

Fighting against Skin Aging: The Way from Bench to Bedside

Cell Transplantation
2018, Vol. 27(5) 729–738
© The Author(s) 2018
Reprints and permission:
sagepub.com/journalsPermissions.nav
DOI: 10.1177/0963689717725755
journals.sagepub.com/home/ccl



Shoubing Zhang^{1,2} and Enkui Duan³

Abstract

As the most voluminous organ of the body that is exposed to the outer environment, the skin suffers from both intrinsic and extrinsic aging factors. Skin aging is characterized by features such as wrinkling, loss of elasticity, laxity, and rough-textured appearance. This aging process is accompanied with phenotypic changes in cutaneous cells as well as structural and functional changes in extracellular matrix components such as collagens and elastin. In this review, we summarize these changes in skin aging, research advances of the molecular mechanisms leading to these changes, and the treatment strategies aimed at preventing or reversing skin aging.

Keywords

skin aging, intrinsic aging, extrinsic aging, extracellular matrix, treatment strategy

Introduction

Skin is the barrier that segregates the body from the outer environment. Besides protecting the body from water loss and microorganism infection, it has an important cosmetic role. Young and beautiful appearance may have a positive influence on people's social behavior and reproductive status¹.

However, aging of organs begins from the time when one is born, and there is no exception for the skin. As the most voluminous organ of the body, the skin shows obvious and visible sign of aging when one becomes older. Therefore, for many people, especially females, a considerable amount of daily expense is occupied by cosmetics and pharmaceuticals attempting to prevent or reverse skin aging². This vast cosmetic need continually promotes research on skin aging and its treatment.

Cutaneous aging is induced by both intrinsic and extrinsic factors. Intrinsic aging is an inevitable physiological process that results in thin, dry skin, fine wrinkles, and gradual dermal atrophy, while extrinsic aging is engendered by external environment factors such as air pollution, smoking, poor nutrition, and sun exposure, resulting in coarse wrinkles, loss of elasticity, laxity, and rough-textured appearance^{3,4}. Notably, long-term exposure to solar ultraviolet (UV) radiation is the primary factor of extrinsic skin aging and is referred to as photoaging⁴. In this review, we will summarize the changes during skin aging, research advances of the molecular mechanisms leading to these changes, and treatment strategies.

Changes in Skin Aging

Exposed directly to the air, skin is not only subject to intrinsic aging but also superimposed by extrinsic aging. These aging processes are accompanied by phenotypic changes in cutaneous cells as well as structural and functional changes in extracellular matrix components such as collagens, elastin, and proteoglycans that are required to provide tensile strength, elasticity, and hydration to the skin, respectively⁴.

Changes in Intrinsic Aging

Intrinsic skin aging is a process of chronologically physiological change. Aging of photoprotected areas for example, the

¹ Department of Histology and Embryology, School of Basic Medical Sciences, Anhui Medical University, Hefei, Anhui, China

² Central laboratory of Molecular and Cellular Biology, School of Basic Medical Sciences, Anhui Medical University, Hefei, Anhui, China

³ State Key Lab of Stem Cell and Reproductive Biology, Institute of Zoology, Chinese Academy of Sciences, Beijing, China

Submitted: November 1, 2016. Revised: July 5, 2017. Accepted: July 14, 2017.

Corresponding Author:

Enkui Duan, State Key Lab of Stem Cell and Reproductive Biology, Institute of Zoology, Chinese Academy of Sciences, 1 Beichen West Road, Chaoyang, Beijing 100101, China.
Email: duane@ioz.ac.cn



Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License (<http://www.creativecommons.org/licenses/by-nc/4.0/>) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (<https://us.sagepub.com/en-us/nam/open-access-at-sage>).

inner side of the upper arm, is mainly due to intrinsic genetic or metabolic factors, whereas exposed skin areas are additionally influenced by extrinsic factors, especially solar UV radiation⁵.

For the intrinsically aged skin, the most remarkable histological changes occur within the basal cell layer. Research finds that as a person ages, proliferation of cells in the basal layer reduces. The epidermis then becomes thinner, and the contact surface area between dermis and epidermis decreases, resulting in a smaller exchange surface for nutrition supply to the epidermis and further weakened ability of basal cell proliferation^{6,7}. This process of decreased proliferative ability of cells including keratinocytes, fibroblasts, and melanocytes is called cellular senescence. In skin samples from human donors of different ages, there was an age-dependent increase in the expression of senescence marker β -galactosidase in dermal fibroblasts and epidermal keratinocytes, indicating that aged skin contains more senescent cells⁸.

In addition, the dermis of photoprotected aged skin shows not only fewer mast cells and fibroblasts than photoprotected young skin but also rarefied collagen fibers and elastic fibers⁹. It is reported that the production of type I procollagen in intrinsically aged human skin is reduced likely because of downregulation of the TGF- β /Smad signaling and its downstream connective tissue growth factor, which is regarded as a regulator of collagen expression¹⁰. Moreover, evidence supports that in intrinsically aged skin, not only fibrous extracellular matrix components including elastin, fibrillin, and collagens but also oligosaccharide are degenerated, which in turn influences the ability of skin to retain bound water¹¹.

Changes in Extrinsic Aging

As early as 1969, it was proposed that besides intrinsic factors, sun exposure also leads to skin aging¹². Exposure to UV radiation is the primary factor of extrinsic skin aging; it accounts for about 80% of facial aging¹³. In contrast to the thinner epidermis in intrinsically aged skin, UV-radiated epidermis thickens¹⁴. As the outermost layer of the epidermis, stratum corneum is mostly affected and thickens because of failure of degradation of corneocyte desmosomes. The expression of differentiation marker involucrin in stratum corneum is increased, which is in accord with the fact that the differentiation process of epidermal keratinocytes is impaired by UV irradiation. In basal cells, the expression of cell-surface protein β 1-integrin, which interacts with extracellular matrix proteins and is regarded as one of the epidermal stem cell markers, is greatly reduced, indicating that proliferation in the aged basal keratinocytes is also impaired^{15,16}.

The expression of type VII collagen in keratinocytes decreased in UV-radiated skin areas. Type VII collagen is the anchoring fibrils at the dermal-epidermal junction. The decrease in its production contributes to wrinkles due to the weakened connection between dermis and epidermis¹⁷. Studies have found that collagen type I diminishes in photoaged

skin^{18,19} due to increased collagen degradation²⁰. Various matrix metalloproteinases (MMPs), serine proteases, and other proteases participate in this degradation activity^{16,21,22}.

For photoaged skin, a striking characteristic is the accumulation of abnormal elastic tissue deep in the dermis²³, a pathologic phenotype named solar elastosis. UV-irradiation elevates the expression of elastin by 4-fold, then elastolysis occurs, characterized by elastic fiber cleavage by proteases mentioned above, resulting in severe deposition of truncated elastic fibers^{4,24}. MMP-2, MMP-3, MMP-7, MMP-9, MMP-12, neutrophil serine proteases cathepsin G, and human leukocyte elastase are known to decompose elastin. Recent research has found that photoaging makes the N-terminal and central parts of the tropoelastin molecules more susceptible to enzymatic cleavage and, hence, accelerates the age-related degradation of elastin⁴.

