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Skin aging: the dermal perspective

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Abstract The world population of adults aged 60 years or more is increasing globally, and this development can impact skin disease morbidity and mortality, as well as being reflected in the health care system organization. There is substantial evidence that the burden from a remarkable number of skin nonmalignant and malignant conditions is greater in the elderly. Dermatologic research and clinical education in dermatology should focus on both challenges and opportunities created by aging. Skin aging due to intrinsic and extrinsic factors can alter significantly epidermal and dermal structure and functions. Dermal aging can be linked to a great number of complications in routine dermatologic conditions, with slow healing as an example of a severe complication in the elderly. This may be attributed to aged dermal fibroblasts modifying the tissue microenvironment via a shift in their soluble factors and extracellular matrix repertoire. This senescence-associated secretory phenotype can explain the particular proclivity of aged skin to develop malignancies.

Change in demography: global aging will affect dermatology practice

The world population of adults aged 60 or more is significantly increasing globally. More important, the population aged 60 or above is growing faster than all younger age groups. This trend was initially apparent in high-income countries. Recently, progressive aging has become apparent elsewhere. By 2050, all regions of the world except Africa will have nearly a quarter or more of their populations aged 60 or more. The number of older persons in the world is projected to be 1.4 billion in 2030, 2.1 billion in 2050, and even 3.1 billion in 2100.[1]

Globally, life expectancy at birth is projected to rise from 71 years in 2010-2015 to 77 years in 2045-2050. For example, Asia and Europe will gain approximately 6 or 7 years of life expectancy by 2045-2050, whereas the United States and Canada are expected to gain 4 to 5 years of longevity.[1]

Historically, such a remarkable increase in life expectancy was initially attributed to the successful management of various infectious diseases via the improved organization and public availability of the health care system, sanitation methods, disinfectants, vaccination, and the use of antimicrobials. Primarily, this was achieved through reduction in mortality particularly in childhood and childbirth. Later, another increment of life expectancy was achieved in adults by new

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options in the treatment of noncommunicable diseases, including cardiovascular disease, metabolic disorders, and malignancies.

The lifetime risks of diseases occurring in the elderly are influenced by increased survival. This may be attributed to the higher number of survivors, where the disease incidence is peaking.[2]

How does this globally extended human life expectancy affect dermatology and health care systems in general? More specifically, how does this impact skin disease morbidity and mortality?

There is substantial evidence that the burden from a remarkable number of nonmalignant skin conditions, including psoriasis, dermatophytoses, and decubitus ulcers, is greater in the elderly.[3] This increasing burden is possible to quantify by using the disability-adjusted life year (DALY).[4] Cutaneous malignancies, including melanoma, also increase with advancing longevity.[5] An elderly population is more likely to develop, for example, skin cancer, and increased age may be a risk factor negatively influencing skin cancer outcomes.[6] Notably, the greatest skin-cancer-related DALY rates occur in individuals older than 75 years.[4]

On the basis of these data, aging—particularly skin aging—is an increasingly important topic. WHO demands that every human being "should have the opportunity to live a long and healthy life"[7] and that "everybody can experience healthy ageing."[7] Dermatologic research and clinical education in dermatology should meaningfully focus on both challenges and opportunities represented by aging. Although multiple efforts have been made to address, for example, the aging skin-related pathologies, studies of this aging-related health system costs are relatively sparse. Active screening for both melanoma and other cutaneous carcinomas is a cost-effective strategy and has been projected for a substantial reduction of 5% in skin cancer mortality during two decades.[8]

In financial terms, poor healing of, for example, decubitus ulcers costs $9.1-$11.6 billion per year in the United States. The cost of individual patient care ranges from $20,900 to $151,700 per decubitus ulcer.[9]

Aging of the epidermis: beyond the intrinsic phenomenon?

Aging is a continuous process. In general, it is very difficult to measure aging precisely, because it is perceived as a complex series of, frequently subtle, physiologic and structural changes that occur over time. These changes are represented by a broad diversity of health and functional states experienced by older people. The range of these changes in the older age group is highly individual and only loosely associated with chronologic age. This diversity is a hallmark of human older age.

Both internal and external factors can influence the onset of age-related changes. Intrinsic (chronologic) and extrinsic (environment induced) aging types are executed through different mechanisms and pathways. Their effects are synergistic for the affected individual. Different mechanisms employed can even result in different structural and functional alterations in the affected organs, including the skin.

