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Skin mirrors human aging

Abstract: Aged skin exhibits disturbed lipid barrier, angiogenesis, production of sweat, immune functions, and calcitriol synthesis as well as the tendency towards development of certain benign or malignant diseases. These complex biological processes comprise endogenous and exogenous factors. Ethnicity also markedly influences the phenotype of skin aging. The theories of cellular senescence, telomere shortening and decreased proliferative capacity, mitochondrial DNA single mutations, the inflammation theory, and the free radical theory try to explain the biological background of the global aging process, which is mirrored in the skin. The development of advanced glycation end-products and the declining hormonal levels are major factors influencing intrinsic aging. Chronic photodamage of the skin is the prime factor leading to extrinsic skin aging. The deterioration of important skin functions, due to intrinsic and extrinsic aging, leads to clinical manifestations, which mirror several internal age-associated diseases such as diabetes, arterial hypertension and malignancies.

Keywords: aging; extrinsic aging; hormones; intrinsic aging; skin.

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Introduction

It is a common truth that biological systems stand as a natural paradox, which in the past was considered to defy the Second Law of Thermodynamics, stating that the entropy of every isolated system should always increase. The existence and maintenance of these systems are based on the development of biochemical mechanisms, with which they struggle to evade or at least delay oxidation that would eventually lead to a lower energy state [1–3]. Under this spectrum, aging can be considered as a natural process of biochemical events, leading to gradual accumulation of damage and resulting in disease and death [4]. Although the manifestations of this damage are masked as far as the inner organs are concerned, the skin surface appears as the first bearer of marks of time as well as an easily accessible model for the assessment and determination of the involved molecular mechanisms [5]. Skin has long been recognized to protect organisms against deleterious environmental factors and is vital for the homeostasis of temperature, electrolyte, and fluid balance of the body [6].

Phenotype of skin aging

Aged skin shows a phenotype of a disturbed lipid barrier, angiogenesis, production of sweat, immune functions, and production of calcitriol as well as the tendency towards development of various benign or malignant diseases [7]. These complex biological processes comprise endogenous factors such as genetic predisposition, cellular metabolic pathways, and qualitative and quantitative hormonal alterations, termed intrinsic aging and exogenous factors, primarily ultraviolet (UV) light exposure and secondarily chemicals, toxins, and pollution, leading to extrinsic aging [8]. The model for the former is skin deriving from areas that are not sun-exposed, mostly the inner side of the upper arm and the buttocks, and for the latter are skin areas constantly sun-exposed, such as facial skin. Intrinsically aged skin appears macroscopically thin and atrophic and exhibits fine wrinkles, loss of underlying fat, reduced elasticity, and prominent dryness, often accompanied by pruritus [9]. On the contrary, extrinsically photoaged skin exhibits deep wrinkles, thickening of the epidermis, dullness, roughness, and mottled discoloration. Telangiectasies and pigmentary discoloration might also be observed in advanced and severe degrees of photoaging [9–14], with the latter being the major skin aging-associated change in Asian populations [15].

The latter observation led to comparative studies between populations of different ethnicity. Caucasians have greater skin wrinkle formation and sagging in comparison with other skin phenotypes, whereas the manifestations have an earlier onset [15]. Furthermore, Caucasians

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are more prone to skin desquamation, which is dependent of age [16]. Afro-American and Caucasian women both have a higher prevalence of age-related dryness compared to other ethnicity groups [17]. Chinese women have more severe periorbital wrinkles in comparison with women from Japan, whereas Thai women were characterized by severe wrinkling of the lower half of their faces [18]. Caucasian females have a higher prevalence of sagging in the subzygomatic area [15]. Wrinkling in each facial area has a later onset in Chinese women in comparison with French women, although age-related pigment spot intensity is the cardinal sign of aging in Chinese women [19]. Lastly, although Asian skin seems to have similar transepidermal water loss and ceramide levels to Caucasian skin, the stratum corneum barrier appears to be more susceptible to mechanical stimuli. Asian skin is more sensitive to exogenous chemicals because of the thinner stratum corneum barrier, higher eccrine gland intensity, and smaller pore areas in comparison with other ethnic groups, indicating the correlation of the latter to the sebaceous gland activity [15]. Because skin aging phenotype varies according to the population, not universal but ethnicity-specific aging characteristics could only be correlated with age-associated diseases. Photographic severity scales and other clinical methods are developed to assess the severity of skin aging features [9, 20].