Also, the function of the microvasculature declines with aging. This is caused by endothelial dysfunction including reduced angiogenic capacity, aberrant expression of adhesion molecules, and impaired vasodilatory function²⁵.

Molecular Mechanisms in Skin Aging

Different models are proposed to explain the molecular basis for skin aging, including the theory of cellular senescence, decrease in cellular DNA repair capacity and loss of telomeres, point mutations of extranuclear mitochondrial DNA, oxidative stress, increased frequency of chromosomal abnormalities, single-gene mutations, reduced sugar, chronic inflammation, and so on¹¹. Some scientists proposed that most of the effects are caused by extrinsic factors, and only 3% of aging factors have intrinsic background²⁶. Here we highlight mainly important models and advances in molecular mechanism research on skin aging.

Oxidative Stress

It is regarded that reactive oxygen species (ROS) play a critical role in dermal extracellular matrix alterations of both intrinsic aging and photoaging. ROS can be produced from different sources including the mitochondrial electron transport chain, peroxisomal and endoplasmic reticulum (ER) localized proteins, the Fenton reaction, and such enzymes as cyclooxygenases, lipoxygenases, xanthine oxidases, and nicotinamide adenine dinucleotide phosphate (NADPH) oxidases²⁷. Under common conditions without ligands, the activity of receptor tyrosine kinases (RTKs) on the cell surface is inhibited by receptor protein tyrosine phosphatases (RPTPs), which dephosphorylate RTKs (Fig. 1A). However, under UV radiation, cellular chromophores absorb the energy and get excited, producing oxidation products and ROS. ROS inhibit the activity of RPTPs by binding to cysteine in the catalytic sites of RPTPs²⁸, elevating the level of phosphorylated RTKs and triggering downstream signaling pathways including the activation of mitogen-activated protein kinase (MAPK) and subsequent nuclear factor- κ B (NF- κ B) and transcription factor

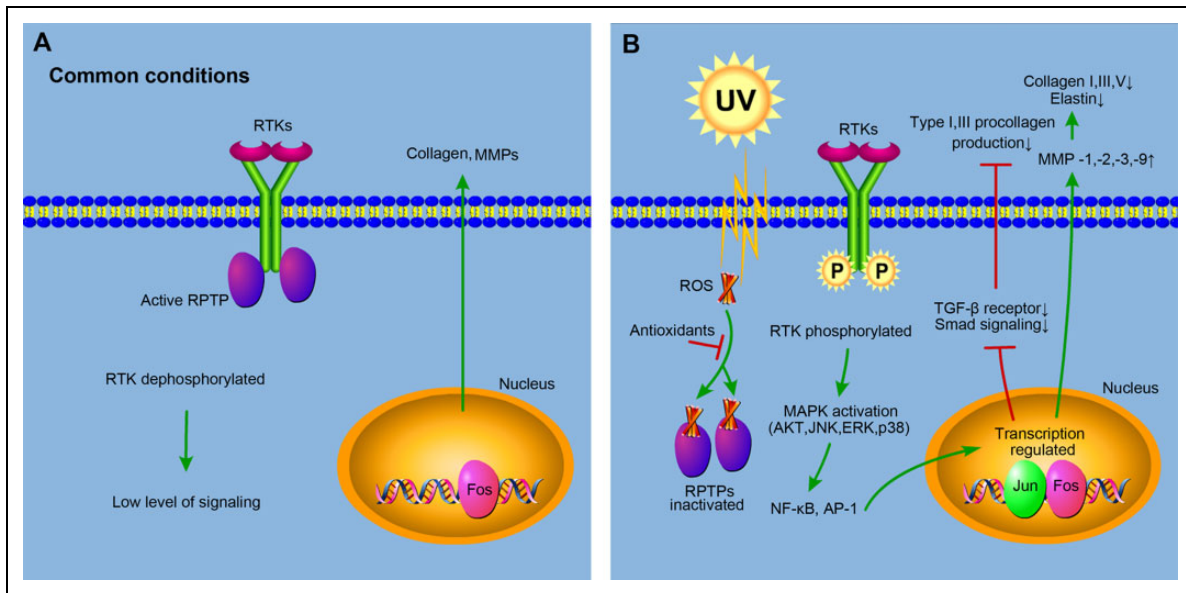


Figure 1. Molecular mechanisms of reactive oxygen species (ROS) in skin aging. (A) Under common conditions without ligands, the activity of receptor tyrosine kinases (RTKs) on the cell surface is inhibited by receptor protein tyrosine phosphatases (RPTPs), which dephosphorylate RTKs and keep low levels of signaling, producing a normal amount of collagen and matrix metalloproteinases (MMPs). (B) Under ultraviolet radiation, ROS are produced, which inhibit the activity of RPTPs by binding to the catalytic sites of RPTPs, elevating the level of phosphorylated RTKs and triggering downstream signaling pathways including the activation of mitogen-activated protein kinase (MAPK) and subsequent nuclear factor- κ B (NF- κ B) and transcription factor activator protein-1 (AP-1). NF- κ B and AP-1 increase MMP gene transcription, and AP-1 downregulates the expression of transforming growth factor- β (TGF- β) type II receptor, resulting in the reduced phosphorylation of transcription factor Smads and the subsequent repression of the collagen production. Thus, the total collagen content in photoaged skin decreases. Antioxidants can neutralize ROS, prevent its binding to RPTPs, and restore the signaling back to normal levels. This diagram is revised from Rittie and Fisher²⁸ and Kammeyer and Luiten²⁹.

activator protein-1 (AP-1). Activated NF- κ B and AP-1 repress collagen production and increase MMP gene transcription, resulting in the decrease of collagen content in photoaged skin²⁹ (Fig. 1B). It's worth noting that NF- κ B was recently found to be activated by mammalian target of rapamycin complexes 2/Akt/I κ B kinase α (mTORC2/Akt/IKK α) pathway in both intrinsic aging and photoaging³⁰.

Surprisingly, other studies found that although significantly higher mitochondrial superoxide levels and oxidative damage exist in *nuo-6* and *isp-1* mutants of *Caenorhabditis elegans*^{31,32} *Mcl1*^{+/-} mice³³, or long-lived naked mole rats^{34,35} than in control ones, these individuals display an increased life span and reduced signs of aging that, at least in *C. elegans*, could be suppressed by the antioxidant treatment³¹. These findings are not consistent with the oxidative stress theory of aging, and researchers suggest that other mechanisms are needed to explain these phenomena³⁴.

DNA Damage

Persistently exposing skin to UV radiation increases DNA damage and mutations and leads to premature aging or carcinogenesis³⁶. When DNA absorbs photons from UV-B, structural rearrangement of nucleotides occurs, resulting in defects of DNA strands³⁷. DNA damage can be repaired in lesser species through removing the lesion by photolyase enzyme, but higher

mammalian and human cells don't have this enzyme. It's accomplished by the nucleotide excision repair pathway³⁸. Once proteins in this pathway suffer from deficiency, DNA damage and premature skin aging will occur³⁹. Many studies provide consistent evidence that use of sunscreen prevents DNA damage in vivo and protects the skin from squamous cell carcinoma and melanoma⁴⁰, which further proves another aspect of the destructive effect of UV radiation on the DNA strand. Detailed description on the mechanism of DNA damage has already been reviewed^{38,41}.

