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Clinical and laboratory skin biomarkers of organ-specific diseases

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ABSTRACT

Intense research during the last few years has elucidated a number of mechanisms of the complex human aging process. Among the body organs, skin has a distinguished role in aging perception both because it constitutes the organ on which the first signs of aging are mostly visible and because skin is recognized as an indicator of human health. Analogous to all other organs, skin undergoes multiple morphological and functional changes with age affected by extrinsic and intrinsic factors. Evaluation of skin morphology as well as of advanced glycation end products, dermal collagen content and alterations of the Wnt signaling pathway may predict – among others - the aging status of the cardiovascular system, the brain and the bones. Increasing knowledge on the association of certain clinical and laboratory characteristics of extrinsic and intrinsic skin aging with organ-specific diseases opens new possibilities for the establishment of clinical and laboratory skin biomarkers for systemic human aging and the course of several internal, organ-specific diseases.

1. Introduction

Population aging is a new challenge for our society (Gilchrest et al., 2015). This is reflected in an increasing share of elderly individuals accompanied by a declining share of the young ones in the total population. In Europe, the so-called population pyramid has nowadays hardly any resemblance to a pyramid form: In the last decade (2006–2016), an increase of 2.4% was observed for the people aged 65 years and older, whereas the share of the population aged less than 15 years decreased by 0.4%. This is due to a steady decline in the birth rate and to the fact that life expectancy is steadily rising (European Statistical System [EUROSTAT] http://epp.eurostat.ec.europa.eu).

Consequently, the study of aging mechanisms has gained more attention in recent years, in an effort to develop strategies to provide a healthy lifespan (Gilchrest et al., 2015). Skin has acquired a distinguished role in aging perception (Vierkötter et al., 2016) because it is the organ on which the first signs of aging are visible, and research, because skin is nowadays recognized as an indicator of human health and may predict a number of systemic diseases(Krutmann et al., 2017). Analogous to all other organs, skin undergoes multiple morphological and functional changes with age, which in turn result in the development of a variety of diseases including benign and malignant skin tumors (Makrantonaki et al., 2017a,b). The pathogenesis of skin aging is rather complex (reviewed in Zouboulis and Makrantonaki, 2011; Krutmann et al., 2016; Makrantonaki et al., 2013) (Fig. 1), however, understanding the underlying mechanisms may open new perspectives in dealing with skin and systemic age-associated diseases (Fig. 2).

2. Extrinsic skin aging

One of the major extrinsic factors that influence skin morphology and appearance is ultraviolet (UV)/infrared (IR) irradiation. Guyuron et al. (2009) investigated 186 identical twin pairs and recorded the differences in the perceived twins' ages and their facial skin features. The perceived age differences were then correlated with multiple factors. Increased sun exposure was associated with an older skin appearance ($p = 0.015$), as was a history of outdoor activities and lack of sunscreen use. Additionally, facial wrinkles were more evident in twins with a history of skin cancer ($p = 0.05$) and in smokers ($p = 0.005$). Pigment defects were more common in twins with a history of smoking ($p = 0.005$) and those with sun exposure ($p = 0.005$) (Fig. 3).

Research has made tremendous progress in deciphering the molecular mechanisms that lead to skin aging and associated skin diseases in the last decades (Krutmann et al., 2012). It was initially postulated that

Abbreviations: AGE, advanced glycated end products; AhR, aryl hydrocarbon receptor; ALS, amyotrophic lateral sclerosis; IR, infrared; MMP, matrix metalloproteinase(s); ROS, reactive oxygen species; UV, ultraviolet

