Journal of Experimental and Basic Medical Sciences 2024;5(1):81-87

Review

Stem Cells in Dermatology and Anti-Aging Care of the Skin

Cengizhan Zerzevatcı[1], Raziye Beyza Kılıçoğlu[1], Mine Ceren Akbulut[1], Oytun Erbaş[1]

ABSTRACT

Dermatology is one of the professions that use stem cells. A lot of significance has recently been placed on using anti-aging products. After recent developments, it has been observed that stem cells have a positive effect on the repair rate of the skin and the healing rate of wounds, and they are used in some medical conditions (vitiligo, chronic ulcers, burns, etc.). Stem cells, used in various methods, will have a significant impact, particularly in dermatology, by delivering very effective outcomes today and in the future for cell renewal and the development of novel formulations. In this chapter, the results of aging and skin aging, the use of stem cells in the skin against skin aging, and the use of stem cell technology in treating skin damage or diseases are mentioned.

Keywords: Anti-aging, dermatology, dermocosmetics, stem cell.

Aging is all of the irreversible structural and functional changes that occur over time, beginning with a person's birth and progressing through the person's physical and mental independence before death in the life cycle at the molecular, cellular, tissue, organ, and system levels. The World Health Organization defines individuals aged 65 and over as elderly and individuals aged 85 and over as very old. On the other hand, Gerontologists categorized old age as early old age, between 65 and 74 years old, middle old age, between 75 and 84 years old, and advanced old age over 85 years old. Aging should be evaluated in terms of psychological, biological, social, and chronological aging. While the calendar age of a person is the primary measure of chronological aging, the vascular age of a person, that is, cardiovascular aging, is the basic measurement unit of biological aging.[1]

While height, aerobic function, cardiovascular function, lean body mass, immunological function, maximum lung capacity, maximal ventilation, and neurotransmitter levels all reduced as life expectancy increased, an increase in adipose tissue and brain atrophy was found. Biomechanical alterations such as decreased muscle size and accompanying loss in muscle strength, slowing and repositioning of bone resorption, and tense ligaments and tendons are noticed in addition to these physiological changes. These physiological changes are most visible on the face, vital for human identity and social interaction. Facial aging begins with scarring in facial wrinkles and skin drooping and is an unavoidable stage in human life.[2]

The arrangement of the eyes, brows, nose, forehead, and chin in conformity with accepted universal aesthetic criteria constitutes the general structure of the face. Aging-related changes are noticed in numerous facial areas, such as the forehead, eyes, nose, midface, and lower face, as well as the general structure of the face. The forehead and brows droop with time in the forehead area, causing a decrease in the eyebrow-eye distance and bunching of the upper eyelid skin. The eyes are the first part of the face to exhibit symptoms of aging. The thinner skin around the eyes has fewer glands and is subjected to friction and pulling as the eye is frequently opened and closed. That is why skin changes around the eyes begin earlier than the rest of

[1]ERBAS Institute of Experimental Medicine, Illinois, USA & Gebze, Türkiye

Correspondence: Cengizhan Zerzevatcı. Institute of Experimental Medicine, 41470 Gebze-Kocaeli, Türkiye

E-mail: zerzevatcic@gmail.com

Cite this article as: Zerzevatcı C, Kılıçoğlu RB, Akbulut MC, Erbaş O. Stem Cells in Dermatology and Anti-Aging Care of the Skin. JEB Med Sci 2024;5(1):81-87.

doi: 10.5606/jebms.2024.1076

Received : September 24, 2023
Accepted : October 5, 2023
Published online : February 26, 2024

the face. The most visible sign of aging in the middle of the face comes when the cheeks sag, resulting in nasolabial wrinkles.[3]