Telomere Shortening

Telomeres are repetitive nucleotide sequences that cap and save the ends of chromosomes from degradation and abnormal recombination. They become shorter with each cell division and ultimately result in cellular senescence and limited numbers of cell division³⁸. Telomerase is an enzyme that adds telomere repetitions to the end to prevent telomeres from getting shorter. Telomerase-deficient mice exhibited accelerated telomere shortening, resulting in defective tissue regeneration. Moreover, proliferation capacity of epidermal stem cells with short telomeres was suppressed, whereas telomerase reintroduction in mice with critically short telomeres is sufficient to correct epidermal stem cell defects⁴². UV radiation leads to excessive ROS production, resulting in telomere mutations and further cell death or senescence⁴³.

MicroRNA (miRNA) Regulation

miRNAs are a class of conserved noncoding RNAs that bind to the 3' untranslated region of target mRNAs to promote their degradation and/or inhibit their translation. In recent years, miRNA dysregulation is found to occur in cellular senescence and organismal aging and is reviewed elsewhere⁵.

Besides these findings reviewed, it's reported that miR-23a-3p causes cellular senescence by targeting hyaluronan synthase 2 (HAS2)⁴⁴. Hyaluronan (HA) is a kind of polysaccharide in the extracellular matrix. Both aged and senescent fibroblasts showed increased miR-23a-3p expression and secreted significantly lower amounts of HA compared with young and non-senescent fibroblasts. Ectopic overexpression of miR-23a-3p in nonsenescent fibroblasts led to decreased HAS2-mediated HA synthesis, upregulation of senescence-associated markers, and decreased proliferation. In vivo, miR-23a-3p was upregulated and HAS2 was downregulated in the skin of old mice compared with young ones. In addition, recent research finds that miR-126, the most abundant miRNA in endothelial cells known to protect blood vessels and induce neovascularization, is significantly downregulated in aged human skin interstitial fluid in accordance with the fact that the number and functionality of capillary structures decreases with age⁴⁵. However, the detailed molecular mechanism needs further investigation.

Advanced Glycation End Product Accumulation

Advanced glycation end (AGE) products are formed by a non-enzymatic process called glycation, during which proteins, lipids, or nucleic acids are covalently bound by sugar molecules such as glucose or fructose, resulting in the inhibition of normal function of target molecules⁴⁶. This is quite different from normal glycosylation, which occurs at defined sites under mediation of enzymes and is necessary for target molecules to fulfill their functions. Glycation is involved in both intrinsic and extrinsic aging. Long-lived proteins in the dermal matrix and cytoskeleton are particularly susceptible to glycation, resulting in tissue stiffening and reduced elasticity⁴⁷. Among extracellular proteins, glycated elastin fibers abnormally aggregate and unusually interact with lysozyme in skin of solar elastosis but not sun-protected sites⁴⁸, indicating that glycation is involved in photoaging. However, glycated collagen is highly resistant to MMP degradation⁴⁹ and thus, it accumulates with age. This deteriorates the condition under the context of increased degradation of functional collagen and decreases collagen production mentioned above. For intracellular proteins, intermediate filament component vimentin was found to be the major intracellular target for N^ε-(carboxymethyl)lysine glycation in fibroblasts of elder human facial skin, whose modification led to a rigorous redistribution of vimentin into a perinuclear aggregate, accompanied by loss of cellular contractile capacity⁵⁰. In addition, recent research found that in sun-exposed old human skin, glyoxalase 2, which detoxifies the detrimental precursors of AGEs, showed drastic lower expression, resulting in a huge accumulation of glycated proteins⁵¹.

Notably, AGEs can also function by binding to cell surface receptors called receptors for AGEs to activate signal pathways, such as MAPKs, NF- κ B, extracellular signal-regulated kinases, and phosphatidylinositol-3-kinase⁵².

Genetic Mutation

Some researchers shed light on gene mutation-caused progeroid syndromes, such as Hutchinson-Gilford progeria syndrome (HGPS), Werner syndrome, Rothmund-Thomson syndrome, Cockayne syndrome, ataxia-telangiectasia, and Down syndrome⁵³. Gene mutation is inherited and causes progeria, a type of premature aging, often showing accelerated skin aging phenotype, including skin atrophy and sclerosis, poikiloderma, alopecia, thinning, and graying of the hair⁵³, for example, HGPS is caused by the mutation of gene *LMNA*⁵⁴, which produces progerin, a mutant protein that impairs many important cellular processes⁵⁵. More work is being done to try to gain insight into genetic variation during the aging process. In 2014 and 2017, different groups identified single-nucleotide polymorphisms associated with skin aging in Caucasians and the Chinese Han population, respectively^{56,57}.

Inflammaging

Chronic, low-grade inflammation is also recognized as a major characteristic of the aging process⁵⁸. This phenomenon is called "inflammaging." Inflammaging plays a role in the initiation and progression of age-related diseases such as type II diabetes, Alzheimer's disease, cardiovascular disease, frailty, sarcopenia, osteoporosis, and skin aging^{59,60}. To explain its occurrence in skin, a model is proposed in 2014 based on previous data⁶⁰. Briefly, UV radiation induces oxidative stress in epidermal cells, resulting in damaged cells with oxidized lipids. Oxidation-specific epitopes on damaged cells and oxidized lipids are recognized by complement system and cause inflammation, leading to infiltration and activation of macrophages to remove the damaged cells and oxidized lipids^{61,62}. Activated macrophages release MMPs to degrade extracellular matrix (Fig. 2A). Repeated UV radiation overactivates the complement system, causing damage to the dermis-epidermis junction, on which they deposit, and macrophages are overburdened with oxidized lipids. Overburdened macrophages release proinflammatory cytokines and ROS^{61,63,64}, the former of which cause chronic inflammation and long-term damage to the dermis, while the latter triggers the oxidative stress-induced damage to the dermal extracellular matrix (Fig. 2B). However, many details of this model need further verification.

