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MINI REVIEW

Protective role of adipose-derived stem cells and their soluble factors in photoaging

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Abstract As individuals age, the skin undergoes changes, such as irregular pigmentation, thinning and loss of elasticity, that are due to both genetic and environmental factors. These changes may worsen, progressing to precancerous and cancerous diseases. Various medical treatments and topical cosmeceuticals have been used to treat some symptoms of photoaging, however, the results have been less than satisfactory. Mesenchymal stem cells within the stromal-vascular fraction of subcutaneous adipose tissue, adipose-derived stem cells (ADSCs), display multi-lineage developmental plasticity and secrete various growth factors that control and manage the damaged neighboring cells. Recently, the production and secretion of growth factors has been reported as an essential function of ADSCs, and diverse regenerative effects of ADSCs have been demonstrated in the skin. For example, conditioned medium from ADSCs (ADSC-CM) stimulated both collagen synthesis and migration of dermal fibroblasts, which improved the wrinkling and accelerated wound healing in animal models. ADSC-CM also inhibited melanogenesis in B16 melanoma cells, and protected dermal fibroblasts from oxidative stress induced by chemicals and UVB irradiation. Therefore, ADSCs and soluble factors show promise for the treatment of photoaging, and this review introduces recent research developments of the ADSCs and ADSC-derived secretory factors regarding this issue.

Keywords Adipose-derived stem cell · Photoaging · Anti-wrinkling · Antioxidant · Whitening

Introduction

Regenerative medicine that uses the body's own stem cells and growth factors is an alternative therapeutic strategy for repair of damaged tissue, and is becoming a predominant cell-based therapy. Adipose-derived stem cells (ADSCs) display multi-lineage developmental plasticity and secrete various growth factors such as vascular endothelial growth factor (VEGF), insulin-like growth factor (IGF), hepatocyte growth factor (HGF) and transforming growth factor-beta1 (TGF-β1), and these proteins control and manage the damaged neighboring cells. Recently, the production and secretion of growth factors has been identified as essential functions of ADSCs (Fig. 1), and diverse rejuvenation effects of ADSCs on skin have been demonstrated [16–19, 26]. For example, we demonstrated that ADSCs and conditioned media from ADSCs (ADSC-CM) stimulated both collagen synthesis and migration of dermal fibroblasts during the wound-healing process [18]. ADSC-CM also inhibited melanogenesis by down-regulation of tyrosinase and tyrosinase-related protein-1 (TRP-1) expression in the B16 melanoma cells [19]. In addition, ADSCs and ADSC-derived secretory factors protected dermal fibroblasts from oxidative stress induced by chemicals and UVB irradiation [16]. In a clinical setting, intradermal injection of processed lipoaspirate cells, which are approximately 20–30% of ADSCs, results in the increase of dermal thickness and the reduction of wrinkles [17, 26]. These evidences support the

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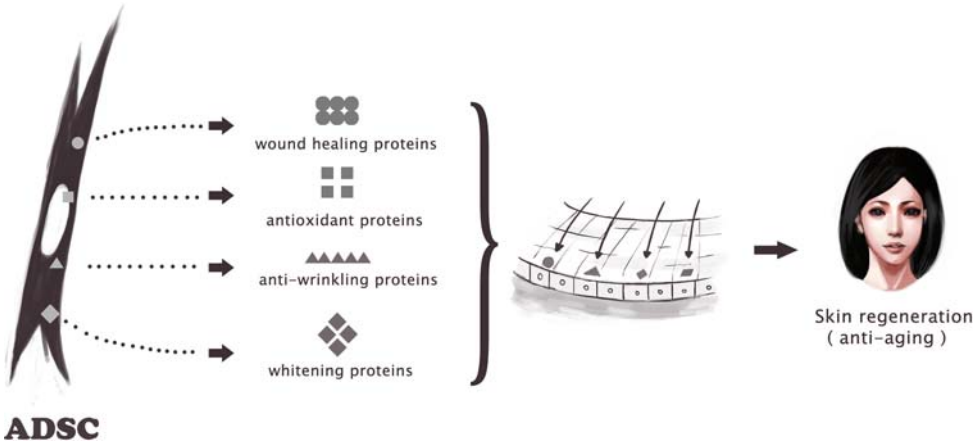

Fig. 1 Paracrine effect of ADSCs and skin regeneration

critical role of ADSCs and their secretory factors in protecting the skin from photodamage.

