PHOTOBIOLOGY/PHOTOMEDICINE

Photoaging

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Photoaging describes those changes in clinical, histologic, and functional characteristics of older skin that can be observed in habitually sun-exposed areas. It consists of chronic sun damage (predominantly) superimposed on so-called intrinsic or programmed aging. Photoaging accounts for most of the unwanted changes in skin appearance over time and also exaggerates or accelerates the loss of physiologic reserve and various protective capacities. The importance of photoaging lies in the enormous consumer demand for agents that can prevent or reverse its stigmata, its strong association with cutaneous malignancies, and the clues it provides regarding the nature of aging itself.

PHOTOAGING ACTION SPECTRUM

Unlike sunburn and suntan, which manifest within hours and days, respectively, after a sufficient exposure to UV light, photoaging develops gradually over decades. This makes experimental determination of the relative contribution of different wavelengths impossible in human skin. Several mouse models have been described, among which, notably, is the rhino mouse, which develops coarse wrinkling following chronic UV exposure. However, substantially, different action spectra have been reported (Yaar and Gilchrest, 2012), and marked anatomic and physiologic differences between human and murine skin suggest that such models may be less informative than hoped.

Short-wave UV photons (UVB, 290–315 nm) are far more energetic than long-wave UV photons (UVA 315–400 nm), and DNA damage—implicated in both aging and photoaging (see below)—is predominantly attributable to UVB. It is therefore presumed that at least some aspects of photoaging, particularly epidermal features, are largely a consequence of UVB irradiation. However, UVA penetrates deeper into the skin, with ~50% of UVA photons, versus <10% of UVB photons, entering the dermis in a fair-skinned individual. It is also noteworthy that UVB constitutes only 0.5% of sunlight on average and is largely restricted to midday and in temperate climates to spring and summer. In contrast, UVA constitutes ~5% of the terrestrial sunlight and, although most abundant at times of peak UVB irradiance, is present in sunlight all day and all year. Unlike UVB, UVA is also transmitted through glass, allowing exposure while driving or while indoors near windows. In combination, these considerations have led many authorities to speculate that UVA has a far larger role in photoaging than in acute effects of UV or in photocarcinogenesis. This speculation has recently been reinforced by certain studies described below. Most probably, UVB and UVA both contribute to specific features of photoaging.

PHOTOAGING CLINICAL FEATURES

As expected, photoaging is generally most pronounced in fair-skinned individuals with many years of regular exposure to intense solar radiation. However, individuals of all skin phototypes can manifest photoaging, with the character, as well as the severity of changes, dependent on as yet poorly understood factors that appear to relate to proficiency of repair for acute DNA damage (Table 1).

EPIDERMAL PHOTOAGING

Other than UV-induced mutations in keratinocytes and melanocytes that ultimately promote development of skin malignancies, little is known about the mechanisms of epidermal photoaging. UV-induced apoptosis of stem cells in the basal layer and hair bulge is postulated to result in epidermal atrophy, slow wound healing, and depigmented pseudoscars, whereas the greater melanin production observed in senescent melanocytes (Bandyopadhya and Medrano, 2000) may be responsible for ''bronzing,'' the permanent ''tan'' observed in photoaged skin of some darker-skinned individuals. However, the molecular events leading to freckling, lentigines, and other pigmentary changes characteristic of photoaged skin are unknown.

DERMAL PHOTOAGING

The photoaging literature overwhelmingly concerns dermal changes, particularly those implicated in wrinkling. This is likely due to a combination of wrinkling's clinical prominence, the ability to quantify wrinkling noninvasively as an end point in clinical studies of anti-aging products, and the ease of dermal fibroblast (vs keratinocyte or melanocyte) culture that has encouraged extensive mechanistic studies on photoaging using this cell type. Type I collagen, produced by fibroblasts, is the most abundant protein in the dermal extracellular matrix (ECM). With age, the amount of collagen decreases (Varani *et al.*, 2004), at least

Table 1. Features of photoaging: influence of skin phototype

Skin photoype I–II
Proliferative exhaustion
Epidermal atrophy
Focal depigmentation
Pseudoscars
Mutation and dysplasia
Freckles
Nevi
Lentigo maligna
Actinic keratoses
Skin phototype III–IV
Protective hyperplasia
Tanning
Lentigines
Epidermal thickening
Coarse wrinkling

Note: the molecular correlates of skin phototype (a subjective rating of ease of sunburning vs tanning) are poorly understood, but they appear related to proficiency of DNA repair and other protective responses to UV irradiation. Typical features of photoaging are strongly influenced by skin phototype and can be conceptualized as dependent on cellular tendency to senescence, apoptosis, or mutation versus adaptive hyperplasia or increased melanogenesis.

