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The role and mechanism of adipose stem cells in facial anti-aging

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Abstract. ADSCs are stem cells found in adipose tissue that can self-renew in vitro and undergo multidirectional differentiation in containers. They may have anti-aging effects through their growth factors as well as their multidirectional differentiation function. In this paper, we searched PubMed, Web Of Science, CNKI, and other databases for related articles in recent years through relevant keywords, and the results showed that ADSCs have significant effects on facial anti-aging such as inhibiting skin wrinkle increase, whitening facial skin, and promoting hair regeneration. This paper presents a multifaceted analysis of the underlying mechanisms of action and related research on the application of adipose stem cells in facial skin anti-aging. It will enable medical aesthetic physicians to have a better understanding of the role and mechanism of ADSCs in facial anti-aging so that they can better provide healthy and standardized medical aesthetic services.

Keywords: adipose stem cells, anti-aging, facial skin, natural aging, photoaging.

1. Introduction

Facial skin aging includes both endogenous and exogenous aging, The main cause is the photo degeneration of the elastin matrix and deep dermal elastin fibers, leading to wrinkles, hyperpigmentation, and other facial skin problems. With the rapid development of the social-economic level, there is a growing concern about the problems associated with anti-aging. Adipose-derived stem cells (ADSCs) are a type of stem cell that is found in adipose tissue, isolated and able to self-expand in vitro, and can multiply. ADSCs are directly involved in the regeneration of facial skin. The paracrine function of ADSCs can secrete various growth factors and inflammatory factors and activates intracellular telomerase to improve the proliferative capacity and differentiation potential of ADMSCs. It has significant effects in the anti-aging of facial skin, whitening, tissue trauma repair, and other aspects of anti-aging. At the same time, ADSCs have become an ideal tool for cell therapy and tissue engineering applications due to their wide source, easy access, low tissue damage, rapid expansion, stable nature, and easy clinical collection.

However, there are relatively few studies on the role and mechanism of ADSC in facial anti-aging. It is reviewed in this paper.

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2. Method

The search terms "ADSCs, Nrip1, paracrine, anti-aging, MTS (multiple tumor suppressor 1), p16, RB gene, skin" and "adipose stem cells, facial, NRIP1, p16 gene, RB gene, facial skin" were used respectively. They were used to search PubMed, SCIE, and CNKI databases for relevant articles and to select articles with reliable arguments and evidence in the same field. The articles were selected from the same field of literature and selected from recent publications or authoritative journals. The aim is to provide a deeper understanding and insight for the general medical aesthetician.

3. Overview of facial skin aging

Facial skin aging is a complex and continuous process with the main clinical manifestations of wrinkles and hyperpigmentation, including endogenous and exogenous aging [1]. Endogenous aging, also known as natural aging, is caused by intrinsic factors in non-exposed areas and is mainly caused by programmed apoptosis, and is influenced by genetic regulation and family history. Exogenous aging, also known as photo-aging, is mainly caused by UV radiation in exposed areas. It causes a decrease in the proliferation and synthesis capacity of fibroblasts (FB), resulting in a thinning of the dermis and aging of the skin.

The cells and tissues of the epidermis, dermis, and skin appendages all change as the body ages, with the most characteristic change being in the composition of the dermis. The dermis is rich in collagen fibers, reticular fibers, elastic fibers, and amino and proteoglycan substrates, of which collagen fibers are the most abundant. During the aging process of the facial skin, the collagen fiber content gradually decreases, the thickness of the dermis thins, and the elastic fibers degenerate, decrease and lose elasticity and tone, leading to a series of external aging manifestations of facial skin aging [2]. This leads to a series of external signs of aging.

Facial skin aging is characterized by wrinkles, dullness, uneven pigmentation, and hair loss [3].

4. Fat stem cells and anti-aging of facial skin

4.1. Adipose stem cells

ADSCs are stem cells that are found in adipose tissue and are capable of self-expansion and multidirectional differentiation in vitro after isolation.

Stem cells have been isolated from tissues and organs for instance bone marrow, skin, peripheral blood, and umbilical cords. However, these stem cells have the disadvantage of being highly invasive, having low tissue collection and low cell yield. In contrast, ADSCs are derived from adipose tissue and obtained by aspiration-assisted lipectomy (i.e. liposuction) [4]. Compared with the above stem cells, ADSCs have less tissue damage [5]. It has the advantages of less tissue damage than the above-mentioned stem cells, a wide range of sources, easy to obtain, and low immunogenicity [6]. At the same time, it avoids the ethical issues associated with other stem cells, for instance, embryonic stem cells [7].

