Clinics in Dermatology (2019) **37**, 296–305

Clinics in Dermatology

Understanding of Mechanisms of Skin Aging

When the skin is in the center of interest: An aging issue

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Abstract The skin represents the first bearer of marks of time as well as an easily accessible model for the assessment and determination of the involved molecular mechanisms. 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 neurodegenerative, cardiovascular, skeletal, and endocrine/metabolic skin diseases. Current molecular data indicate that skin aging, especially intrinsic aging, mirrors age-related deficiencies in the entire human body. These data and the development of new biologic technologies highlight the importance of the skin in aging research and should enable future interdisciplinary projects on internal diseases, which could barely have been performed until recently due mainly to the lack of respective tissue.

Introduction

Aging can be considered a natural process of biochemical events that leads to the gradual accumulation of damage and results in disease and death.[1–3] The skin appears as the first bearer of the marks of time as well as an easily accessible model for the assessment and determination of the involved molecular mechanisms.[4] Skin has long been recognized as the protecting organ against deleterious environmental factors and is vital for the homeostasis of body temperature, electrolytes, and fluid balance.[5]

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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 toward development of various benign or malignant diseases.[6,7] These complex biologic processes comprise endogenous factors, such as genetic predisposition, cellular metabolic pathways, and qualitative and quantitative hormonal alterations, and exogenous factors, primarily ultraviolet light exposure and—secondarily—chemicals, toxins, and pollution that lead to extrinsic aging.[8–10] The model for the former is the skin from areas that are not sun-exposed, mostly the inner aspect of the arm and the buttocks, and for the latter, it is the skin from areas constantly sun-exposed, such as the face (Figure 1).

https://doi.org/10.1016/j.clindermatol.2019.04.004
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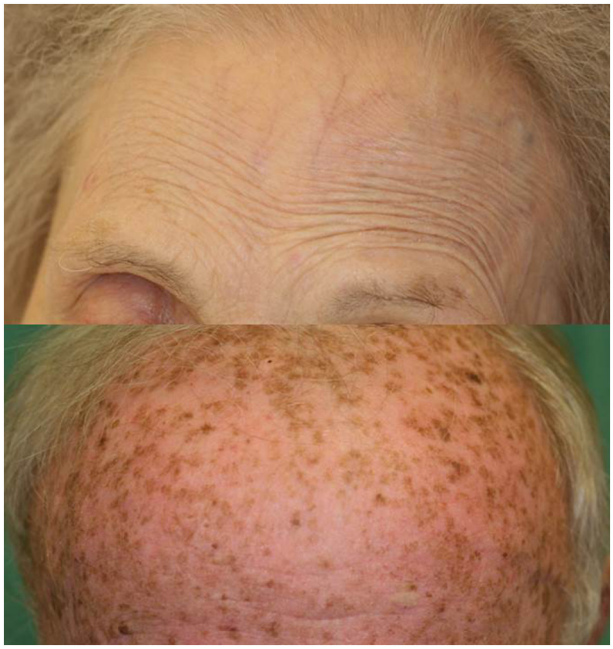

Fig. 1 Deep wrinkles and pigmentary discoloration, two of the characteristic signs of extrinsically aged skin.

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.[3,9] Opposed to these observations are extrinsically photoaged skin with 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,[8–12] which is the major skin aging–associated change found in Asian populations.[13,14]

The latter observation led to comparative studies among populations of different ethnicities (Table 1). Because skin aging phenotype varies according to the population, only ethnicity-specific aging characteristics could be correlated with age-associated diseases. As a result, photographic severity scales and other clinical methods have been developed to assess the severity of skin aging features.[9,18]

Intrinsic aging

Many theories have tried to explain the different pathophysiologic aspects of intrinsic aging. Among them are the theories of cellular senescence, telomere shortening and decreased proliferative capacity, chronic inflammation, mitochondrial DNA single mutations, and free radicals.[3,19–24] The process of aging is mirrored in the skin, and it comprises multifactorial processes, including extracellular matrix skin components and cells as well as cell-cell and cell-matrix interactions (Figure 2).[25]