The nasolabial folds are the lines that run from the corners of the nose to the corners of the lips. The nose lengthens with age in the nose area. Elongation is commonly caused by thinning soft tissue and lack of elasticity, which causes the "tip of the nose to drop." As the face ages, facial tissues generate downward vertical lines in the lower facial area. "Laugh Lines" are the names given to these lines. The corners of the mouth may droop and form "Puppet Lines" around the chin. Ridges occur when the cheeks hang around a specific position along the chin, where the facial muscles link to the jawbone. The platysma muscle is a layer of facial muscles that extends into the neck. With age, this provides a stratified appearance on the neck.[4]

There are two processes of skin aging: internal and external. Intrinsic aging is thought to be influenced by genetic predisposition over time. By definition, this type of aging is unaffected by changes in human behavior. External factors impacting the human body, including smoking, excessive alcohol use, poor food, and long-term sun exposure, significantly impact extrinsic aging. Exposure to these substances, which are usually optional, although sometimes mandatory, is not inevitable and causes skin aging, triggering effects if care is not taken. Sunlight, one of the main factors in skin aging, is thought to affect 80% of skin aging. As life expectancy has increased in many parts of the world, a youthful appearance has become even more valuable. Therefore, serious efforts are made to improve the skin. Facial aging primarily causes an increase in the prominence of the nasolabial folds, as well as thinning of the tissues superficial to the levator labii superioris and zygomaticus major muscles, loss of malar fat, including medial, middle, and lateral temporal cheek fat, and sagging of the skin above the malar fold.[5,6]

SKIN AGING

Chronic skin aging is a natural phenomenon. Such aging characteristics result from dysregulation of the dermal and epidermal components of elastosis and components linked to heliodermatitis. As seen in Figure 1, fine wrinkles and deep grooves begin to form on the skin. The skin can be observed as dry and pale. Collagen and elastin, two fibrin proteins, are found in lower amounts in the skin as people age. Collagen production is dropping, which causes the skin to loosen. The epidermis thins due to the slowing of cell renewal, which also causes a drop in glycosaminoglycans and proteoglycans, and the skin begins to fold and wrinkle. Elastic fiber loss and aging are observed in all body parts containing connective tissue. Therefore, bruises can quickly occur on the skin. The senses of pressure, heat, and cold in the hands and feet also seem to be diminished, along with the sensitivity of touch receptors.[7]

Skin aging is observed in two different ways:

a) Intrinsic aging (natural aging that progresses over time): It is the period that begins with a slowdown in cell renewal and continues with its cessation due to chronological and genetic reasons. Over time, the amount of keratinocytes and fibroblasts accumulated in the skin increases, and the rate of aging increases. The tissue hardens, and wrinkles appear.

b) Extrinsic aging (premature aging of the skin that develops due to various time-independent factors): Aging can occur with environmental factors such as climatic conditions, air pollution, sun rays, or unconscious use of products in contact with the skin. Exposure to UV rays causes free radical formation and damages the collagen tissue and elastin network. Thus, cell renewal decreases and hyperpigmentation, dryness, and wrinkles occur.[8,9]

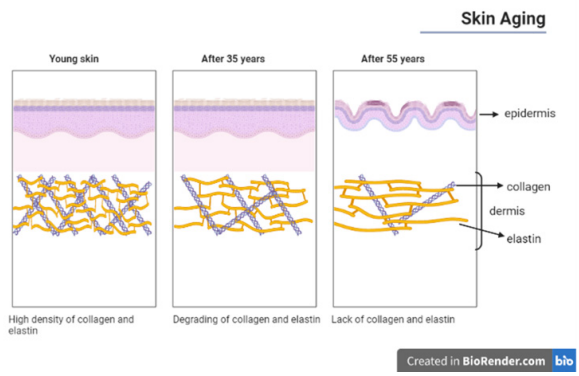

Figure 1. The amount of collagen and elastin in the skin aging process and the condition of the epidermis.

