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Review

Mesenchymal stem cells for sweat gland regeneration after burns: From possibility to reality

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ABSTRACT

Sweat glands play important roles in homeostasis maintenance and body temperature regulation. In patients with deep burns, the injury can reach the muscle tissues and damage sweat glands. However, the plasticity of mesenchymal stem cells (MSCs) may offer the possibility to regenerate sweat glands after severe burn. In particular, recent studies have changed the possibility to reality. Here, we analyze the barriers of sweat gland regeneration *in situ* after deep burns, propose the possibilities of MSCs in regeneration of sweat glands, summarize the recent researches into sweat gland regeneration with MSCs, and sum up the possible mechanisms during this process. In addition, the advantage and disadvantage of sweat gland regeneration with MSCs from different tissues have been discussed. So this review will provide meaningful guidance in the clinic for sweat gland regeneration with MSCs.

Contents

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Abbreviations: SGL, sweat-gland-like; BM-MSCs, bone marrow mesenchymal stem cells; UCB, umbilical cord blood; WJ, Wharton's jelly; ERK, extracellular regulated protein kinase; MAPK, mitogen-activated protein kinase; EGF, epidermal growth factor; FGF-10, fibroblast growth factor-10; HGF, hepatocyte growth factor; EDAR, Ectodysplasin-A1 receptor; HED, hypohidrotic ectodermal dysplasia; EDARADD, EDAR-associated death domain; NF, nuclear factor; IKK, IκB kinase.

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1. Introduction

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 [1]. Sweat gland is a kind of important appendage of the skin, which plays some key roles in homeostasis maintenance and body temperature regulation. The skin of patients with an extensive deep burn is repaired by a hypertrophic scar [2] without regeneration of sweat glands, and therefore loses the function of perspiration. Burns survivors feel the heat very much and have to rest at home in summer, which affects their quality of life. Therefore, regeneration of sweat glands in the skin has become a focus of modern medical study [3].

Meanwhile, the recent progress in stem cell research in regenerative medicine is remarkable [4–6]. Cell therapy with MSCs holds enormous promise for the treatment of damaged organs using regenerative technology [7]. MSCs can be obtained from adult tissue such as bone marrow [8,9], adipose tissue [10], umbilical cord [11] and others. Under suitable conditions, MSCs can differentiate into various types of cells such as neural cells [12,13], osteocytes [14,15], adipose cells [16], muscle cells [17] and vascular endothelial cells [18]. The unique property of MSCs highlights the potential for sweat gland regeneration. In this review, we focus on the barriers of sweat gland regeneration after deep burns and the possibilities, recent researches and possible mechanisms of MSCs in regeneration of sweat glands after deep burns.

2. Regeneration barriers of sweat glands after deep burns

The sweat glands develop from the cells in epidermis during embryonic development [19]. Recent studies indicated that mature sweat glands still contain stem cells or progenitor cells [20–23]. However, in most cases of deep burns, above 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 loss of sweating function in the wound healed with scarring. Therefore, understanding the effects 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 called the stem cell niche [24]. 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 [25]. 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 [26]. However, under the condition of scar formation after deep burns, the internal and external environments for self-renewal of the stem cells have 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 were expressions of carcinoembryonic antigen and cytokeratin 8, which are thought to be markers of sweat gland cells, in the scar tissue [27]. 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 re-construction 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 deep burn patients, scar needs to 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 are trying to obtain sweat gland cells from mesenchymal stem cells.

3. Possibility of MSCs in regeneration of sweat glands

MSCs have proved to be an attractive cell type for various cell therapies due to their ability to differentiate into various cell lineages, multiple donor tissue types, and relative resilience in *ex vivo* expansion, as well as immunomodulatory effects during transplants. Recent findings of both experimental studies and clinical trials demonstrated that MSCs were able to repair skin. First, MSCs can differentiate into epidermal-like cells [28] and enhance the reepithelialization during wound repair. Animal autografting experiments with MSCs showed the increased number of epidermal ridges and thickness of the regenerated epidermis [29]. It is interesting to find in one animal experiment that GFP-labeled marrow stem cells were noted in hair follicle, epidermis, and sebaceous glands [30]. Second, MSCs can promote revascularization of the wound