

REVIEW

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Chemical consequences of cutaneous photoageing

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Abstract

Human skin, in common with other organs, ages as a consequence of the passage of time, but in areas exposed to solar ultraviolet radiation, the effects of this intrinsic ageing process are exacerbated. In particular, both the severity and speed of onset of age-related changes, such as wrinkle formation and loss of elasticity, are enhanced in photoaged (also termed extrinsically aged) as compared with aged, photoprotected, skin. The anatomy of skin is characterised by two major layers: an outer, avascular, yet highly cellular and dynamic epidermis and an underlying vascularised, comparatively static and cell-poor, dermis. The structural consequences of photoageing are mainly evident in the extracellular matrix-rich but cell-poor dermis where key extracellular matrix proteins are particularly susceptible to photodamage. Most investigations to date have concentrated on the cell as both a target for and mediator of, ultraviolet radiation-induced photoageing. As the main effectors of dermal remodelling produced by cells (extracellular proteases) generally have low substrate specificity, we recently suggested that the differential susceptibility of key extracellular matrix proteins to the processes of photoageing may be due to direct, as opposed to cell-mediated, photodamage.

In this review, we discuss the experimental evidence for ultraviolet radiation (and related reactive oxygen species)-mediated differential degradation of normally long lived dermal proteins including the fibrillar collagens, elastic fibre components, glycoproteins and proteoglycans. Whilst these components exhibit highly diverse primary and hence macro- and supra-molecular structures, we present evidence that amino acid composition alone may be a useful predictor of age-related protein degradation in both photoexposed and, as a consequence of differential oxidation sensitivity, photoprotected, tissues.

Introduction

Human skin undergoes extensive changes in appearance (e.g. wrinkle formation) and mechanical function (loss of both compliance and resilience) with age [1–3]. Whilst these structural and functional changes eventually manifest in elderly, photoprotected skin, their age of onset is accelerated and their severity is exacerbated by exposure to environmental factors such as smoking and ultraviolet radiation (UVR) [4–6]. Exposure to UVR, in particular, induces extensive changes in the composition and architecture of the extracellular matrix (ECM)-rich dermis [7,8]. Although UVR undoubtedly influences the viability and phenotype of cutaneous cells, the ability of these cells to selectively remodel key elements of the ECM via

production of low substrate specificity proteases may be limited [9]. In this review, we discuss: i) the composition of healthy skin; ii) the effects of UVR exposure on skin structure and function; iii) experimental evidence that UVR directly and differentially degrades skin biomolecules and; iv) the potential for amino acid composition alone (as opposed to higher order structures) to predict the susceptibility of key ECM proteins to direct (via UVR absorption) and indirect (via photodynamically produced reactive oxygen species [ROS]) degradation.

Structure and function of young, healthy skin

Skin is divided into two regions: an external epidermis and internal dermis, which differ profoundly in structure and hence function. The largely cellular epidermis acts as a barrier which blocks and/or mediates the passage of water, pathogens, heat and UVR [10,11]. In order to

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perform these functions, keratinocyte stem cells at the base of the epidermis undergo mitotic division to produce a supply of sequentially differentiating daughter keratinocytes which are ultimately shed a few weeks later as keratin-rich enucleated cells in a process known as desquamation [12].