Extrinsic aging

Chronic photodamage of the skin is the prime factor leading to skin aging, exerting its manifestations through induction of DNA damage and alterations through ultraviolet-mediated reactive oxygen species, including interference with the cutaneous immune system.[24] In addition, exposure to tobacco smoke has become a widely accepted factor, as it accelerates extrinsic aging processes[26–28] and targets mainly the elastin network of the skin.[29] Cigarette smokers' wrinkle formation depicts a distinctive pattern with prominent perioral lines and sharply contoured crow's feet, known as "smoker's face." In addition, advanced glycation elements (AGE) are also involved in extrinsically aged skin. AGE accumulation is mainly associated with solar elastosis, indicating that ultraviolet irradiation affects AGE precipitation *in vivo*.[30–32]

Age-associated skin diseases

Aging, both intrinsic and extrinsic, induces several skin manifestations.[3] There are a number of important skin functions that deteriorate with increasing age, including epidermal regeneration capacity, synthesis of sebum and sweat, dermoepidermal adhesion, wound healing, thermoregulation, and the speed of natural elimination of potentially hazardous chemical factors.[7,10] In addition, several age-associated diseases, such as diabetes, arterial hypertension, and malignancies, are reflected by skin changes[9,10,24] (Table 2).

Skin as a tool for understanding global aging

Apart from skin-associated intrinsic and extrinsic alterations and skin diseases usually related to the aging

Table 1 Comparison of skin aging characteristics among women of different ethnicity

	Caucasian	African American	Chinese	Japanese	Thai	Reference
Skin wrinkle formation	Greater, earlier	Less, later				14
Age-related skin dryness	Higher	Higher	Lower	Lower		15
Periorbital wrinkles			Severe	Mild		16
Wrinkles at the lower face area			Mild	Mild	Severe	16
Sagging in the subzygomatic area	Higher prevalence		Lower prevalence			17
Age-related pigment spots	Less		More			17
Sensitivity to exogenous chemicals	Lower		Higher			17