Treatments for Skin Aging

Antioxidants

Antioxidants as reducing agents can relieve skin aging by neutralizing ROS that have already formed. ROS activates MAPK pathway and subsequently increase MMP production

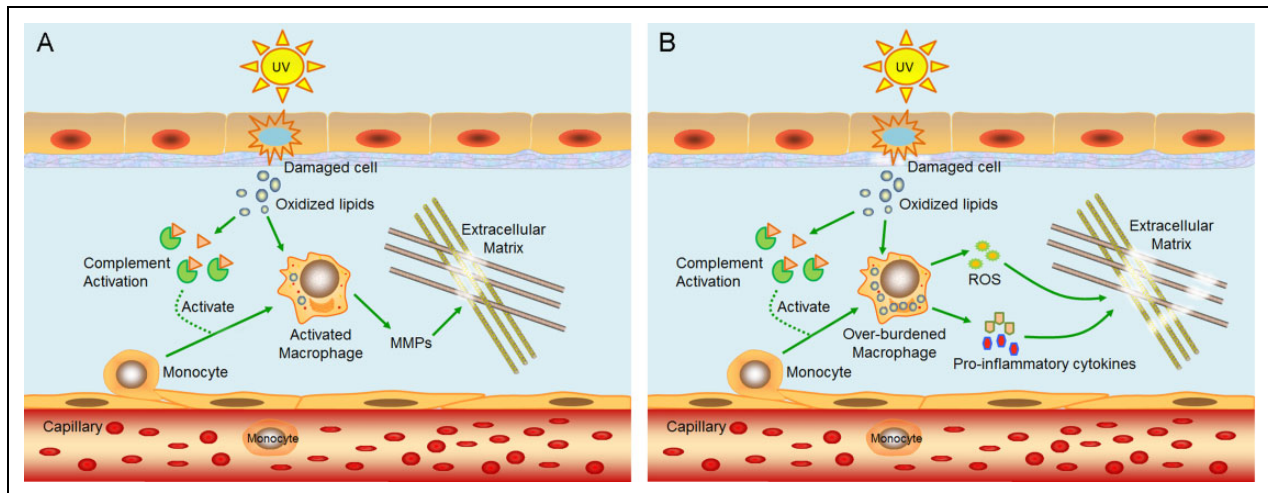


Figure 2. A model proposed to explain the mechanism of inflammaging in skin. (A) Ultraviolet (UV) radiation induces oxidative stress in epidermal cells, resulting in damaged cells with oxidized lipids. Oxidation-specific epitopes on damaged cells and oxidized lipids activate complement systems and cause inflammation, leading to infiltration and activation of macrophages. Activated macrophages release metalloproteinases (MMPs) to degrade extracellular matrix. (B) Repeated UV radiation overactivates the complement system, causing damage to the dermis–epidermis junction, on which they deposit, and macrophages are overburdened with oxidized lipids. Overburdened macrophages release proinflammatory cytokines and reactive oxygen species (ROS), the former of which cause chronic inflammation and long-term damage to the dermis, while the latter triggers the oxidative stress-induced damages to the dermal extracellular matrix. This schematic diagram is revised from Zhuang and Lyga⁶⁰.

that degrades collagen. This can be prevented by antioxidants (Fig. 1B), such as vitamin C and vitamin E, or antioxidative enzymes, such as superoxide dismutase, catalase, glutathione peroxidase, and coenzyme Q10^{65,66}. Some plants can also be used as natural source of antioxidants, such as green tea and aloe vera⁶⁶. A recent example is that epigallocatechin gallate (EGCG), a kind of catechin in green tea, prevents skin aging via the epidermal growth factor receptor (EGFR) pathway in an aging mouse model, resulting in better skin structure than the control⁶⁷. Moreover, *N*-acetylcysteine, the precursor to the antioxidant glutathione, seems to be successful in the treatment of vascular and nonvascular neurological disorders as well as against age-related decline in tissue regeneration^{68,69}, indicating its prospective antiaging application in skin.

However, it's notable that some researchers suggest that antioxidant supplements do not possess preventive effects to chronic diseases, and excessive supplementation of β -carotene and vitamins A and E is potentially harmful with unwanted side effects^{70,71}, especially in well-nourished populations, and the optimal source of antioxidants seems to come from our diet not from antioxidant supplements in pills or tablets⁷². And a previous study found that EGCG induced significant death and DNA damage in human lung and skin normal cells through a reductive mechanism⁷³. The aim of antioxidant treatment is to restore oxygen homeostasis instead of completely eliminating all oxidants because they have their physiological functions⁷⁴. Thus, for necessary clinical application of antioxidants, the doctor should evaluate the status of the patient before giving a prescription. It's not desirable to completely inactivate all ROS, and antioxidant treatment seems to be beneficial for aging (including skin aging) only if the ROS level is reduced to those of healthy cells.

Stem Cell Therapy

Stem cell transplantation is a promising therapy for the treatment of skin aging. Adipose tissue transplantation could improve skin quality at the recipient site in addition to increasing skin volume⁷⁵. Further experiments demonstrate that adipose-derived stem cells (ADSCs) contribute to the regeneration of skin during aging^{76,77}. In recent clinical tests, autologous fat grafting rejuvenates aging skin and enhances the volume of periorcular and perioral skin in recipients with an average age of 50 years^{78,79}. Data show that ADSCs produce a series of growth factors, such as vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), transforming growth factor (TGF)- β 1, TGF- β 2, hepatocyte growth factor (HGF), keratinocyte growth factor (KGF), platelet-derived growth factor AA (PDGF-AA), and placental growth factor (PGF)⁸⁰, reminding us that ADSCs may influence surrounding cutaneous cells through these secretions. It seemed that ADSC may also transdifferentiate into epithelial stem cells that express epithelial stem cell marker p63 after fat grafting⁸¹. This work provides clues into the understanding of how fat grafts may rejuvenate overlying skin.

Retinoids

Retinoids are chemically similar to vitamin A, and tretinoin is the first retinoid approved for clinical use. Topical application of tretinoin inhibits AP-1, thus suppressing the expression of MMPs and preventing the degradation of collagen⁸². An increase in epidermal thickness and anchoring fibrils is observed, and intrinsically aged skin may also benefit from the topical application of retinoids⁸³.

Hormone Replacement Therapy

In addition to being used in the treatment of symptoms caused by menopause, hormone replacement therapy (HRT) is used to slow the skin aging process. HRT improve skin thickness, collagen content, and elasticity and it enhances hydration. However, there are studies suggesting that HRT increases the risk of developing breast cancer⁸⁴.

Telomere Modification

Although telomerase activation seems to be an ideal approach to reverse skin aging, and indeed high-level expression of telomerase reverse transcriptase (TERT) in skin fibroblasts and keratinocytes results in a significantly enhanced proliferative capacity⁸⁵, but risks of epidermal carcinogenesis increase meanwhile⁸⁶. Therefore, further investigation is needed to evaluate the safety of the enhanced proliferation brought by the lengthened telomere.

Diet Restriction

Because it's still technically infeasible to reverse glycosylated proteins to their original state, currently the primary strategy still stays on the prevention of proteins from glycation. But the problem is that diet provides not only sugars such as glucose and fructose but also preformed AGEs, and the latter have a large amount in grilled, fried, or roasted food but very low content in foods prepared by water-based cooking such as boiling and steaming⁴⁶. Therefore, low-sugar food cooked with water would decrease the intake of preformed exogenous AGEs and endogenous production of physiologically glycosylated proteins. In the future, finding medicines of deglycation capability would be an expected breakthrough discovery.

Some scientists believe that some culinary herbs and spices, such as cinnamon, cloves, oregano, and allspice, can inhibit fructose-induced glycation⁸⁷, and some compounds, including ginger, garlic, α -lipoic acid, carnitine, taurine, carnosine, flavonoids (e.g., green tea catechins), benfotiamine, α -tocopherol, niacinamide, pyridoxal, sodium selenite, selenium yeast, riboflavin, zinc, and manganese^{52,87-89}. More investigation is needed to further validate these findings and reveal their inhibitory mechanisms.