In contrast to the dynamic epidermis, the structure of the dermis is characterised by a low density of fibroblast cells and a relatively static ECM [13]. Unlike intracellular proteins, which have half-lives measured in days, ECM proteins in human tissue are required to fulfil their mechanical and biochemical functions over a time course of many years in the absence of mechanisms to prevent or repair accumulated damage [14–17]. These proteins include members of the collagen super-family whose structures are characterised by the presence of at least one Gly-X-Y repeat domain (where X and Y are frequently proline and hydroxyproline amino acid residues respectively) which is able to form homo- or heterotypic triple helices [18,19]. Although all collagens share a triple helical region, these otherwise structurally diverse proteins perform distinct and disparate mechanical roles. The network and anchoring collagens IV and VII for example are localised at the dermal-epidermal junction (DEJ) where they play key roles in binding the tissue layers together [20,21]. In contrast, the widely distributed fibrillar collagens I and III, form covalently bonded fibrils which resist tensile forces [22–24]. In order to withstand compressive forces human skin relies on hydrophilic glycosaminoglycans (GAGs) including dermatan, chondroitin, heparin and keratin sulphate [25,26]. With the exception of hyaluronic acid, these unbranched disaccharide oligomers are located on post-translationally glycosylated proteins (proteoglycans) such as aggrecan, decorin and versican [27,28]. Finally, and in common with tissues of the cardiovascular and pulmonary systems, which are subjected to cyclic loads, human skin is rich in elastic fibres which drive passive recoil [29,30]. In young healthy skin, the architecture and relative abundance of the two major components of this system: the cross-linked, hydrophobic and highly compliant elastin core and the outer mantle of biochemically active and potentially mechanically stiff fibrillin-rich microfibrils is precisely controlled [31–33]. It is this elastic fibre system, and in particular the microfibrillar fraction which appears to be most sensitive to the effects of photoageing [9,34,35] (Figure 1).

Ageing skin

All tissues in the human body exhibit some manifestations of intrinsic (chronological) ageing. Aged, yet photoprotected skin is characterised by a late onset of fine wrinkles, increased fragility and stiffness and by decreased elastic recoil [2,36,37]. These functional changes are correlated with

structural remodelling (flattening) of the DEJ, a decrease in fibroblast numbers and dermal thickness and a generalised atrophy of dermal collagens, proteoglycans and elastic fibre components [38–41]. Although a consensus is yet to be achieved as to which cellular and molecular mechanisms play central causative roles in mediating intrinsic ageing: cell senescence, telomere shortening and oxidative stress have all been implicated in the process [42–46].

Compared with the slow, generalised atrophy of uncertain causation which characterises intrinsic skin ageing, extrinsically aged skin is characterised by a rapid and differential remodelling of diverse ECM components which is thought to be driven primarily by cellular responses to UVR [5,47]. Specifically, UVA radiation (315–400nm), which penetrates to a greater depth than UVB radiation (280–315nm), may be primarily responsible for chronic photoageing [5,48,49]. Clinically, photoaged skin appears deeply wrinkled and mottled and is characterised by reduced compliance and recoil [2,8]. Histologically these gross functional and structural differences are associated with: i) the loss of fibrillar collagens from the dermis as a whole and specifically with the localised loss of the elastic fibre associated proteins fibrillin (Figure 1) and fibulin-5 from the papillary dermis and: ii) the accumulation and often co-localisation of disorganised elastotic (elastic fibre containing) material and GAGs such as hyaluronic acid and chondroitin sulphate in a process known as solar elastosis [4,6,8,35].

To date, attention has focussed primarily on UVR-mediated activation and up-regulation of proteolytic enzymes and in particular the matrix metalloproteinases (MMPs) as the key causative mechanism of ECM degradation in photoaged skin [47,50,51]. Collectively, however, the implicated MMPs (-1, -2, -3, -7, -8, -9, -12 and -13) are capable of degrading most dermal ECM components [9,52]. We therefore recently suggested that acellular (i.e. direct UVR interaction with ECM proteins), rather than cellular (UVR mediated synthesis of ECM proteases) mechanisms may be responsible for the selective degradation of elastic fibre associated glycoproteins in early photoageing (Figure 2).

Degradation of biomolecules by UVR

Irrespective of whether direct UVR/molecule interactions alone or downstream perturbations in cell-mediated homeostasis are primarily responsible for photoageing, the process will be initiated by the absorption of photon energy by endogenous chromophores in the skin (Grotthuss–Draper law). Whilst, by definition, the term chromophore should be used only to refer to molecular regions which absorb visible or UV radiation, in many cases entire molecules or even molecular families are often referred to as UVR chromophores [53]. On absorption of photon energy, chromophores within

