
Publication: Naidoo K, Birch-Machin MA.

**[Oxidative Stress and Ageing: The Influence of Environmental Pollution,
Sunlight and Diet on Skin.](#)**
***Cosmetics* 2017, 4 (1), 1-8.**

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DOI link to article:

<http://dx.doi.org/10.3390/cosmetics4010004>

Date deposited:

24/02/2017



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Review

Oxidative Stress and Ageing: The Influence of Environmental Pollution, Sunlight and Diet on Skin

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Academic Editor: Johanna Maria Gillbro

Received: 25 November 2016; Accepted: 3 January 2017; Published: 10 January 2017

Abstract: Skin ageing is a complex process that is determined by both intrinsic and extrinsic factors, which leads to a progressive loss of structure and function. There is extensive evidence indicating that oxidative stress induced by reactive oxygen species plays an important role in the process of human skin ageing. Mitochondria are the major source of cellular oxidative stress and are widely implicated in cutaneous ageing. Extrinsic skin ageing is driven to a large extent by environmental factors and external stressors such as ultraviolet radiation (UVR), pollution and lifestyle factors which have been shown to stimulate the production of reactive oxygen species and generate oxidative stress. The oxidative damage from these exogenous sources can impair skin structure and function, leading to the phenotypic features of extrinsic skin ageing. The following review highlights the current evidence surrounding the role of mitochondria and oxidative stress in the ageing process and the influence of environmental factors such as ultraviolet radiation, pollution and diet on skin ageing.

Keywords: skin ageing; reactive oxygen species; ROS; oxidative stress; pollution; UVR; sunlight; diet

1. Introduction

Ageing is marked by a progressive functional decline of an organism over time, which leads to increased susceptibility to age-related diseases, and eventually the death of an organism [1]. Skin ageing is a complex process that is determined by both intrinsic and extrinsic factors, which leads to a progressive loss of structural integrity and physiological function. Intrinsic ageing is largely genetically determined and occurs as a natural consequence of physiological changes over time [2]. Intrinsic ageing is clinically characterised by skin atrophy, prominence of vasculature, loss of elasticity and fine wrinkles [3]. Extrinsic ageing is related to the cumulative effects of environmental factors such as ultraviolet radiation (UVR), smoking and environmental pollution. Extrinsicly aged skin is characterised by deep wrinkles, rough texture, telangiectasia and irregular pigmentation [4]. The severity of extrinsic ageing depends on skin type, with the features being more prominent in type I or II skin and less noticeable in type III or higher skin [5].

Many studies have been performed to elicit the cause of ageing; however, the exact mechanism remains unknown. During the past century several theories of ageing have been proposed including the “wear and tear theory of ageing”, the “antagonistic pleiotropy theory of ageing” and the “disposable soma theory of ageing”. There have been a large number of studies examining the involvement of mitochondria in the ageing process. Mitochondria are dynamic double-membrane-bound organelles found within the cytoplasm of eukaryotic cells. The primary function of mitochondria is the production of cellular energy, through a process termed oxidative phosphorylation, in the form of adenosine triphosphate (ATP) [6]. Oxygen metabolism in the mitochondria leads to the generation of reactive oxygen species (ROS). The formation of ROS is a natural consequence of oxygen metabolism and ROS have integral physiological roles in cell signalling and oxygen homeostasis [7]. Mitochondria

are considered to be the predominant source of intracellular ROS and are believed to contribute 90% of the ROS generated within the cell [8]. In addition to mitochondria, the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase system has been identified as an important source of intracellular ROS and a key player in the generation of oxidative stress. NADPH oxidases, also known as NOX enzymes, act by catalysing the transfer of electrons from NADPH to molecular oxygen to generate superoxide and other forms of ROS [9,10]. NOX enzymes can be found in various membranes including the plasma membrane, the endoplasmic reticulum and the mitochondria [11]. They were initially discovered as the enzyme responsible for producing large amounts of ROS as a first line of defense against invading pathogens during the immune response; however, it is now thought that they play roles in other physiological processes including cell signalling [12]. Antioxidants are produced to counteract oxidative stress generated by excess ROS; however, in times of environmental stress, elevated ROS levels can overwhelm endogenous cellular antioxidant mechanisms [7]. This can lead to an imbalance in tissue oxygen homeostasis, with oxidant effects outweighing antioxidant effects, and as a consequence the cellular environment becomes oxidatively stressed [7]. Free radicals can cause oxidative damage via a variety of mechanisms. Oxidation of lipids by ROS can damage cellular structures and result in premature cell death [13]. In addition, interaction with nuclear and mitochondrial nucleic acids results in mutations that predispose them to strand breaks [13].