Intrinsic aging

Nowadays, many theories have been developed to explain different pathophysiologic aspects of aging. Among them are the theory of cellular senescence, telomere shortening and decreased proliferative capacity, the inflammation theory, mitochondrial DNA single mutations, and the free radical theory [21–26]. The process of aging is being mirrored in the skin and it comprises multifactorial processes,

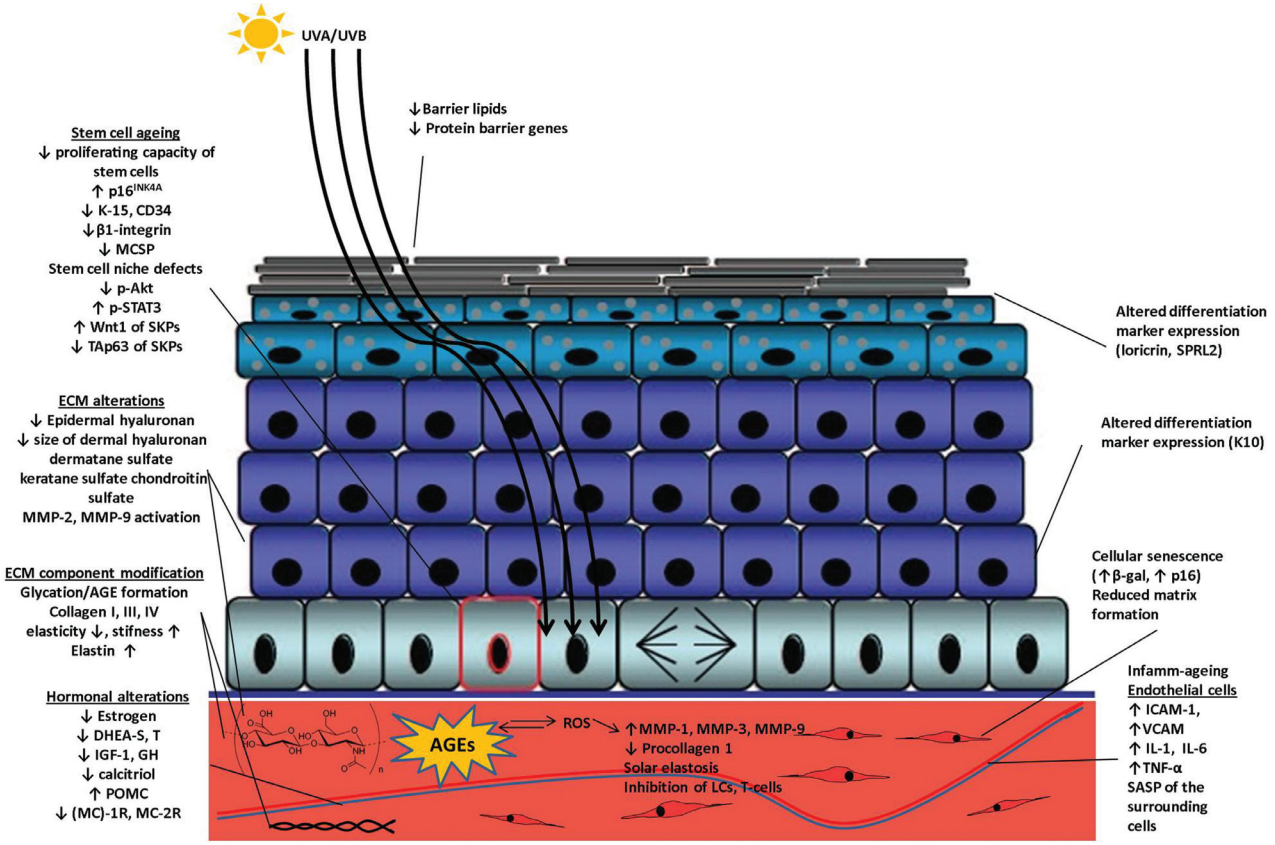

Figure 1 Intrinsic and extrinsic factors of skin aging.
β-gal, β-galactosidase; AGEs, advanced glycation end-products; DHEA, dehydroepiandrosterone; GH, growth hormone; ICAM-1, intercellular adhesion molecule-1; IGF-I, insulin growth factor-I; IL, interleukin; K-15, keratin-15; LCs, Langerhans cells; MC-1R, melanocortin-1-receptor; MC-2R, melanocortin-2-receptor; MCSP, melanoma-associated chondroitin sulfate proteoglycan; MMP, matrix metalloproteinase; POMC, proopiomelanocortin; SASP, senescent-associated secretory phenotype; SKPs, skin-derived precursors; SPRL2, small proline-rich-like protein 2; T, testosterone; VCAM-1, vascular cell adhesion molecule-1.

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including extracellular matrix (ECM) skin components, cells, as well as cell-cell and cell-matrix interactions [27].

Cellular senescence

As far as cellular senescence is concerned, human dermal fibroblasts after many series of passages in vitro were shown to exhibit enlarged cell bodies and were often positive for the myofibroblast marker α-smooth actin and the senescence markers β-galactosidase and p16, in comparison with early-passage fibroblasts. The fibroblasts were in a subsequent step used for the generation of human skin equivalents (HSE). HSE formation with late-passage fibroblasts resulted in a thinner dermis with reduced matrix formation and a weaker expression of the differentiation marker keratin-10 [28], highlighting the effects of aging in ECM quality, keratinocyte differentiation, and strata formation. However, the changes regarding epidermal proliferation and the basement membrane, which are observed in vivo, are lacking [29]. Janson et al. [30] used high-passage fibroblasts, deriving from the papillary and reticular dermis, and used them for the reconstruction of artificial skin in vitro. HSE deriving from reticular fibroblasts showed impaired differentiation patterns and areas of incomplete cornification of the epidermis. The expression of the epidermal differentiation markers loricrin, filaggrin and small proline-rich protein 2 in the stratum granulosum and corneum of the HSE deriving from papillary fibroblasts was more intense in comparison with reticular fibroblast-derived ones. Moreover, the presence of papillary fibroblasts resulted in a higher number of Ki67-positive basal keratinocytes. Papillary fibroblast senescence led to a more reticular-like fibroblast phenotype [30].