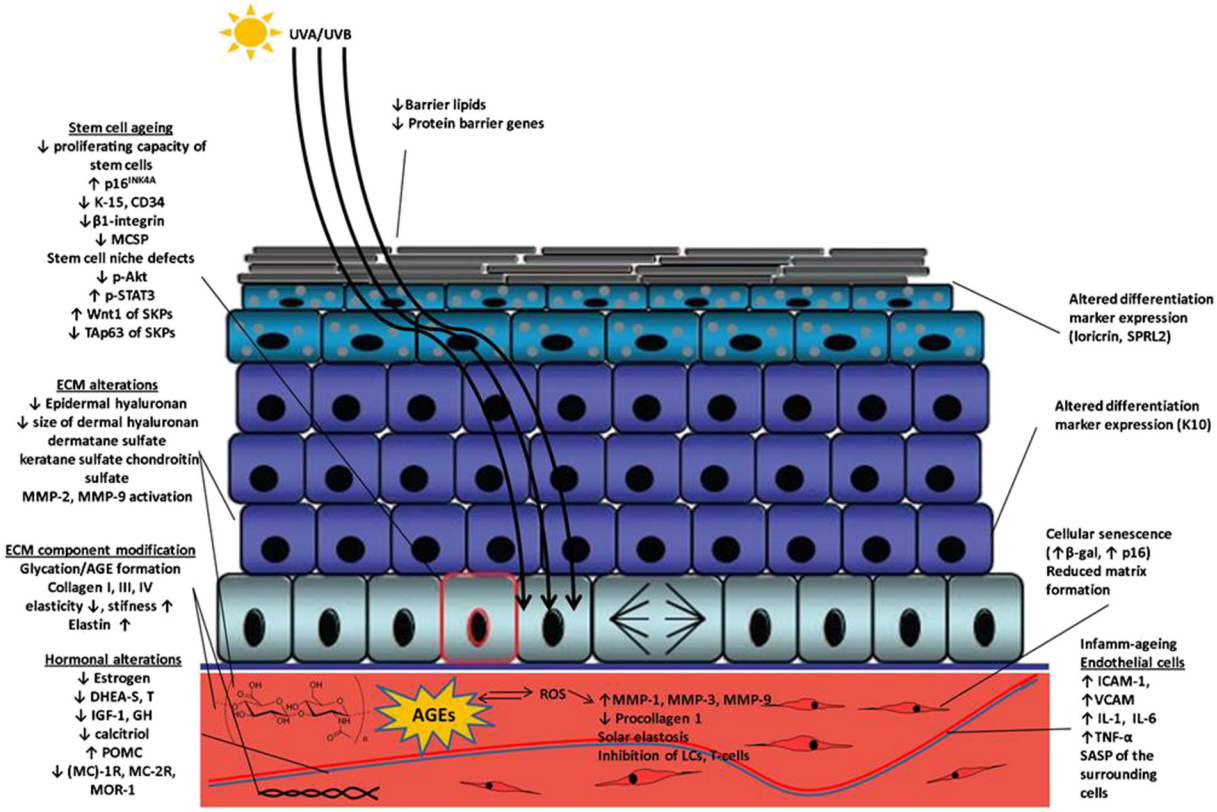

Fig. 2 Intrinsic and extrinsic factors of skin aging. AGEs, advanced glycation end products; DHEA, dehydroepiandrosterone; GH, growth hormone; ICAM-1, intercellular adhesion molecule 1; IGF-1, insulin growth factor-1; IL, interleukin; K-15, keratin-15; LCs, Langerhans cells; MC-1 R, melanocortin-1-receptor; MC-2 R, melanocortin-2-receptor; MCSP, melanoma-associated chondroitin sulfate proteoglycan; MMP, matrix metalloproteinase; MOR-1, microtubule organization 1 protein; 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; β-gal, β-galactosidase. Reproduced with permission from Nikolakis et al.[24]

process, ongoing research advances the use of skin as a model for age-associated pathologic conditions of various systems, such as the nervous, skeletal, cardiovascular, and endocrine systems. The skin's capacity to efficiently mirror age-associated inner organ alterations or deficiencies is further highlighted by the prominent skin signs of

Table 2 Common age-associated skin diseases or diseases whose prevalence and manifestation are modified in elderly patients

Function	Diseases
Wound healing	Leg ulcers
	Decubitus ulcers
Impaired epidermal barrier	Skin infections
	Bacterial (impetigo, intertrigo, folliculitis, furunculosis, carbunculosis, erysipelas)
	Viral (zoster)
	Fungal (tinea unguum, oral candidosis)
Age-related immune system alterations	Bullous pemphigoid
	Pemphigus (vulgaris, foliaceous, paraneoplastic)
	Psoriasis (mild, erythrodermic)
	Seborrheic dermatitis
	Rosacea
Progressive loss of melanocytes	Pigmentary disorders (vitiligo)
Cellular DNA alterations	Seborrheic keratosis
	Precanceroses (actinic keratosis, Bowen's disease, solar lentigo)
	Epithelial skin tumors (squamous cell carcinoma, Bowen's disease, basal cell carcinoma)
	Melanocyte-derived skin tumors (malignant melanoma)