There is increasing evidence that oxidative stress induced by ROS is a major contributing factor to the ageing process. The “free radical theory of ageing” proposed by Harman postulated that free radicals cause cumulative oxidative damage to biological structures, which eventually leads to loss of cellular function and phenotypic ageing [14]. Within this theory Harman included the “vicious cycle theory of ageing” which summarises how the characteristics of mitochondria can contribute to ageing [14]. Mitochondrial DNA is located in close proximity to the site of ROS production, making it highly vulnerable to oxidative damage. This is exacerbated by the fact that mitochondria do not possess efficient DNA repair mechanisms [13]. As the integrity of mitochondrial DNA is essential for mitochondrial function, errors in gene expression may in result in dysfunctional mitochondrial subunits [15]. This leads to a continuous “vicious cycle” where dysfunctional mitochondria contribute to further ROS production, which can lead to further ROS-mediated oxidative damage to mitochondria [8]. Mitochondrial dysfunction is heavily implicated in the ageing process and the pathogenesis of age-related diseases such as Alzheimer’s disease (AD) [16]. In AD it is believed that the accumulation of amyloid beta peptide interacts with mitochondria, leading to mitochondrial dysfunction. The resulting aberrant mitochondrial function leads to increased oxidative stress and neuronal damage and cognitive decline [17]. Recently, a novel concept termed mitohormesis has been introduced in the field of mitochondria and ageing [18,19]. Studies have shown that there is a nonlinear relationship between ROS production and ageing and that different levels of oxidative stress may have opposite outcomes. Low concentrations have been demonstrated to have a protective effect by inducing cellular defense mechanisms, whilst higher concentrations promote damage to cellular structures [18]. While there is extensive evidence which links increased levels of oxidative stress with ageing, mitohormesis introduces the interesting notion that low levels may have the reverse effect and may actually prevent ageing.

Cellular senescence refers to the irreversible arrest of proliferation, which acts as a tumour-suppressive mechanism to inhibit cells with potentially cancerous mutations from undergoing replication [1]. The induction of senescence is a stress response which occurs in cells which are exposed to unfavourable physiological conditions, or those with mutations leading to oncogenic activation [13]. Cells which undergo senescence remain viable but are unable to divide, which is contrast to biological ageing, where there is progressive decline of an organism which eventually leads to death [13]. Despite these differences between the two processes, there is increasing evidence that cellular senescence plays a prominent role in ageing [1]. Senescent cells accumulate with increasing age in many organisms including humans and are seen with increased frequency in prematurely aged skin [20]. Furthermore, studies have shown that senescent cells are implicated in the genesis of

age-related diseases such as AD and atherosclerosis [1]. Mitochondrial dysfunction is thought to play a role in the increased levels of senescent cells seen with advancing age [21]. Studies have shown that mice with knocked-down manganese superoxide, an antioxidant that protects against mitochondrial oxidative damage, have higher levels of mitochondrial ROS production and an increased number of senescent cells [22]. Interestingly, the mice developed epidermal thinning, an established feature of aged skin, providing evidence for a causal relationship between mitochondrial dysfunction, cellular senescence and the phenotypic manifestations of skin ageing [22]. Recently, mitochondrial complex II activity has been implicated in senescence and ageing. Bowman et al. demonstrated that complex II activity decreases with age in human skin fibroblasts, an effect only observed in senescent cell populations [23]. The authors speculated that the observed decrease in complex II activity contributes to the ageing process by leading to an increase in ROS which results in mitochondrial dysfunction and oxidative stress.

2. Environmental Sources of Oxidative Stress

Human skin is continuously exposed to ROS generated from a combination of intrinsic and extrinsic sources. The skin serves as an interface between the body and the external environment and is in constant contact with external stressors such as UVR and ambient pollutants. Exposure to these exogenous factors has been shown to be a major contributing factor to the production of ROS and the generation of oxidative stress [24]. The resultant ROS-mediated oxidative damage from these sources can impair skin structure and function, leading to the phenotypic features of extrinsic cutaneous ageing.