Immunologic alterations

Although age is usually associated with a gradual deterioration of the immune system and immunologic shifts named immunosenescence, it is also reported to correlate to an hyperinflammatory state, termed inflamm-aging [31]. The immune system undergoes certain alterations, making it susceptible to certain infections, autoimmune diseases, and malignancies. Interleukin-1 dysregulation mechanisms and potentially every molecule that can induce the synthesis of the intercellular adhesion molecule-1 and the subsequent recruitment of circulating immune cells in the dermis are aging factors. In a subsequent step, these inflammatory cells release proteases and radical oxygen species, which provoke long-term damage in cutaneous cells [32–35]. Senescent cells are believed to force the surrounding cells in acquiring the so-called "senescent-associated secretory phenotype" (SASP) by the secretion of various proinflammatory factors [36]. Furthermore, there is increasing evidence that chronic inflammation correlates with normal aging and impairs stem cell dysfunction [37].

Disruption of epidermal barrier

With advancing age, the epidermis develops an abnormality of the barrier homeostasis, which is even more prominent in photoaged skin [38]. This can be explained by an overall reduction of stratum corneum lipids and a disturbance regarding the cholesterol and fatty acid synthesis [39]. Not only the "mortar" of the skin barrier but the "bricks" as well are affected by aging; genes associated with keratinocyte differentiation, including keratins and cornified envelope components, undergo an age-related down-regulation [40].

Intrinsically aged skin reflects age-related pathophysiologies

Not only keratinocytes and fibroblasts but also all skin cell types seem to be affected by intrinsic and extrinsic aging factors. Sebaceous gland cells also show a profound decrease of secretory output, which is age related, as well as a decrease of the size of sebaceous cells [41–43]. These data were confirmed after in vitro treatment of human sebocytes with a hormone mixture consisting of androgens, estrogens, and growth factor levels correlating to the average serum levels of 20- and 60-year-old women. The treatment with the latter resulted in a significant reduction of sebaceous lipogenesis in comparison with the former, showing remarkable biological correspondence to the in vivo phenotype. The hormone mixtures resulted in differential gene expression, according to the age correspondence of the mixture used. Genes that were shown to be regulated were involved in DNA repair and stability, mitochondrial processes, oxidative stress, cell cycle and apoptosis, ubiquitin-induced proteolysis, and other pathways. The most significantly altered pathway was that of tumor growth factor-β, known for its association with malignancies [44]. Furthermore, key genes associated with the pathogenesis of neurodegenerative diseases were shown to be expressed in human sebaceous glands and showed a regulation of their expression after hormone treatment. Considering the fact that

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skin and nervous system are both ectodermal derivatives, this finding led to the assumption that skin maybe used as a tool for investigating aging of the nervous system. Additional experiments, in which the whole genome of human skin biopsies from young and elderly males and females was investigated, confirmed this hypothesis. Skin expresses several genes associated with age-associated diseases of the nerve system and these genes are regulated with increasing age and maybe due to the accompanying hormone decline [45].

Dermal aging

During aging, the proportion of skin glycosaminoglycans (GAGs) changes, as it was depicted in corneal keratinocytes and skin-derived fibroblasts. Among the matrix components involved, hyaluronan appears to play a special role [46, 47]. Hyaluronan is a GAG with the unique ability to bind and retain water molecules [48], contributing directly to skin hydration [49]. Hyaluronan was shown to affect the expression of matrix metalloproteinases (MMPs), special proteases regulating physiologic and pathologic skin processes, such as tissue remodeling, morphogenesis, wound healing, and tumor progression [50]. MMP activity is regulated in the level of transcription and level of activation of the inactive zymogen forms, by proteases such as trypsin, plasmin, or other MMPs. Hyaluronan increases expression and activation of MMP-2 and MMP-9 of skin explant cultures [51]. Epidermal hyaluronan disappears from aged skin, whereas reduction of the size of polymers may also result in an overall reduction of skin moisture [52, 53]. As far as skin explant cultures are concerned, other ECM components, such as dermatane sulfate, keratane sulfate, and chondroitin sulfate, can up-regulate MMP-9 activation, thus being of pathophysiologic significance for skin remodeling [27].

The ECM of the skin is a complex structure composed of a combination of collagens, elastic fibers, and GAG-rich proteoglycans. The ECM is constantly under structural modification and remodeling, with main components the collagen I and III, which offer skin its tensile strength [54]. The elastic properties of the skin are offered by other ECM molecules with slow turnover rate, mainly elastin and fibrillin-1, which form an elastin core and a microfibrillar scaffold. Fibrillin-1 is one of the potential biomarkers for the objective assessment of aging [54, 55]. The fact that many ECM molecules are not rapidly regenerating makes them excellent potential immunohistochemical targets for quantifying dermal aging.