The epidermis is a rapidly proliferating tissue. The pool of proliferating cells is located in the basal layer anchored to the basement membrane. Epidermal stem cells occupy a well-defined region of the hair follicle (the bulge region) and less clearly defined regions in interfollicular epidermis.[10] The epidermis and also its appendageal organs undergo frequent turnover to replace physiologically shed cells. In pathologic conditions, these organs also contribute to the rapid repair of externally induced wounds.

The epidermis is also a self-renewing tissue that is required throughout the whole lifespan of an organism. Cells are able to divide for only a restricted number of times, before they undergo permanent cell division arrest lasting until their death. This phenomenon is known as replicative senescence.[11] Telomere shortening acts as a mitotic clock to prevent unregulated cell proliferation.[12] This would also restrict proliferation in transit-amplifying cells and their progeny in the epidermis. Telomere shortening occurs during every normal DNA replication due to so-the called end replication problem and telomere end processing; however, there are several strategies to allow circumventing of this mechanism. This is frequently observed in cancer, including epidermal carcinomas and melanoma.[13]

Normal epidermal stem cells must stringently guide the number of mitotic divisions engaged. This is compensated by the high proliferative capacity of daughter populations (transit-amplifying cells) after asymmetric stem cell division. Low frequency of stem cell cycling is, therefore, a highly effective preventive strategy to avoid the permanent incorporation of randomly occurring genetic alterations into the genome.[14] Such a genetic mutation in self-renewing stem cells could potentially lead to devastating consequences, including tumor formation. This mechanism of cancer prevention, however, is believed to come at a cost that is senescence. A crucial question, therefore, is what controls the balance of epidermal proliferation and epidermal differentiation; however, the identity of the human epidermal stem cell has remained a matter of some controversy.[10]

Complete exhaustion of the stem cell pool has been described in a mouse model, where, for example, long-term activation of Wnt causes cell senescence and the depletion of the stem cell compartment by the persistent activation of mTOR.[15] Despite several critical differences in telomere structure, mouse models of telomerase deficiency also provided evidence that telomere shortening may be important for skin aging. Mice with critically short telomeres exhibited problems with highly proliferative tissue, including epidermal abnormalities such as poor wound healing, spontaneous ulcerative skin lesions, early hair loss, and early hair graying.[16]

There are several conditions where mutations in telomerase components result in human disease, for example, in

dyskeratosis congenita.[17] Accelerated telomere shortening leads to premature loss of tissue self-renewal capacity and untimely death, most frequently due to a fatal bone marrow failure. Common skin findings in dyskeratosis congenita include irregular pigmentation, nail dystrophy, poikiloderma with epidermal atrophy and prominent telangiectasias, and oral leukoplakia. Other cutaneous findings may include alopecia involving the scalp, eyebrows, and eyelashes with premature graying.[18] This genetic disorder, therefore, offers multiple accentuated facets of skin aging for observation; however, we have not observed a complete loss of epidermal self-renewal capacity in such patients. In addition, we also have not observed absolute loss of skin regeneration in centenarians in a clinical setting. The aged epidermis is frequently associated with multiple important structural and functional impairments. These include, for example, epidermal atrophy due to decreased cellular turnover, slow re-epithelization, weaker barrier function, lower mechanical resistance, decreased DNA repair capacity, and lower sweat and sebum production.[19]

On the contrary, the clinically relevant complete exhaustion of skin regenerative capacity is achieved by extensive exposure to radiation or chemicals, either accidental or therapeutic. These harmful external agents also trigger cellular senescence in response to DNA damage without respect to the actual extent of telomere attrition in the affected cell. It was shown that activated oncogenes are responsible for this arrest; therefore, this type of senescence was termed *oncogene-induced senescence*.[20]

There is good evidence that keratinocyte progenitors are relatively radiosensitive cells, whereas epidermal stem cells appeared to be relatively radioresistant.[21] In this study, which used radiation lower than 2 Gy, colony-forming assays showed that 82% of stem cells survived at 2 weeks, compared with only 29% for the progenitors; however, after high doses of radiation, toxicity and cell death take over the adaptive responses of the cells. This catastrophic scenario leads to depletion of the stem cell pool, which can impair skin regeneration in the long-term.[22] Dermatologists are aware of the slow healing of the so-called moist desquamation, which may occur after radiotherapy, once a cumulative dose exceeding 8 Gy was administered.[23] Less frequently, radiation therapy may sometimes lead to severe adverse effects in irradiated tissue known as radiation-induced cutaneous ulcerations, which are extremely resistant to healing.[24]

