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Current issues of skin aging and strategies for its correction

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ABSTRACT

The review analyzes current experimental and clinical data on skin aging. One of skin aging phenomena is the aging of its cells. Senescent cells produce a broad spectrum of cytokines that alter the microenvironment of tissues. The results of recent studies show that the microenvironment affects the functional activity of stem cells, which is accompanied by impairment in skin regeneration and recovery.

KEY WORDS: *skin aging; skin stem cells; senescent cells; senolytics*

Human aging is a destructive process that is associated to some extent with structural changes and reduced functional activity at all levels of biological organization, including the skin [5, 68, 78]. The skin has unique properties compared to other tissues, performing a number of functions: barrier, protective, immune, thermoregulatory, secretory and others. The skin is an external organ that comes into direct contact with the environment, protecting tissues and organs from mechanical damage and UV radiation [48].

Recently, a number of scientists have identified a new function of the skin – socio-psychological. Young and attractive skin has a positive effect on social behavior, reproductive status, provides a sense of confidence, promotes professional and career growth. Therefore, understanding the pathogenetic mechanisms of age-related changes in human skin, development and application of techniques and drugs, which help restore the beauty, youth and function of the skin, has become extremely important at the present stage of our society [56]. Changes in the skin are simultaneously affected by a combination of factors of endogenous (genetics, cellular metabolism, hormones and metabolic processes) and exogenous origin (chronic exposure to light, pollution, ionizing radiation, chemicals, toxins). The complex action of these factors together leads to structural and physiological transformations that occur in the epidermis, skin-epidermal junction, dermis and epidermal appendages, including hair follicles, sebaceous glands, sweat ducts and glands [7, 33, 75].

The skin is of scientific and clinical interest to experts in aesthetic and regenerative medicine, because it is the most accessible organ for both diagnosis (e.g., skin biopsy) and medical interventions, as it is convenient to apply cosmetics and pharmacotherapeutic agents locally. The most promising to date are the study of cellular mechanisms of aging associated with a decrease in the functional activity of skin stem cells (SCs) and an increase in the number of senescent cells in the dermis.

NICHES OF DERMAL STEM CELLS

The skin, like other soft tissues, is restored and renewed due to the presence of regional tissue-specific stem cells [1]. According to the literature, stem cells are located in specific sites – niches of the body. The term niche was proposed in 1978 by Schofield. A niche is understood as a microenvironment of stem cells, which provides their activity, self-renewal and differentiation. The microenvironment itself protects stem cells and is an important factor for tissue homeostasis in the epidermis, as well as in other tissues [69]. The niche performs a trophic function, and is a signaling medium for SCs interaction [52]. Anatomical and biochemical microenvironment protects the pool of SCs from depletion, regulates the transition of cells from undifferentiated to terminally differentiated [6]. The niche consists of neighboring cells, components of the intercellular matrix (collagen, elastin), chemokines of Wnt signaling pathways, growth factors (epidermal growth factor, transforming growth factor beta, fibroblast growth factor, insulin-like growth factor), surrounding capillaries, physical parameters (hypoxia, pH) [2, 19 , 20, 35, 80].

Skin SCs are located in the following niches: epidermal, dermal and adipose. The epidermal stem niche consists of at least three cell populations of the SC: the bulge region of the hair follicle, sebaceous glands and the basal layer of the interfollicular epithelium [31]. Basal stem cells are transformed into transient amplifying and terminal differentiated keratinocytes. They are responsible for the physiological regeneration and repair of the epidermis during injuries caused by trauma and disease. SCs of the bulge region are differentiated into epitheliocytes of the inner and outer root sheath of the hair follicle and hair shaft cells, regulating the processes of hair folliculogenesis and hair follicle regeneration. The population of melanocytic SCs of the bulge region are responsible for the melanogenesis in dermis and hair pigmentation. SCs which differentiate into sebocytes are localized near the sebaceous glands. [19, 52, 36]. The composition of the dermal stem niche includes multipotent stem cells of the hair follicle, dermal papilla, perivascular cells located mainly near the hair follicles, which have the properties of mesenchymal stem cells. These cell populations can give rise to dermal cells, induce hair morphogenesis, participate in skin repair during traumatic injuries and diseases [73, 79, 88]. The adipose niche of the dermis is represented by adipose-derived stem cells, which can be isolated from the stromal-vascular fraction of adipose tissue. They are actively involved in the mechanisms of subcutaneous adipose tissue regeneration [41]. SCs and microenvironment simultaneously form a dynamic system that determines the regenerative abilities of organisms [6].