Glycation

Glycation is the nonenzymatic reaction between sugars and proteins, lipids, and nucleic acids. A long-standing hyperglycemic condition in rats was shown to decrease epidermal lipid synthesis, lamellar body production, and antimicrobial peptide expression [56]. The role of advanced glycation end-products (AGEs) and their impact in aging has been highlighted over the recent years. Their formation involves many steps and begins with the Maillard reaction, which ends with the production of a non-stable Schiff base (or an Amadori product after further rearrangements) after reaction of the sugar carbonyl groups with amino groups of protein amino acid residues [57]. Stable products might result also after protein adduct formation or cross-linking of Schiff base or Amadori products. AGEs exert their actions both per se and through interaction with specific receptors (RAGE - Receptor for AGEs). This is a pattern recognition receptor, also binding various other molecules such as S100, β-amyloids, and β-sheet fibrils [58, 59]. Binding of AGEs leads to activation of nuclear factor-κB and transcription of various inflammatory genes [60]. AGEs are accumulated at a slow rate with aging. Increased levels of AGEs are the result of diseases such as diabetes mellitus, the excessive production of reactive oxygen species (ROS), dietary factors, and smoking [58, 61]. AGEs deposition in peripheral tissues is implicated in many diseases, such as diabetes-related macular degeneration, osteoarthritis, and diabetic angiopathy [62–65]. Total content of AGEs accumulated in the organism is also defined from their removal rate, in both the glutathione-dependent system of glyoxalase I and II and the fructosyl-amine oxidases and the fructosamine kinases [66, 67]. Proteins with a slow turnover rate, such as collagen types I and IV, are mainly susceptible to glycation during intrinsic aging [68, 69]. Collagen glycation leads to intermolecular crosslink formation of adjacent collagen fibers, leading to decreased flexibility and stiffness [70]. Moreover, AGE-induced collagen modification makes collagen resistant to MMP proteolysis, thus hindering its degradation and substitution with new and functional fibers [71]. Other ECM protein targets are elastin and fibronectin [68, 69, 72]. AGEs mediate their effects also direct on cells by reducing the proliferation and inducing apoptosis of dermal fibroblasts [73], decrease keratinocyte cell viability and migration [74] and the premature cellular senescence of both [75–77]. In a recent study, Hoffmann et al. illustrated that AGE-associated skin autofluorescence mirrors the vascular function [76]. The authors analyzed the AGE modifications in collagens obtained from residual bypass graft material via hydroxyproline assay and AGE intrinsic

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fluorescence and correlated their findings with skin autofluorescence measured by an autofluorescence reader. In addition, they measured pulse wave velocity, which reflects vessel stiffness, and correlated the findings. They found that skin autofluorescence and pulse wave velocity significantly correlate with the AGE contained in graft material; therefore, both techniques can be used as adequate predictors of vessel function in patients suffering from coronary heart disease.

Skin stem cell aging

Stem cells are cells that have the ability to self-renew by undergoing multiple cycles of self-division while retaining their undifferentiated phenotype [78, 79]. Embryonic stem cells are multipotent cells and are able to give rise to all other cell types, whereas adult stem cells have more restricted potentials. The latter also have high proliferative capacity and are required for tissue renewal throughout the organism's lifespan [80]. As far as the skin is concerned, epidermal stem cells are known to reside within the stratum basale and give rise to transient amplifying cells and differentiating progenitors, forming functional epidermal proliferative units, extending from the basal to the corneal layer [81]. Furthermore, dermal stem cells are also of great importance for skin homeostasis, because they produce the progeny responsible for ECM synthesis and growth factors. Although they derive from the mesoderm, they can give rise to endodermal liver cells and ectodermal nerve cells, suggesting the potential for giving birth to a broader palette of cell type progenitors [80, 82, 83]. Because they comprise the pool of tissue regeneration, stem cells also came in to the focus of the aging research as a potential target of intrinsic and extrinsic aging factors, which could potentially affect the number and the function of these cells. On the contrary, the potential therapeutic effects of utilization of stem cells, and especially the abundant and easy way to access adipose-derived stem cells, are also being examined [84, 85].

The epidermal turnover rate is 28 days in young individuals, whereas it varies between 40 and 60 days in the elderly [86]. Epidermal stem cells are considered unique in comparison with other adult stem cells in their ability to resist aging. They show no effects associated with increased ROS levels, perhaps as a result of maintaining high levels of superoxide dismutase [87]. Interestingly, stem cell numbers do not necessarily decline with age [88]; however, their functional role, which is their ability to produce differentiated progeny, to be impaired [89]. Wound healing is a prime example, because keratinocytes isolated from older donors give rise to a lower proportion of holoclones in comparison with younger ones [90]. This fact, as well as the higher level of the cell cycle arrest molecule $p16^{INK4A}$ of human epidermal cells of senior individuals [91], suggests an impairment of stem cell mobilization with age as well the inability to respond to proliferating signals. In accordance with these results, the molecule 12-*O*-tetradecanoylphorbol-13-acetate, known as an inducer of stem cell activation and proliferation, led to an increase of the number of stem cells from young mouse dorsal back skin, whereas it depleted old skin-derived cells, which expressed the stem cell markers keratin-15 and CD34 [92]. Furthermore, epidermal stem cells of older individuals express lower levels of the stem cell markers β1-integrin and melanoma-associated chondroitin sulfate proteoglycan, which are correlated with the higher self-renewal capacity [93].