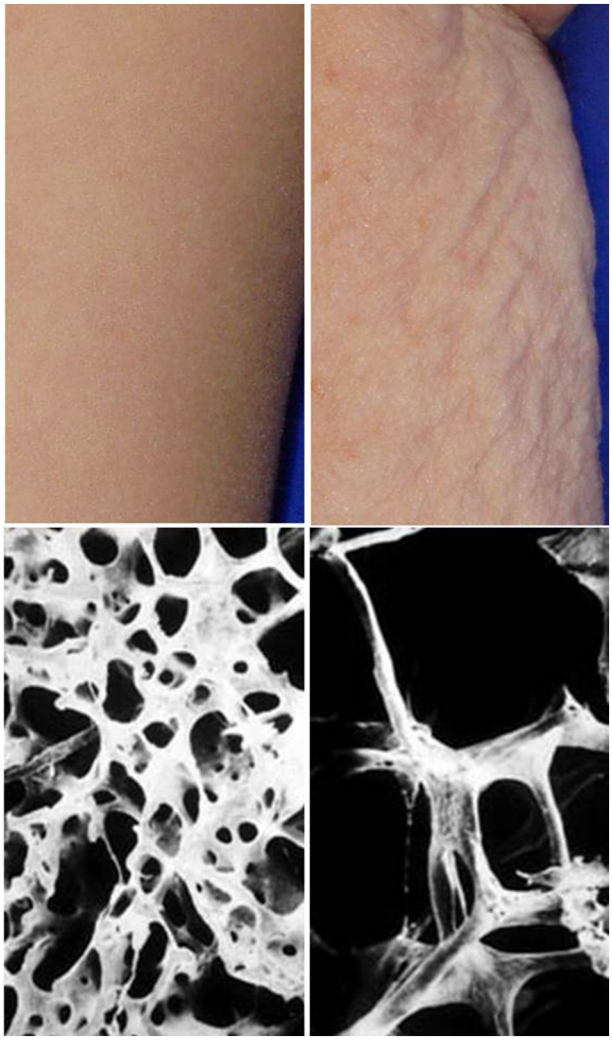

Fig. 3 Intrinsic skin aging (*upper panel*) at inner aspect of the arm of a 45-year-old (*left*) and a 70-year-old woman and bone aging (*lower panel*) of similarly aged women. Collagen content (collagen/protein) correlates well with bone mineral density (hydroxyapatite/cm^2).

genetic diseases, which may resemble aspects of aging at early age.

Neurodegenerative diseases

Due to the common ectodermal origin of the nervous system and the skin, the use of the skin as a model of evaluation of aging has been recently highlighted.[23] cDNA microarray analysis of immortalized sebocytes, treated with a hormonal mixture of growth factors and sex steroids resembling those of 20- and 60-year-old women, resulted in the regulation of 899 genes, which are related to significant metabolic pathways associated with aging.[5,33]

Specific genes found with the pathomechanism of neurodegenerative diseases, such as Parkinson's disease, Huntington's chorea, Alzheimer's disease, dentatorubral pallidoluysian atrophy, and amyotrophic lateral sclerosis, have also been documented to alter their expression during skin aging.[33] The amyloid precursor protein, when expressed, plays a role in human epidermal formation,[34] whereas the expression of β-amyloid and tau proteins has been detected in skin mast cells, providing additional proof of skin reflecting neural degeneration.[35] Melanocytes undergo apoptosis after treatment for β-amyloid, whereas nerve growth factor attenuates the action of the latter and exerts a protective effect.[36]

Osteoporosis

Skin collagen content (collagen/protein) correlates well with bone mineral density (hydroxyapatite/cm^2)[37] (Figure 3), and hormone replacement treatment in menopausal women leads to a parallel increase of skin thickness and bone remineralization,[38] indicating the role of skin parameters for the evaluation of bone health and osteoporosis.

Cardiovascular diseases

Accumulation of AGE in the skin has also been shown to serve as a strong and independent predictor of arterial stiffness in older adults[39,40] as well as arteriosclerosis and cardiovascular mortality in diabetic or hemodialysis patients[41,42]; moreover, AGE in the skin are good markers to assess vascular aging of patients with coronary heart disease and peripheral arterial disease.[43,44] In addition to being a marker of senescence, AGE accumulation in the dermis represents a prognostic factor in cardiac surgery, which may be used as a predictor of surgical outcome.[45]

Hormone deficiency

Patients suffering from multiple hormone deficiency or insulin growth factor-1deficiency may present with a phenotype of premature aged skin, because insulin growth factor–age-related decline affects sebocyte differentiation and epidermal thickness.[46] Important aspects of growth hormone or insulin growth factor-1deficiency are hyperglycemia, obesity, osteopenia, hypercholesterolemia, decrease of lean mass, cardiovascular diseases, and premature mortality.[23,47–49]

Metabolic diseases

In diabetes mellitus, the impairment of the skin barrier, namely, decreased epidermal lipid synthesis and antimicrobial peptide expression, has been correlated with hemoglobin A1c levels in a chronic hyperglycemia mouse model.[50] Diabetic mice exhibit a reduced hydration state of the stratum corneum and a decrease of the activity of the sebaceous gland, resembling senile xerosis.[51] Diabetic skin depicts

abnormalities of the elastic cutaneous network and results in age-associated laxity.[52] Diabetic skin, as well as aged skin, shows a reduction of blood flow in rest and in response to sustained heat.[53,54]

Progeria syndromes

Hutchinson–Gilford progeria syndrome is a rare genetic disorder with clinical features of premature aging. Clinical manifestations of this syndrome include bone abnormalities, joint stiffness, and growth retardation. There are also skin signs, namely, scleroderma-like skin changes, alopecia, and lack of subcutaneous fat. The average lifespan of patients with Hutchinson–Gilford progeria syndrome is 13 years, with atherosclerotic heart disease being the most common cause of death.[55,56] 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. Progerin is also abundant in the dermis of healthy aged individuals.[57,58] It 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.[59]