STEM CELLS

Stem cells are undifferentiated cells that have the ability to self-renew, differentiate into specialized cells, and transform into many different cell types in the body or the appropriate laboratory environment. As seen in Figure 2, there are five essential criteria to define any cell as a stem cell. These criteria are, respectively, long-term division (proliferation), self-renewal ability (self-renewal), not being specialized (undifferentiated), being able to originate from specialized cells and differentiating

to them (plasticity, differentiation), and regenerating the source tissue to function when transferred to the damaged recipient.[10]

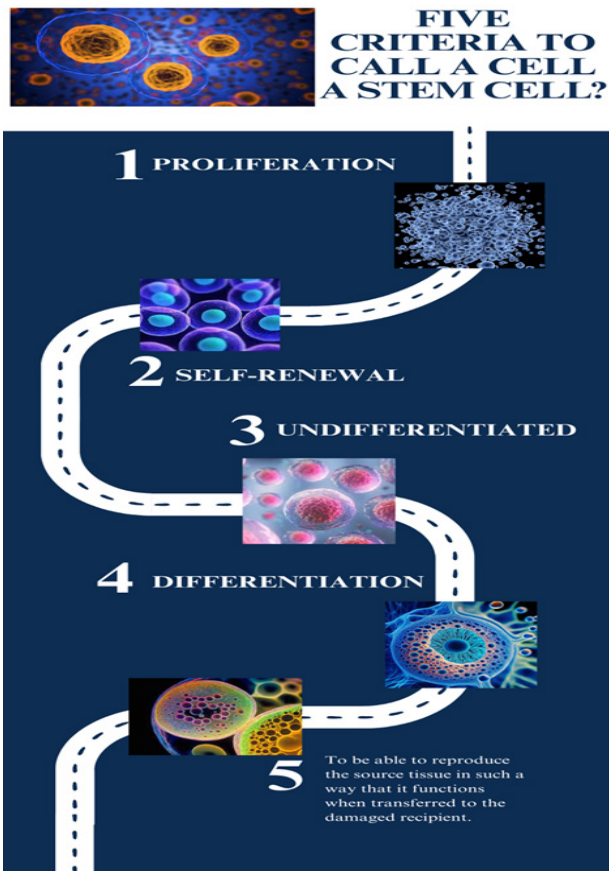

Figure 2. Characteristics of stem cells.

Stem cells are examined as embryonic stem cells and adult/somatic stem cells. Embryonic stem cells are pluripotent, capable of transforming into all cells in an adult organism. Human embryonic stem cells are located in the inner cell part of the embryo at the blastocyst stage. Each of these stem cells has the capacity to become an embryo. However, in order to obtain these cells, an existing embryo must be destroyed. Adult/somatic stem cells, on the other hand, are called multipotent since they lose their ability to transform into all cells in the organism. Such cells are usually found in tissues and can transform into more than one cell type typically found in tissue.[11]

Stem Cells in the Skin

As the largest organ of the body, the skin contains many different cells. There are stem cells within these cells, and as seen in Figure 3, they can be listed mainly as melanocytic stem cells, dermal stem cells, and adipocytic cells.

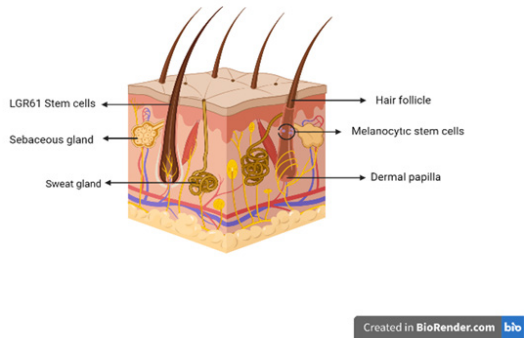

Figure 3. Stem cells in the skin.

Melanocytic stem cells

The hair follicle melanocytes multiply and differentiate closely with the hair regrowth cycle. The bulbus pili, hair bud, basal layer of the interfollicular epidermis, and dermis all contain melanocytic stem cells. Mature melanocytes are produced by melanocytic stem cells. The age-related decline in melanocytic stem cells triggers the whitening of the hair process.[12]

Dermal stem cells

Dermal stem cells are observed, especially in the dermal papilla and dermal sheath under the hair follicle. Dermal stem cells play critical roles in the development of the hair follicle, its growth, and its maintenance. Multipotent stem cells in the dermis originate from these and can form smooth muscle, neurons, glial cells, and adipocytes. Additionally, stem cells from the dermal papilla and dermal sheath play a significant part in the restoration of the dermis during wound healing.[13]

Adipose-derived stem cells

Adipose-derived stem cells are observed in white adipose tissue. They have the capacity to differentiate into osteoblasts and chondrocytes in addition to mature adipocytes. These cells are known to influence hair growth, according to observations.[14]

Do Stem Cells Age?