Chronic UV radiation damages human skin, affecting skin tone and resiliency and leading to premature aging (photoaging), the symptoms of which include leathery texture, wrinkles, mottled pigmentation, laxity and sallowness, and in the long run precancerous (actinic keratoses, letigo maligna) and cancerous change. However, conventional anti-aging skin treatments are less than satisfactory, because their primary mechanism is mainly inducing new collagen synthesis via activation of dermal fibroblasts. On the basis of our previous studies that demonstrated the wound healing, antioxidant, antiwrinkle and skin-whitening effects of ADSCs and their secretory factors (Fig. 1), they may be good candidates for the treatment of photoaging [16–19, 26]. Therefore, this brief review describes our recent research developments on the anti-aging effects of ADSCs and ADSC-derived growth factors.

Adipose-derived stem cells and skin regeneration

The aim of tissue engineering is to repair and regenerate damaged organs using a combination of cells, biomaterials and cytokines. The limited availability of human cells that are capable of self-renewal and differentiation into multiple cell types is a barrier to expansion and development of tissue engineering. Stem cells and progenitor cells offer a potential solution to this dilemma. Especially, ADSCs have been used in skin regeneration with satisfactory results.

Adipose-derived stem cells and paracrine effects

Due to the lack of a specific and universal molecular marker for adult stem cells, functional assays for multiple differentiations must be used to identify stem cells in a tissue. Mesenchymal stem cells (MSCs) were first characterized in bone marrow, but many studies have reported the existence of MSCs in the connective tissue of several organs [12, 29]. The role of these cells is not entirely clear, but they are generally believed to constitute a reserve cellular fraction for tissue maintenance and repair. The most abundant and accessible source of adult stem cells is adipose tissue, and observations under physiologic and pathologic conditions suggest that MSCs exist in human adipose tissue. The yield of stem cells from adipose tissue is approximately 40-fold greater than that from bone marrow, and ADSCs are available in liposuction aspirate [3, 11, 13].

Recent phase I and II clinical trials indicate that stem cell treatment is safe, practical and effective for repair of damaged tissue [33, 34]. Despite rapid translation to the bedside, the mechanism of action is not well characterized. It was initially hypothesized that immature stem cells migrate to the injured area, differentiate into the phenotype of injured tissue, repopulate the diseased organ with healthy cells, and subsequently repair the tissue (building-block function). However, the levels of engraftment and survival of engrafted cells are too low, i.e., <5%, to be therapeutically relevant [38]. In addition, acute stem cell-mediated improvement within days or even hours makes it difficult to fully explain the mechanisms by which regeneration occurs [8, 40]. Importantly, much of the functional improvement and attenuation of injury afforded by stem cells can be achieved by treatment with cell-free conditioned media derived from stem cells [27]. Thus, it can be deduced that stem cells may exert their beneficial effects via complex paracrine actions (manager function) in addition to building-block function.

Wound-healing effects of ADSCs and ADSC-derived growth factors

Several studies of the pathophysiology of photoaging have detected similarities with certain aspects of chronic wounds [10, 39]. Histologically, photo-aged skin shows marked

alterations in ECM composition [17, 44]. The collagenous component of dermal ECM is responsible for the strength and resiliency of skin and is intimately involved in the pathology of photoaging and wound. Although chronic wounds are common in degenerative diseases, treatment of these disabling conditions remains limited and largely ineffective. Recently, autologous MSCs were found to accelerate wound healing in human cutaneous wounds. Wu et al. [42] showed that injection of bone marrow-derived mesenchymal stem cells (BMSCs) near the wound significantly enhanced wound healing in normal and diabetic mice compared with injection of allergenic neonatal dermal fibroblasts. Notably, conditioned medium from BMSCs contains paracrine effectors for wound healing, and has mediated wound healing in diverse experimental systems [5].

ADSCs have surface markers and gene profiling similar to BMSCs and their soluble factors are not significantly different [12, 18]. Given their convenient isolation compared with BMSCs and extensive proliferative capacities ex vivo, ADSCs hold great promise for use in wound repair and regeneration. However, there is little evidence demonstrating the wound-healing effects of ADSCs [1, 18]. Our group first demonstrated that ADSCs accelerate skin wound healing, especially with regard to fibroblast activation [18]. ADSCs promote proliferation of dermal fibroblasts, not only by direct cell-to-cell contact, but also by paracrine activation through secretory factors. Furthermore, ADSC-CM enhanced secretion of type I collagen from dermal fibroblasts and stimulated fibroblast migration in in vitro wound-healing models. ADSCs secreted a variety of growth factors such as basic fibroblast growth factor (bFGF), keratinocyte growth factor (KGF), TGF-β1, HGF and VEGF, into the conditioned medium, which might mediate the wound-healing effect of ADSCs. In addition to the in vitro evidence, the wound-healing effect of ADSCs was also verified in an animal study, which showed that topical administration of ADSCs significantly reduced the wound size (34% reduction) and accelerated the re-epithelialization at the wound edge (Fig. 2). Similar to ADSC treatment, ADSC-CM treatment also accelerated wound healing in laser-induced burn animal models (our unpublished data).