AGE-RELATED ASPECTS OF THE SKIN STEM CELL NICHE

Ge Y. et al. in *in vivo* studies using immunofluorescence microscopy showed that in young mice the bulge region has a two-bulge structure at second telogen in contrast to the older animals, which had a single bulge. There was also a consistent tendency to the decrease in nephronectin (NPNT) regulation in hair follicle stem cells in older organisms compared to young ones. The severity of hair loss correlated with the prevalence of the phenotype with a single bulge structure. In addition, an age-related decrease in the number of hair follicle stem cells (HFSCs) was found, especially in mice with alopecia. [81].

The arrector pili muscle was separated from the wall of the hair follicle above the buldge in older hair follicles, in contrast to young hair follicles, where it attaches to the bulge's upper convexity. Arrector pili muscle attachment is mediated by NPNT expressed by stem cells [32].

On the murine skin during hair growth (anagen), the structure of a single bulge was identified, which corresponds to the potential ability of hair follicle stem cells to generate the growth of new hair. In contrast, on old hairless skin, the ability to hair grow was noticeably reduced. These observations suggest that despite the presence of HFSCs within the old bulges, they are much less able to affect the new hair growth cycle. This coincides with the study of other researchers that the effect of the old bulge on the initiation of new hair growth is reduced [47, 81].

A decrease in the total number of T-cells, $CD4^+$ and regulatory T-cells in the skin of older mice has been proved [81]. According to Ali N. et al., in young mice, regulatory T-cells of the hair follicle promote the function of the hair follicle SCs [14]. Thus, reducing the number of regulatory T-cells of the hair follicle may affect the activity of SCs and hair growth.

In the experiment, shaving hair in the telogen phase and modelling of a wound on the skin of the mice's back led to the restoration of hair growth and pigmentation of the injured area of skin in a young mouse. In contrast, in the old mouse, no restoration of hair growth was observed even after two months of the study, and the area of skin injury remained pale because the pigmentation did not restore. The transplantation of young and old HFSCs in combination with neonatal dermal cells resulted in the formation of numerous hair follicles in the skin of nude mice. In contrast, the transplantation of young and old HFSCs in combination with old dermal cells did not result in the appearance of hair follicles in the nude mice skin in any of the cases. The obtained data convincingly support the opinion that the microenvironment of old skin is the main barrier to the full activity of hair follicle stem cells. Moreover, they demonstrate that the microenvironment of the neonatal dermis promotes the rejuvenation of old HFSCs and the restoration of hair growth [81].

SENESCENT CELLS AND THEIR EFFECT ON SKIN AGING

With age, the ability of SCs to maintain tissue homeostasis and tissue repair decreases due to several mechanisms: shortening of telomere length, reducing telomerase activity, reducing proliferative potential, weakening antioxidant protection of cells and/or increasing oxidative stress, disruption of genome DNA repair, and cells [25, 30, 70, 87]. Today the age-related decrease in the functional activity of the epidermis and hair follicle SCs is well known [26, 34, 55].

Gradually, the cells lose their functional properties; there is cellular aging – senescence. Senescent cells are located in different organs, the gradual increase in their number with age is one of the phenomena of human aging [10, 53]. Senescent cells are not capable of replication, increase in size, are resistant to apoptosis, but retain metabolic activity [3]. In addition, they produce a number of biologically active molecules, such as proinflammatory cytokines, proteolysis factors, extracellular matrix proteases, which together form a senescence-associated secretory phenotype (SASP) [9, 22]. The secretome of senescent cells can damage the local environment, change the functional activity of neighboring differentiated cells, stem and progenitor cells, as well as accelerate the aging of tissues [8, 54].