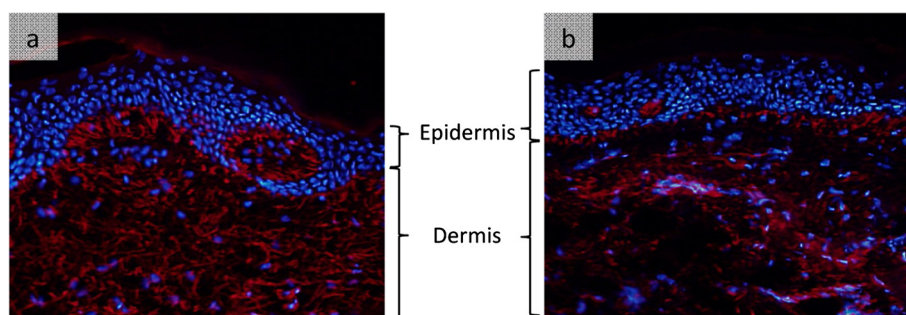


Figure 1 The structure of skin is dominated by a highly cellular epidermis and a relatively acellular dermis. Photoprotected (a) and photoaged (b) skin biopsies collected from the buttock and forearm respectively, of a 75 year old individual were immunofluorescently stained for the key elastic fibre component fibrillin-1 using a primary monoclonal antibody (clone 11C1.3) and a red fluorescently-labelled secondary antibody. Cellular DNA was visualised with diamidino-2-phenylindole (DAPI) which stains cell nuclei with blue fluorescence. In both photoprotected and photoexposed skin the cellular population is concentrated in the epidermis whilst in the dermis, fibroblasts are sparsely distributed. As a consequence, marked ECM remodelling in photoexposed skin (in this case loss of the red fibrillin-1 fluorescence) may be spatially separated from cells and hence from potential cell-derived mediators of tissue homeostasis.

ECM proteins enter a highly energetic but short lived, singlet excited state which may result in direct perturbations to protein structure [54]. In turn, this singlet state may undergo intersystem crossing to yield the longer lived triplet state which can act as an intra-molecular photosensitiser. Such photosensitisers are capable of undergoing type I (electron transfer) reactions to form radical species and/or type II (energy transfer) reactions with molecular O_2 , resulting in the formation of singlet O_2 (1O_2) which is a major photo-oxidiser of other protein moieties [55,56]. As the main ECM chromophores (see following sections) primarily absorb in the UVB (280-315nm) region it is this waveband that is mainly responsible for ECM damage via the ECM singlet state and intra-molecular photosensitisation [54]. Whilst some collagen photosensitised production of ROS has been reported to occur on absorption of UVA (315-400nm) radiation, it is unclear whether an intra-molecular ECM chromophore or an endogenous chromophore (e.g. pyridinoline) was responsible [57]. Photosensitisation by extra-molecular chromophores (i.e. non-ECM chromophores associated with ECM proteins such as Advanced Glycation End products (AGEs)) is likely to play a major role in UVA-induced, and primarily 1O_2 -mediated, photo-oxidative ECM protein damage *in vivo* [57]. However, as the exact nature of these ECM-associated, extra-molecular photosensitisers is yet to be established, this is an exciting area of current research.

Intracellular and epidermal chromophores

Predominant amongst skin chromophores are DNA, melanin, urocanic acid and proteins which have wavelength/photon energy specific absorption spectra (usually maximal in the UVB part of the solar UVR spectrum) [54]. Absorption of UVR by DNA results in the formation of

photoproducts, including highly mutagenic cyclopyrimidine dimers, which if formed in crucial tumor suppressor genes (e.g. p53) and/or oncogenes (e.g. ras) may initiate skin tumorigenesis [58]. Melanin produced by epidermal melanocytes, absorbs UVR and acts as a natural sunscreen, protecting DNA and proteins of the basal layer cells, particularly stem cells. Urocanic acid (UCA) which is produced in the upper epidermal cell layers, also has a

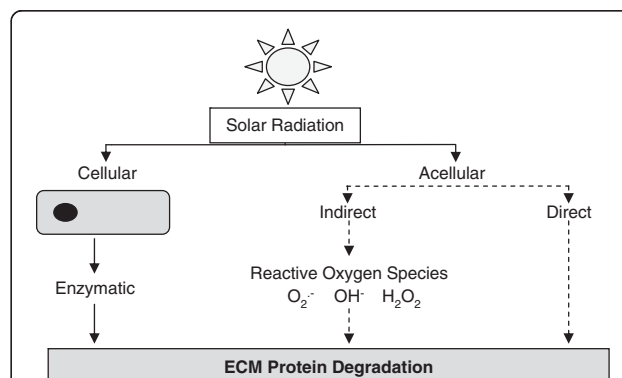


Figure 2 Potential pathways of UVR-induced protein degradation.