Werner syndrome is a premature aging disorder associated with an increased occurrence of inflammatory diseases, cataract, diabetes mellitus type II, and atherosclerosis. Restrictive respiratory disease, hyperuricemia, proteinuria, and primary hypogonadism may also occur.[60] Skin manifestations and hair graying precede the inner organ defects. Skin fibroblasts *in vitro* are characterized by premature cellular senescence correlated with genomic instability resulting in stress kinase activation.[61]

Skin stem cell aging

Epidermal stem cells reside within the basal cell layer and give rise to transient amplifying cells and differentiating progenitors. These form functional epidermal proliferative units, extending from the basal to the corneal layer.[62,63] Dermal stem cells are also of great importance for skin homeostasis, because they produce the progeny responsible for extracellular matrix 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 producing a broader palette of cell type progenitors.[62,64,65] Because they compose the pool of tissue regeneration, stem cells also come in focus of the aging research.

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 reactive oxygen species levels, perhaps as a result of maintaining high levels of superoxide dismutase.[66] Despite these factors, the epidermal turnover rate is 28 days in young individuals, whereas it varies between 40 and 60 days in the elderly.[67] Stem cell numbers do not necessarily decline with age[68]; however, their functional role, which is their ability to produce differentiated progeny, has been documented to be disturbed.[69]

There is the possibility of impairment of stem cell mobilization with age, as well the inability to respond to proliferating signals.[70,71] Epidermal stem cells of older individuals express lower levels of the stem cell markers β1-integrin and melanoma chondroitin sulfate proteoglycan, which are correlated with a higher self-renewal capacity.[72] Multiple mechanisms are involved in stem cell exhaustion.[24]

Table 3 Comparison of gene expression between old and young skin in areas of intrinsic and extrinsic aging[73]

	Intrinsic ageing	Extrinsic ageing
Biologic Processes		
Lipid biosynthesis	↓↓↓	(↓)
Steroid biosynthesis	↓↓↓	
Cholesterol metabolism	↓↓↓	↓↓
Epidermal cell differentiation	↓↓↓	
Development of epidermis	↓↓↓	
Organisation and biosynthesis of extracellular matrix		↑↑↑
Reaction after wounding	↑	↑↑↑
Wound healing		↑↑↑
Immune response		↑
Endogenous immune response		↑↑
Inflammatory reaction	(↑)	(↑)
Cell adhesion	↑↑↑	↑↑↑
Molecular functions		
Cytokine activity	↑↑	↑
Trypsin activity		(↑)
Oxyreductase activity	↓↓	
Cellular components		
Keratinisation	↓↓	
Keratin elements	↓↓↓	
Extracellular matrix	↑↑	↑↑↑

Intrinsic aging mostly affects procedures in the epidermal tissue (blue letters), whereas extrinsic aging procedures in the dermis (red letters).

Table 4 Genes exhibiting sex-independent differential regulation in skin aging[33]