Mammalian tissue's capacity for replication noticeably deteriorates with age. According to some theories, a drop in stem cell activity in numerous organs with aging may be linked to a decline in regenerative abilities. Cell function assays could not be carried out in most breast tissues due to difficulties such as the inability to isolate stem cells, homogeneity, and lack of pattern.[15]

USAGE OF STEM CELLS IN DERMATOLOGY

Chronic Ulcers

Chronic ulcer is an essential and common public problem. Venous insufficiency, tissue hypoxia, local pressure, malnutrition, immunological disorders and infections play a role in the etiopathogenesis of chronic ulcers. Stem cell capabilities decline as we age, and persistent systemic inflammation is a common illness. In this case, the elderly's wound healing system may slow down or worsen. Negative pressure therapy, the use of antimicrobial medications, the bioengineering creation of biological scaffolding, hyperbaric oxygen therapy, maggot debridement therapy, and growth hormones are known treatments for chronic ulcers. However, these treatments provide a limited effect, so new treatment methods are needed.

Stem cell therapies are one of the emerging therapy techniques. Mesenchymal stem cells (MSCs) can be used to treat chronic ulcers. These stem cells can be obtained from various tissues, especially from many tissues such as bone marrow, adipose tissue, umbilical cord blood, dermis, and nervous tissue. Most clinical investigations employ MSCs that are generated from bone marrow. In diabetic ulcers, MSCs originating from adipose tissue and umbilical cord are preferred. Stem cells have effects such as accelerating wound healing, secreting paracrine signaling molecules, increasing re-epithelialization, showing plasticity, and regulating angiogenesis, through the trophic mediators and immunomodulatory molecules they secrete, by making the ulcer microenvironment suitable for healing in both acute and chronic ulcer treatment, and by making the wound microenvironment of endogenous progenitor cells suitable for wound healing. It has been observed that when applied locally to the wound, it reduces ulcer size, increases vascularization and dermal thickness, and accelerates wound healing. Immunogenicity issues arise during stem cell therapies. However, when patient stem cells are used, the issue is resolved. The most suitable stem cell collection should be selected and given to the skin with the most suitable carrier for the treatment to be effective. Another problem with stem cell therapy is its limited use in the clinic due to its complex and costly production.[16,17]

Burns

Heat, frostbite, electricity, chemicals, radiation, friction, and other factors can all result in burn injuries. The damaged tissue, intensity, and repercussions of burn injuries vary greatly.[18] Stem cells were first used in treating burns in humans in 2004. As seen in Figure 4, in a patient with extensive burns, it was observed that bone marrow-derived MSCs accelerated wound healing on the burned surface and increased angiogenesis compared to routine healing. While it was observed that the application of autologous adipose-derived MSC on the wound surface decreased the pain in burns caused by radiation and accelerated wound healing by preventing necrosis, it was found that the same effect was not observed when allogeneic stem cell application was applied. Loss of skin appendages and contractures negatively impact the patient's quality of life in burn patients. Using autologous MSC produced from bone marrow, graft contractures in patients can be minimized. In patients with advanced severe burns, sweat gland loss is possible. With the help of the MSC application, this loss can be prevented.[19]