Multiple mechanisms are involved in stem cell exhaustion. DNA repair mechanism deficits are implied as one of the causes. Deletion of the DNA repair gene ataxia-telangiectasia and Rad3-related resulted in progeroid phenotypes in adult mice, such as development of alopecia, kyphosis, osteoporosis, thymic involution, and fibrosis [94]. Experiments with mouse skin have shown that epidermal stem cells are resistant to cellular aging [95, 96], highlighting the role of the microenvironment (stem cell niche) in age-related stem cell exhaustion [80, 88, 97]. Accumulation of 53BP1 foci throughout the highly compacted heterochromatin of aged hair-follicle stem cells confirmed that DNA damage is between the primary mechanisms of stem cell exhaustion [98].

Jak-Stat and Notch pathways are involved to age-associated epidermal stem cell alterations [92]. More specifically, cells of the aging epidermis as well as the epidermal stem cell population express high levels of phosphorylated Stat3, which is also involved in tumor progression [92, 99–101], whereas skin was used as a model to provide insights in the way that aging is linked with age-associated pathophysiologic events, including inflammation and tumorigenesis. The Wnt and mTOR pathway is also involved in skin aging [45]. Persistent expression of Wnt1 led to rapid growth of hair follicles followed by epithelial stem cell senescence, apoptosis, and epidermal stem cell exhaustion [102]. Lastly, the phosphatidylinositol 3-kinase/Akt pathway is involved in the senescence of embryonic neural crest-derived or somite-derived multipotent progenitor cells with properties of stem cells of the dermal compartment, termed skin-derived precursors (SKPs). These cells were shown to contribute to wound

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healing, maintenance of the dermis, and hair follicle morphogenesis [103]. Separation of these cells from their niche led to accelerated senescence together with a profound decrease of Akt activity. Similar cell phenotypes were obtained after blocking the aforementioned pathway with several inhibitors [104].

The p63 protein in both its isoforms, with (TAp63) and without (ΔNp63) in its transactivation domain, was demonstrated to have multiple functions during skin development and a protective role against premature aging through maintenance of SKPs as well as a fundamental role in cardiac development. TAp63$^{-/-}$ mice display a phenotype with severe ulcerations, kyphosis, hair loss, and impaired wound healing. Interestingly, small interfering RNA-specific knockdown of Tap63 prevented the formation of beating cardiomyocytes in mice [105–107].

Although mechanisms related to age-related defects in stem cell polarity and asymmetrical damage protein segregation have been described in bacteria and yeast, data from humans are still lacking [108, 109].

Hormonal alterations

One of the major factors influencing intrinsic aging is the progressive decrease of various hormone levels with age, which manifest themselves with various skin changes [110]. Estrogens and testosterone, growth hormone, and insulin growth factor-I (IGF-I), melatonin, T3 and thyroid-stimulating hormone, dehydroepiandrosterone (DHEA), and DHEA sulfate (DHEA-s) decrease with aging, leading to menopause and androgen deficiency of the aging male [5, 111–114]. Testosterone has been shown to enhance the keratinization of epidermal cells and promote human foreskin angiogenesis. On the contrary, DHEA increases procollagen synthesis and inhibits collagen synthesis by regulating MMPs and up-regulating the tissue inhibitor of MMP-1 in normal human fibroblasts [115–118]. Decrease of testosterone or loss of its circadian rhythm has been observed in aged men, with various manifestations, such as general weakness, erectile dysfunction, reduced muscle and bone mass, and reduced erythropoiesis. Furthermore, it increases the prevalence of depression, coronary disease, and osteoporosis. Free bioavailable testosterone increases approximately 2% per year, whereas the sex-hormone binding globulin also increases [119]. Testosterone deficiency is correlated with diabetes mellitus type 2 and obesity [114]. DHEA-s levels decline in blood as a result of aging and are unrelated to menopause status. Interestingly, the response of DHEA to adrenocorticotropin-releasing hormone or corticotropin-releasing hormone is age dependent [120].

Estrogens stimulate the proliferation of normal human epidermal keratinocytes, by promoting the expression of cyclin D2, which facilitates the cell transition from G1 to S phase [121, 122]. They increase the production of ECM components, such as acid mucopolysaccharides, hyaluronic acid, and collagen I and III synthesis [123, 124], promote wound healing through acceleration of keratinocyte granulocyte-macrophage colony-stimulating factor secretion [125], protect from photoaging [126], and prevent wrinkle formation and skin dryness of postmenopausal women [127]. Cell viability of both HaCaT keratinocytes and fibroblasts presents a formidable resistance to hydrogen peroxide and to counteract DNA damage, as investigated with an antibody against 8-oxo-2′-deoxyguanosine [128]. Selective antioxidants are believed to mediate their effects through estrogen receptor-β activation in the skin [129]. Surprisingly, 5α-dihydrotestosterone appears as an inhibitor of wound repair, because it inhibits the migration of epidermal keratinocytes by regulating the expression of β-catenin [130, 131]. IGF-I declining with age might be involved in the reduction of skin surface lipids and thickness of the epidermis [132]. Its decreased expression is combined with an inappropriate UVB response of elderly volunteers [133].