A nonhealing wound is frequently complicated by such afflictions as diabetes-induced and nondiabetic neuropathies, chronic venous insufficiency, arterial disease, nutrition deficiency, decubitus ulcers due to immobility, and so on. Successful treatment of an underlying causative disease stimulates skin healing. Chronologic aging of the epidermis and resulting poor re-epithelization seems an unlikely explanation. There might be a significant age-dependent difference in the proportion of highly clonogenic keratinocytes in human interfollicular epidermis.[25] Using a similar feeder technique, gradual age-related decrease, but not complete absence, was also confirmed by others in the case of follicular keratinocytes.[26] Keratinocyte culture methods have developed over decades and shifted to various chemically defined, low/no serum, feeder-free variants. Studies using improved cell culture methods suggest that no differences in keratinocyte doubling capacity were found among cells isolated from the skin of different body areas (thorax, breast, abdomen) or donors of different ages (here ranging from 15-58 years).[27]

The plausible explanation of these conflicting data is most likely not found in the epidermis *per se*, but it is coming from the cell culture environment. The difference in the type of feeder cells or surface coating by biomolecules, serum content, growth supplements, and so on, significantly influences the maintenance of epidermal stemness *in vitro*.[28] All these factors mimic more or less successfully the so-called tissue microenvironment. Our current incapability of reliable reconstruction of tissue microenvironment recently represents the most critical bottleneck in the broader implementation of cell-based treatment methods in clinical praxis; however, there is a steadily increasing demand for autologous adult stem-cell-based therapies or artificial organs.

One group[27] followed their expansion for more than 100 population doublings (regardless of the age of the actual donor), without reaching signs of replicative senescence in keratinocytes. Taking this possibility into account, it seems that we usually do not have a chance to meet the physical limits of epidermal proliferative capacity even in extremely aged individuals. We usually do not live long enough.

In irradiation studies,[23] the presence of, for example, fibroblast growth factor 2 (FGF2) in the irradiated microenvironment is critical for stem cell survival. Stem cell protection by its microenvironment (the so-called *niche*) is an essential factor for tissue homeostasis in the epidermis and also in other tissues. The mutual interactions between epithelial cells and their microenvironment are therefore critical.[29] It seems likely that this microenvironment could be the next therapeutic target.

Dermal fibroblasts: seemingly invisible differences

Skin is the outermost organ of the body. The barrier function is dominantly executed by epidermis as noted above. Although the primary function of the dermis is to form a protective layer, it must also cope with the environment and mechanical forces. The dermis is not a passive extracellular-matrix-rich scaffold providing mechanical support to the overlying epidermis. Dermal architecture and function depend on diverse populations of cells, predominantly on dermal fibroblasts. Minor dermal populations are represented by, for example, various cells of immune system, endothelial cells, and pericytes. Reciprocal communication via growth factors, cytokines, and chemokines across the basement membrane between the epidermis and dermis plays a key role in skin development, homeostasis, and repair.

With simple histologic methods, the dermis can be reliably distinguished as early as week 5 to 6 of human development.

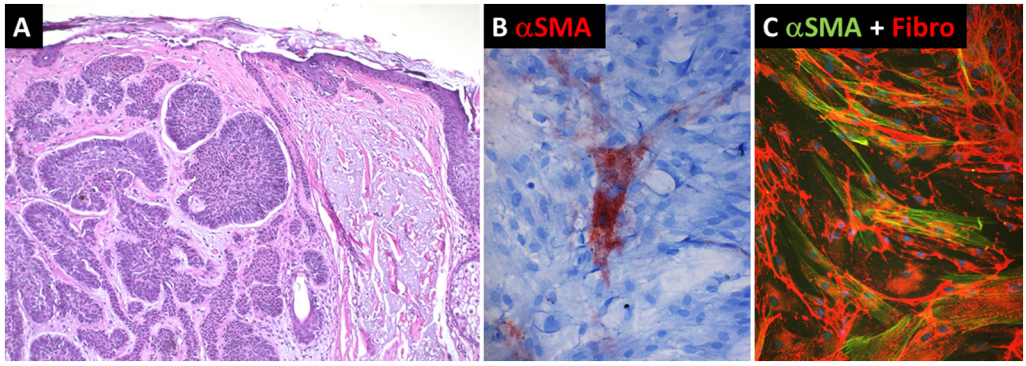

Fig. 1 **(A)** Basal cell carcinoma (on the left), surrounded by a grayish zone of heavily altered dermis (solar elastosis, on the right). **(B)** Cancer-associated fibroblasts (isolated from an elderly patient with basal cell carcinoma) in tissue culture; AEC (red) highlighted alpha-smooth muscle actin (αSMA)–positive myofibroblasts; cells are counterstained with Gill hematoxylin (blue). **(C)** Immunocytochemical analysis reveals multiple αSMA-positive cells (green) surrounded by a dense meshwork of extracellular-matrix-containing fibronectin (Fibro, red).