Name	Accession Nr.	Description	Ratio/male	P-value	Ratio/female	P-value
SIRT6	NM_016539.1	sirtuin (silent mating type information regulation 2 homolog) 6 S.cerevisiae	1.246	0.030	1.762	0.027
RDH16	NM_003708.2	Homo sapiens retinol dehydrogenase 16 (all-trans and 13-cis) (RDH16), mRNA	1.016	0.014	1.186	0.048
CPT1B	NM_152246.1	carnitine palmitoyltransferase 1B (muscle), transcript variant 3	1.000	0.013	1.021	0.007
MGC3101	NM_024043.2	homo sapiens hypothetical protein MGC3101 (MGC3101), mRNA	0.796	0.001	1.446	0.043
C9orf112	NM_138778.1	homo sapiens chromosome 9 open reading frame 112 (C9orf112), mRNA	0.690	0.000	0.479	0.050
STK40	NM_032017.1	homo sapiens serine/threonine kinase 40 (STK40), mRNA	0.621	0.011	-0.419	0.023
TOM1L2	NM_001033551.1	homo sapiens target of myb1-like 2 (chicken) (TOM1L2), transcript variant 1, mRNA	0.601	0.001	0.674	0.033
CINP	NM_032630.2	cyclin-dependent kinase2-interacting protein	0.584	0.002	0.503	0.029
PGLS	NM_012088.2	phosphogluconolactonase	0.541	0.000	0.533	0.028
FLJ20920	NM_025149.3	hypothetical protein FLJ20920	0.519	0.009	0.604	0.009
CYHR1	NM_032687.2	cysteine/histidine-rich 1	0.511	0.016	0.708	0.002
TAF10	NM_006284.2	TAF10RNA polymerase II, TATA box binding protein (TBP)-associated factor, 30 kDa	0.503	0.024	0.385	0.014
GAMT	NM_000156.4	homo sapiens guanidinoacetate N-methyltransferase (GAMT), transcript variant 1, mRNA	0.496	0.003	0.738	0.042
NOL3	NM_003946.3	nucleolar protein 3 (apoptosis repressor with CARD domain)	0.487	0.016	0.476	0.050
PET112L	NM_004564.1	PET112-like (yeast)	0.472	0.005	0.617	0.010
OR52N2	NM_001005174.1	homo sapiens olfactory receptor, family 52, subfamily N, member 2 (OR52N2), mRNA	0.458	0.001	-0.403	0.018
MFSD3	NM_138431.1	homo sapiens major facilitator superfamily domain containing 3 (MFSD3), mRNA	0.452	0.028	0.595	0.034
C19orf24	NM_017914.2	Homo sapiens chromosome 19 open reading frame 24 (C19orf24), mRNA	0.395	0.049	0.627	0.043
FGFR1OP2	NM_015633.1	homo sapiens FGFR1 oncogene partner 2 (FGFR1OP2), mRNA	0.384	0.013	-0.590	0.001
TRIM33	NM_033020.2	homo sapiens tripartite motif-containing 33 (TRIM33), transcript variant b, mRNA	-0.396	0.002	-0.515	0.048
SDCCAG33	NM_005786.3	serologically defined colon cancer antigen 33	-0.397	0.017	-0.699	0.003
LRIG3	NM_153377.3	homo sapiens leucine-rich repeats and immunoglobulin-like domains 3 (LRIG3), mRNA	-0.398	0.002	-0.650	0.029
DOCK9	NM_015296.1	homo sapiens dedicator of cytokinesis 9 (DOCK9), mRNA	-0.415	0.014	-0.815	0.009
ABCG1	NM_004915.3	ATP-binding cassette, subfamily G (WHITE),member 1, transcript variant 4	-0.434	0.028	-0.577	0.046
NLGN2	NM_020795.2	homo sapiens neuroligin 2 (NLGN2), mRNA	-0.436	0.025	-0.476	0.049
LGR4	NM_018490.1	leucine-rich repeat-containing G protein-coupled receptor 4	-0.442	0.000	-0.417	0.028
PTGFRN	NM_020440.2	homo sapiens prostaglandin F2 receptor negative regulator (PTGFRN), mRNA	-0.457	0.003	-0.681	0.035
MIB1	NM_020774.2	mindbomb homolog 1 (drosophila)	-0.539	0.002	-0.935	0.019
B3GALT3	NM_003781.2	homo sapiens UDP-Gal:betaGlcNAc beta 1,3-galactosyltransferase, polypeptide 3 (B3GALT3), transcript variant 1, mRNA	-0.590	0.043	-0.575	0.043
AXIN2	NM_004655.2	axin 2 (conductin, axil)	-0.617	0.008	-1.039	0.006
FZD7	NM_003507.1	homo sapiens frizzled homolog 7 (drosophila)	-0.915	0.045	-0.910	0.026
TUBAL3	NM_024803.1	homo sapiens tubulin, alpha-like 3 (TUBAL3), mRNA	-0.915	0.029	0.673	0.043
MMP27	NM_022122.2	matrix metalloprotease 27	-0.982	0.048	-1.579	0.001
COL1A1	NM_000088.2	collagen type 1, alpha 1	-1.144	0.038	-2.349	0.001
MATN4	NM_003833.2	matrilin 4, transcript variant 1	-1.393	0.014	-1.823	0.003
TMEM46	NM_001007538.1	transmembrane protein 46	-1.436	0.026	-1.626	0.038
CPZ	NM_001014447.1	carboxypeptidase Z, transcript variant 1	-1.674	0.008	-1.945	0.014
WIF1	NM_007191.2	WNT inhibitory factor 1	-1.929	0.026	-2.247	0.019
CORIN	NM_006587.2	homo sapiens corin, serine peptidase (CORIN), mRNA	-1.935	0.035	-3.216	0.014