in part due to increased activity of the matrix metalloproteinases (MMPs), collagenase, 92-kd gelatinase, and stromelysin (Fisher *et al.*, 1996), responsible for collagen turnover. MMPs are further activated by even small doses of UVB (Fisher *et al.*, 1996), leading to the breakdown of existing dermal collagen. This secondarily reduces synthesis of new collagen by reducing the ECM-exerted tension on fibroblasts attached to collagen fibers, which appears to stimulate new collagen synthesis (Varani *et al.*, 2004, 2006). Prolonged elevation of MMP activity results from even intermittent modest UV exposures (Fisher *et al.*, 1997). These effects in combination are believed to contribute substantially to the loss of collagen and wrinkling observed in the photoaged skin. Conversely, treatments that reduce wrinkling in photoaged skin increase the rate of synthesis and the total amount of type I collagen in the dermis. The best studied, of these treatments, retinoic acid, does so at least in part by blocking UV-induced MMP activation (Fisher *et al.*, 1996, 1997) while having no effect on the level of the tissue inhibitor of MMP (Fisher *et al.*, 1997).

Elastosis, the accumulation of partially degraded elastin fibers in the upper dermis, is the hallmark of photoaging. The lysosomal protease cathepsin K, the most potent of the elastin-degrading enzymes (Chapman *et al.*, 1997), was recently shown to be induced by UVA irradiation of cultured dermal fibroblasts derived from young but not old donors (Codriansky *et al.*, 2009). Young fibroblasts were also shown to be capable of internalizing and digesting extracellular elastin, a reaction inhibited by a cathepsin K inhibitor. Together, these data support an important role for UVA-induced fibroblast-derived cathepsin K in clearing elastin that has been partially degraded by MMPs in the ECM. This function appears to be lost with age, leading to clinical and histologic elastosis.

PAN-CUTANEOUS PHOTOAGING CONTRIBUTORS

Although photoaging research has been focused on changes in the ECM attributable to combined effects of aging and chronic UV irradiation, logic dictates that intracellular changes ultimately drive the process. One requirement for normal cellular function is energy production within the mitochondria. However, the mitochondrial electron transport chain that generates energy in the form of ATP also generates reactive oxygen species (ROS) that can damage the mitochondrial DNA (Ballard and Dean, 2001), classically producing a 4,977 base pair deletion (Cortopassi *et al.*, 1992). This so-called common deletion is up to 10-fold more prevalent in photoaged than in sun-protected skin and exposure of cultured dermal fibroblasts derived from sun-protected skin; exposure to physiologic doses of UVA can induce this mutation (Berneburg *et al.*, 2000). The resulting compromise of energy production is postulated to contribute to clinical signs of photoaging, whereas leakage of ROS from mitochondria into the cytoplasm and extracellular space damages many critical molecules, further compromising tissue function.

Very recent findings offer intriguing ties among the rare premature aging disorder Hutchinson Gifford progeria (HGP), normal intrinsic aging, and photoaging. In HGP, a mutation of the gene encoding lamin-A, a nuclear envelope protein, activates a cryptic splice site, resulting in a nonfunctional truncated protein and impaired nuclear function, including impaired DNA repair (Eriksson *et al.*, 2003). The abnormal protein, termed progerin, is responsible for accelerated aging-like changes in many organs including the skin and a life expectancy for HGP patients of only 10–15 years (Scaffifi and Misteli, 2006). Progerin has also been shown to be produced by cells of normal elderly individuals (McClintock *et al.*, 2007), suggesting a role for compromised nuclear envelope function in normal aging. In a recent study, repeated UVA irradiation of cultured dermal fibroblasts led to progerin production and changes in nuclear morphology, just as observed in fibroblasts from HGP patients and old donors (Takeuchi and Ruenger, 2013). UVB irradiation caused similar but less-striking changes. These data support an interpretation of photoaging as an exaggeration and/or an acceleration of intrinsic aging (see below).

AGENTS THAT EXACERBATE PHOTOAGING CHANGES

UV irradiation appears overwhelmingly responsible for changes observed in habitually exposed older skin. However, well-controlled studies have repeatedly documented more pronounced coarse wrinkling in the facial skin of heavy cigarette smokers (Joffe, 1991; Smith and Fenske, 1996), and this appears also to be the case for women with greater exposure to air pollution, due to heavy traffic (Krutmann and Schroeder, 2009). Whether the more

pronounced photoaging changes can be attributed primarily to DNA-damaging agents such as carcinogens in tobacco smoke and gasoline fumes or to other UV-additive insults is unknown. However, in this context it is of interest that at least in the case of smoking, the risk of skin cancer as well as coarse wrinkling is increased in individuals otherwise well matched for complexion and total sun exposure (Davis and Koh, 1992).