The dermis is derived from mesenchyme of lateral plate mesoderm (for the limbs and body wall) and also of the paraxial mesoderm (dermis of the back). Besides this purely mesodermal components, the ectomesenchyme originating from the neural crest cells forms the dermis and connective tissues of the face and neck.[30] Despite these differences in embryologic origin, the histologic arrangement of the adult dermis is otherwise uniform across the body.

Conventional histology recognizes the superficial papillary dermis and more deeply located reticular dermis with adjacent adipocyte-rich hypodermis. Dermal thickness can be variable in different body sites. This otherwise uniform dermal structure attracted the little to no attention of the researchers over decades. Such structural uniformity of the source tissue has been inappropriately extrapolated also on all fibroblasts derived from this tissue. In later years, more light has been shed on the diversity of dermal fibroblasts under physiologic and pathologic conditions.

[31] on the address of the principal cells in stroma of various tissues, collectively called fibroblasts: "*a catch-all designation that belies their diversity*."????

Fibroblasts are somewhat difficult to identify positively morphologically. In cell culture, fibroblasts are identified based on their spindle shape and loose growth pattern. This can be combined with positive immunohistochemical staining for the mesenchymal marker vimentin along with the absence of staining for epithelial cell markers (eg, keratins) or other mesenchymal cell types, such as desmin (for muscle cells), GFAP (for glial cells), CD34 (for hematopoietic cells), CD68 (for macrophages), and S100 P (neural crest-derived cells). Extensive production of representatives of the extracellular matrix such as collagen type I or III as well as of fibronectin (Figure 1C) can also be employed for *in vitro* recognition of fibroblasts. Thorough understanding of fibroblast phenotype can aid our insight into various processes significantly, not only in the skin but also in other organs; however, this approach is based on a combination of several markers and therefore has just limited applicability.[32] Also, the cell phenotype *in vitro* is frequently different from the phenotype observed in normal tissue context.[33,34]

The possibility of defining differences in fibroblasts by cell function more than by cell phenotype was noted in the context of skin tissue by e in the early 1990s.[33] In these already classic experiments, dermal papilla fibroblasts were implanted alone into footpad skin under controlled conditions in a murine model. New pelage-type follicles were induced by transdifferentiation of the footpad epidermis afterward. At this moment, the dermal compartment of the follicle, the dermal papilla, was for the first time recognized as the key signaling center. Dermal papilla fibroblasts were acknowledged for being responsible for maintaining hair growth and controlling the complex system of hair follicle cycling. It was suggested later that these dermal cells could have a great regenerative potential even outside of the hair follicle, and their role in, for example, wound healing was proposed.[35] Approximately at the same time, there was a proposal that the same epidermal organ (hair follicle) could host another pool of stem cells of different origin, the neural crest-derived stem cells.[36] The obvious need for more robust cell definition based on gene signatures shifted all these fibroblast-targeted studies inevitably to the era of transcriptomics.

Using gene microarrays in later years, fibroblasts from each body site displayed distinct and characteristic transcriptional patterns.[31] In tissue culture, adult fibroblasts maintained key features of *HOX* gene expression patterns established during embryogenesis. This observation suggests positional memory in fibroblasts. Next, these data suggest that fibroblasts at different locations in the body should be considered as distinctly differentiated cell types separable by their gene expression profiles.[31] Microarray studies have become an extensively used technique in skin research, and it has offered an excellent tool for deciphering fibroblast functional heterogeneity. It is possible to determine the typical expression profile of, for example, various skin-cancer-associated fibroblasts[37–40] or from fibroblasts activated during healing process,[41] and so on; however, all those microarray-generated data must be interpreted stringently.

Great care must be dedicated to the design of the study and appropriate control selection. It was observed that several genes defective in genetic syndromes were prominently expressed in fibroblasts originating from sites most affected in that diseases.[31] These false discoveries are worrisome. As approximately 81% of newborn boys in the United States are circumcised,[42] the residual foreskin is frequently used as a source of tissue in dermatologic research; however, the dermis and its resident fibroblasts are anatomically more heterogeneous than was previously thought.