Following exposure to UVR radiation, ECM remodelling in human skin may occur as a result of: i) cell mediated mechanisms via the synthesis of ECM proteases such as MMPs or ii) acellular pathways. Whilst cellular mechanisms undoubtedly play a role in downstream ECM remodelling, we recently demonstrated that physiologically attainable doses of UVR are capable of differentially degrading key ECM components in a cell-free environment. It remains to be determined whether this protein degradation occurs as a consequence of *direct* photon absorption by amino acid residues or the *indirect* action of UVR-induced ROS.

sunscreening role but paradoxically, absorption of UVR results in the production of a photoisomer (*cis*-UCA) which has immunosuppressive properties and may increase the progression of skin cancers [59].

Dermal extracellular chromophores

UVR absorbing epidermal molecules such as melanin and UCA appear to play a protective role in absorbing UVR and both DNA and short-lived intracellular proteins are, at least partially, protected from the long term effects of UV-mediated damage by endogenous mechanisms which detect and repair or rapidly replace defective molecules [15,46,60]. In contrast, individual dermal ECM proteins and supra-molecular assemblies must continue to function in potentially harmful environments for many years [61]. For example, aspartic acid racemisation methods estimate the half-life of human dermal collagen as 15 years whilst pulmonary elastic fibre components are retained for the lifetime of the individual [16,62]. Such extended molecular life-spans provide ample opportunity for the accumulation of damage via external influences such as UVR [14,63]. Type I collagen for example, may be fragmented and rendered less thermally stable by exposure UVR, whilst hydrolysed and irradiated elastin undergoes extensive photodegradation [64–67]. Similar UVR exposure can also affect key molecular functions including collagen fibril assembly and protease susceptibility [65,68,69]. Crucially however, in order to influence the structure and biological function of isolated type I collagen and elastin, these studies employed either supra-physiological UVR doses (measured in J/cm² as compared to the 50 mJ/cm² required to induce minimal erythema [47]) and/or the use of sources emitting non-physiologically relevant wavelengths (i.e. UVC radiation <280nm which is not a component of solar UVR).

In contrast to these studies, we recently demonstrated that exposure to a UVB radiation dose of 50 mJ/cm² had no detectable effect on the electrophoretic mobility (in both denaturing and native conditions) of monomeric type I collagen [9]. In the same study, we established that fibrillin microfibrils extracted from the elastic fibre system, undergo extensive and apparently stochastic ultrastructural modification following exposure to doses of UVB radiation as low as 20mJ/cm², whilst a dose of 100mJ/cm² is sufficient to induce aggregation of dimeric fibronectin. We suggested therefore that the differential susceptibility exhibited by these key dermal ECM components to UVR exposure *in vitro* may: i) explain the selective degradation of elements of the elastic fibre system (fibrillin-1 and fibulin-5) *in vivo* and ii) be mediated by their relative amino acid (and hence similar UVR in title chromophore) composition.

Amino acid composition as a predictor of UVR susceptibility

Relative UVR absorption is determined by molecular structure. Therefore, for highly heterogeneous polymeric molecules, the potential consequences of UV irradiation are likely to differ between molecular species. In the case of proteins only a subset of amino acid residues: cysteine, histidine, phenylalanine, tryptophan and tyrosine act as potent UV chromophores for solar UVR (280-400nm) [70]. Hence the relative UVR susceptibility of individual proteins may be mediated primarily by their differential amino acid composition (Table 1).