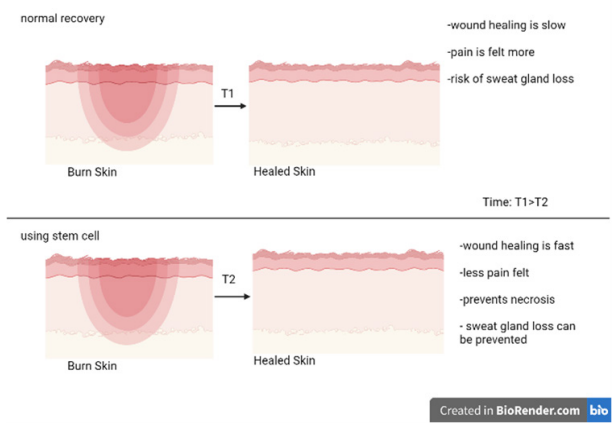

Figure 4. Comparison of the normal healing process of the burned skin and the use of stem cells.

Vitiligo

The estimated prevalence of vitiligo, a common depigmentation skin disorder, in the worldwide population is 0.5-2%. The disease is characterized by selective loss of melanocytes resulting in chalk-white macules that are not typically scaly.[20] Successful results have been obtained in vitiligo treatment using cell suspensions containing melanocyte stem cells in the outer root sheath.[21]

Methods of Delivery of Stem Cells to the Skin

The type of stem cell that will be used in stem cell treatments as well as how it will be administered to the treatment location are both crucial factors. Since it might be challenging to deliver stem cells

to the desired tissue when given systemically, local administration of stem cells has lately gained popularity. Stem cell effects can be altered by unfavorable conditions such as hypoxia, oxidative stress, and inflammation in the wound area. The number and density of the cells delivered to the wound in spray form, one of the topical delivery modalities, need to be clarified, making it difficult to establish the appropriate therapeutic dose. The application method should also work in this circumstance since stem cells diverge quickly. On the other hand, the local injection method is an invasive one and not the best for treating the condition since the stem cells could be harmed as the needle passes through them.[22]

Biological Scaffolds

Recently, several regenerative medicine applications have been effective in using decellularized tissues and organs. Several decellularization techniques that successfully remove cells from the tissue to be treated can be used to create a biological scaffold from the extracellular matrix.[23]

Biological scaffolds produced from synthetic or natural materials such as collagen and hyaluronic acid, which result from bioengineering design, support cells such as extracellular matrices. They also act as wound dressings by providing a microenvironment. Due to these properties, biological scaffolds are effective in many dermatological diseases, especially in ulcer treatments. In addition, these structures control the differentiation of stem cells and contribute to the preservation of their unique characteristics.[24]

STEM CELLS IN ANTI-AGING THERAPY

In recent years, the use of stem cells in anti-aging therapies has gained popularity. First up is the stem cell facelift technique, which encourages the patient's stem cells to produce collagen and fibroblasts when injected into the face. Other techniques involve adding ingredients derived from stem cell-conditioned media and plant stem cell-conditioned media to cosmetic products and formulations. Animal and plant stem cells have the ability to speed up the healing of wounds and promote skin regeneration, but since living stem cells cannot survive in cosmetic formulations, stem cell extracts are utilized instead. There needs to be more clinical research on the effectiveness and safety of anti-aging treatments involving stem cells, despite claims that they regenerate cells, shield them from aging damage, and boost filagrin levels.[25,26]

THE EFFECT OF STEM CELLS AND MITOCHONDRIA ON AGING

Aging is defined by diminished organ and tissue function, which is frequently accompanied by increased oxidative stress and mitochondrial dysfunction. For this reason, it is known that mitochondria have an important role in the signaling pathway caused by aging. Since dormant stem cells appear less metabolically active, they are exposed to many by-products of cellular metabolism, including reactive oxygen species (ROS). Reactive oxygen species can damage the deoxyribonucleic acid (DNA) of the mitochondria, which is the site of oxidative metabolism, and itself. Furthermore, it has been proposed that the loss of stem cell activities is linked to this damage to the mitochondrial DNA, which can be passed down through generations. Based on this knowledge, it can be inferred that stem cells can use mitochondria as an anti-aging mechanism to circumvent the limitations of cellular longevity.[27,28]