Juvenile dermis: quick and smooth inspiration for rapid healing?

Dermal fibroblasts are highly proliferative during embryonic development. The cellularity of the dermis is much higher at this developmental stage,[43] which corresponds with the rapid growth of the body.[44] On the contrary, the adult dermal fibroblasts are typically quiescent cells[45]; however, these quiescent fibroblasts can be activated again by various external stimuli to divide in response and to maintain tissue homeostasis, if necessary.

Regeneration in adult mammals (including humans) is generally highly limited in comparison with some invertebrates and amphibians.[46] There is an indication that this loss of regenerative capacity can result from our evolutionary strategy. Due to improved obstetric care in 1970s, several anecdotal reports introduced the appealing topic of human fetal scarless healing.[47] These reports indicated that surgical incisions or even limb amputations (spontaneous, mostly due to constriction bands) in the human fetus heal rapidly and do not result in scar formation (of course without regeneration of missing limb). Notably, no acute inflammatory process and no granulation tissue formation were observed at any of the amputation sites. This was also confirmed in other mammalians.[48]

An initial hypothesis was postulated that factors present in the uterus, such as complete sterility[49] or low oxygen tension,[50] could be beneficial to, or directly responsible for, scarless healing.[48] These potential factors were extensively studied to establish a treatment method through which scarless healing could be achieved even in adults.[51] Unfortunately, later experiments and trials concluded that these factors proved to be sufficient to be meaningfully implemented into routine therapy.

Results of fetal healing are nearly indistinguishable from the uninjured tissue. It was extensively documented using robust scientific methods, for example, confocal microscopy.[52] It was assumed that these features are typical for early phases of fetal development before 24th week of gestation.[53] More recently, it was confirmed that highly favorable healing result could be achieved even in newborns within the first week of postnatal life.[54,55] These studies performed on newborns undergoing lip clef surgery highlighted the importance of the intrinsic tissue factors.

The early timing of this surgery seems to be a crucial factor. It is evident that the rate of tissue maturation/aging is rapid in this case. Of note, this excellent healing capacity is readily lost even in slightly older children. Nevertheless, such a rapid decrease of healing capacity observed in newborns within a few weeks offers acquisition of material with highly contrasting differences that could be easily studied by molecular analysis of transcriptome[56] and presumably also epigenome.[42]

What are the most critical features of fetal and newborn skin? Extracellular matrix is an obvious first target. The principal component of extracellular matrix in human dermis is collagen deposited here by dermal fibroblasts. The adult human dermis contains an excess of collagen type I,[57] whereas in rat fetal dermis content of collagen type III exceeded content of collagen type I.[58] Notably, this switch roughly coincides with the decrease of fetal-type healing capacity in the skin of newborns.[57] The adult dermis also contains, for example, more decorin. Decorin regulates collagen fibrillogenesis.[53] The 3-D arrangement of collagen bundles is therefore different in fetal dermis, as the collagen bundles are finer more reticular. There are conflicting data regarding the other components of the extracellular matrix, for example, tenascin or fibronectin expression. Differences in temporospatial expression profile were suggested.[53] One group[41] could not confirm quantitative differences in, for example, fibronectin production in fibroblast cell cultures. The extracellular matrix is also a highly dynamic structure with a variable turnover.

Various models of skin aging suggested that progressive accumulation of senescent fibrocytes in the aged dermis is leading to a subsequent reduction of collagen I production and loss of its volume, which is also associated with local overproduction of matrix metalloproteinases.[57] This turnover can be further modulated by, for example, epithelial-mesenchymal interactions during wound healing.[41] It was possible to show such enhancement via coculture methods where keratinocytes significantly enhanced the proliferative and migratory potential of the fibroblasts that was linked to changes in expression of matrix metalloproteinase MMP-2 and MMP-9.[41,59]

Another prominent component of dermal extracellular matrix is glycosaminoglycans such as hyaluronic acid. Hyaluronic acid gained a great deal of attention in dermatology and cosmetics in previous years. These molecules are extremely hydrophilic and bind an excessive amount of water. The increase in levels of glycosaminoglycans changes the rheology of the matrix toward a more pliable one. Low stiffness of the extracellular matrix is known to influence mesenchymal cell phenotype and affect cell survival; this may be also critical for the scarless healing.[60] Hyaluronic acid can also bind growth factors and cytokines form their depot and thus create temporal and spatial gradients of these molecules.[61] This might be important also in modulation of local pro-/antiinflammatory environment. Particular attention was

dedicated to the levels of growth factors, namely, TGF-β, PDGF, EGF, basic FGF, VEGF, and IL-6/IL-8/CXCL1.[56,62]