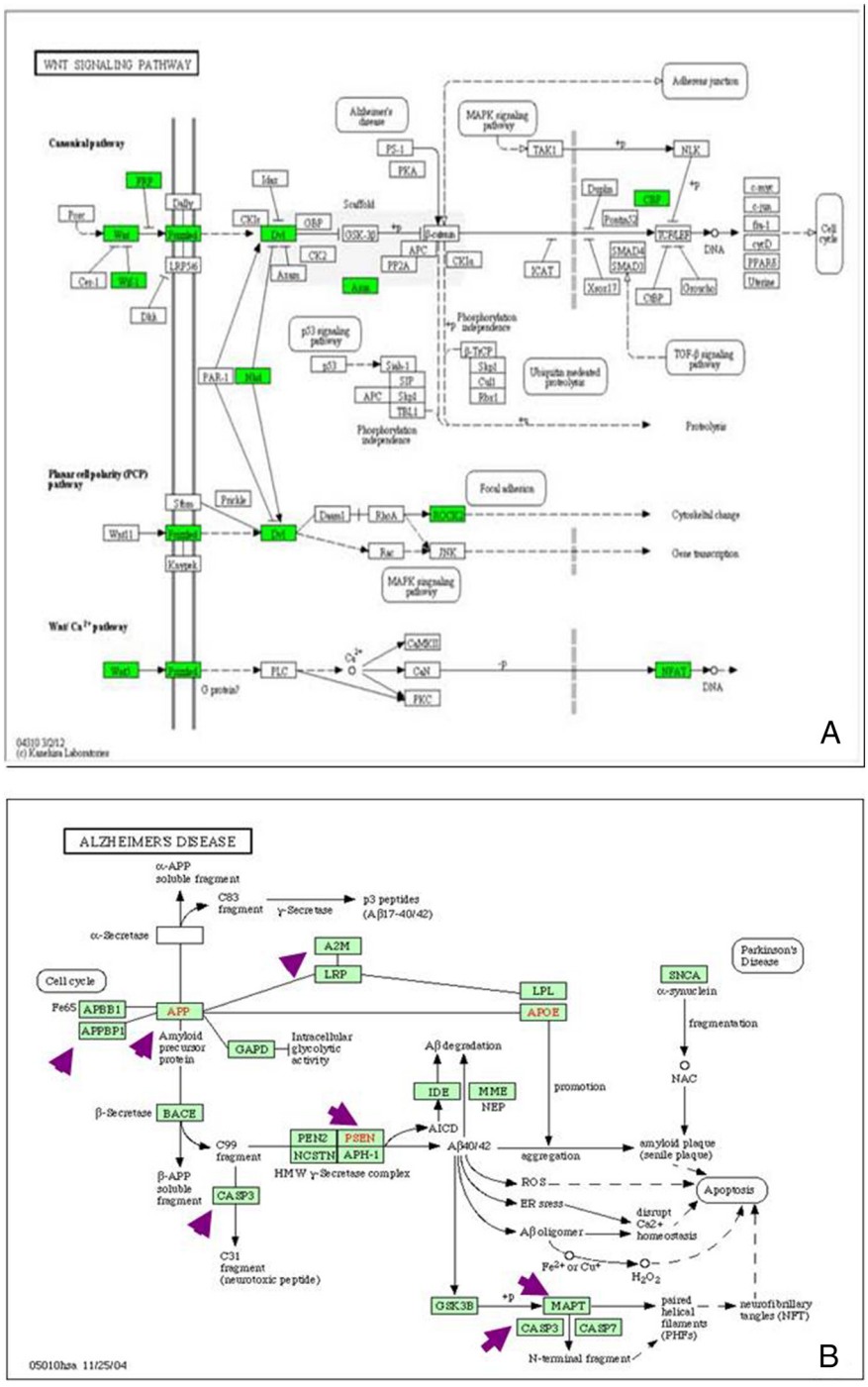

Fig. 4 **(A)** The Wnt pathway (KEGG; https://www.genome.jp/kegg/) with the genes involved in healthy intrinsic skin aging depicted in green. Reproduced with permission from Makrantonaki et al.[33] **(B)** The pathway of genes involved in Alzheimer's disease (KEGG; https://www.genome.jp/kegg/). The genes depicted by arrowheads are also differentially regulated in healthy intrinsic skin aging.