4.2. Potential mechanisms of ADSCs in anti-aging of facial skin

During the aging process, external factors such as UV light induce an increase in matrix metalloproteinase-1 (MMP-1) activity in human dermal fibroblasts (HDFs), leading to increased collagen degradation and reduced regeneration [8], while a decrease in the synthesis of HDFs induces a decrease in the production of type I collagen. Stimulation of HDFs with ADSCs may induce a decrease in MMP-1 expression and collagen hydrolase synthesis [9]. This may increase collagen content and enhance the stability of the extracellular matrix (ECM) [10].

In addition to their differentiation potential, ADSC can also secrete various growth factors（Fig.1）. These growth factors and inflammatory factors can signal to surround tissues and cells, enhance cell proliferation and migration, and promote angiogenesis and anti-apoptosis, thus improving skin fibroblast damage caused by exogenous aging and showing a constructive effect on the anti-aging of facial skin.

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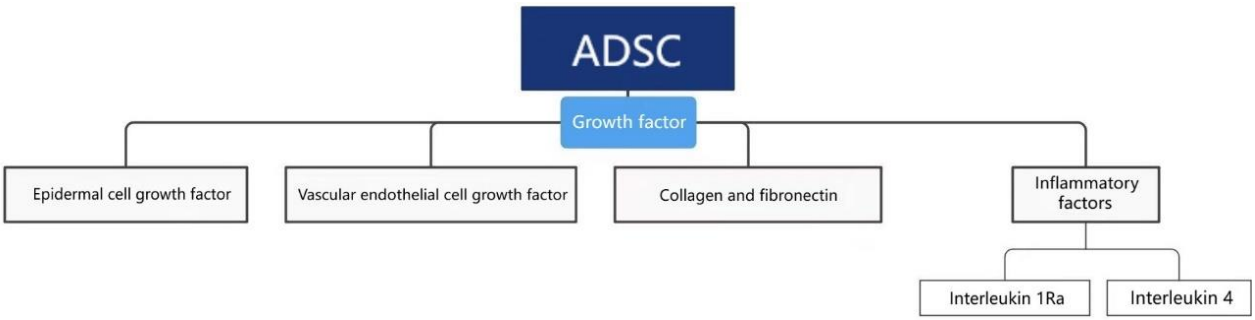

Figure 1. Secretion of common growth factors by adipose stem cells.

5. Application of ADSC in anti-aging of facial skin

5.1. The mechanism of ADSCs in the anti-wrinkle of facial skin

Exogenous aging processes such as UV radiation, increase MMP expression and contribute to ECM degradation [11]. This leads to the degradation of collagen and changes the deposition of elastic tissue. This is manifested by the formation of wrinkles in the facial skin [12].

In addition, exposure of facial skin to UV light increases the level of reactive oxygen species (ROS), which activates the cytoplasmic signal transduction pathway of fibroblasts, depleting and disrupting the skin's non-enzymatic and enzymatic antioxidant defense mechanisms, leading to the formation of wrinkles due to oxidative impairment.

The most important skin regeneration process in photodamage is collagen remodeling and the most significant cells in the collagen remodeling process are HDFs. （Figure 2）

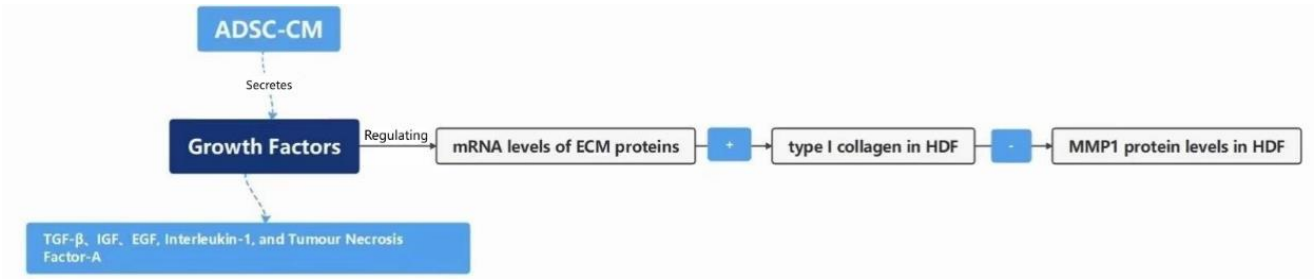

Figure 2. Schematic diagram of the anti-wrinkle mechanism of action of ADSCs.