Antiprogeria Strategies

Currently, therapies targeting HGPS are mostly investigated. Because the farnesyl group in the mutant protein progerin was regarded as the predominant deleterious and toxic component, the original therapies are designed to inhibit the farnesylation process⁹⁰. Farnesyltransferase inhibitor lonafarnib was used in a clinical trial to treat 25 HGPS patients for 2 years, resulting in improved vascular stiffness, bone structure, and audiological status⁹¹. Another strategy using the combination of 2 compounds, statin and aminobisphosphonate, efficiently inhibited both farnesylation and geranylgeranylation of progerin and prelamin A and markedly improved the aging-like phenotypes

of *Zmpste24*-deficient progeria mice model including growth retardation, loss of weight, lipodystrophy, hair loss, and bone defects⁹². A clinical trial using the same therapy was carried out, but the results are not published yet⁹³. A recent clinical trial combining lonafarnib with prenylation inhibitor pravastatin and zoledronic acid on 37 HGPS patients reveals additional bone mineral density benefit but no added cardiovascular benefit⁹⁴.

Also other alternative therapies not targeting farnesyl group have been proposed in recent years. Mammalian targets of the rapamycin (mTOR) pathway inhibitor rapamycin treatment of HGPS fibroblasts reverses premature aging and the lobulated nuclei by increasing progerin clearance through macroautophagy-related pathways⁹⁵. After that, antioxidant sulforaphane is also found to enhance progerin clearance by autophagy and to reverse the cellular hallmarks of HGPS⁹⁶. In addition, a small molecule called remodelin was found to improve nuclear architecture, decrease DNA damage, and reverse cell proliferation defects in HGPS cells⁹⁷. More recently, retinoids were identified as a novel class of compounds that reverse aging phenotypes in HGPS patient skin fibroblasts in a high-throughput screening⁹⁸.

For HGPS patients, to gain a longer life span is the biggest priority. That's the reason why most work mentioned here wasn't aimed at skin specifically. Nevertheless, this work has provided possible hints for future research.

Anti-inflammaging

Given that the mechanism of skin inflammaging is far from being thoroughly understood, little progress is made to develop targeted treatments. Suh et al. reported that treatment of the human fibroblast cell line using UV-absorbing compound mycosporine-like amino acids (MAAs) suppressed cyclooxygenase-2 (COX-2) gene expression, which is typically increased in response to inflammation in skin⁹⁹. Moreover, the expressions of skin aging-related proteins elastin and procollagen C-proteinase enhancer, which is an important determinate of procollagen processing in the regulation of collagen deposition in the skin, are strongly suppressed after UV irradiation but restored after MAAs treatment to normal levels as in the control⁹⁹. Also, there are other reported anti-inflammaging additives, such as vitamins A, C, D and E, green tea, and so forth, that are already summarized^{100,101}.

It's noteworthy here that although some treatments may help to relieve skin aging, prevention of extrinsic aging from occurring is still the best approach, because skin wrinkles are formed mainly by changes in the dermal part of the skin and there is still difficulty for antiaging agents in topical treatment to penetrate into deep dermis, although different delivery methods are developed.

Concluding Remarks

There is a contradiction between the irreversibility of skin aging and people's thirst for eternal young appearance. From

ancient to modern times, many efforts were made trying to understand the truth of cutaneous aging and to prevent or even reverse the aging process. This review summarizes the structural changes in both intrinsically and extrinsically aged skin, main molecular mechanisms proposed to explain these phenotypes, and advances in treatment research. It seems that skin aging is brought about by the comprehensive effect of different mechanisms, and it's difficult to develop an integrated theory to string different models together. Ambiguity in the molecular mechanism of skin aging, as well as controversy in viewpoints, retarded the progress of targeted therapy, although some therapeutic attempts have proven to be effective. As people's cosmetic requirements increase, more research efforts should persist to fully elucidate the molecular basis of the deteriorative changes during skin aging.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by Grants for Scientific Research of BSKY (No. XJ201224) from Anhui Medical University and the National Natural Science Foundation of China (31471287 and 31671568).