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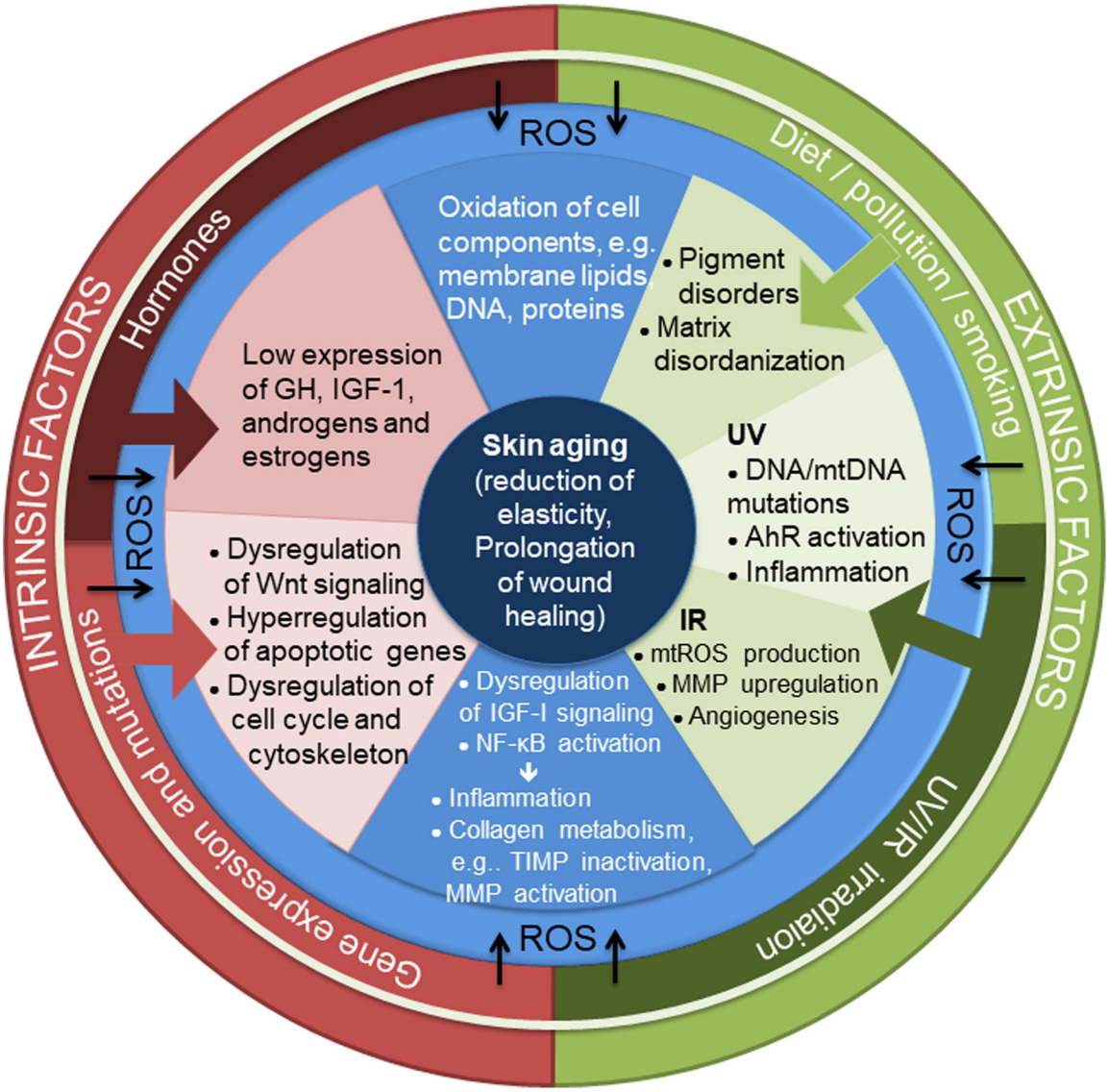

Fig. 1. Schematic presentation of extrinsic and intrinsic factors on skin aging. ROS, reactive oxygen species, mtDNA, mitochondrial DNA, GH, growth hormone, IGF-I, insulin-like growth factor I, UV, ultraviolet, IR, infrared, AhR, arylhydrocarbon receptor, mtROS, mitochondrial reactive oxygen species, MMP, matrix metalloproteinases, TIMPs, tissue metalloproteinase inhibitors, Wnt, Wnt signaling pathway, NF-kB, nuclear factor-kappa-light chain-enhancer. (Translated an modified from Makrantonaki, E. et al. Hautarzt 66, 730–7, 2015).