PHOTOAGING: A TRUE ACCELERATION OF AGING?

Many lines of evidence implicate DNA damage or poor DNA repair in the intrinsic aging process (reviewed in Yaar and Gilchrest, 2007, 2012). For example, essentially all progeroid syndromes result from the loss of function of proteins involved in DNA repair. These diseases include HGP, Werner syndrome, ataxia telangiectasia, xeroderma pigmentosum, and Cockayne syndrome (Reddy and Gilchrest, 2011). The so-called longevity genes, whose overexpression extends the life span in lower species, encode proteins that reduce environmental stress from such factors as UV irradiation and oxidative damage. Cumulative DNA damage is likewise a well-documented consequence of repeated UV irradiation.

Mechanisms of intrinsic aging and extrinsic aging, which is largely photoaging, thus appear to have substantial overlap and to prominently feature DNA damage. This is consistent with the widely accepted notion, first put forward in the 1960s by Leonard Hayflick, that aging at the cellular level, termed cell senescence, is Nature's safeguard against cumulative genomic damage, of which the most remarkable manifestation is malignancy (Campisi, 1996). Over the past two decades, great advances have been made in understanding the molecular mechanisms of cellular senescence and organism aging overall. Much of this work focuses on telomeres, the widely acknowledged ''biologic clock.''

As DNA polymerase cannot replicate the final bases at chromosome ends, chromosomes shorten slightly with each round of cell division. After a finite number of cell divisions, related to passage of time in proliferative tissues and characteristically increased after injury, including after UV irradiation, telomeres shorten to a critical short length and, in the case of fibroblasts, the cell enters a permanently nondividing or senescent state (Harley *et al.*, 1990). This is now known to involve DNA damage signaling through ATM, ATR, and p53 (reviewed in Gilchrest *et al.*, 2009). The same signaling drives other cell types, such as keratinocytes, to apoptosis. Critically, p53 signaling initially mediates a variety of protective cancer-preventative responses that include antioxidant defenses to reduce ROS, inhibition of the inefficient aerobic glycolysis that characterizes malignant cells (Li *et al.*, 2012), enhanced DNA repair capacity, transient cell-cycle arrest, and in skin also melanogenesis (reviewed in Gilchrest *et al.*, 2009). Senescence or apoptosis follows only when the cell perceives persistently unrepaired DNA damage. A corollary of this central p53 role as ''guardian of the genome'' is that when a cell enters senescence, this p53 signaling ceases, leaving viable but nonproliferative cells (such as dermal fibroblasts) in a state of chronic oxidative stress that promotes the proinflammatory environment characteristic of old skin and particularly of photoaged skin (Yaar and Gilchrest, 2012). It has also been well documented experimentally that acute DNA damage activates the same signaling pathways and, unless the DNA damage is adequately repaired, also drives cells to senescence or apoptosis (von Zglinicki *et al.*, 2005; Gilchrest *et al.*, 2009).

In the case of undamaged proliferative cells, the ''Hayflick limit'', or the number of serial cell divisions required for critical telomere shortening, is rarely reached during an individual's life span. However, in the face of frequent UV insults with frequent DNA damage, epidermal keratinocytes may reach this ''limit.'' UV-irradiated keratinocytes frequently undergo apoptosis, detected as ''sunburn cells'', followed by a wave of increased division by surrounding cells to replace lost cells and to increase epidermal thickness, a presumptive protection of basal layer stem cells from future UV damage. In time, the loss of stem cells is postulated to lead to epidermal atrophy and compromised wound healing relative to sun-protected areas. Surviving mutated cells, including stem cells, may also begin to divide inappropriately, giving rise, for example, to actinic keratoses. However, they also reach the maximal number of cell divisions and then cease dividing unless sufficient mutations have already occurred to defeat this fundamental safeguard.

Although cell senescence or apoptosis driven by repeated UV injury is understood to be more prominent in the epidermis, where most UV photons are absorbed, the same process may also affect the upper dermis. Fibroblasts typically undergo senescence rather than apoptosis after either acute DNA damage or multiple rounds of cell division, and the dermis of photoaged skin does contain fibroblasts that are senescent as defined by expressing senescence-associated β-galactosidase positivity (Dimri *et al.*, 1995).