Notably, many efforts have been made to closely determine the role of, for example, transforming growth factor-beta (TGF-β) isoforms, and their receptors in the wound healing process. Their roles in scarless wound repair observed in are still not well understood.[56] TGF-β signaling is usually referred to be context dependent. It is dependent on the available amount of the TGF-β itself in various isoforms, its receptors, and also by signal duration and cytokine temporal availability and receptor internalization.

In fetal wound healing, there is a rapid induction of TGF-β, but it is in lower total levels than in adults.[63] It was suggested that fetal healing has a more rapid clearance from the wound site compared with adult wounds.[63] TGF-β is also linked to fibroblasts differentiation into the myofibroblast phenotype (Figure 1B, C). Upon injury, the fibroblasts are stimulated mechanically by inflammatory mediators to undergo this process. Examination of this phenomenon in cultured fibroblasts from newborns and adults has shown that fibroblasts can undergo this more efficiently once specific components of extracellular matrix, namely, galectin-1.[64]

Myofibroblast contraction is rather long lasting and results in a permanent tissue retraction that closes the wound. This also leads to stabilization of extracellular matrix, and it could explain the characteristic favorable tissue remodeling activity observed in the case of healing of fetal skin. This seems to be dependent on precise temporal regulation of TGF-β activity.[63] On the contrary, extended TGF-β1-mediated signaling has been implicated in diseases characterized by excessive collagen deposition, including keloids and scleroderma[65]; however, we were not able to identify quantitative differences of myofibroblasts in fibroblast cultures from various donors based on their age.[55] TGF-β1 appears as an important target to control myofibroblast activity.[66]

Similarly, conflicting data were reported by us for IL-6. It was detected on RNA and protein level in a surprisingly higher amount in fibroblasts[55] isolated from newborns compared with adult skin-derived fibroblasts. This finding was explained later by the difference in their developmental origin (trunk from mesenchyme vs face from ectomesenchyme).[56]

Aging of the dermis: wrinkled? weak? worrisome?

Dermal aging can sometimes be highly evident in routine histology. Ultraviolet radiation from natural and artificial sources is the principal environmental factor of skin damage that is accumulated by the tissues over the years of life; therefore, this damage is generally also reported as the photodamage. Structurally, complex of these changes is known as solar elastosis (or dermal elastosis, actinic elastosis; Figure 1A). There are a variety of clinical manifestations of solar elastosis. Commonly, solar elastosis manifests as yellowish, thickened, coarsely wrinkled skin. This visual aspect has a substantial impact on tissue esthetics and health. The occurrence of solar elastosis can be used as a biomarker of cutaneous photoaging.

Additional extrinsic factors corroborating this effect include other types of radiation, reactive oxygen radicals, chemical pollution, smoking, and repetitive muscle movements; in a more general sense, also lifestyle and diet can act as accelerators or intensifiers of aging signs.[67] Evaluation of the overall effect of these changes and their scoring is difficult and subjective. For purposes of comparative studies, the Beagley-Gibson grading system was developed. It evaluates skin changes and generates an individualized, objective estimate of cumulative, lifetime ultraviolet radiation (UVR) exposure.[68]

Additionally, extrinsic factors, including UV radiation, pollution, nicotine use, repetitive muscle movements, lifestyle, and diet, can act as accelerators or intensifiers of aging sign

Additional extrinsic factors, including other types of radiation, chemical pollutants (eg, released during nicotine smoking), repetitive physical stimulation (due to, e.g., movements), lifestyle, and diet, can act as accelerators or intensifiers of aging signs.

The detectable loss of elastic properties is caused by changes in elastin production, increased degradation, and modified processing. The fibroblasts are a principal group of cells in the dermis involved in the so-called elastogenesis. This process occurs predominantly in the superficial dermis, which corresponds to the natural distribution of elastin in the dermis. Elastic fibers consist of two morphologically distinct components: Microfibrils and polymerized elastin. The precursor, tropoelastin, is secreted into the extracellular space, where it becomes highly crosslinked by the activity of the copper-requiring enzyme known as lysyl oxidase.[69]

Several studies from the 1980s showed that decrease of production is associated to fibroblast aging and occurs already after approximately 30 population doublings.[70] Comparing multiple donors, a significant fall of tropoelastin production appeared in donor chronologically aged 70 years[70]; however, these tissues were from previously more sun-protected areas (from foreskins and trunk skin). Clinically notable photodamage frequently comes at much younger age. This can be explained as the real photoaging. Ultraviolet radiation can induce alternative splicing of the elastin gene, which leads to the inadequate synthesis of the proteins required for the correct assembly of elastic fibers.[71] The elastin content is estimated to be only 2% of the total dermal protein mass. Despite the relatively modest content, elastin is highly important for mechanical tissue properties.