the UVB stress nuclear response of cells is initiated by DNA damage (Bender et al., 1997), as DNA is the major chromophore of UVB. However, it has been recognized since then that much of the UVB stress response occurs outside the nucleus by clustering and internalizing cell membrane-bound growth factor receptors, such as the epidermal growth factor receptor. Fritsche et al. (2007) demonstrated that aryl hydrocarbon receptor (AhR; also called dioxin receptor) plays a key role in initiating internal signaling cascades after UVB irradiation. In epidermal keratinocytes, UVB irradiation leads to the formation of a range of photoproducts from tryptophan, which is freely present in the cytoplasm. These photoproducts serve as natural ligands of the AhR and lead to its activation. Subsequently, inflammation-associated genes, such as cyclooxygenase-2 are up-regulated. These amplify the expression of matrix metalloproteinases (MMP) 1 and 3 in addition to other proteases (Herrmann et al., 1993; Brenneisen et al., 1996, 2002) and stimulate melanocyte proliferation and melanin synthesis (Jux et al., 2011). Since AhR activation plays a special role in the development of Treg (Quintana and Cohen, 2008) and γ / δ-T cells (Kadow et al., 2011), cutaneous immune status is also indirectly impaired. In addition, UV-induced stress may contribute to mtDNA damage, with mtDNA damage being more responsible for the chronic effects of UV irradiation on aging pathogenesis (Schroeder et al., 2008).

IR irradiation is most strongly absorbed in the mitochondria with copper serving as a chromophore in complex IV of the respiratory chain (Karu, 2008). For this reason, IR irradiation rapidly leads to an increase in reactive oxygen species (ROS) (Schroeder et al., 2007). ROS can induce multiple signaling cascades in skin cells. Among others, it can increase the intracytoplasmic calcium level and activate the MAPK / ERK signaling pathway (Krutmann and Schroeder, 2009). Calles et al. (2010) demonstrated that IR irradiation is able to regulate 600 genes by increasing intramitochondrial ROS production in human dermal fibroblasts. Some of the strongly upregulated signaling pathways following IR irradiation are the ERK1/2, p38, JNK, PI3K/AKT, STAT3, and IL-6 signaling pathways. Important functions of the skin, such as angiogenesis (Chung and Eun, 2007; Blaudschun et al., 2002) and mast cell production (Kim et al., 2009) are also affected by IR exposure. Another notable phenomenon is that while IR does not induce tumorigenesis in the skin to the same extent as UVB, it is associated with more aggressive tumor growth (Jantschitsch et al., 2011).

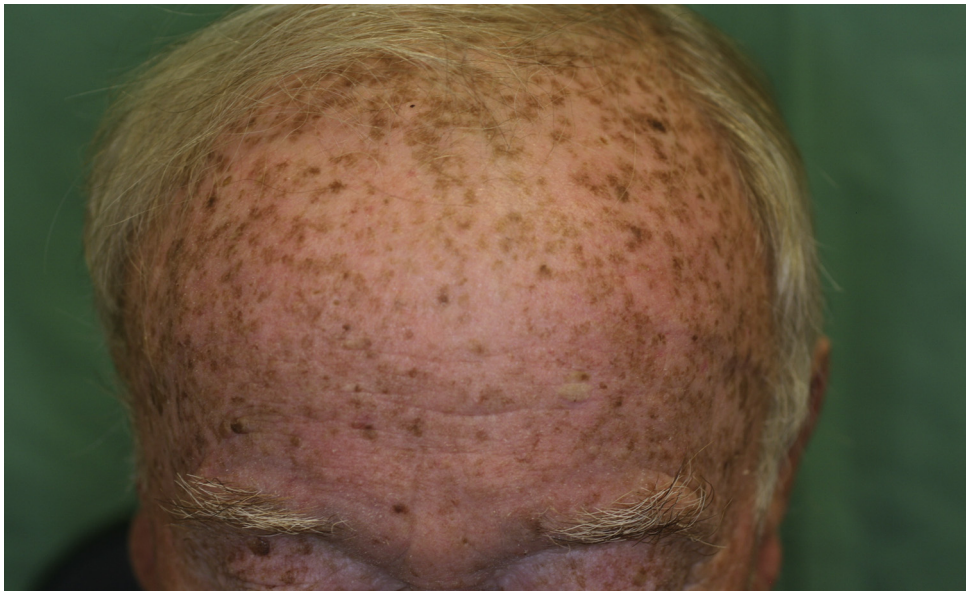

Fig. 2. Disseminated skin pigment abnormalities (actinic lentigines) and focal epithelial acanthosis with few atypic cells (actinic keratosis) on the forehead of in a 94-year old male patient with fair skin due to extrinsic skin aging.