The study of senescent dermal fibroblasts has shown an increase in the expression of the senescence-related marker p16INK4A (a protein involved in the mechanisms of cell division encoded by the CDKN2A gene) *in vitro* [15]. Later, Ressler et al. have shown that there is an increase in p16INK4A protein gene expression in dermal fibroblasts and skin epidermis of the elderly compared to the younger group of people. The p16INK4A protein directly correlates with the chronological aging of human skin, and, therefore, may be a biomarker for assessing human aging [60].

In an *in vitro* study, senescent fibroblasts have a reduced ability to activate in response to the impact of transforming growth factor b-1, which can lead to impaired collagen synthesis and wound healing [29, 67].

Analyzing the telomere dysfunction as a biomarker of aging, Herbig et al. proved that the number of senescent fibroblasts in the skin of old baboons increases exponentially, reaching the level of 15-20 % of all cells [39].

According to the results of immunohistochemical study Victorelli et al., there is an increase in the number of melanocytes expressing p16INK4A in the skin of the elderly *in vivo*. Senescent melanocytes also have reduced expressions of the cytokine mediator high-mobility group protein B1 (HMGB1), sirtuin 1 (SIRT1) and dysfunctional telomeres, but without their shortening. Melanocyte SASP reduces the proliferation of surrounding cells by increasing the production of mitochondrial active oxygen species. Finally, older melanocytes impair basal keratinocyte proliferation and contribute to epidermal atrophy *in vitro* [84].

The study of Victorelli et al. proved an increase in the number of C-X-C chemokine receptor type 3 (CXCR3) for human interferon-inducible protein 10 (IP-10). IP-10 is secreted by macrophages and fibroblasts in response to interferon-γ production. It is also expressed on the membrane of senescent melanocytes of the epidermal basal layer of the elderly skin *in vitro*. The addition of recombinant human IP-10 to the culture of dermal fibroblasts has led to the increased production of mitochondrial reactive oxygen species, which disrupt the function of telomeres.

The addition of the conditioned medium of senescent melanocytes to the culture of dermal fibroblasts caused telomere dysfunction on the 2^{nd} and 30^{rd} days of the study. In addition, dermal fibroblasts increased the production of the cyclin-dependent kinase p16 inhibitor, which is expressed in senescent cells, and the senescence-associated β-galactosidase (Sen-β-Gal). Both markers are considered biomarkers of aging [84].

Another experiment used an *in vitro* model of the epidermal equivalent consisting of proliferating or senescent melanocytes and young keratinocytes cultured in a ratio of 1:10, which during 10 days formed a multilayered highly differentiated equivalent of the epidermis. The reduce in the number of senescent melanocytes by adding the ABT-737 inhibitor molecule of the BCL-2 family of antiapoptotic proteins to such an epidermal equivalent resulted in a decrease in the percentage of p16-positive keratinocytes, which was compared with the relative content of p16-positive keratinocytes of melanoderma with young melanocytes. The obtained data testify that SASP factors of senescent melanocytes can cause telomere dysfunction by paracrine way and impair proliferation of surrounding cells accelerating the aging of neighboring epidermal cells [84].

MORPHOHISTOLOGICAL AGE-RELATED CHANGES IN THE SKIN

One of the key factors of morphological changes in the epidermis and dermis during chronological aging is decrease of cellular regeneration. There is an imbalance between cell division and differentiation as well as their death. With age, the proliferative potential of keratinocytes of the epidermis decreases, resulting in the thinning of the epidermis, as well as the number and functional activity of melanocytes [27, 65, 74, 77]. The density of antigen-presenting Langerhans cells decreases in the skin, the ability to migrate in them is significantly reduced [71, 74]. The number of T-lymphocytes also decreases and they become less sensitive to specific antigens [50]. The epidermal-dermal junction of old skin becomes 35 % thinner than the epidermal-dermal junction of young skin [62].