Collagens are the main extracellular component of the dermis. Fibril-forming collagens (eg, collagen types I, III, and V) assemble into 3-D scaffolds in the dermis. This is the structural base of multiprotein networks with other matrix proteins such as the elastin fibers and nonfibrillar matrix. The nonfibrillar matrix also contributes as a visco-elastic material and prevents any motion of the network. The disorganization of collagen fibers associated with solar irradiation and aging was documented.[72] Collectively, all these components determine the mechanical behavior of the dermis and other collagen-rich tissues with clinical consequence.[68]

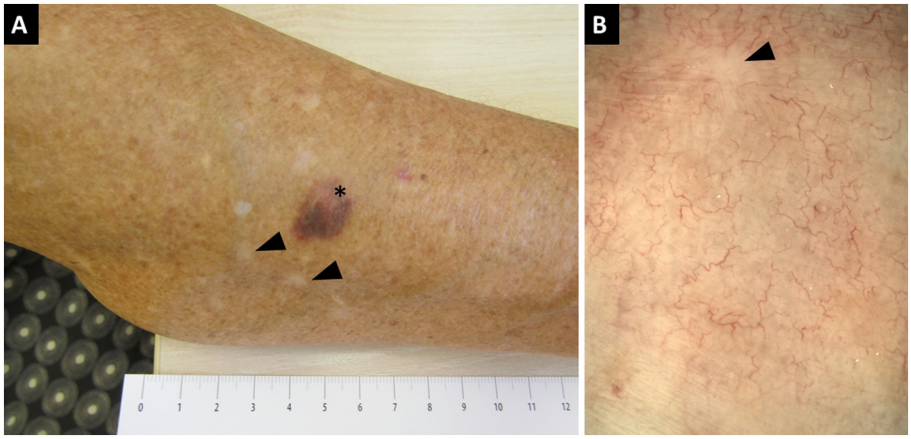

Fig. 2 Forearm of 86-year-old Caucasian woman, phototype II, with prominent signs of dermatoporosis. Stellate pseudoscars (black arrowheads **A, B**) and skin atrophy with irregularities of dermal vessels (the detailed view in dermatoscopy, **B**). Hematomas, linear skin tears, and lacerations might occur after minimal trauma in patients with dermatoporosis. Hematoma (asterisk) is not dissecting here.

In 2007, the word *dermatoporosis* was created to give an umbrella name to the chronic cutaneous fragility of aging skin.[73] The leading features of dermatoporosis include skin atrophy (both epidermal and dermal), with solar purpura and whitish scarlike changes present on the extremities of elderly patients (Figure 2). Skin lacerations and delayed healing are frequent features in dermatoporotic skin, leaving affected patients susceptible to bleeding complications and cutaneous infections.[68] The prevalence of dermatoporosis is surprisingly high as estimated recently (37.5% in French subjects aged ≥65 years; 27.5% men versus 43.9% women).[74]

All such common clinical phenomena can be linked to changed dermal architecture. The increased stiffness in aged dermis frequently reported in the literature can be attributed to the increased crosslinking between fibers, which results in increased stiffness of the whole collagen network.[75] Easier breaking is also possible due to the shortening of the fibrils in the fibers, which will then separate more easily. The degradation of proteoglycans further leads to a loss of water and impedes sliding of fibrils inside the fibers. This finally results in a more substantial increase of inner shear per fiber contributing to increased mechanical fragility.[75]

The aged dermis is obviously vulnerable; however, there are other invisible risks associated with aging. As mentioned earlier, cellular senescence occurs in culture and in the organism as a response to excessive extracellular or intracellular stress. There are several methods of senescence assessment in cultured cells and also in tissues. Senescence-associated β-galactosidase activity, detectable at pH 6.0, gained much attention in the last decades. The method based on enzyme histochemistry offers the advantages of being quantitative and relatively sensitive.[76] The interpretation of the results is sometimes problematic and it is not easy to implement, for example, in diagnostic procedures.