MOLECULAR MECHANISMS OF STEM CELL ANTI-AGING

Hypoxia-Induced by the Microenvironment

Stem cells are kept in their natural state in a hypoxic or low-oxygen environment. Generally, 5% of the partial oxygen pressure (pO_2) is the physiologically relevant O_2 concentration in the stem cell microenvironment. When exposed to the microenvironment of 5% of pO_2, it was observed that Wharton Jelly-derived MSC cultures were less differentiated and tended towards a more primitive phenotype. It also supported and stabilized the expression of octamer-binding transcription factor 4-A (OCT4A), NANOG, sex-determining region Y-box 2 (SOX2), and REX1 in induced pluripotent stem cells. Since 2% O_2 reduces mitochondrial DNA content, hypoxia-induced stem cell rejuvenation may depend on energy metabolism via mitochondria. Under the 1% O_2 condition, activation of hypoxia-inducible factor-1 (HIF-1) led to a reduction of extracellular signal-regulated kinase followed by decreased expression of p16. Decreased expression of the aging marker p16 helped MSC survive cellular senescence *in vitro*. In another recent study, 1% O_2 was also down-regulated. This result means that DNA is susceptible to molecules including ataxia-telangiectasia-mutated (ATM)/Rad3-related (ATR), checkpoint kinase 1 (Chk1), and checkpoint kinase 2 (Chk2), as well as senescence-related-beta (β)-galactosidase, H3K9me3, confirmed that

it damages cellular aging markers, including heterochromatin protein 1 gamma (γ).[29,30] The results showed that the bone marrow MSC developed under hypoxia (3% pO_2) for 15 days, and telomere length was conserved; nevertheless, telomere length reduced with time under normoxia. Telomere length reduction is typically associated with cellular aging.

Recently, it was reported that a significant pathway preventing MSC aging due to hypoxia is the HIF-1alpha-TWIST pathway downregulating E2A-p21. In addition, hypoxia induced an immediate and concerted downregulation of genes involved in DNA repair and damage response pathways [including the mutL homolog 1 (MLH1), RAD51, Breast cancer gene 1 (BRCA1), and Ku80 genes], suggesting that hypoxia contributes to genomic stability. There is also the possibility that p53 may suppress HIF-1 translation by targeting the pro-myelocytic leukemia protein, which activates the mammalian target of rapamycin (mTOR) to induce senescence. Conversely, HIF-1 interacts with the senescence marker p53, leading to p53 stabilization leading to the pro-aging phenomenon. In summary, hypoxia provides an anti-aging microenvironment to stem cells and is necessary for the progression of healthy aging.[27,31]

Genome Stability Induced by Microenvironment Stress

Mortimer and Johnston discovered in the 1950s that genome instability accompanies aging in yeast. In principle, there are three different types of genome instability. These can be listed as mutations, mismatch repair deficiency, and chromosomal instability.[32] Mechanisms of genome instability associated with mammalian aging are stress-induced ROS, telomere loss, and germline genetic variations for DNA repair. In addition, DNA damage caused by ROS has been reported to cause temporary growth arrest, apoptosis, and cellular senescence.

In adult hematopoietic stem and progenitor cells, histone deacetylase sirtuin 1 (SIRT1) has been observed in association with the accumulation of DNA damage and loss of progenitor cells. Under the stress of SIRT1 ablation, hormone-sensitive prostate cancers increased the expression of the homeobox protein Hox a9 (Hox a9), leading to increased DNA damage.[33,34] Another sirtuin family protein, SIRT6, likewise slows aging and coordinates genomic stability. To maintain genome integrity during DNA double-strand break repair, SIRT6 encouraged DNA end resection. Interestingly, the p53 family member TAp63 prevented premature senescence in skin cells, as seen in TAp63-/- mice, by retaining the characteristics of epidermal and dermal progenitors. The most prominent evidence linking genome stability with aging is the observed disease in humans known as progeroid syndrome. Defects in the DNA repair system known as transcription-coupled excision repair (TCER) cause progeroid syndrome; here, lesions in the replicated active gene strand are repaired with defective TCER. Contrary to popular belief, stem cells have a propensity to acquire DNA damage when they are in a condition of stasis. A prior study demonstrated that stem cells use the non-homologous end joining (NHEJ) repair system during quiescence in response to DNA damage. However, in hematopoietic stem cells, the NHEJ response is typically linked to abnormalities such as genome rearrangement. In summary, genomic stability is crucial for maintaining stem cells.[27,35]