Secreted proteins such as SOD and some cytokines in the conditioned medium of ADSCs (ADSC-CM) may mediate HDFs to enhance the activity of superoxide dismutase (SOD) and glutathione peroxidase (GPx) in HDFs, thereby resisting tert-butyl hydroperoxide (tbOOH)-induced free radical damage. This in turn reduces wrinkle formation [13].

Won-Seok Kim et al. 5-week-old female hairless mice were subjected to wrinkle induction by UVB dorsal irradiation. The results showed that injection of ADSCs had an anti-wrinkle effect on UVB-induced wrinkles [14]. Kikap Kim et al. grouped 44 female nude mice in controls and showed that adipose-treated and ADSCs significantly reduced wrinkles with the adipose-treated group and could synergistically affect collagen synthesis and neointima formation [15]. ADSCs were extracted from the tissue of female donors (n = 2, mean age 27 yrs) by liposuction reagents. Extracted ADSCs were injected subcutaneously into the skin of one side of the mice and controls were injected subcutaneously with HBSS into the skin of the other side. The results showed that ADSCs increased dermal thickness, collagen density, and fibroblast numbers [5].

The results of the above study illustrate the possible efficacy of ADSC in anti-wrinkle facial skin, but there are some limitations. Firstly, the period assessed after 4 weeks of injection is relatively short and no definite conclusions can be drawn about long-term efficacy [16]. Secondly, only simple

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cellular injections were used during the trial, but the injection of cytokines and growth factors may have caused dissimilar effects. Thirdly, the study mostly used mice as test subjects, albeit mice are generally considered to be acceptable animal models for studying natural aging and photoaging of facial skin. Fourthly, the trial suffered from the inadequate sample size, and further expansion of sample size or more clinical studies are urgently needed to investigate the role of ADSC in anti-wrinkle in depth.

5.2. The mechanism of ADSCs in the whitening of facial skin

One of the specific signs of facial aging is the gradual darkening of the skin tone due to the growth of pigmentation. Facial skin melanin is produced by melanocytes in the basal layer of the facial epidermis. When the facial skin is exposed to external stimuli (UVB exposure, chemical stimuli, emotional stress, etc.), the tyrosinase activity in the melanocytes is increased, which is the main enzyme that limits the rate of conversion of tyrosine to melanin, resulting in increased melanin synthesis and darkening of the facial skin [17].

Secretory factors of ADSCs can down-regulate the expression of tyrosinase which is mediated principally by Transforming growth factor-β1 (TGF- β 1) and TRP1 to inhibit melanin synthesis. In addition, Interleukin 6 (IL-6) produced in significant quantities by ASCs is capable of mediating microphthalmia-associated transcription factor (MITF) to down-regulate and reduce the tyrosinase protein levels to inhibit hyperpigmentation caused by exogenous aging or pigmented skin diseases [18].

Won-Serk KIM et al, extracted ADSC from human subcutaneous adipose tissue and prepared ADSC-CM, melanoma B16 cells were incubated by ADSC-CM, and finally measured melanin expression levels in melanoma B16 cells by protein blotting. The findings demonstrated that the released factor of ADSC reduced the production of tyrosinase and TRP1, which was mostly mediated by TGF-β1 to inhibit melanin synthesis [19]. As a control, UVB irradiation was only administered to the dorsal side of the mice (HRM-2 hairless mice treated with melanin), while the contralateral side received both UVB irradiation and an injection of ADSCs. Tyrosinase activity and melanin concentration in the epidermis of the mouse facial skin were measured to investigate the impact of ADSCs on the melanogenic activity of the facial skin. The results showed that ADSCs injected subcutaneously into the dorsal side of mice reduced skin tone deepening after UVB irradiation by inhibiting tyrosinase activity [20]. C57BL/6 mice's adipose tissue was used to separate and culture the ADSCs. And injected the ADSCs into the back of the right ear and a balanced salt solution (HBSS) is injected in the left ear as a control. After 7 days, each ear received three UVB (150 mJ/cm2) treatments in a single day, with each third irradiation being two days apart from the next. The study's findings demonstrated that ADSCs inhibited UVB-induced melanin formation [21].