The senescence program drives the cells into a cell-cycle arrest, but it does not eliminate them from the tissues and leaves them viable and functional. Senescence, therefore, prevents the spread of genetic damage, but it does not lead to numeric atrophy of the tissues. Senescent cells have been shown to accumulate during the lifetime in various animals and also in humans.[76]

Once introduced, senescence leads to extensive changes in gene expression of affected cells. The repertoire of these changes is conserved. Critical differences between the transcriptome of presenescent and senescent were observed in products of genes encoding the secretory proteins. Collectively, this complex of changes constitutes to the so-called senescence-associated secretory phenotype.[77] This secretory phenotype includes several families of soluble and insoluble factors. Soluble signaling molecules include interleukins, chemokines, and growth factors (Table 1).

Next, senescence also contributes to changes of secreted proteases and secreted insoluble proteins of the extracellular matrix. In the next step, the changes of extracellular matrix can modify the effect of soluble molecules by their stabilization or sequestration as discussed earlier. All these factors of senescent cells can, therefore, modify the tissue microenvironment. So far, the senescence growth arrest has been shown to promote activities of the major tumor-suppressor cellular mechanisms.[77] Unfortunately, this is only the bright side of the story.

Epidemiologic studies have shown that markers of chronic sun exposure increase the risk of both melanoma and nonmelanoma skin cancer.[67] It is a broadly accepted idea that cumulative exposure to ultraviolet light is etiologically relevant, for example, basal cell carcinoma, squamous cell carcinoma, and malignant melanoma.[78] Ultraviolet radiation induces DNA damage, and it is responsible for the development of mutations and consecutive carcinogenesis in skin. On the other hand, ultraviolet radiation is a potent inducer of stress in the tissue and penetrates deep and reaches the dermis. Considerable attention was dedicated to environmental factors supporting the growth of the cancer cells in last years. We have accumulated evidence that tissue microenvironment is a critical factor for cancer progression. It was suggested that the so-called cancer-

Table 1 Factors extensively produced by fibroblasts with senescent phenotype, myofibroblasts, and cancer-associated fibroblasts

Category of product	Factor
Interleukins	IL-1 (a,b)
	IL-6
	IL-7
	IL-13
	IL-15
Chemokines (CXCL, CCL)	IL-8
	GRO-a (b, g)
	MCP-2
	MCP-4
	MIP-1 a
	MIP-3 a
	HCC-4
	Eotaxin-3
Other inflammation supporting factor	GM-CSE
	MIF
Growth factors	Amphiregulin
	Epiregulin
	Heregulin
	EGF
	bFGF
	HGF
	KGF(FGF7)
	VEGF
	Angiogenin
	SCF
	SDF-1
	PIGF
	NGF
	IGFBP-2 (3, 4, 6, 7)

Modified from multiple studies.[77,82,83,86]

associated fibroblast are highly biologically active population in, for example, basal cell carcinoma, squamous cell carcinoma,[37,38,79] and also in melanoma and other various types of tumors.[80,81] Cancer-associated fibroblast were suggested as clinically important modifiers of oncological therapy response.[40]

The activity of cancer-associated fibroblast is not cancer-type specific, and released molecules are secreted regularly as an important component of cancer-supporting environment.[80,82,83]

Surprisingly, we have identified that this repertoire is significantly overlapping with the repertoire of cytokines present in senescent cells. Most frequently we have detected interleukins, for example, IL-6 and IL-8. This overlap represents a double-edged sword. In this light, the protective factors of senescence become corrupted and can be engaged in tumor progression.[84] This mechanism is also attracting research attention with therapeutic potential. These principal components of cancer microenvironment also offer a potential target for future therapy.[85]

Conclusions

The association between aging and cancer seems to be more than apparent.[14] Respecting the ongoing global shift in demographics, the further increase of the epidemiclike incidence of malignant tumors in a population can be expected soon. The increased incidence of cancer will demand the attention of governmental authorities to establish an adequate economic base necessary for the expensive treatment of numerous patients.[14,46]

In this light, we should support the implementation of aging-risk-based skin cancer screening guidelines internationally. The elderly population should be the audience of such targeted screening because the essential phenotypic cancer risk factors are present in higher age. In this context, the role of cancer stroma in controlling multiple biologic properties of tumors is a prospective target for translational research with potential therapeutic outcomes.

This situation represents an excellent starting point for the development of innovations in cancer prevention and therapy.

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