References

- Blanpain C, Fuchs E. Epidermal stem cells of the skin. *Annu Rev Cell Dev Biol.* 2006;22:339–373.
- Kazanci A, Kurus M, Atasever A. Analyses of changes on skin by aging. *Skin Res Technol.* 2016;23(1):48–60.
- Krutmann J, Bouloc A, Sore G, Bernard BA, Passeron T. The skin aging exposome. *J Dermatol Sci.* 2017;85(3):152–161.
- Mora Huertas AC, Schmelzer CE, Hoehenwarter W, Heyroth F, Heinz A. Molecular-level insights into aging processes of skin elastin. *Biochimie* 2016;128–129:163–173.
- Mancini M, Lena AM, Saintigny G, Mahe C, Di Daniele N, Melino G, Candi E. MicroRNAs in human skin ageing. *Ageing Res Rev.* 2014;17:9–15.
- Makrantonaki E, Zouboulis CC, William J. Cunliffe Scientific Awards. Characteristics and pathomechanisms of endogenously aged skin. *Dermatology.* 2007;214(4):352–360.
- Moragas A, Castells C, Sans M. Mathematical morphologic analysis of aging-related epidermal changes. *Anal Quant Cytol Histol.* 1993;15(2):75–82.
- Dimri GP, Lee X, Basile G, Acosta M, Scott G, Roskelley C, Medrano EE, Linskens M, Rubelj I, Pereira-Smith O, et al. A biomarker that identifies senescent human cells in culture and in aging skin in vivo. *Proc Natl Acad Sci U S A.* 1995;92(20):9363–9367.
- Kohl E, Steinbauer J, Landthaler M, Szeimies RM. Skin ageing. *J Eur Acad Dermatol Venereol.* 2011;25(8):873–884.
- Quan T, Shao Y, He T, Voorhees JJ, Fisher GJ. Reduced expression of connective tissue growth factor (CTGF/CCN2) mediates collagen loss in chronologically aged human skin. *J Invest Dermatol.* 2010;130(2):415–424.
- Naylor EC, Watson RE, Sherratt MJ. Molecular aspects of skin ageing. *Maturitas.* 2011;69(3):249–256.
- Kligman AM. Early destructive effect of sunlight on human skin. *JAMA.* 1969;210(13):2377–2380.
- Friedman O. Changes associated with the aging face. *Facial Plast Surg Clin North Am.* 2005;13(3):371–380.
- Kligman LH. Photoaging. Manifestations, prevention, and treatment. *Clin Geriatr Med.* 1989;5(1):235–251.
- Bosset S, Bonnet-Duquennoy M, Barre P, Chalou A, Lazou K, Kurfurst R, Bonte F, Schnebert S, Disant F, Le Varlet B, et al. Decreased expression of keratinocyte beta1 integrins in chronically sun-exposed skin in vivo. *Br J Dermatol.* 2003;148(4):770–778.
- Makrantonaki E, Zouboulis CC. Molecular mechanisms of skin aging: state of the art. *Ann N Y Acad Sci.* 2007;1119:40–50.
- Contet-Audonneau JL, Jeanmaire C, Pauly G. A histological study of human wrinkle structures: comparison between sun-exposed areas of the face, with or without wrinkles, and sun-protected areas. *Br J Dermatol.* 1999;140(6):1038–1047.
- Griffiths CE, Russman AN, Majmudar G, Singer RS, Hamilton TA, Voorhees JJ. Restoration of collagen formation in photo-damaged human skin by tretinoin (retinoic acid). *N Engl J Med.* 1993;329(8):530–535.
- Trautinger F, Mazzucco K, Knobler RM, Trenz A, Kokoschka EM. UVA- and UVB-induced changes in hairless mouse skin collagen. *Arch Dermatol Res.* 1994;286(8):490–494.
- Varani J, Spearman D, Perone P, Fligiel SE, Datta SC, Wang ZQ, Shao Y, Kang S, Fisher GJ, Voorhees JJ. Inhibition of type I procollagen synthesis by damaged collagen in photoaged skin and by collagenase-degraded collagen in vitro. *Am J Pathol.* 2001;158(3):931–942.
- Brenneisen P, Oh J, Wlaschek M, Wenk J, Briviba K, Hommel C, Herrmann G, Sies H, Scharffetter-Kochanek K. Ultraviolet B wavelength dependence for the regulation of two major matrix-metalloproteinases and their inhibitor TIMP-1 in human dermal fibroblasts. *Photochem Photobiol.* 1996;64(5):877–885.
- Fisher GJ, Wang ZQ, Datta SC, Varani J, Kang S, Voorhees JJ. Pathophysiology of premature skin aging induced by ultraviolet light. *N Engl J Med.* 1997;337(20):1419–28.
- Bonta M, Daina L, Mutiu G. The process of ageing reflected by histological changes in the skin. *Rom J Morphol Embryol.* 2013;54(Suppl 3):797–804.
- Bernstein EF, Chen YQ, Kopp JB, Fisher L, Brown DB, Hahn PJ, Robey FA, Lakkakorpi J, Uitto J. Long-term sun exposure alters the collagen of the papillary dermis. Comparison of sun-protected and photoaged skin by northern analysis, immunohistochemical staining, and confocal laser scanning microscopy. *J Am Acad Dermatol.* 1996;34(2 Pt 1):209–218.
- Scioli MG, Bielli A, Arcuri G, Ferlosio A, Orlandi A. Ageing and microvasculature. *Vasc Cell.* 2014;6:19.
- Poljsak B, Dahmane RG, Godic A. Intrinsic skin aging: the role of oxidative stress. *Acta Dermatovenerol Alp Pannonica Adriat.* 2012;21(2):33–36.

27. Rinnerthaler M, Bischof J, Streubel MK, Trost A, Richter K. Oxidative stress in aging human skin. *Biomolecules*. 2015; 5(2):545–589.
28. Rittie L, Fisher GJ. Natural and sun-induced aging of human skin. *Cold Spring Harb Perspect Med*. 2015;5(1):a015370.
29. Kammeyer A, Luiten RM. Oxidation events and skin aging. *Ageing Res Rev*. 2015;21:16–29.
30. Choi YJ, Moon KM, Chung KW, Jeong JW, Park D, Kim DH, Yu BP, Chung HY. The underlying mechanism of proinflammatory NF- κ B activation by the mTORC2/Akt/IKK α pathway during skin aging. *Oncotarget*. 2016;7(33):52685–52694.
31. Yang W, Hekimi S. A mitochondrial superoxide signal triggers increased longevity in *Caenorhabditis elegans*. *PLoS Biol*. 2010;8(12):e1000556.
32. Yang W, Hekimi S. Two modes of mitochondrial dysfunction lead independently to lifespan extension in *Caenorhabditis elegans*. *Ageing Cell*. 2010;9(3):433–447.
33. Lapointe J, Hekimi S. Early mitochondrial dysfunction in long-lived *Mclk1*^{+/-} mice. *J Biol Chem*. 2008;283(38):26217–26227.
34. Andziak B, O'Connor TP, Qi W, DeWaal EM, Pierce A, Chaudhuri AR, Van Remmen H, Buffenstein R. High oxidative damage levels in the longest-living rodent, the naked mole-rat. *Ageing Cell*. 2006;5(6):463–471.
35. Labinskyy N, Csiszar A, Orosz Z, Smith K, Rivera A, Buffenstein R, Ungvari Z. Comparison of endothelial function, O₂-* and H₂O₂ production, and vascular oxidative stress resistance between the longest-living rodent, the naked mole rat, and mice. *Am J Physiol Heart Circ Physiol*. 2006;291(6):H2698–H2704.
36. Tsatsou F, Trakatelli M, Patsatsi A, Kalokasidis K, Sotiriadis D. Extrinsic aging: UV-mediated skin carcinogenesis. *Dermatoendocrinol*. 2012;4(3):285–297.
37. Ravanat JL, Douki T, Cadet J. Direct and indirect effects of UV radiation on DNA and its components. *J Photochem Photobiol B*. 2001;63(1–3):88–102.
38. Panich U, Sittithumcharee G, Rathviboon N, Jirawatnotai S. Ultraviolet radiation-induced skin aging: The role of DNA damage and oxidative stress in epidermal stem cell damage mediated skin aging. *Stem Cells Int*. 2016;2016:7370642.
39. Kamenisch Y, Berneburg M. Progeroid syndromes and UV-induced oxidative DNA damage. *J Investig Dermatol Symp Proc*. 2009;14(1):8–14.
40. Olsen CM, Wilson LF, Green AC, Biswas N, Loyalka J, White-man DC. Prevention of DNA damage in human skin by topical sunscreens. *Photodermatol Photoimmunol Photomed*. 2017; 33(3):135–142.
41. Nakanishi M, Niida H, Murakami H, Shimada M. DNA damage responses in skin biology—implications in tumor prevention and aging acceleration. *J Dermatol Sci*. 2009; 56(2):76–81.
42. Siegl-Cachedenier I, Flores I, Klatt P, Blasco MA. Telomerase reverses epidermal hair follicle stem cell defects and loss of long-term survival associated with critically short telomeres. *J Cell Biol*. 2007;179(2):277–290.
43. Buckingham EM, Klingelhutz AJ. The role of telomeres in the ageing of human skin. *Exp Dermatol*. 2011;20(4):297–302.
44. Rock K, Tigges J, Sass S, Schutze A, Florea AM, Fender AC, Theis FJ, Krutmann J, Boege F, Fritsche E, et al. miR-23a-3p causes cellular senescence by targeting hyaluronan synthase 2: possible implication for skin aging. *J Invest Dermatol*. 2015; 135(2):369–377.
45. Fiedler J, Gronniger E, Pfanne A, Bronneke S, Schmidt K, Falk CS, Wenck H, Terstegen L, Thum T, Winnefeld M. Identification of miR-126 as a new regulator of skin aging. *Exp Dermatol*. 2017;26(3):284–286.
46. Danby FW. Nutrition and aging skin: sugar and glycation. *Clin Dermatol*. 2010;28(4):409–411.
47. Farrar MD. Advanced glycation end products in skin ageing and photoageing: what are the implications for epidermal function? *Exp Dermatol*. 2016;25(12):947–948.
48. Yoshinaga E, Kawada A, Ono K, Fujimoto E, Wachi H, Harumiya S, Nagai R, Tajima S. N(varepsilon)-(carboxymethyl)-lysine modification of elastin alters its biological properties: implications for the accumulation of abnormal elastic fibers in actinic elastosis. *J Invest Dermatol*. 2012;132(2):315–323.
49. Dunn JA, McCance DR, Thorpe SR, Lyons TJ, Baynes JW. Age-dependent accumulation of N epsilon-(carboxymethyl)lysine and N epsilon-(carboxymethyl)hydroxylysine in human skin collagen. *Biochemistry*. 1991;30(5):1205–10.
50. Kueper T, Grune T, Prahl S, Lenz H, Welge V, Biernoth T, Vogt Y, Muhr GM, Gaemlich A, Jung T, et al. Vimentin is the specific target in skin glycation. Structural prerequisites, functional consequences, and role in skin aging. *J Biol Chem*. 2007; 282(32):23427–23436.
51. Radjei S, Gareil M, Moreau M, Leblanc E, Schnebert S, Friguet B, Nizard C, Petropoulos I. The glyoxalase enzymes are differentially localized in epidermis and regulated during ageing and photoageing. *Exp Dermatol*. 2016;25(6):492–494.
52. Nguyen HP, Katta R. Sugar sag: glycation and the role of diet in aging skin. *Skin Therapy Lett*. 2015;20(6):1–5.
53. Makrantonaki E, Bekou V, Zouboulis CC. Genetics and skin aging. *Dermatoendocrinol*. 2012;4(3):280–284.
54. Gonzalo S, Kreienkamp R, Askjaer P. Hutchinson-Gilford Progeria Syndrome: A premature aging disease caused by LMNA gene mutations. *Ageing Res Rev*. 2017;33:18–29.
55. Vidak S, Foisner R. Molecular insights into the premature aging disease progeria. *Histochem Cell Biol*. 2016;145(4):401–417.
56. Naval J, Alonso V, Herranz MA. Genetic polymorphisms and skin aging: the identification of population genotypic groups holds potential for personalized treatments. *Clin Cosmet Investig Dermatol*. 2014;7:207–214.
57. Gao W, Tan J, Huls A, Ding A, Liu Y, Matsui MS, Vierkotter A, Krutmann J, Schikowski T, Jin L, et al. Genetic variants associated with skin aging in the Chinese Han population. *J Dermatol Sci*. 2017;86(1):21–29.
58. Franceschi C, Bonafe M, Valensin S, Olivieri F, De Luca M, Ottaviani E, De Benedictis G. Inflamm-aging. An evolutionary perspective on immunosenescence. *Ann N Y Acad Sci*. 2000; 908:244–254.
59. Fougere B, Boulanger E, Nourhashemi F, Guyonnet S, Cesari M. Chronic inflammation: accelerator of biological aging. *J Gerontol A Biol Sci Med Sci*. 2017;72(9):1218–1225.