The above findings suggest a possible mechanism of action of ADSC in facial skin whitening, but some limitations remain. Firstly, still lacks an ideal experimental model for immunosuppression and UVB-induced melanin production. Secondly, although current studies suggest that the whitening effect of ADSC is mainly mediated by TGF-β1, the exact mechanism needs to be further investigated. For example, there are speculations that the secreted factor of ADSC compensates for the down-regulation of MITF expression by TGF-β1, but there is no clear mechanism to elucidate the reason why MITF expression is not significantly altered during the action.

5.3. Promotes hair growth

Hair growth is a cyclical process. During the normal cycle, a large number of hair follicle stem cells (HF-SC) remain in the stem cell compartment of the hair follicle to continue producing follicle cells. In contrast, during senescence, the lack of division of HF-SC during prolonged resting phases leads to hair loss (Figure 3.) [22].

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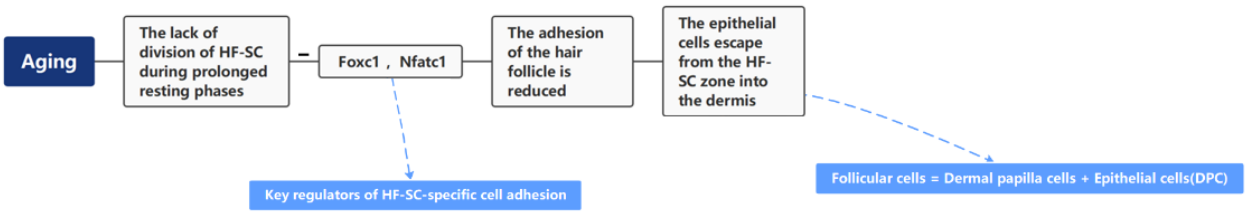

Figure 3. Schematic diagram of the mechanism of hair loss during aging.

The mechanism of action of ADSCs on hair production may be threefold. Firstly, studies have shown that ADSCs secrete growth factors. (Fig. 4) In a mouse model, PDGF induces and maintains the anagen phase of the hair cycle [23], and single-chain HGF stimulates hair follicle elongation. VEGF fosters hair growth and proportions through follicular vascularization [24], and IGF-1 improves hair follicle cell migration, livability, and multiplication [25].

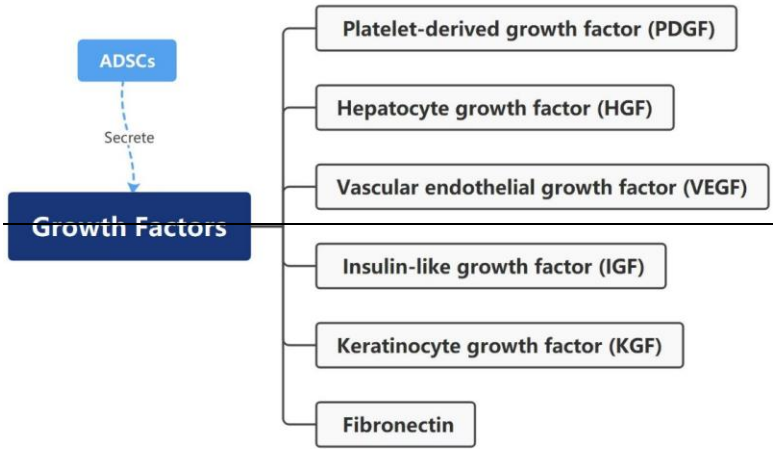

Figure 4. Growth factors secreted by ADSCs that are effective against hair loss.

Secondly, Changes in the hair cycle can also cause hair growth, artificially altering the follicular cycle (FGC) to promote hair growth, such as prolonging the anagen phase, delaying the regression phase, and promoting the conversion of the resting phase to the anagen phase [26]. ADSCs may be able to facilitate hair growth by altering the cell growth cycle of human hair papilla cells (HDPC). After ADSC-CM treatment the anagen phase (G1 phase) of HDPCs is shortened and DNA synthesis (S phase) and mitosis (G2-M phase) are prolonged. This may have the function of regulating FGC and promoting hair growth.

Finally, hair growth is usually achieved through the multiplication of follicular cells, which are primarily made up of dermal papilla cells and epithelial cells (DPC). ADSC-CM may facilitate the multiplication of both epithelial cells and DPCs for hair growth.