Common molecular markers

Differential gene expression in the skin of older versus younger individuals, at areas of intrinsically and extrinsically aging skin, revealed that intrinsic aging affects the epidermal tissue, whereas extrinsic aging affects the dermis[73] (Table 3).

The investigation of the expression of 2,135 genes in the light-protected foreskin of 5 children (aged 3-4 years) and 5 adults (aged 68-72 years) has shown that 5% of the examined genes exhibited a differential expression, implicating the *insulin* gene and *STAT3* signaling, the cell cycle (eg, *CDKs*, *GOS2*) and the extracellular matrix (eg, *PI3*,

S100A2, *S100A7*, *S100A9*, *SPRR2B*) pathways;[74] furthermore, there was an up-regulation of pro-apoptotic genes in the aged individuals, which can be partly due to a dysregulation of *FoxO1*. Moreover, a reduction of the expression of *jos* and *fos* family members has been observed. Genes of the cytoskeleton (eg, *keratin 2A*, *keratin 6A*, and *keratin 16A*) have also been shown to be affected by aging.

Not only keratinocytes and fibroblasts but all skin cell types seem to be affected by intrinsic aging. Sebaceous glands also show a profound decrease of secretory output, which is age related, as well as a decrease in the size of their cells.[75] Data initially obtained in human sebaceous gland cells cultured with aging-associated hormone levels[12,76] have been confirmed in comparisons of intrinsically aged human skin with that of young individuals (8 men and 8 women aged 20 and 60 years, respectively)[33]; 523 genes were differentially regulated in the aged skin of the women and 401 genes in the aged skin of the men in comparison with their younger counterparts. Of these genes, 183 were upregulated and 340 downregulated in the women, whereas in the men 210 genes showed an increased and 191 a reduced expression with age. Of the ~44,000 genes (and gene variants) studied, 39 genes showed overlapping and were similarly regulated in both sexes (Table 4). The involved genes, among others, were involved in DNA repair and stability, mitochondrial processes, oxidative stress, cell cycle and apoptosis, and ubiquitin-induced proteolysis.

The most significantly altered pathways involved the *tumor* growth *factor-β* in vitro and the *Wnt* pathways (Figure 4), whereas the *Wnt* signaling pathway was significantly suppressed in the skin of elderly individuals in both sexes, at both RNA and protein levels.[33] The *Wnt/β-catenin* pathway has currently been associated with severe abdominal aortic calcification,[77] osteoporosis,[78] sphincter muscle dysfunction, fibrosis,[79] and neurodegenerative diseases[33,80,81] in aging individuals. Increased activity and expression of metalloproteinases (MMP), such as MMP-9, have been reported in association with skin aging[82] and with the progression of amyotrophic lateral sclerosis in the nervous system and in the skin in amyotrophic lateral sclerosis animal models.[83]

Studies in 856 twin women in the age range of 39-85 years have detected differential expression with age in 1,672 genes in skin and 188 genes in adipose tissue.[84] Genes significantly regulated by age were compared with expression profiles in 10 brain regions from 100 postmortem brains aged 16 to 83 years. Only one age-related gene commonly upregulated in the three tissues (*TMRM178*) and 12 genes showing differential expression with age in both skin and brain tissue (*PROCR*, *HSD11B1*, *PTPN3*, *CA9*, *PLCH2*, *NETO2*, *MT1G*, *SLC7A5*, *MYOT*, *HEY2*, *TMEM178*, *MS4A6A*), as well as two common genes to adipose and brain tissues (*ZBTB16*, *WWC2*) were identified.

Conclusions

Current molecular data indicate that skin aging, especially intrinsic aging, mirrors age-related deficiencies for the entire human body and correlates well with certain systemic diseases. These data and the advent of new biologic technologies, such as the detection of the body-wide transcriptome[85] and the development of induced pluripotent stem cells from skin cells,[86,87] highlight the importance of the skin in aging research. This should enable future interdisciplinary projects for internal diseases, which previously could barely have been performed due to lack of respective tissue.

Acknowledgements

This work was partially supported by the German Federal Ministry of Education and Research through the Explorative Project 0313359 ‘The genetic etiology of human longevity’ of the German National Genome Research Network 2 to CCZ and the 7th LIERAC research award 2010 on skin ageing to EM.

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