Hypoxia amplifies the paracrine effects of ADSCs by enhancing the secretion of certain growth factors [20, 21, 32]. For example, ADSCs improved perfusion in hindlimb ischemia induced by the ligation of femoral arteries and ADSC function was enhanced by hypoxic culture conditions [20]. Because inflammation and oxidative stress near the wound area in the skin evokes an oxygen deficit, the wound-healing effect of ADSCs was investigated in hypoxia (in press). As expected, secretomes of ADSCs cultured in hypoxia significantly reduced the wound area compared with those in normoxia. Furthermore, mRNA and protein measurements showed that hypoxia up-regulated some growth factors such as VEGF and bFGF. An inhibition study using neutralizing antibodies of VEGF and bFGF resulted in delayed wound healing, which indicates that VEGF and bFGF, at least partially, account for the hypoxia-enhanced function of ADSCs. These results suggest that wound-healing effect of ADSC is at least partially mediated by secretory factors, and increased by hypoxia.

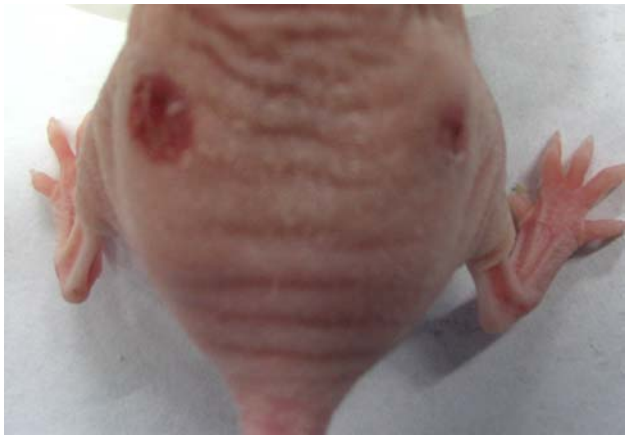

Fig. 2 Wound-healing effects of ADSCs in nude mice. Artificial wounds were made using a 6-mm punch biopsy and ADSCs were topically applied. The wounded area was significantly reduced in the ADSC-treated group (right side of the back) 7 days after surgery

Antioxidant effects of ADSCs

Currently, a hot topic in dermatology is the exploration of every possible means to counteract the injurious effects of anatomical–functional damage to the skin. Of great interest are substances that prevent skin damage from free radical-induced skin damage. Although there are only a few reports on the antioxidant action of ADSCs, some evidence supports a protective effect of secretomes of ADSCs during oxidative injury. For example, IGF reportedly protects fibroblasts and intestinal epithelial cells from free radicals [2, 30]. HGF protects the retinal pigment epithelium against oxidative stress induced by glutathione depletion [35]. Pigment epithelium-derived factor (PEDF) is an anti-angiogenic/neurotropic factor and has been shown to have antioxidant effects [37]. Interleukin-6 (IL-6) reduces the epithelial cell death induced by hydrogen peroxide [14]. These evidences suggest that ADSCs exhibit an antioxidant effect, however, the mechanism of protective effect is yet to be determined.

As ADSCs are located under the skin, particularly beneath dermal fibroblasts, they may play significant roles in skin damage involving oxidative stress. Therefore, the antioxidant effects of ADSC-CM on dermal fibroblasts were investigated in an oxidative injury model. In a ADSC-CM,

various antioxidant proteins, such as IGF binding proteins, IL-6, PEDF, SOD2 and HGF, were detected by proteomic analysis and enzyme-linked immunosorbent assay. Both morphological changes and a cell-survival assay revealed that incubation with ADSC-CM protected dermal fibroblasts against free radicals induced by tbOOH. In addition, activities of both SOD and glutathione peroxidase were enhanced in dermal fibroblasts after treatment with ADSC-CM. Cell cycle analysis demonstrated that ADSC-CM treatment reversed the apoptotic cell death induced by ROS, as evidenced by a significant decrease of sub-G1 phase dermal fibroblasts (Fig. 3).