In 2010, Won et al. applied a conditioned medium of ADSCs (ADSC-CM) to the multiplication of human dermal papilla cells (HDCP) and immortalized keratinocytes (HaCaT) cells in vitro, and cell cycle experiments showed that ADSCs secretion accelerated the hair follicle cycle, thereby promoting hair growth [27]. In a stochastic, double-blind, carrier-controlled clinical trial, 38 patients (29 males) with androgenetic alopecia (AGA) were allocated to the intervention group (IG), where an adipose stem cell topical solution component extract (ADSC-CE) was self-applied to the scalp twice daily, the fingers, or the control group (CG). The study's findings suggest that using ADSC-CE topical solution has a high potential for increasing hair density and thickness are increased while treatment safety is maintained [28]. Isolated ADSC and isolated adipose-derived stem cell exosomes (ADSC-Exos). Randomly divided 12 nude mice into two groups (n=6 per group), for the control group, a combination of isolated DC and EC was transplanted. For the ADSC-Exos group, an admixture of DC, EC, and

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ADSC-Exos was transplanted, resulting in the control group's relatively immature hair follicles and the ADSC-Exos group's distinct terminal hairs. The findings indicate that ADSC-Exos can stimulate hair follicle regeneration in vivo [29].

Even though many laboratory experiments and animal studies have been conducted to investigate the effects of ADSC on hair growth, and have recognized its possible optimistic effects in advancing hair regrowth, there are still some limitations. Firstly, clinical trials still suffer from inadequate sample sizes. Secondly, the duration of the clinical trials was relatively short. Therefore, the data may not be adequate to conclude the long-term effects of ADSC-CE applications.

5.4. Questions about the safety and efficacy of ADSCs in facial skin anti-aging therapy

Although stem cell therapy is clinically available in many countries around the world and is at the stage of formal clinical trials, there is an urgent need for more in-depth research on the safety and long-term complications of adipose stem cell therapy, and there are many problems with the use of ADSCs for anti-aging of facial skin.

Whether ADSCs can maintain paracrine function after entry into the body, and how the types and concentrations of cytokines they secrete are regulated according to the body's needs.

Whether the cell clumps formed by ADSCs entering the circulation have the potential to obstruct blood vessels and what to do with the cell clumps of ADSCs.

Although adipose stem cells are effective in the anti-aging of facial skin, the current sample size of clinical trials is insufficient, and an increase in clinical data is urgently required to assess their effectiveness and to determine their exact role and safety.

There is currently no standardized measurement standard for ADSCs in facial skin anti-aging, and a standardized measurement standard is needed to ensure the safety of adipose stem cell treatment. For example, in the extraction of ADSCs, different extraction protocols will affect the quality and quantity of the final ADSCs obtained, so it is important to develop a unified criterion for the extraction of adipose stem cells and a unified standard extraction method.

Future research is needed on the extraction criteria of ADSCs and the safety, efficacy, and long-term complications of the treatment.

6. Conclusion

In this paper, the possible mechanisms of action of ADSCs in the anti-aging of facial skin are described. Although the anti-aging effects and mechanisms of ADSCs in the facial skin have been confirmed by several animal studies, there are still inadequate sample sizes and no standardized criteria for intervention doses. At the same time, there are still few relevant clinical trials, and more in-depth clinical studies are urgently required to further clarify the role and efficacy of ADSCs in anti-aging.

References

[1] Ganceviciene R, Liakou AI, Theodoridis A, et al. Skin anti-aging strategies. Dermatoendocrinol. 2012;4(3):308-319.

[2] Robert L, Labat-Robert J, Robert AM: Physiology of skin aging. Clin Plast Surg 2012, 39(1):1-8.

[3] Helfrich YR, Sachs DL, Voorhees JJ: Overview of skin aging and photoaging. Dermatol Nurs 2008, 20(3):177-183; quiz 184.

[4] Zuk PA, Zhu M, Mizuno H, et al. Multilineage cells from human adipose tissue: implications for cell-based therapies. Tissue Eng. 2001;7(2):211-228.

[5] Kim JH, Jung M, Kim HS, et al. Adipose-derived stem cells as a new therapeutic modality for aging skin. Exp Dermatol. 2011;20(5):383-387.

[6] McIntosh K, Zvonic S, Garrett S, et al. The immunogenicity of human adipose-derived cells: temporal changes in vitro. Stem Cells. 2006;24(5):1246-1253.