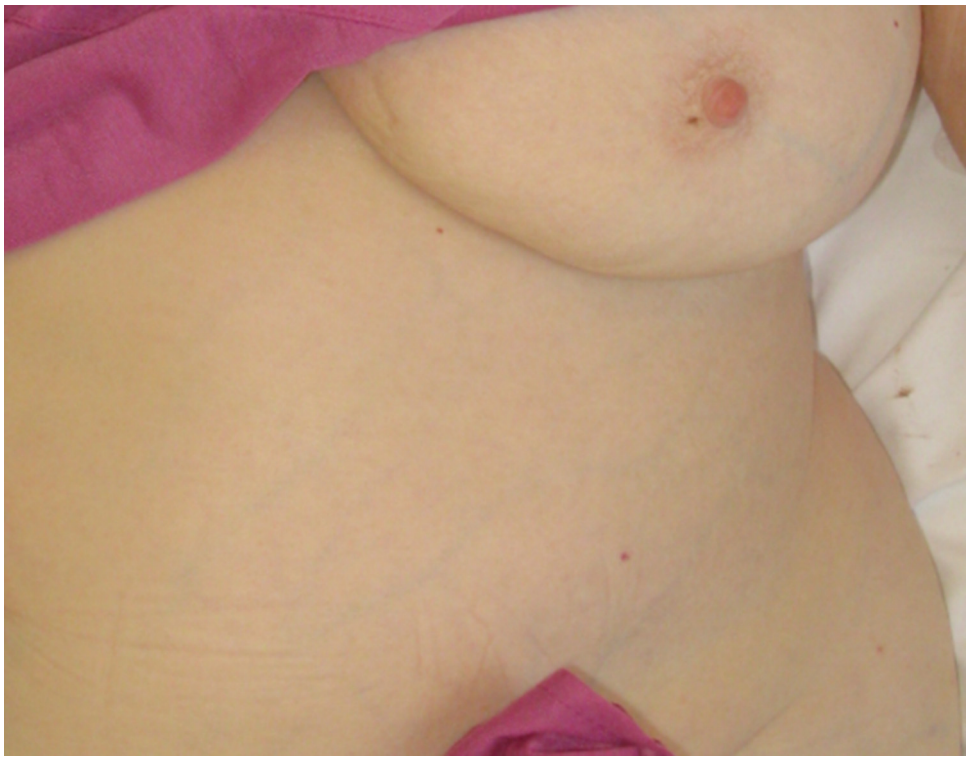

Fig. 3. Apparently normal-looking light-protected abdominal skin - despite the expected intrinsic aging - in a 102-year old female patient.

3. Extrinsic skin aging and biomarkers of organ-specific diseases

With increasing age skin accumulates several defects, which are in the most cases visible (Krutmann et al., 2016). In a recent pilot study, we ascertained the skin status of elderly patients hospitalized in a geriatric clinic with several systemic diseases. One hundred and ten multimorbid geriatric inpatients at a Geriatric Hospital in Berlin were examined to determine the prevalence of skin diseases in this age group, according to the gender and their possible correlation with their genral health status and treatment success. Among a variety of different skin diseases, infectious diseases were found to be most common in both female and male patients (55% and 58%, respectively) followed by vascular diseases (46.7% and 54%, respectively). Wound healing disorders (e. g. leg ulcers, pressure ulcers) were observed in 28.3% of women and 22% of men. Precancerous skin lesions and epithelial skin cancer were more frequent in men than in women (20% vs. 6.7%, $p < 0.037$ and 34% vs. 13.3%, $p < 0.010$, respectively), indicating that elderly men need a closer monitoring by dermatologists.