In general, stem cells are regarded as the origin of malignant cells and stem cells induce tumor growth in various systems [28, 31, 36]. However, the inhibition of tumor growth by MSCs has been reported in the skin of animal models [22, 23]. For example, Maestroni et al. [23] first demonstrated that melanoma B16 cells were inhibited by BMSC injection, but the mechanisms were not characterized. Recently, we discovered that ADSC-CM inhibited the proliferation of B16 melanoma cells without induction of apoptosis. Although the mechanism responsible for the anticancer effects of ADSC-CM are yet to be fully characterized, secretory factors of ADSCs prolonged the G1 phase in B16 cells (G1 arrest), delaying the progression of cancer (our unpublished data). Considering the antioxidant and anticancer effects of ADSC-CM, it is reasonable to assume that ADSCs play a key defensive role against the oxidative stress in the skin.

Potential application of ADSC in photoaging

Sun exposure harms the skin due to the effects of UV radiation. UVA and UVB reportedly alter specific cellular pathways leading to different consequences. UVB radiation causes redness of the skin, whereas UVA penetrates deeper into the dermis where it causes more DNA damage. Exposure to UV radiation has a significant effect on collagen production and pigmentation and is responsible for skin thickening, mottled pigmentation and wrinkling [43]. However, ADSCs protect the skin against UV irradiation, improve wrinkling and reduce pigmentation.

Anti-wrinkling effects of ADSCs

Topical application of growth factors stimulates the repair of photo-damaged skin, resulting in new collagen synthesis, epidermal thickening and the clinical appearance of smoother skin with less visible wrinkling [4, 9]. A cell-based treatment

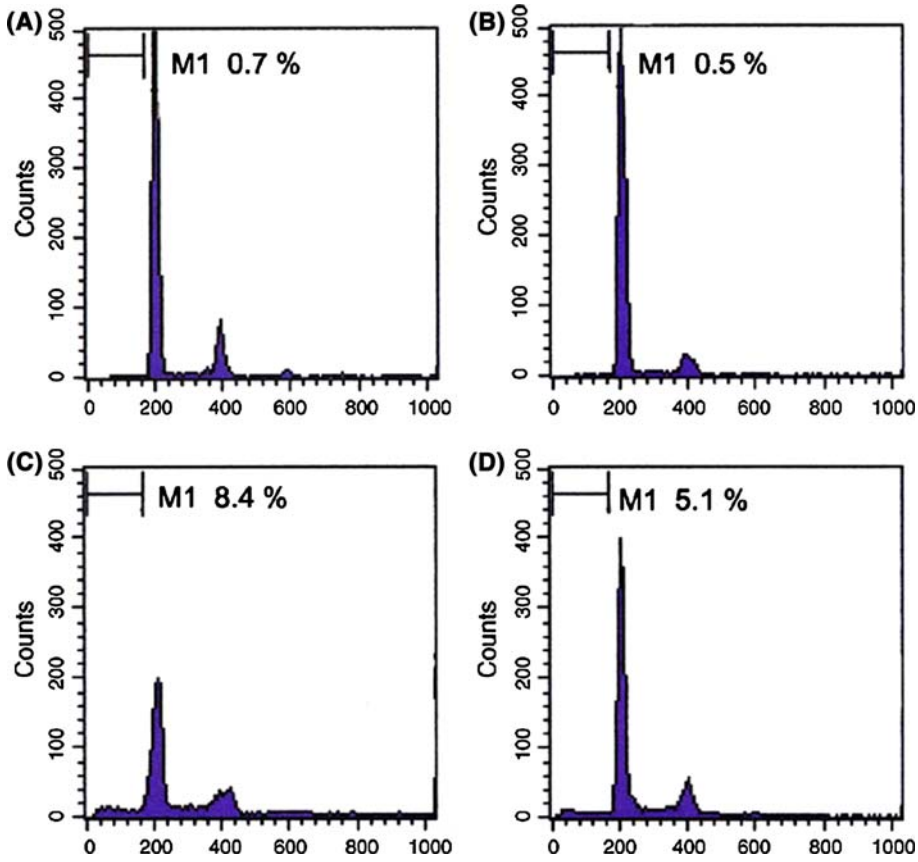

Fig. 3 Antioxidant effects of ADSCs. Untreated dermal fibroblasts and fibroblasts incubated with ADSC-CM showed similar distributions among cell cycle phases (**a** and **b**, respectively). tbOOH-treated cells exhibited a significant increase in the sub-G1 phase, which is indicative of apoptotic cell death (**c**). However, this phenomenon was reversed by pre-treatment with ADSC-CM (**d**)