HYPOTHETICAL TELOMERE-BASED PHOTOAGING MECHANISM

Experimentally, cell senescence may result from the disruption of the normal telomere loop structure that then initiates telomere-based signaling through ATM, ATR, p53, and their classic downstream DNA damage signaling pathways (van Steensel *et al.*, 1998; Eller *et al.*, 2006; Denchi and de Lange, 2007). It is also well established that oxidative damage due to aerobic metabolism or exogenous insults, including UVA irradiation, drives cell senescence by similar or identical signaling (von Zglinicki *et al.*, 2005).

Telomeres are composed of tandem repeats of 5′-TTAGGG-3′ and its complementary sequence ~7,000–10,000 base pairs long in human cells, with a terminal 5′ overhang of the 5′-TTAG GG-3′ repeat of up to a few hundred bases (reviewed in Gilchrest *et al.*, 2009). Interestingly, the 5′-TTAGG G-3′ tandem repeat sequence of telomeric DNA is conserved through all

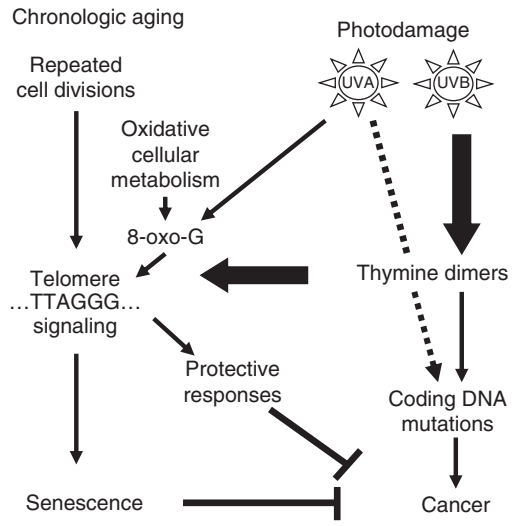

Figure 1. Convergence of intrinsic and extrinsic aging pathways at the telomere. Chronologic or intrinsic aging comprises, at least in part, cell senescence, the result of progressive telomere shortening that causes cells to enter a permanently nondividing state (senescence) postulated to result from exposure of the 5′-TTAGGG-3′ telomere sequence. Cell aging is also understood to result partly from chronic low-grade oxidative damage, for example, due to aerobic metabolism, expected to produce 8-oxo-guanine (8-oxo-G), a form of DNA damage expected to enhance signaling through the telomere pathway. Extrinsic aging in skin is largely the consequence of UV irradiation. Both UVB and UVA cause DNA damage: UVB primarily through the production of photoproducts such as thymine dimers and UVA in large part through indirect oxidative damage of guanine bases. Such damage can lead to mutation of key regulatory genes and cumulatively to skin cancer. Lesions produced in telomeric DNA, however, are postulated to induce signaling through ATM, ATR, p53, and their downstream effectors. Such signaling can lead to cell senescence. However, a variety of adaptive or protective responses also occur, as described in the text, creating a balance that varies strikingly among individuals of different phototype. In all cases, however, the result is genome protective, reducing cancer risk. Adapted from Halachmi *et al.*, (2005) and reproduced with permission (Gilchrest *et al*, 2009).

mammalian species despite the fact that it does not encode proteins. It is also of interest that this sequence contains the principal target sequences for all DNA-damaging agents: thymine dinucleotides (TT) that are obligate substrate for UV-induced thymine dimers and guanine (G) residues that are damaged by all oxidative insults and by chemical carcinogens, a few of which also form adducts at adenine–guanine (AG) dinucleotides. It has been repeatedly observed that exposing cells to DNA-damaging agents results in a larger burden of damage in the telomeres than in the remainder of the genome (reviewed in Gilchrest *et al.*, 2009). In combination with experiments documenting a key role of telomere ''dysfunction'' or disruption in initiating DNA damage–like signaling from telomeres as cells enter replicative senescence (Li *et al.*, 2004), these observations strongly suggest that intrinsic aging and extrinsic aging (largely photoaging) may result from activation of the same core aging mechanism (Figure 1).

CONCLUSIONS

Over the past two decades, detailed work by many groups has substantially elucidated the mechanisms of photoaging particularly in the dermis, suggesting both preventive and therapeutic interventions. Advances in telomere biology and basic gerontology have allowed the development of a unifying hypothesis for intrinsic and extrinsic skin aging pathways consistent with their understood biologic importance as genome-protective strategies.

CONFLICT OF INTEREST

The author states no conflict of interest.

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