On the other hand, pruritus - a very common symptom in the elderly, that accompanies a variety of systemic diseases, such as liver cirrhosis and renal insufficiency - showed a positive correlation with the duration of hospitalization and a negative correlation with the

Barthel index and Tinetti score on the day of discharge, indicating that pruritus may have a significant impact on the physical condition of elderly multimorbid patients and on the static and dynamic balance abilities (Makrantonaki et al., 2017a,b).

Skin is very susceptible to increased inflammatory parameters and disturbed endocrine microenvironment. As a consequence, it can mark the first signs of an ongoing systemic disease. For instance, wound healing disorders are often associated with several internal diseases, among others vascular and coagulation diseases (e.g. peripheral artery disease, venous insufficiency, protein C deficiency, protein S deficiency, APC resistance, factor Leiden V mutation, antiphospholipid antibodies syndrome), metabolic diseases (e.g. diabetes mellitus, amyloidosis), hematologic disorders (e.g. sickle cell disease, spherocytosis and thalassemia), myeloproliferative disorders (e.g. polycythemia vera, multiple myeloma) and internal infections (Makrantonaki et al., 2017a,b). Dermatological findings such as hirsutism, striae, alopecia, and easy bruising may lead to the diagnosis of metabolic disorders such as Cushing disease (Lefkowitz et al., 2017) or polycystic ovary syndrome (reviewed in Lause et al., 2017).

Vierkötter et al. (2010) investigated the influence of air pollution on skin aging characteristics. For this purpose, 400 Caucasian women between the ages of 70 and 80 years were recruited and examined by a Score of Intrinsic and Extrinsic Skin Aging (SCINEXA). The results of the score was correlated with the traffic-related exposure at the residence of the women examined. An increase in soot (per 0.5×10^{-5}/ m) and particles from traffic (per 475 kg/ year and km^2) was associated with 20% more pigment spots on forehead and cheeks. It was thus possible to establish a significant correlation between air pollution and signs of skin aging. The detrimental effects of air pollution on the health status in terms of impaired lung and cognitive function have been established by the same group (Vierkötter et al., 2018).

Indoor air pollution constitutes another risk factor for skin aging as shown in two cross-sectional studies in China (n = 1262 women), in which the association between cooking with solid fuels and signs of skin aging have been assessed. The analysis showed that cooking with solid fuels was significantly associated with a 5–8% more severe wrinkle appearance on face and an 74% increased risk of having fine wrinkles on back of hands in both studies combined, independent of age and other effects on skin aging. Some of the proposed theories for the pathogenesis suggest an increased generation of cytoplasmic ROS, direct mitochondrial damage and activation of the AhR signaling pathway (Li et al., 2015; Xia et al., 2015).

Previous work has documented an association between nicotine abuse, wrinkling, and airway obstruction (Patel et al., 2006). Thus, the level of skin aging may serve as a marker for the effects of smoking on the lung. In the population-based cohort SALIA study, wrinkling was assessed in 697 elderly women by SCINEXA and airway obstruction by spirometry (Ratio FEV1 / FVC). Women with significant airway obstruction also showed significantly increased wrinkling. Carriers of MMP 1–2 G or MMP 3–6 A allele were particularly susceptible. This is an example of a possible genetic predisposition exhibiting a negative effect on the activity of exogenous agents (Vierkotter et al., 2015). However, skin wrinkling and other signs of extrinsic skin aging should be assessed in the absence of airway obstruction and the latter in the absence of signs of extrinsic aging in order to prove skin wrinkling as specific predictors of airway obstruction diseases.

4. Intrinsic skin aging

Several theories have been developed to explain different pathophysiologic aspects of intrinsic aging. The theories of cellular senescence, telomere shortening and decreased proliferative capacity, inflammation, mitochondrial DNA single mutations and free radical are among them (reviewed in Nikolakis et al., 2013). The process of aging is being mirrored in the skin and it comprises multifactorial processes, including extracellular matrix skin components, cells, as well as cell-cell and cell-matrix interactions.

