain in summer, which affects their quality of life. Therefore, recovery is incomplete. In addition, many genetic diseases are associated with abnormal development and function of the sweat glands [4–6] and cannot be treated with the use of modern medicine. Therefore, regeneration of sweat glands in the skin has become a focus of modern medical study.

According to differentiation potential, stem cells can be divided into totipotent stem cells (for example, embryonic stem cells [ESCs] and induced pluripotent stem cells [iPSCs]), multipotent stem cells (for example, adipose stem cells) and unipotent stem cells (for example, epidermal stem cells). According to advent order during embryonic development, stem cells can be divided into ESCs and adult stem cells (for example, bone marrow mesenchymal stromal cells [BM-MSCs]). Recently, with in-depth study of stem cell biology and regenerative medicine, therapies that use stem cells have shown a high

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capability for tissue regeneration such as muscle regeneration by ESCs [7], neural regeneration by BM-MSCs [8,9] and cardiac regeneration by iPSCs [10,11]. These studies highlight the potential for sweat gland regeneration using stem cells. In this review, we focus on some of the significant advances made recently in sweat gland regeneration.

Difficulties of sweat gland regeneration after deep burns

The sweat glands develop from epidermal cells during embryonic development [12]. Mature sweat gland is composed of a ductal portion and a secretory portion. The duct portion opens at the orifice across the epidermis. Larger ducts that coil together form a secretory portion that locates in subcutaneous tissue. Luminal cells of sweat glands take in water and electrolytes from blood and convert them into sweat. Glands are surrounded by myoepithelial cells, whose contractions can help to exhaust sweat. Recent studies indicated that mature sweat glands still contain stem cells or progenitor cells [13–16]. There were four populations of stem cells within glandular skin including epidermal progenitors, ductal progenitors, luminal progenitors and myoepithelial progenitors. In the process of wound repair, ductal progenitors participated in regenerating the sweat duct orifice and epidermal progenitors adjacent to the wound focused on epidermal repair. In engineered mice, diphtheria toxin selectively induced the apoptosis of luminal and myoepithelial cells in sweat glands. In response, surviving myoepithelial progenitors proliferated to replace damaged myoepithelial cells and surviving luminal progenitors proliferated to replace damaged luminal cells, and sweat production was then restored [13]. However, in most cases of deep burns, stem cells in the injured sweat glands cannot achieve the regeneration of sweat glands. Furthermore, after scar healing, the new epidermal stem cells also fail to differentiate into sweat gland cells, which results in the functional loss of perspiration of the healed wound with scarring. Therefore, understanding the effect of scar healing on sweat gland regeneration by epidermal stem cells will be helpful to guide the study of sweat gland regeneration.

The microenvironment surrounding the stem cells is also called the stem cell niche [17]. Modulation of proliferation and differentiation of epidermal stem cells by the stem cell niche mainly involves cell-cell and cell–extracellular matrix interactions. In addition, cytokines play important roles in transmitting information between cells and the extracellular matrix [18]. Regeneration of sweat gland cells is also regulated by the above factors because the sweat gland cells are homologous with the basal epidermal stem cells [19]. However, under the conditions of scar formation after deep burns, the internal and external environments for self-renewal of the stem cells have been changed. First, the cell quantity and types in the scar are different from those in normal skin. Second, the extracellular matrix metabolism related to sweat gland development is disordered. Third, the basal membrane of scar tissues loses the normal structure and function. All these factors will affect sweat gland regeneration by endogenous stem cells in scars.

After wound healing by scarring, the absence of perspiration in healed areas does not necessarily indicate that there is no sweat gland tissue in the scar. A previous study indicated that there was an expression of carcinoembryonic antigen and cytokeratin 8, which are thought to be markers of sweat gland cells, in the scar tissue [20]. Therefore, it has been proposed that there is a biological basis and potential for sweat gland regeneration in the wound after burns. The reason for the lack of reconstruction of sweat glands in proliferative scars is related to the excessive speed of scar repairing over sweat gland regeneration. The proliferative scar then forms a barrier that prevents sweat gland regeneration. To solve the difficulty of perspiration in patients with deep burns, scarring must be removed, followed by transplantation of sweat gland cells or tissue-engineered skin containing sweat gland cells. However, the sweat gland cells in patients are very few and seriously damaged, therefore, researchers have tried to obtain sweat gland cells from several stem cell types.

iPSC reprogramming and direct reprogramming

Somatic cell reprogramming holds tremendous potential for cell therapy and regenerative medicine. There are two different reprogramming strategies. Induced pluripotent stem cell technology was invented in 2006 that established the exciting field of cellular reprogramming [21]. In this technology, forced expression of OCT4, KLF4, SOX2 and C-MYC reprogrammed fibroblasts to yield pluripotent stem cells that could later be coaxed *ex vivo* to differentiate into certain cell types. Other studies followed, with the aim of reducing the number of transcription factors required, and showed that the generation of iPSCs was possible without the oncogene C-MYC [22,23] and under specific culture conditions by transduction of the single transcription factor OCT4 alone [24]. Although iPSCs can be used to derive a desired cell type, a limitation of this technology is the length of time it takes to first reprogram the cells and then subsequently direct them to the preferred state. Because the procedure of