Amino acids residues (Cys/Cys-Cys, His, Phe, Trp, Tyr)

Whilst the absorption peaks of these amino acids lie in the UVC (<280nm) region, which is not part of terrestrial solar radiation, all have absorption tails that all have absorption tails that extend into the UVB and UVA regions. The rank

Table 1 Relative amino acid composition of three key dermal ECM proteins. Monomeric type I collagen ($\alpha 1(I)$ $\alpha 2(I)$), accession numbers P02452 ($\alpha 1$) and P08123 ($\alpha 2$) is rich in Gly and Pro but contains few UV-B chromophores (Cys, His, Phe, Trp and Tyr). In contrast, fibronectin, (accession number P02751) and in particular fibrillin-1 (accession number P35555), are rich in UV-B chromophores and in the case of Fibrillin-1 Cys residues [9].

Amino Acid	Collagen I (%)	Fibronectin (%)	Fibrillin-1 (%)
Ala (A)	11.2	4.0	3.2
Arg (R)	5.1	5.2	4.5
Asn (n)	1.5	4.2	6.6
Asp (D)	2.8	5.1	6.0
Cys (C)	0.0	2.6	12.7
Gln (Q)	2.6	5.5	3.6
Glu (E)	4.6	5.9	7.0
Gly (G)	33.1	8.2	10.7
His (H)	0.6	2.2	1.7
Ile (I)	1.0	4.7	5.2
Leu (L)	2.4	5.2	4.8
Lys (K)	3.4	3.2	3.9
Met (M)	0.6	1.1	1.8
Phe (F)	1.3	2.2	2.9
Pro (P)	21.8	7.9	6.2
Ser (S)	3.5	8.0	6.0
Thr (T)	1.7	10.8	5.8
Trp (W)	0.0	1.7	0.5
Tyr (Y)	0.3	4.2	3.3
Val (V)	2.6	8.0	3.8
Total chromophore content (%)	2.2	12.9	21.1

order of absorption at the longer wavebands is Trp > Tyr > Phe > Cys > His which, in combination with their relative susceptibility to oxidation, is an important factor when considering their relative contribution to protein photodegradation (reviewed in [54]). The complex photochemistry that follows excitation of these amino acids has been studied using steady state and time-resolved techniques [71]. Illustrative of these photo-processes are those observed for Trp and indeed, fluorescence from the Trp singlet state is predominant in proteins containing this amino acid. Inter-system crossing competes with this process to generate the Trp triplet which in turn photosensitises the production of ROS; O₂ radicals by electron transfer or ¹O₂ by energy transfer [54]. The quenching of ¹O₂ by Trp, His, Tyr, Met, and Cys side-chains can result in a number of modifications to ECM-protein structure and therefore function (reviewed in [56]). Many structural proteins in the ECM are stabilised by intra-chain disulphide bonds which may be photodegraded directly or as a consequence of a radical cascade initiated by electron transfer from nearby Trp or Tyr residues [63].

Differential amino acid composition of key dermal proteins

The early and specific degradation of fibrillin-rich microfibrils and fibulin-5 from the photoexposed papillary dermis suggests that these ECM components may share structural similarities which pre-dispose them to UVR-mediated degradation [34,35]. The tertiary structures of many elastic fibre associated proteins, including fibrillins 1–3, fibulins 1–5 and the latent transforming growth factor β binding proteins (LTBPs) 1–4, are dominated by heavily disulphide bonded, calcium-binding epidermal growth factor (cbEGF)-like domains [72]. We suggested therefore, that the unequal distribution of UV chromophores and in particular Cys residues may explain both the differential degradation of fibrillin-rich microfibrils and fibronectin (but not collagen I or elastin) *in vitro* and the loss of fibrillin-rich microfibrils and fibulin-5 in the upper dermis following exposure to UVR [9,34,35]. Analysis of amino acid composition may therefore indicate which proteins are most likely to undergo direct UVR or, photodynamic and hence ROS-mediated degradation (Figure 3) [73].