The great progress in genome analysis has provided a deeper insight into the molecular events of aging of various model organisms. Lener et al (2006) investigated the expression of 2135 genes in the light-protected foreskin of 5 children (age 3–4 years) and 5 adults (age 68–72 years). Five percent of the examined genes showed a differential expression, implicating the insulin and STAT3 signaling pathway, the cell cycle (e.g. CDKs, GOS2) and the extracellular matrix (e.g., PI3, S100A2, A7, A9 SPRR2B). Furthermore, there is an up-regulation of pro-apoptotic genes, which can be partly due to a dysregulation of FoxO1. Underexpression of jos and fos family members has been observed. Genes of the cytoskeleton (e.g., keratin 2 A, 6 A, and 16 A) have also been shown to be affected by aging.

The changes of the extracellular matrix, which occur with increasing age are due to functional protein defects. This is mainly due to non-enzymatic glycation of proteins, lipids, and nucleic acids by the increased glucose levels, leading to the formation of advanced glycation end products (AGEs) (Paul and Bailey, 1996). AGE formation is a stepwise process and starts 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 (Singh et al., 2014). Stable products are then built after protein adduct formation or cross-linking of Schiff base or Amadori products. AGEs are a very heterogeneous group of molecules. Since the discovery of the first glycated protein, i.e. glycated hemoglobin in diabetes, numerous other AGEs have been detected.

5. Intrinsic skin aging and biomarkers of organ-specific diseases

AGEs many exhibit characteristic autofluorescent properties, which simplifies their identification in situ or in vivo (Singh et al., 2014). Their accumulation in the dermis has been involved in the pathogenesis of skin diseases in diabetic patients (Makrantonaki et al., 2017a,b), whereas ethnic and gender differences have been detected in AGEs measured by skin auto-fluorescence (Mook-Kanamori et al., 2013). AGEs, in addition to being a marker of senescence, have been shown to represent a prognostic factor in cardiac surgery, which can be used as a predictor of patient outcome (Simm et al., 2007). Indeed, accumulation of AGEs in the skin has been also shown to serve as a strong and independent predictor of arterial stiffness in older adults (Llauradó et al., 2014; Mayer et al., 2016) as well as arteriosclerosis and cardiovascular mortality in diabetics and hemodialysis patients (Lutgers et al., 2009; McIntyre et al., 2011). In addition, AGEs in the skin are a good marker to assess vascular aging of patients with coronary heart disease and peripheral arterial disease (Noordzij et al., 2012; Hofmann et al., 2013).

Not only keratinocytes and fibroblasts but all skin cell types seem to be affected by intrinsic aging. Sebaceous gland cells also show a profound decrease of secretory output, which is age related, as well as a decrease of the size of their cells (Zouboulis and Boschnakow, 2001). These data were confirmed in human skin and after in vitro hormone treatment of human sebocytes (Makrantonaki et al., 2006, 2012). Genes that were shown to be regulated were involved – among others - in DNA repair and stability, mitochondrial processes, oxidative stress, cell cycle and apoptosis, ubiquitin-induced proteolysis. The most significantly altered pathways were that of tumor growth factor-β in vitro and of the Wnt in vivo. Indeed, the Wnt/β-catenin pathway has currently been associated with severe abdominal aortic calcification (female population; Touw et al., 2017), osteoporosis (Mäkitie et al., 2018) and sphincter muscle dysfunction and fibrosis (Rajasekaran et al., 2017) in aging individuals. In aging animals, the Wnt pathway has been associated with osteoarthritis (Lietman et al., 2018), brain and bone changes in experimental Alzheimer's disease (Dengler-Crish et al., 2018) and in aging cell culture models of Parkinson's disease (Colini Baldeschi et al., 2018).