60. Zhuang Y, Lyga J. Inflammaging in skin and other tissues—the roles of complement system and macrophage. *Inflamm Allergy Drug Targets*. 2014;13(3):153–161.
61. Takahara M, Kang K, Liu L, Yoshida Y, McCormick TS, Cooper KD. iC3b arrests monocytic cell differentiation into CD1c-expressing dendritic cell precursors: a mechanism for transiently decreased dendritic cells in vivo after human skin injury by ultraviolet B. *J Invest Dermatol*. 2003;120(5):802–809.
62. Yoshida Y, Kang K, Berger M, Chen G, Gilliam AC, Moser A, Wu L, Hammerberg C, Cooper KD. Monocyte induction of IL-10 and down-regulation of IL-12 by iC3b deposited in ultraviolet-exposed human skin. *J Immunol*. 1998;161(11):5873–5879.
63. Handoko HY, Rodero MP, Boyle GM, Ferguson B, Engwerda C, Hill G, Muller HK, Khosrotehrani K, Walker GJ. UVB-induced melanocyte proliferation in neonatal mice driven by CCR2-independent recruitment of Ly6c(low)MHCII(hi) macrophages. *J Invest Dermatol*. 2013;133(7):1803–1812.
64. Hammerberg C, Duraiswamy N, Cooper KD. Active induction of unresponsiveness (tolerance) to DNFB by in vivo ultraviolet-exposed epidermal cells is dependent upon infiltrating class II MHC+ CD11bbright monocytic/macrophagic cells. *J Immunol*. 1994;153(11):4915–4924.
65. Masaki H. Role of antioxidants in the skin: anti-aging effects. *J Dermatol Sci*. 2010;58(2):85–90.
66. Tanuja Y, Mishra S, Das S, Aggarwal S, Rani V. Anticedants and natural prevention of environmental toxicants induced accelerated aging of skin. *Environ Toxicol Pharmacol*. 2015;39(1):384–391.
67. Chen J, Li Y, Zhu Q, Li T, Lu H, Wei N, Huang Y, Shi R, Ma X, Wang X, et al. Anti-skin-aging effect of epigallocatechin gallate by regulating epidermal growth factor receptor pathway on aging mouse model induced by d-Galactose. *Mech Ageing Dev*. 2017;164:1–7.
68. Bavarsad Shahripour R, Harrigan MR, Alexandrov AV. N-acetylcysteine (NAC) in neurological disorders: mechanisms of action and therapeutic opportunities. *Brain Behav*. 2014;4(2):108–122.
69. Geissler S, Textor M, Schmidt-Bleek K, Klein O, Thiele M, Ellinghaus A, Jacobi D, Ode A, Perka C, Dienelt A, et al. In serum veritas-in serum sanitas? Cell non-autonomous aging compromises differentiation and survival of mesenchymal stromal cells via the oxidative stress pathway. *Cell Death Dis*. 2013;4:e970.
70. Bjelakovic G, Nikolova D, Gluud LL, Simonetti RG, Gluud C. Antioxidant supplements for prevention of mortality in healthy participants and patients with various diseases. *Cochrane Database Syst Rev*. 2012(3):CD007176.
71. Marosz A, Chlubek D. The risk of abuse of vitamin supplements. *Ann Acad Med Stetin*. 2014;60(1):60–64.
72. Bjelakovic G, Nikolova D, Gluud C. Antioxidant supplements and mortality. *Curr Opin Clin Nutr Metab Care*. 2014;17(1):40–44.
73. Lu LY, Ou N, Lu QB. Antioxidant induces DNA damage, cell death and mutagenicity in human lung and skin normal cells. *Sci Rep*. 2013;3:3169.
74. Rhee SG. Cell signaling. H₂O₂, a necessary evil for cell signaling. *Science*. 2006;312(5782):1882–1883.
75. Mojallal A, Lequeux C, Shipkov C, Breton P, Foyatier JL, Braye F, Damour O. Improvement of skin quality after fat grafting: clinical observation and an animal study. *Plast Reconstr Surg*. 2009;124(3):765–774.
76. Kim WS, Park BS, Kim HK, Park JS, Kim KJ, Choi JS, Chung SJ, Kim DD, Sung JH. 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.
77. Zhang S, Dong Z, Peng Z, Lu F. Anti-aging effect of adipose-derived stem cells in a mouse model of skin aging induced by D-galactose. *PLoS One*. 2014;9(5):e97573.
78. Bernardini FP, Gennai A, Izzo L, Zambelli A, Repaci E, Baldelli I, Fraternali-Orcioni G, Hartstein ME, Santi PL, Quarto R. Superficial enhanced fluid fat injection (SEFFI) to correct volume defects and skin aging of the face and periocular region. *Aesthet Surg J*. 2015;35(5):504–515.
79. Gennai A, Zambelli A, Repaci E, Quarto R, Baldelli I, Fraternali G, Bernardini FP. Skin rejuvenation and volume enhancement with the micro superficial enhanced fluid fat injection (M-SEFFI) for skin aging of the periocular and perioral regions. *Aesthet Surg J*. 2017;37(1):14–23.
80. Park BS, Jang KA, Sung JH, Park JS, Kwon YH, Kim KJ, Kim WS. Adipose-derived stem cells and their secretory factors as a promising therapy for skin aging. *Dermatol Surg*. 2008;34(10):1323–1326.
81. Derby BM, Dai H, Reichensperger J, Cox L, Harrison C, Cosenza N, Yang M, Bueno RA, Neumeister MW. Adipose-derived stem cell to epithelial stem cell transdifferentiation: a mechanism to potentially improve understanding of fat grafting's impact on skin rejuvenation. *Aesthet Surg J*. 2014;34(1):142–153.
82. Fisher GJ, Datta SC, Talwar HS, Wang ZQ, Varani J, Kang S, Voorhees JJ. Molecular basis of sun-induced premature skin ageing and retinoid antagonism. *Nature*. 1996;379(6563):335–339.
83. Kafi R, Kwak HS, Schumacher WE, Cho S, Hanft VN, Hamilton TA, King AL, Neal JD, Varani J, Fisher GJ, et al. Improvement of naturally aged skin with vitamin A (retinol). *Arch Dermatol*. 2007;143(5):606–612.
84. Verdier-Sevrain S, Bonte F. Skin hydration: a review on its molecular mechanisms. *J Cosmet Dermatol*. 2007;6(2):75–82.
85. Ramirez RD, Morales CP, Herbert BS, Rohde JM, Passons C, Shay JW, Wright WE. Putative telomere-independent mechanisms of replicative aging reflect inadequate growth conditions. *Genes Dev*. 2001;15(4):398–403.
86. Gonzalez-Suarez E, Geserick C, Flores JM, Blasco MA. Antagonistic effects of telomerase on cancer and aging in K5-mTert transgenic mice. *Oncogene*. 2005;24(13):2256–2570.
87. Dearlove RP, Greenspan P, Hartle DK, Swanson RB, Hargrove JL. Inhibition of protein glycation by extracts of culinary herbs and spices. *J Med Food*. 2008;11(2):275–281.