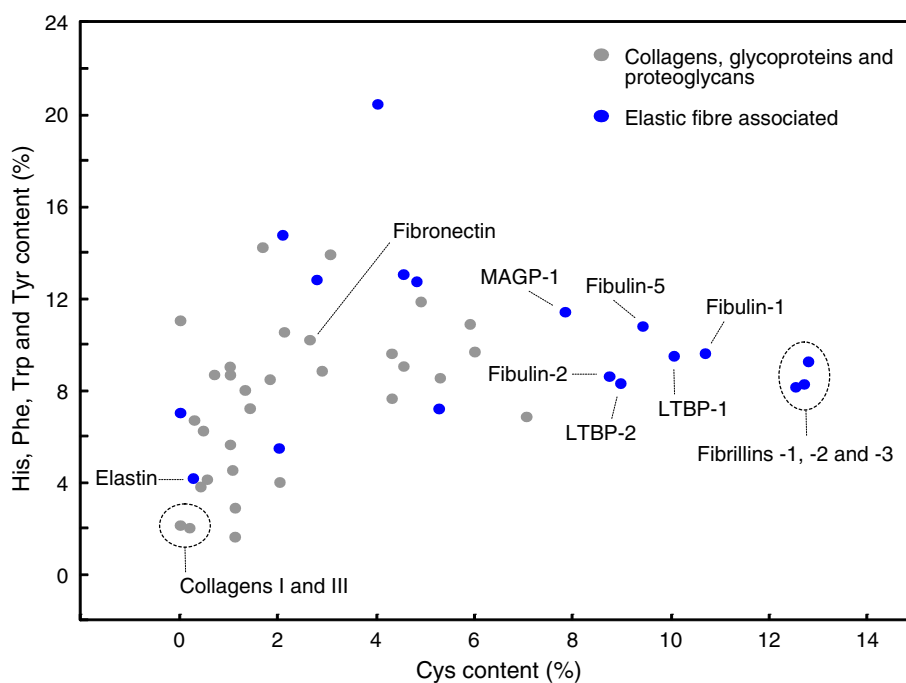


Figure 3 Differential amino acid composition of major dermal ECM components. Compared with the non-elastic fibre associated proteins (collagen: I, III, IV, V, VI, VII, VIII, XII, XIII, XIV, XVI, XVII, XXII and XXIII; the proteoglycans: fibromodulin, decorin, biglycan, perlecan, agrin, versican and aggrecan; and the glycoproteins: thrombospondin-1 and -2, tenascin-C and -X, osteopontin, fibronectin, laminin-5 and -6, vitronectin) elastic fibre components in general (MAGP-1 and -2, LTBP-1 and -2, MFAP-1, elastin, LOX, LOXL1, 2, 3 and 4, Fibulin-1, -2 and -3, emilin-1 and EBP) and the fibrillins in particular, are enriched in Cys residues. Furthermore, most of these in latter proteins are associated with the disulphide bonded microfibrils which are: i) degraded in the papillary dermis of mildly photoaged skin and ii) abundantly distributed in the elastotic material which characterises the deeper dermis of severely photoaged skin [34,74]. In contrast, the major structural components: dermal fibrillar collagen and elastin are almost devoid of UVR sensitive amino acids (Cys and His, Phe, Trp and Tyr residues).

Conclusions

Skin presents an ideal model system in which to study the effects of ageing, whether due to the passage of time alone, or to the action of exogenous accelerating factors. Although the extensive structural remodelling which characterises the ageing process has profound consequences for cutaneous function, the primary causative mechanisms remain to be determined. We have discussed the evidence that selective UVR/molecule interactions alone may be sufficient to drive many of the characteristic remodelling events in photoaged skin.

Acknowledgments

This work was supported by a programme grant from Alliance Boots, Nottingham, UK and by a Senior Age UK Fellowship awarded to MJS. CEMG is supported in part by the NIHR Manchester Biomedical Research Centre.

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Received: 11 November 2011 Accepted: 25 April 2012

Published: 25 April 2012

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doi:10.1186/s1752-153X-0-302

Cite this article as: Thurstan *et al.*: Chemical consequences of cutaneous photoaging. *Chemistry Central Journal* 2012 **6**:34.

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