that use autologous cultured dermal fibroblasts was developed to improve skin texture with relatively satisfactory results in clinical applications [41]. Because several growth factors involved in skin regeneration are secreted from ADSCs, and characteristics of ADSCs are similar to fibroblasts, it was hypothesized that ADSCs may improve UVB-induced wrinkling. In our experiments, wrinkles were induced by an 8-week regimen of UVB irradiation and the antiwrinkle effects of ADSCs were investigated following the subcutaneous injection of ADSCs in hairless mice. Wrinkling was reduced following subcutaneous injection of ADSCs (greater than 1×10^4 cells) (Fig. 4). In addition, dermal thickness and collagen content in the dermis were increased in the ADSC-injected animals, as confirmed by H&E and Masson's trichrome staining. To examine the paracrine mediators of the antiwrinkle effects of ADSCs, dermal fibroblasts were incubated in ADSC-CM. UVB irradiation reduced the proliferation of dermal fibroblasts, but this was reversed by pretreatment of ADSC-CM. Cell cycle analysis revealed that secretomes of ADSCs decreased UVB-induced apoptotic cell death, as evidenced by a reduction in the sub-G1 phase of fibroblasts. In addition, the ADSC-CM increased the protein expression of type I collagen and decreased the protein level of MMP 1 in fibroblasts, which may explain the increased collagen content of the dermis in an animal experiment.

To study the antiwrinkle effects of ADSCs in the skin of micropigs, we twice injected ADSCs and ADSC-CM intradermally into the back of micropigs. Histological evaluation showed a small but indefinite increase in dermal thickness at the ADSC- and ADSC-CM-injection sites. However, a distinct increase in collagen expression in the skin injected with ADSCs and ADSC-CM was demonstrated using Western blot analysis [26]. Moreover, in a pilot study, intradermal injections of purified autologous processed lipoaspirate cells (1×10^6 cells in 1 ml HBSS solution), which were approximately 20–30% of ADSCs, were tested in the photo-aged skin of one patient. The female patient was administered two successive injections. Two months after the second injection, the patent showed improvement in general skin texture and wrinkling. Collectively, these results indicate that ADSCs and their ADSC-derived secretory factors are effective anti-wrinkle treatments.

Whitening effects of ADSCs

Clinically, photo-aged skin is coarsely wrinkled and exhibits associated dyspigmentation and telangiectasia. In Asians, the principal manifestation of photodamage is pigmentary change rather than wrinkling [6, 7]. Antioxidants inhibit the chemical reactions that lead to melanin formation, change the type of melanin formed, and interfere with the distribution of pigment and melanosome transfer. Therefore, they are good candidates for skin whitening agents. In addition, some growth factors reportedly regulate melanogenesis and are major regulators of tyrosinase and TRPs [15, 24, 25]. Because ADSC-CM has potent antioxidant