[7] Wang JV, Schoenberg E, Zaya R, et al. The rise of stem cells in skin rejuvenation: A new

frontier. Clin Dermatol. 2020;38(4):494-496.
[8] Fisher GJ, Datta SC, Talwar HS, et al. Molecular basis of sun-induced premature skin aging and retinoid antagonism. Nature. 1996;379(6563):335-339.
[9] Song SY, Jung JE, Jeon YR, et al. Determination of adipose-derived stem cell application on photo-aged fibroblasts, based on paracrine function. Cytotherapy. 2011;13(3):378-384.
[10] Stevenson S, Taylor AH, Meskiri A, et al. Differing responses of human follicular and nonfollicular scalp cells in an in vitro wound healing assay: effects of estrogen on vascular endothelial growth factor secretion. Wound Repair Regen 2008, 16(2):243-253.
[11] Kim HH, Lee MJ, Lee SR, et al. Augmentation of UV-induced skin wrinkling by infrared irradiation in hairless mice. Mech Ageing Dev. 2005;126(11):1170-1177.
[12] Watson RE, Griffiths CE: Pathogenic aspects of cutaneous photoaging. J Cosmet Dermatol 2005, 4(4):230-236.
[13] Kim WS, Park BS, Kim HK, et al. Evidence supporting antioxidant action of adipose-derived stem cells: protection of human dermal fibroblasts from oxidative stress. J Dermatol Sci. 2008;49(2):133-142.
[14] Kim WS, Park BS, Park SH, et al. Antiwrinkle effect of adipose-derived stem cell: activation of dermal fibroblast by secretory factors. J Dermatol Sci. 2009;53(2):96-102.
[15] Kim K, Fan Y, Lin G, et al. Synergistic Effect of Adipose-Derived Stem Cells and Fat Graft on Wrinkles in Aged Mice. Plast Reconstr Surg. 2019;143(6):1637-1646.
[16] Szadvari I, Krizanova O, Babula P: Athymic nude mice as an experimental model for cancer treatment. Physiol Res 2016, 65(Suppl 4): S441-S453.
[17] Pillaiyar T, Manickam M, Namasivayam V: Skin whitening agents: medicinal chemistry perspective of tyrosinase inhibitors. J Enzyme Inhib Med Chem 2017, 32(1):403-425.
[18] Choi H, Ahn S, Lee BG, et al. Inhibition of skin pigmentation by an extract of Lepidium apetalum and its possible implication in IL-6 mediated signaling. Pigment Cell Res. 2005;18(6):439-446.
[19] Kim WS, Park SH, Ahn SJ, et al. Whitening effect of adipose-derived stem cells: a critical role of TGF-beta 1. Biol Pharm Bull. 2008;31(4):606-610.
[20] Jeon BJ, Kim DW, Kim MS, et al. Protective effects of adipose-derived stem cells against UVB-induced skin pigmentation. J Plast Surg Hand Surg. 2016;50(6):336-342.
[21] Chang H, Park JH, Min KH, et al. Whitening effects of adipose-derived stem cells: a preliminary in vivo study. Aesthetic Plast Surg. 2014;38(1):230-233.
[22] Zhang, C., Wang, D., Wang, J. et al. Escape of hair follicle stem cells causes stem cell exhaustion during aging. Nat Aging 1, 889–903 (2021).
[23] Tomita Y, Akiyama M, Shimizu H: PDGF isoforms induce and maintain anagen phase of murine hair follicles. J Dermatol Sci 2006, 43(2):105-115.
[24] Yano K, Brown LF, Detmar M: Control of hair growth and follicle size by VEGF-mediated angiogenesis. J Clin Invest 2001, 107(4):409-417.
[25] Gentile P, Garcovich S: Advances in Regenerative Stem Cell Therapy in Androgenic Alopecia and Hair Loss: Wnt pathway, Growth-Factor, and Mesenchymal Stem Cell Signaling Impact Analysis on Cell Growth and Hair Follicle Development. Cells 2019, 8(5).
[26] Watabe R, Yamaguchi T, Kabashima-Kubo R, et al. Leptin controls hair follicle cycling. Exp Dermatol. 2014;23(4):228-229.
[27] Won CH, Yoo HG, Kwon OS, et al. Hair growth-promoting effects of adipose tissue-derived stem cells. J Dermatol Sci. 2010;57(2):134-137.
[28] Tak YJ, Lee SY, Cho AR, et al. A randomized, double-blind, vehicle-controlled clinical study of hair regeneration using adipose-derived stem cell constituent extract in androgenetic alopecia. Stem Cells Transl Med. 2020;9(8):839-849.
[29] Wu J, Yang Q, Wu S, et al. Adipose-Derived Stem Cell Exosomes Promoted Hair Regeneration. Tissue Eng Regen Med. 2021;18(4):685-691