The vitamin D system plays also an important role in aging [134]. In vitro experiments demonstrated that UVB apoptosis of epidermal keratinocytes is suppressed by pretreatment of the cell population with 1 μM $1,25(OH)_2D_3$ over 24 h [135, 136]. The $1,25(OH)_2D$ treatment of HaCaT keratinocytes results in the promotion of sphingomyelin hydrolysis via expression of the tumor necrosis factor-α, which leads to proapoptotic ceramide production [137, 138]. Interestingly, physiologic concentrations of $1,25(OH)_2D$ stimulate keratinocyte proliferation, whereas pharmacologic doses seem to attenuate it [139].

Pro-opiomelanocortin (POMC) and its receptors are also undergoing age-related changes in keratinocytes. POMC gene expression exhibits an increase with age, whereas the melanocortin receptors MC-1R and MC-2R are down-regulated in human skin epidermis in both protein and mRNA levels. The decrease of the receptor expression is believed to be compensated by the increase of POMC expression [140].

Skin is a major target and source of hormones and the correlation of its phenotype with altered hormone levels can provide insights to other hormone decline-associated comorbidities.

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Extrinsic aging

Chronic photodamage

Chronic photodamage of the skin is the prime factor leading to skin aging, exerting its manifestations through induction of DNA damage and UV-mediated ROS. ROS formation induces the transcription factor c-Jun via mitogen-activated protein kinases, leading to an overexpression of MMP-1, MMP-3, and MMP-9 and inhibition of procollagen-1 [141]. The cutaneous manifestations of this process are pigmentary changes and wrinkling [48]. Apart from the similarities with endogenously aged skin, thickened epidermis and the hyperplasia of elastic tissue, namely solar elastosis, characterize the extrinsic aging of the skin [7, 14]. The level of sun exposure determines the level of hyperplastic response, with the accumulation of abundant dystrophic elastotic material in the dermis considered to be pathognomonic for this condition [142, 143]. Photoaged skin accumulates more mutations of mitochondrial DNA in comparison with photoprotected skin [144]. The role of the 1000-fold repeats of TTAGGG sequences, termed telomeres, has been implicated in photoaging, as the photoexposed epidermis exhibits shorter telomere length in the epidermis than in the dermis [145].

UV radiation interferes with the cutaneous immune system – action that has also therapeutic implications in many cases in dermatology. On the contrary, inhibition of action of certain immune cells (Langerhans cells and T cells) might hinder the blocking mechanisms of early cell tumorigenic progression [146].

Smoking

Exposure to tobacco smoke is also a widely accepted factor that accelerates extrinsic aging processes [147–149], targeting mainly the elastin network of the skin [150]. Cigarette smokers wrinkle formation depict a distinctive pattern with prominent perioral lines and sharply contoured crows feet, termed the “smoker’s face”. The physical movement of the lips and face while inhaling the smoke is the natural explanation for their formation. Facial wrinkles radiate typically at right angles from the lips and eyes and a thinning of the facial features are also observed [147, 151].

Glycation

AGEs are also involved in extrinsically aged skin. It was shown from studies of young individuals that AGE accumulation was mainly colocalized with solar elastosis, indicating that UV irradiation affects AGE precipitation in vivo [60, 69, 72]. Using photoexposed and photoprotected skin specimens, a significant increase of lower molecular mass of hyaluronan was observed in photoexposed skin, with a concomitant down-regulation of its receptors CD44 and RHAMM [152].

Age-associated skin diseases

Aging, both intrinsic and extrinsic, comprises a major variable of many cutaneous manifestations. There are a number of important skin functions that deteriorate with increasing age, such as epidermal regeneration capacity, synthesis of sebum and sweat, dermoepidermal adhesion, wound healing, thermoregulation, and the speed of natural elimination of potentially hazardous chemical factors [153]. In addition, several age-associated diseases such as diabetes, arterial hypertension, and malignancies indicate their subtle manifestation through skin, for example, through disturbance of wound healing processes and chronic ulcerations or paraneoplastic syndromes.

Based on these characteristics, we present some common age-associated skin diseases or diseases whose prevalence and manifestation have specific characteristics when appearing in elderly patients.

Wound healing

The prevalence of leg ulcers, as a result of an end-stadium venal insufficiency, affects a great number of elderly patients, with 4% of the population suffering from healed or active venous ulcers. Apart from the chronic pain, immobility of the patients, depression, and decreased quality of life characterize the disease [154–156]. Multimedication of the elderly can be also the cause for their development [157]. Leg ulcers and decubital ulcers constitute a major financial problem for the health system, because they require longer inpatient care, until they are sufficiently treated, compared with other age-related skin disorders [158].