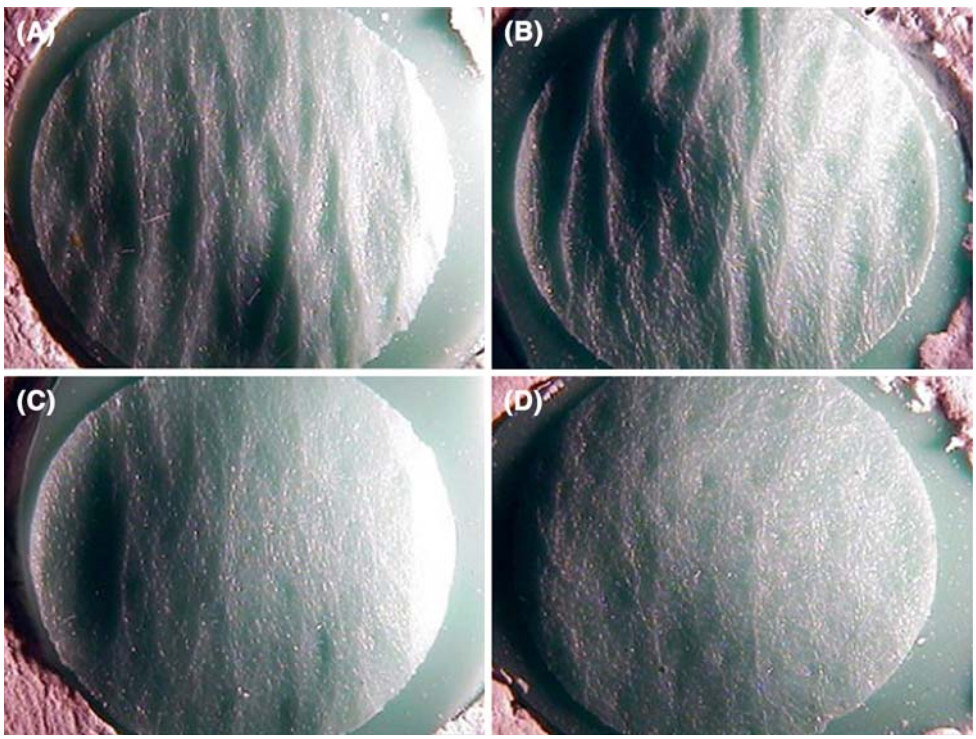

Fig. 4 Anti-wrinkling effects of ADSCs. Wrinkles were induced by 8 weeks of UVB irradiation and ADSCs were subcutaneously injected three times. Wrinkles were evaluated by replica analysis. Control (**a**), 1×10^3 cells (**b**), 1×10^4 cells (**c**), and 1×10^5 cells (**d**)

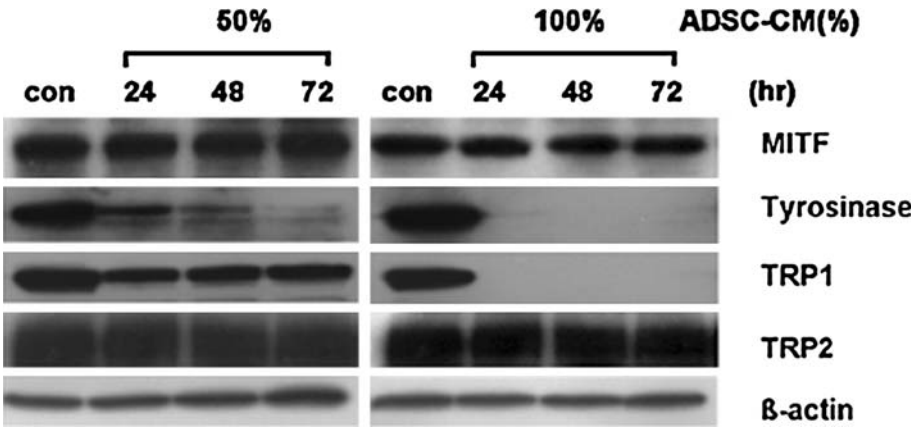

Fig. 5 Skin-whitening effect of ADSC-CM. Expression of MITF and TRP2 was unchanged, but expression of tyrosinase and TRP1 was down-regulated by ADSC-CM treatment in B16 melanoma cells

activity and contains whitening growth factors, the whitening effects of ADSC were investigated [19]. ADSC-CM was harvested and its inhibitory effects were studied in melanoma B16 cells. ADSC-CM treatment inhibited both the synthesis of melanin and the tyrosinase activity in a dose-dependent manner. To clarify the underlying mechanisms of the whitening action of ADSC-CM, melanogenic proteins were qualified using Western blot. Although expression of microphthalmia-associated transcription factor (MITF) and TRP2 remained unchanged, expression of tyrosinase and TRP1 was down-regulated by ADSC-CM treatment (Fig. 5). TGF-β1, a potent regulator of melanogenic proteins, was neutralized by the addition of a blocking antibody to ADSC-CM, and the down-regulation in tyrosinase and TRP1 was nearly reversed. Although the mechanism responsible for the whitening effect of ADSCs has not been fully characterized, secretory factors may down-regulate the expression of melanogenic enzymes and TGF-β1 plays an important role.

Perspective

The pharmacology of ADSCs and ADSC-derived secretory factors that are involved in anti-aging was reviewed in this paper. To date, application of ADSCs and their secretory factors have been investigated mainly in vitro and with animal models, so clinical trials in humans are needed. Because ADSCs and ADSC-derived secretory factors have anti-wrinkling, antioxidant and skin-whitening effects, they are promising anti-aging agents. However, since ADSCs are difficult both to handle and to commercialize, methods to overcome these barriers are needed. Instead, ADSC-derived secretory factors have numerous advantages over cell-based therapies and have great potential. Therefore, isolation and characterization of ADSC-derived secretory factors that have anti-aging effects will be the next goal of our research, as identification of these factors will suggest new strategies for anti-aging therapies.

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