In the dermis, the number and functional activity of cells, collagen and elastin fibers, skin appendages change. The main cellular population of skin – fibroblasts – decreases, their biosynthetic functions also change

[4]. Mature fibroblasts gradually turn into fibrocytes. Compared with fibroblasts, fibrocytes produce much less mucopolysaccharides, collagen, elastin, and the dermis becomes atrophic [11, 28]. According to Varani et al., the number of skin fibroblasts at the age of 80 years is reduced by 35 % compared to the skin at the age of 30 years, and the ability to produce collagen is reduced by an average of 75 % [83].

At a young age (20-30 years), collagen fibers are tightly packed, well organized. At the age of 80, they become fragmented, their orderly orientation, characteristic of young skin, disappears [62]. This is due to the increased activity of zinc-dependent matrix metalloproteinases (MMPs), which destroy collagen and elastin molecules. The studies of Baroni et al. demonstrate that in women 's skin there is a decrease in the percentage of collagen type 1 and 3, its fragmentation and disorganization, especially after the age of 60 [17].

Age-related hair changes affect the color and number of hair follicles. According to Giacometti et al., there is a decrease in the number of hair follicles on the scalp on average from 615 per 1 cm^2 at the age of 20-30 to 435 per 1 cm^2 at the age of 80-90 [28]. The hair becomes thin, loses its color. By the age of 60, approximately 50 % of the population has half gray hair on the body and a higher percentage of gray/white hair on the head. The change of the color to gray is explained by a gradual decrease in the number and function of melanocytes located both in the area of hair follicles and external root sheath [23].

It is known that significant changes during aging occur in capillaries and small blood vessels. Capillaroscopy and native microscopy revealed a decrease in the number of vertical capillary loops in the papillary layer of the dermis, as well as a decrease in vascular density per area [86]. The functional activity of both mature and stem cells of the skin is impaired, gradually increasing atrophic and dystrophic changes in all its structures [1, 61].

DERMATOPOROSIS – A SYNDROME OF SKIN AGING

Skin aging has long been seen largely as an aesthetic problem. The correction of age-related skin changes was carried out mainly with the help of cosmetics. As life expectancy increases, we begin to experience skin changes that progress with age and become not only cosmetic but also functional – the skin gradually loses its functions (protective, barrier and others). Therefore, in order to study the chronic changes that occur during aging and are accompanied by the development of chronic skin insufficiency syndrome, as well as the development of means to restore skin function in elderly patients, scientists have proposed the term dermatoporosis [46].

According to the etiological classification, there are:

- primary dermatoporosis, which is the most common and occurs due to chronological aging and long-term exposure to sunlight in unprotected areas.
- secondary iatrogenic dermatoporosis, which occurs during long-term intake of systemic and/or local corticosteroids for the treatment of various diseases [12, 46].

Among main diagnoses used to describe the clinical picture of aging of the face and skin, ICD-10 distinguishes two nosologies associated with age-related skin changes: chronoaging – "senile skin atrophy" (code L 57.4) and photoaging – "skin changes due to chronic exposure to nonionizing radiation" (code L 57).

The first signs of dermatoporosis appear around the age of 60, but the disease develops between the ages of 70 and 90. The clinical manifestations of both types do not differ from each other, but iatrogenic dermatoporosis may occur earlier and be more severe in patients susceptible to primary dermatoporosis.

Manifestations of dermatoporosis are divided into:

- clinical – skin atrophy, senile purpura, stellate pseudoscars, trophic ulcers;
- functional – reduced wound healing, damage/frequent ruptures of the skin from minor injuries, non-healing of atrophic ulcers and subcutaneous bleeding with the formation of hematomas, leading to necrosis [46, 72].

In its turn, the clinical signs of atrophic process at the level of the epidermis and dermis of human skin are manifested by the appearance of superficial and deep wrinkles, as well as pigmented spots, the formation of gravitational ptosis, decreased sebum and sweat production, the development of dry skin [27, 28].