Skin infections

Skin and soft-tissue infections are frequent in senior patients also because of the impaired epidermal skin barrier. *Staphylococcus aureus* and β-hemolytic

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streptococci are often the causative organisms leading to infections such as impetigo, folliculitis, furunculosis, carbunculosis, and erysipelas. Comorbidities such as lymphedema and deep vein thrombosis play an important role in facilitating skin infections. Excoriations caused from pruritus of the elderly as a result of the barrier impairment or underlying conditions such as renal disease or diabetes mellitus might provide the ground for bacterial superinfections [159]. Herpes zoster manifests itself after reactivation of the varicella zoster virus, usually after a "blow" to the immune system (e.g., infection and operation) based on already existing age-related immune alterations [160].

Immunologic diseases

The increase of certain immunologic skin disorders, correlated to age-related immune system alterations, is a possible explanation for the prevalence of such diseases. A prime example is the shift of T cells from the naïve to the memory phenotype, their reduced proliferation after activation, Langerhans cell number reduction, and the cytokine profile alterations, which make skin cells more susceptible to endotoxins [161, 162]. Bullous pemphigoid is clinically characterized by tense skin blistering and crusts usually on erythematous skin [163] and pemphigus is a chronic blistering disease characterized histologically by intraepidermal bulla formation. The latter has three types: vulgaris, foliaceous, and paraneoplastic. Pemphigus vulgaris mostly affects older adults of 40 to 70 years, whereas bullous pemphigoid peaks at 80 years [153, 164, 165]. On the contrary, immunologic skin senescence might explain why the manifestations of psoriasis of the elderly are mild in comparison with young patients. Erythrodermic psoriasis has a higher prevalence in those patients, whereas the scalp skin of the elderly patients with plaque psoriasis is more frequently affected. On the contrary, younger patients usually present with erythematosquamous plaques on the knees and elbows [153, 166–168].

Pigmentary disorders

Vitiligo is a disorder of progressive loss of melanocytes from the skin and hair follicle. It was recently shown that melanocytes in vitiligo are accumulating an increased number of p16, which does not correlate to the age of the donor, and several active proteins of the senescence-associated secretory phenotype, implying a pathophysiologic mechanism of premature cellular senescence [169].

Skin tumors

A high rate of skin cancers (90%) is attributed to sun exposure [170]. Among them, actinic keratosis is a form of noninvasive intraepithelial skin neoplasm, characterized by atypical proliferation of suprabasal keratinocytes and a frequent reason for dermatologic consultation. This lesion occasionally evolves to squamous cell carcinoma (SCC) and is currently defined as an in situ SCC [171]. Actinic keratoses occur in UV-exposed skin and develop in older, fair skined individuals [172]. The darker the skin type is, the smaller is the risk for the development of actinic keratoses. Apart from sun exposure, drugs such as thiazide diuretics are also contributing to the genesis of the lesions [173].

Basal cell carcinoma (BCC) and SCC appear on sun-exposed skin, and Fitzpatrick skin types II and III are more prone to their development [146]. BCC is the most common skin cancer of Caucasians and comprises a locally invasive cancer, deriving from the basaloid cells, resembling the undifferentiated basal cells of the epidermis and its appendages. Eighty-five percent of all BCCs are localized on the head-and-neck area [174]. Its prevalence increases with age and sun exposure [175]. SCC is the second most common nonmelanoma skin cancer, occurring more often in men in comparison with women. It is characterized by the malignant transformation of suprabasal keratinocytes. It shows a higher metastatic potential than the BCC, and its incidence rises after the age of 40. Factors correlated with UV exposure, such as agricultural work, sun burns, solarium, PUVA therapy play an important role in its pathogenesis, as well as factors, such as ionizing radiation, chemical carcinogens, immunosuppression/immunosenescence [176], and human papilloma virus infection [153, 177].

Malignant melanoma is a melanocyte-derived skin tumor. Melanoma is also more prevalent in senior patients, because half of the patients with the disease in Europe, the US, and Australia are more than 65 years old [178–180]. A retrospective study of 610 patients showed that patients older than 70 years appear to have thicker melanomas, higher local/transit metastases, and a higher mitotic ratio [181]. For all histologic subtypes, except lentigo maligna melanoma, men more than 50 years old were most likely to be diagnosed with thick (≥2.0 mm) tumors [182]. In contrast, younger women had fewer thick melanomas in all histologic subtypes. In addition, ulceration is more common in the aged population. Interestingly, de novo melanomas are more common in the elderly, whereas it is more probable that a malignant tumor will develop based on a preexisting single naevus in the elderly, also

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due to the decrease of naevus counts in this population [182]. Older age is considered an independent poor prognostic factor, whereas it is unclear if conditions, such as impaired host defenses and a change in the disease's pathophysiology, have a confounding role [183].

Skin as a tool for understanding global aging

Apart from the skin-associated intrinsic and extrinsic alterations and the skin diseases usually related to the aging process, there is an ongoing interest of the utilization of the skin as a model for age-associated pathologic conditions of various systems, such as the nervous and endocrine systems. The way that skin can efficiently mirror inner organ alterations or deficiencies which come with age is also highlighted by the prominent skin signs of genetic diseases, which resemble aspects of aging at a very early age.

Hormone deficiency

IGF age-related decline affects sebocyte differentiation and epidermal thickness [132]. Patients suffering from conditions of multiple hormone deficiency or IGF-I deficiency present with a phenotype of premature aged skin. Important aspects of the growth hormone/IGF-I deficiency are hyperglycemia, obesity, osteopenia, hypercholesterolemia, decrease of lean mass, cardiovascular diseases, and premature mortality [26, 184–186].