In conclusion, when people age, their skin begins to display the signs of aging. Stem cells have been shown to be able to reverse the symptoms of aging on the skin, and they are sometimes used to cure disorders (such as vitiligo, chronic ulcers, and burns) in order to improve the appearance of the skin. When using anti-aging stem cells, it is crucial to consider the hypoxia caused by the microenvironment at the beginning of the anti-aging processes as well as the stability of the genome caused by the stress caused by the surrounding conditions.

Acknowledgments

The Figures (Figure 1, Figure 2, Figure 3, and Figure 4) used in this chapter were created with BioRender (BioRender.com).

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The authors received no financial support for the research and/or authorship of this article.

REFERENCES

1. Beğer T, Yavuzer H. Yaşlılık ve Yaşlılık Epidemiyolojisi. Klinik Gelişim. 2012;25:1-3.
2. Karakaş S, Yaşlanmanın anatomisi. The Journal of Turkish Family Physician. 2012 3:23-9.
3. Pala HG, Pala EE, Artunc Ulkumen B, Aktug H, Yavasoglu A, Korkmaz HA, et al. The protective effect of granulocyte colony-stimulating factor on endometrium and ovary in a rat model of diabetes mellitus. Gynecol Obstet Invest. 2014;78:94-100.
4. Hall G, Phillips TJ. Estrogen and skin: the effects of