CD44 expression and hyaluronic acid levels are reduced in the epidermis and dermis of patients with dermatoporosis compared to the skin of young people, therefore, some researchers consider this fact as one of the potential molecular mechanisms of involutive skin changes and the clinical picture of dermatoporosis [45]. According to Kaya G. et al., the regulation of keratinocyte proliferation in response to extracellular stimuli and maintenance of local homeostasis have been shown to be key functions of CD44 in mouse skin [43]. Keratinocytes with the loss of CD44 expression have a defect in their ability to proliferate in response to various stimuli, which is accompanied by the development of the atrophy of mice epidermis both *in vivo* and *in vitro* [43, 45].

MODERN APPROACHES IN THE TREATMENT OF SKIN AGING

For the treatment of age-related skin changes, there are used:

- cosmetics and daily skin care (creams, masks, sunscreens);
- topical pharmacotherapeutic agents (retinoids, antioxidants);
- invasive procedures (biorevitalization, mesotherapy, chemical peelings);
- hardware techniques (laser therapy, Intense Pulse Light therapy – IPL, Radio Frequency Lifting – RF therapy);
- systemic therapy (hormone replacement therapy, antioxidants);
- regenerative cell technologies: platelet-rich plasma (PRP therapy), stem cells.

In addition, it is extremely important to avoid bad habits (smoking and alcohol consumption), stress control, providing the necessary nutrients, adequate sleep and exercise, dietary and caloric restrictions [33, 56].

Retinoids and their derivatives are widely used in the complex treatment of involutive skin changes. According to Kaya G. et al., topical application of retinaldehyde increases the expression of CD44 and hyaluronic acid synthase in the skin of mice [44]. Topical application of retinaldehyde and hyaluronic acid increased the level of these molecules in the skin of patients with dermatoporosis and corrected skin atrophy, demonstrating a synergistic effect at both molecular and clinical levels [46]. Vitamin A (retinol) and its derivatives (retinaldehyde and tretinoin) have an antioxidant effect, can induce collagen biosynthesis and reduce the expression of MMP-1 [42]. Tretinoin is a non-aromatic first-generation retinoid approved in the United States for use as an anti-aging agent [66].

Involutive skin changes are very closely related to stem cell function, so the use of these cells in anti-aging strategies, as well as the treatment of patients with stem cells or their differentiated derivatives can be a universal technique in regenerative and aesthetic medicine [24, 70]. Subcutaneous adipose tissue is the most available source of mesenchymal stem cells isolation for transplantation. In dermatology and aesthetic medicine today, lipoaspirate, stromal-vascular fraction and cultured adipose tissue stem cells are widely used to correct age-related skin changes.

For example, according to Park B. et al., the administration of lipoaspirate intradermally into the skin of patients with the signs of photoaging led to a decrease in wrinkle depth, significant improvement in skin texture, increase in dermis thickness, as evidenced by ultrasonography, two months after the last injection [57]. In the study of Amirkhani et al., subcutaneous administration of adipose-derived stem cells in the nasolabial folds 6 months after the injection shows an increase in the density of the dermis, its thickness, a decrease in transepidermal water loss [16]. The injection of autologous fat enriched with stromal-vascular fraction in patients diagnosed with androgenic alopecia showed a doubling of hair growth density compared with the patients who received only injections of their autologous fat without SVF [58]. 126 patients participated in the study of rejuvenating and volumizing effects of stromal-vascular gel (SVF-gel). All participants noted an improvement in facial contours, reduction of wrinkles [82].

However, the clinical application of stem cells has a number of limitations: they are contraindicated in pregnancy, cancer, HIV/AIDS. Stem cell treatment is more costly and time consuming than the use of pharmaceuticals, as they require special reagents and equipment to isolate, grow, control the quality of cells and their subsequent transplantation. The use of allogeneic cells requires some caution about the risk of infection transmission. In the case of the latest autologous induced pluripotent cell (iPSC) technology, there are some safety concerns due to their ability to provoke the development of teratomas [13].