Neurodegenerative diseases

In addition to the common ectodermal origin of the nervous system and the skin, the use of the second as a model of detection of hormone-associated aging has been highlighted recently. cDNA microarray analysis of immortalized sebocytes treated with a hormonal mixture of growth factors and sex steroids resembling the one of 20- and 60-year-old women resulted in the regulation of 899 genes, which have been related to significant metabolic pathways related to aging [6, 45]. Furthermore, specific genes associated with the pathomechanism of neurodegenerative diseases, such as Parkinson's disease, Huntington's disease, Alzheimer's disease, dentatorubral pallidoluysian atrophy and amyotrophic lateral sclerosis were also documented to alter their expression. Amyloid precursor protein was expressed and found to play a role in human epidermis [187], whereas the expression of β-amyloid and τ protein was detected in skin mast cells, bearing another proof of skin reflecting neural degeneration [188]. Moreover, skin melanocytes undergo apoptosis after treatment with β-amyloid, whereas nerve growth factor attenuates the action of the latter and exerts a protective effect [189].

Progeria syndromes

Hutchinson-Gilford progeria syndrome (HGPS) is a rare genetic disorder with clinical features of premature aging. Clinical symptoms of this syndrome include scleroderma-like skin changes, bone abnormalities, alopecia, lack of subcutaneous fat, growth retardation, bone abnormalities, and joint stiffness. The average lifespan of HGPS patients is 13 years, with atherosclerotic heart disease being between the most common cause of death [190, 191]. The disease occurs due to a single nucleotide mutation, which results in the production of a truncated mRNA transcript encoding a prelamin A protein with an internal deletion of 50 amino acids, known as progerin. Surprisingly, the discovery of progerin in normal cells suggests mechanisms of progeria in normal aging [192, 193]. Progerin is more abundant in the dermis of senior individuals and in late-passage skin cells. The way that progerin builds up in normal skin with age and is detected in the papillary dermis, spreading to reticular dermis with age and a few terminally differentiated keratinocytes in the elderly, confirms how skin can accurately function as a model, reflecting human aging [194]. In vivo and in vitro data implicate the premature exhaustion of stem cells as a major reason for the progeria phenotype. Skin was again the means to confirm stem cell impairment, because cells isolated from all known stem cell-rich skin areas of a progeria mouse model (bulge region, sebaceous gland) showed reduced clonogenic capacity in comparison with controls. In addition, progeria skin keratinocytes exhibited lower levels of the stem cell markers α6-integrin and CD34 [195]. HGPS skin fibroblasts exhibit nuclear defects, such as altered gene expression, nuclear blebbing, disorganization of the underlying heterochromatin, stem cell dysfunction, increased DNA damage, cellular senescence, and high $p16^{INK4A}$ levels [196].

Werner syndrome is a premature aging disorder associated with increased occurrence of inflammatory diseases, cataract, diabetes mellitus type 2, and atherosclerosis. Surprisingly, skin manifestations and hair graying precede the inner organ defects. Skin fibroblasts

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in vitro are characterized by premature cellular senescence correlated to genomic instability resulting in stress kinase activation, such as p38 [197]. Restrictive respiratory disease, hyperuricemia, proteinuria, and primary hypogonadism are also findings of premature aging syndromes [198].

These and several other syndromes associated with premature aging phenotypes (Bloom syndrome, Cockayne syndrome, trichothiodystrophy, ataxia-telangiectasia, Rothmund-Thomson syndrome, and xeroderma pigmentosum) have contributed to important findings regarding aging and cancer [196].

Metabolic diseases

Diabetes mellitus is a common disease affecting multiple organs of the elderly and skin can be an attractive model of combining the cutaneous manifestations of uncontrolled chronic hyperglycemia with skin defects. Chronic hyperglycemia leads to an increase of AGEs, thus enhancing the aging process [60]. Specifically, the impairment of the skin barrier, namely decreased epidermal lipid synthesis and antimicrobial peptide expression, was shown to be correlated with hemoglobin A1c levels in a chronic hyperglycemia mouse model [56]. Diabetic mice were shown to exhibit a reduced hydration state of the stratum corneum and a decrease of the activity of the sebaceous gland, resembling senile xerosis [199]. Diabetic skin depicts abnormalities of the elastic cutaneous network, resulting in age-associated laxity [200]. Diabetic skin as well as aged skin showed reduction of blood flow in rest and in response to sustained heat [201, 202]. Skin autofluorescence as a measure of AGEs in skin is a marker that was reported to correlate with hyperglycemia, age, adiposity, vascular damage, and the metabolic syndrome [203], suggesting a promising noninvasive method for patients in risk for developing complications [204].

Conclusion

The above data present the mechanisms involved in skin aging and confirm the fact that skin aging comprises the mirror of age-related deficiencies for the entire human body. Interdisciplinary research projects can further facilitate and highlight the utilization of the skin as a robust predictor of age-associated disease and offer the possibility for the early diagnosis of pathophysiologic conditions, such as heart disease and cancer.

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