estrogen, menopause, and hormone replacement therapy on the skin. J Am Acad Dermatol. 2005 Oct;53:555-68.
5. Erdeo F, Hisar F. Yüz Egzersizlerinin Cilt Yaşlanması Üzerine Etkisi. Sağlık ve Toplum. 2021;31:45-51.
6. Godic A. The role of stem cells in anti-aging medicine. Clin Dermatol. 2019 Jul-Aug;37:320-25.
7. Zhang S, Duan E. Fighting against Skin Aging: The Way from Bench to Bedside. Cell Transplant. 2018 May;27:729-38.
8. Tüzün Y, Dolar N. Fotoyaşlanma ve kronolojik yaşlanma arasındaki farklar. T Klin J Int Med Sci. 2005;1:16.
9. Csekes E, Račková L. Skin Aging, Cellular Senescence and Natural Polyphenols. Int J Mol Sci. 2021 Nov 23;22:12641.
10. Romito A, Cobellis G. Pluripotent Stem Cells: Current Understanding and Future Directions. Stem Cells Int. 2016;2016:9451492.
11. Dahl MV. Stem Cell Cosmeceuticals. Cosmeceuticals and Cosmetic Practice. 2013:192-9.
12. Qiu W, Chuong CM, Lei M. Regulation of melanocyte stem cells in the pigmentation of skin and its appendages: Biological patterning and therapeutic potentials. Exp Dermatol. 2019 Apr;28:395-405.
13. Yang CC, Cotsarelis G. Review of hair follicle dermal cells. J Dermatol Sci. 2010 Jan;57:2-11.
14. Zhang P, Kling RE, Ravuri SK, Kokai LE, Rubin JP, Chai JK, et al. A review of adipocyte lineage cells and dermal papilla cells in hair follicle regeneration. J Tissue Eng. 2014 Oct 27;5:2041731414556850.
15. Schultz MB, Sinclair DA. When stem cells grow old: phenotypes and mechanisms of stem cell aging. Development. 2016 Jan 1;143:3-14.
16. Wong VW, Levi B, Rajadas J, Longaker MT, Gurtner GC. Stem cell niches for skin regeneration. Int J Biomater. 2012;2012:926059.
17. Sen CK, Gordillo GM, Roy S, Kirsner R, Lambert L, Hunt TK, et al. Human skin wounds: a major and snowballing threat to public health and the economy. Wound Repair Regen. 2009 Nov-Dec;17:763-71.
18. Evers LH, Bhavsar D, Mailänder P. Yanık yaralanmasının biyolojisi. Deneysel dermatoloji. 2010;19:777-783.
19. Francis E, Kearney L, Clover J. The effects of stem cells on burn wounds: a review. Int J Burns Trauma. 2019 Feb 15;9:1-12
20. Bergqvist C, Ezzedine K. Vitiligo: A Review. Dermatology. 2020;236:571-92.
21. Kumar A, Mohanty S, Sahni K, Kumar R, Gupta S. Extracted hair follicle outer root sheath cell suspension for pigment cell restoration in vitiligo. J Cutan Aesthet Surg. 2013 Apr;6:121-5.
22. Duscher D, Barrera J, Wong VW, Maan ZN, Whittam AJ, Januszyk M, et al. Stem Cells in Wound Healing: The Future of Regenerative Medicine? A Mini-Review. Gerontology. 2016;62:216-25.
23. Üçgül İ, Aras S. Deselülerizasyon yöntemleri ve dokularda kullanımı. ANKA e-dergi. 2017;2:19-34.
24. Krishani M, Shin WY, Suhaimi H, Sambudi NS. Development of Scaffolds from Bio-Based Natural Materials for Tissue Regeneration Applications: A Review. Gels. 2023 Jan 23;9:100.
25. Rodop BB, Erbaş O. Mitochondrial dysfunction in aging and disease: The role of nutrition. D J Med Sci 2023;9:43-55.
26. Zarei F, Abbaszadeh A. Application of Cell Therapy for Anti-Aging Facial Skin. Curr Stem Cell Res Ther. 2019;14:244-8.
27. Wong TY, Solis MA, Chen YH, Huang LL. Molecular mechanism of extrinsic factors affecting anti-aging of stem cells. World J Stem Cells. 2015 Mar 26;7:512-20.
28. Taub AF, Pham K. Stem Cells in Dermatology and Anti-aging Care of the Skin. Facial Plast Surg Clin North Am. 2018 Nov;26:425-37.
29. Bernardi R, Guernah I, Jin D, Grisendi S, Alimonti A, Teruya-Feldstein J, et al. PML inhibits HIF-1alpha translation and neoangiogenesis through repression of mTOR. Nature. 2006 Aug 17;442:779-85.
30. Dal BN, Altuntaş İ, Erbaş O. Genetic Aspects of Aging and Anti-Aging Strategies. JEB Med Sci 2023;4:156-64.
31. Drela K, Sarnowska A, Siedlecka P, Szablowska-Gadomska I, Wielgos M, Jurga M, et al. Low oxygen atmosphere facilitates proliferation and maintains undifferentiated state of umbilical cord mesenchymal stem cells in an hypoxia inducible factor-dependent manner. Cytotherapy. 2014 Jul;16:881-92.
32. Mortimer RK, Johnston JR. Life span of individual yeast cells. Nature. 1959 Jun 20;183:1751-2.
33. Lombard veritabanı. Sirtuinler kırılma noktasında: DNA onarımında SIRT6. Yaşlanma (Albany NY). 2009 Ocak 20;1:12-6.
34. Singh SK, Williams CA, Klarmann K, Burkett SS, Keller JR, Oberdoerffer P. Sirt1 ablasyonu, stres kaynaklı epigenetik ve genomik hematopoietik kök ve progenitör hücre bakım kaybını teşvik eder. J Uzm Med. 2013 Mayıs 6;210:987-1001.
35. Su X, Paris M, Gi YJ, Tsai KY, Cho MS, Lin YL, et al. TAp63 prevents premature aging by promoting adult stem cell maintenance. Cell Stem Cell. 2009 Jul 2;5:64-75.