Wnt signaling has been shown to be one of the most crucial

morphogens in development (Bernkopf and Behrens, 2018) and during the maturation of central nervous system (Naito et al., 2012; Folke et al., 2018; Oliva et al., 2018). Its action is relevant during the establishment and maintenance of synaptic structure and neuronal function. The dysfunction of Wnt signaling has been considered to be linked with human aging (Bernkopf and Behrens, 2018; Siegle et al., 2018) and with several neurodegenerative diseases and neurological disorders (Makrantonaki et al., 2010; Nikolakis et al., 2013; Folke et al., 2018; Oliva et al., 2018). The facts that skin and nervous system are embryonically both ectodermal derivatives and because key genes associated with the pathogenesis of neurodegenerative diseases were shown to be expressed in the skin and especially the human sebaceous glands and showed a regulation of their expression after hormone treatment (Makrantonaki et al., 2006, 2012) have led to the assumption that skin may be used as a tool for investigating aging of the nervous system, including neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis (ALS) (Makrantonaki et al., 2010; Nikolakis et al., 2013). In own preliminary work, the entire genome of light-protected skin of healthy, Caucasian young and elderly women and men was examined by means of the Illumina array platform. A total of 523 genes were differentially regulated in the female skin and 401 genes in the male skin with progressing age. Of these, 183 genes were upregulated and 340 downregulated in the women, while in the men 210 genes showed an increased and 191 a reduced expression with age. Of all the genes studied, only 39 genes showed to be overlapping and were regulated in both sexes. These genes could serve as a battery of sex-independent biomarkers of endogenous skin aging. Interestingly, the Wnt signaling pathway was significantly suppressed in the skin of elderly subjects in both sexes, both at the RNA and protein levels (Makrantonaki et al., 2012). The Wnt signaling pathway regulates various processes during embryonic development but can also lead to tumorigenesis. These results emphasize the role of this signaling pathway in the aging process. These initial human data were currently confirmed in animal and in vitro experiments (Choi et al., 2018; Holguin and Silva, 2018; Huang et al., 2018; L'Episcopo et al., 2018).

Increased activity and expression of MMP, such as MMP-9, have been reported in association with skin aging (Tzellos et al., 2009) and with the progression of ALS both in the nervous system and the skin in ALS animal models (Fang et al., 2010).

Moreover, skin collagen content correlates well with bone mineral density, i.e. the amount of hydroxyapatite in bone mass (Castelo-Branco et al., 1994) and hormone replacement treatment in menopausal females leads to a parallel increase of skin thickness and bone remineralisation (Brincat et al., 1985) indicating the predictive role of skin parameters for the evaluation of bone health and osteoporosis.

The analysis of complex methylation patterns in skin samples from younger and older donors has also illustrated significant differences. An increase in DNA hypermethylation has been found in the samples of older donors (Gronniger et al., 2010). Furthermore, recent findings indicate the important role of accumulated defective proteins in skin cells and have associated the progressive dysregulated function of the proteosome and lysosome with aging (Chondrogianni et al., 2015). Dysregulation of adult stem cells in the skin may also contribute to aging. Possible causes for this could be an impaired expression of chromatin regulators, such as sirtuins (Mohrin and Chen, 2013) or "long noncoding RNAs", and a dysfunctional NF-κB signaling pathway (Gilchrest et al., 2015).

Finally, our knowledge regarding biomarkers of skin aging and their association with internal disease has been widened by the observation of known progeroid syndromes. Studies of progeroid syndromes such as the Hutchinson-Gilford progeria syndrome, Werner's Syndrome (WS), Rothmund-Thomson and Cockayne syndrome, telangiectatic ataxia and Down syndrome have highlighted the importance of biological processes such as DNA replication, recombination, repair and transcription as well as mitochondrial function, cell cycle and apoptosis, ubiquitin-induced proteolysis and cellular metabolism in endogenous aging. People suffering from these syndromes are characterized by typical signs of skin aging such as hair loss and alopecia, skin atrophy, sclerotic skin changes, telangiectasia, poikilodermia, increased prevalence of skin tumours and a great number of internal systemic diseases among them joint abnormalities, cognitive dysfunction, arteriosclerosis, high risk for heart attack and stroke (Burtner and Kennedy, 2010; Kamenisch and Berneburg, 2009). These serious complications can worsen over time and are life-threatening for affected individuals.

6. Conclusion

Increasing knowledge on the association of certain clinical and laboratory characteristics of extrinsic and intrinsic skin aging with organ-specific diseases opens new possibilities for the establishment of skin biomarkers for systemic human aging. Such a development may facilitate in the future both primary and secondary prevention of aging-related organ-specific diseases and the evaluation of their course under treatment.

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