88. Thirunavukkarasu V, Nandhini AT, Anuradha CV. Fructose diet-induced skin collagen abnormalities are prevented by lipoic acid. *Exp Diabetes Res.* 2004;5(4):237–244.
89. Tarwadi KV, Agte VV. Effect of micronutrients on methylglyoxal-mediated in vitro glycation of albumin. *Biol Trace Elem Res.* 2011;143(2):717–725.
90. Lo Cicero A, Nissan X. Pluripotent stem cells to model Hutchinson-Gilford progeria syndrome (HGPS): current trends and future perspectives for drug discovery. *Ageing Res Rev.* 2015;24(Pt B):343–348.
91. Gordon LB, Kleinman ME, Miller DT, Neuberger DS, Giobbie-Hurder A, Gerhard-Herman M, Smoot LB, Gordon CM, Cleveland R, Snyder BD, et al. Clinical trial of a farnesyl-transferase inhibitor in children with Hutchinson-Gilford progeria syndrome. *Proc Natl Acad Sci U S A.* 2012;109(41):16666–16671.
92. Varela I, Pereira S, Ugalde AP, Navarro CL, Suarez MF, Cau P, Cadinanos J, Osorio FG, Foray N, Cobo J, et al. Combined treatment with statins and aminobisphosphonates extends longevity in a mouse model of human premature aging. *Nat Med.* 2008;14(7):767–772.
93. Cau P, Navarro C, Harhour K, Roll P, Sigaudy S, Kaspi E, Perrin S, De Sandre-Giovannoli A, Levy N. Nuclear matrix, nuclear envelope and premature aging syndromes in a translational research perspective. *Semin Cell Dev Biol.* 2014;29:125–147.
94. Gordon LB, Kleinman ME, Massaro J, D'Agostino RB Sr., Shappell H, Gerhard-Herman M, Smoot LB, Gordon CM, Cleveland RH, Nazarian A, et al. Clinical trial of the protein farnesylation inhibitors lonafarnib, pravastatin, and zoledronic acid in children with Hutchinson-Gilford progeria syndrome. *Circulation.* 2016;134(2):114–125.
95. Cao K, Graziotto JJ, Blair CD, Mazzulli JR, Erdos MR, Krainc D, Collins FS. Rapamycin reverses cellular phenotypes and enhances mutant protein clearance in Hutchinson-Gilford progeria syndrome cells. *Sci Transl Med.* 2011;3(89):89ra58.
96. Gabriel D, Roedl D, Gordon LB, Djabali K. Sulforaphane enhances progerin clearance in Hutchinson-Gilford progeria fibroblasts. *Aging Cell.* 2015;14(1):78–91.
97. Larrieu D, Britton S, Demir M, Rodriguez R, Jackson SP. Chemical inhibition of NAT10 corrects defects of laminopathic cells. *Science.* 2014;344(6183):527–532.
98. Kubben N, Brimacombe KR, Donegan M, Li Z, Misteli T. A high-content imaging-based screening pipeline for the systematic identification of anti-progeroid compounds. *Methods.* 2016;96:46–58.
99. Suh SS, Hwang J, Park M, Seo HH, Kim HS, Lee JH, Moh SH, Lee TK. Anti-inflammation activities of mycosporine-like amino acids (MAAs) in response to UV radiation suggest potential anti-skin aging activity. *Mar Drugs.* 2014;12(10):5174–87.
100. Suggs A, Oyetakin-White P, Baron ED. Effect of botanicals on inflammation and skin aging: analyzing the evidence. *Inflamm Allergy Drug Targets.* 2014;13(3):168–76.
101. Goncalves de Carvalho CM, Ribeiro SM. Aging, low-grade systemic inflammation and vitamin D: a mini-review. *Eur J Clin Nutr.* 2017;71(4):434–440.