Given the above, we can assume that the microenvironment will be the next promising therapeutic strategy to influence age-related skin changes. However, the current state of research demonstrates the inability to reliable and long-term recovery of tissue microenvironment, which will contribute to the normalization of the functional activity of stem cells and surrounding cells, resulting in a decrease in the level of senescent cells [69]. Under these conditions, there are prospective means that improve the tissue microenvironment of cells, which will restore the functional activity of cells.

One of the means of therapeutic strategy aimed at the treatment of age-related diseases and skin rejuvenation is the widespread use of senotherapy in the treatment of cellular aging. They are divided into:

- senolytics – drugs that reduce the number of senescent cells;
- senomorphics – drugs that reduce the secretion of SASP-associated cytokines;
- geroprotectors – means to prevent aging, which reduce the manifestations of oxidative stress and telomere damage [51].

For example, according to Zhu et al., the combination of the proapoptotic drug dasatinib and the bioflavonoid quercetin significantly reduced the number of senescent C12FDG-positive primary mouse embryonic fibroblasts compared to these drugs alone [76]. According to Hickson et al., the treatment with the combination of dasatinib and quercetin in patients with diabetic nephropathy caused a decrease in epidermal cells expressing p16ink4A and p21CIPI, circulating SASP factors, including IL-1a, IL-6, MMPs-9 and MMPs-12, and senescent-dependent adipocytes protein inhibitor (p16ink4A) and cyclin-dependent kinase inhibitor 1 (p21CIP1) [40].

Another well-known drug is resveratrol (3,4,5-trihydroxystilbene, RSV), a natural polyphenolic compound with antioxidant properties found in red grapes, berries and some vegetables. Multiple protective effects on the human body (lowering glucose levels, improving insulin sensitivity, lowering the level of C-reactive protein, triglycerides) allow us to consider resveratrol as a means of slowing down the aging process of the body and skin in particular [85]. Resveratrol as a geroprotector is increasingly used in clinical practice and demonstrates a reduction in clinical markers of aging in human skin at systemic use. The intake of 8 mg of resveratrol for 60 days in the study group resulted in improved skin hydration and elasticity, reduced wrinkle depth, roughness and pigment spot intensity compared with the placebo control group [21]. According to histological examination, the addition of resveratrol gel to the skin of rats after pre-surface peeling for 15 days caused the thickening of the epidermis and dermis [37].

The first clinical and experimental data on the use of senotherapy allow us to consider them as a new anti-aging strategy. However, the widespread application of senotherapy in clinical practice requires additional study of a number of issues:

- the interaction of senotherapeutics with each other and with medicines as well as with non-drug treatments;
- the identification of side effects;
- doses, schemes, the duration of treatment for various diseases;
- the rate of accumulation of aging cells after their removal in different diseases, in different tissues and at different ages [49].

CONCLUSION

The microenvironment affects the functional activity of human skin stem cells. The functional activity of old stem cells can be restored, which provides new promising ways for regenerative and aesthetic dermatology.

Research is needed to identify and correct a key microenvironmental factor that negatively affects stem cell functions, and to develop effective therapeutic strategies to preserve skin function and restore it in old age. The latest data contribute to the further development of geriatric dermatology and better treatment of age-associated skin diseases.

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Сучасні уявлення про старіння шкіри та способи його корекції

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РЕЗЮМЕ

У статті проаналізовані сучасні експериментальні та клінічні дані щодо старіння шкіри. Один із феноменів старіння шкіри – це старіння її клітин. Сенесцентні клітини продукують спектр цитокінів, що змінюють мікрооточення тканин. Результати останніх досліджень показують, що мікрооточення впливає на функціональну активність стовбурових клітин шкіри, що супроводжується погіршенням її регенерації та відновлення.

КЛЮЧОВІ СЛОВА: *старіння шкіри; стовбурові клітини шкіри; сенесцентні клітини; сенолітики*