2.1. Sunlight

Solar radiation is comprised of UVR, visible light and infrared with relative contributions of 6%, 40% and 54%, respectively. UVR forms can be subdivided into three categories according to wavelength; UVA (320–400 nm), UVB (280–320 nm) and UVC (100–280 nm) [7]. UVR is the primary environmental factor in the development of extrinsic skin ageing. Excessive exposure to UVR can result in cellular, genetic and molecular changes in the skin, which can lead to accelerated skin ageing also known as photoageing. The rate of UVR-induced skin ageing depends on the balance between the frequency, intensity and duration of exposure and the natural protection by skin pigmentation [5]. Both UVA and UVB have been shown to contribute to UVR-induced ageing; however, due to its ability to penetrate deeper into the dermis, UVA has been shown to cause disproportionately more damage [5]. Exposure of skin to UVR is known to stimulate the photochemical generation of ROS, which includes superoxide anions and hydrogen peroxide [6]. Although ROS are continuously produced in the skin and are involved in physiological processes, there is accumulating evidence for the harmful effects of high ROS concentrations following exposure to UVR [5]. Antioxidants are produced by the skin to counteract the harmful effects of ROS; however, the higher concentrations of ROS generated following UVR exposure can induce an imbalance in cellular antioxidant defence systems, leading to oxidative stress [6]. UVB can also be directly absorbed by DNA, leading to direct induction of damage within cells. Mitochondrial DNA is particularly vulnerable to damage following exposure to UVR as mitochondria have limited DNA repair mechanisms [8]. A recent study looking at the action spectrum of UVR-induced mitochondrial damage showed that mitochondrial DNA is more vulnerable to damage at UVR wavelengths >320 nm when compared with nuclear DNA [25]. Damage to mitochondrial DNA can lead to mitochondrial dysfunction which may subsequently increase the production of ROS. This leads to a continuing vicious cycle whereby the generation of ROS may lead to further mitochondrial DNA damage [6]. This is of particular importance as there is increasing evidence that alterations in mitochondrial function can adversely impact skin health and lead to skin disease [26]. UVR is therefore able to increase oxidative stress by both direct and indirect means, either by potent stimulation of ROS or by direct DNA damage [8]. This increase in oxidative stress can impair cellular functions, leading to the phenotypic manifestations of extrinsic skin ageing.

2.2. Environmental Pollution

Ambient pollution is increasing significantly worldwide and the impact of pollutants on human health is a growing concern. The majority of ambient pollutants are derived from anthropogenic sources such as motor vehicle emissions, fossil fuel combustion, forest fires and industrial facilities. This combination of sources produces a complex mixture of toxic pollutants including particulate matter and gases such as nitrogen dioxide and ozone [27]. Although there is comparatively less research investigating the cutaneous effects of environmental pollutants, there is growing recognition of the adverse effects on skin health. Numerous studies have demonstrated that ambient pollutant exposure is linked with the development of the signs of extrinsic skin ageing [28]. A cohort study conducted in Germany examined the association between ambient pollutant exposure and skin ageing in Caucasian women. Their results showed that chronic exposure to particulate matter significantly correlated with signs of extrinsic ageing, in particular pigment spots and more pronounced nasolabial folds [29]. The generation of ROS and induction of oxidative stress is implicated as one of the mechanisms by which particulate matter exert their deleterious effects [30]. Particles measuring $<0.1 \mu\text{m}$ in diameter are defined as ultrafine particles and are associated with vehicle exhaust emissions [31]. Ultrafine particles are particularly harmful due to their ability to penetrate tissues more easily and localise in the mitochondria [32]. Once absorbed, ultrafine particles are able to induce oxidative stress and mitochondrial damage [32]. Ground-level ozone, a major component of smog, is a highly reactive environmental pollutant that is capable of inducing oxidative stress in cutaneous tissues. Ozone mediates its noxious effects through free radical reactions that are achieved either directly by oxidation of biomolecules to generate ROS or by the production of cytotoxic non-radical molecules [33]. Experimental animal studies have shown that exposure to ozone results in signs of oxidative stress including significant depletion of cutaneous antioxidants [34,35]. Furthermore, it has been demonstrated that topical application of the antioxidants vitamin C and E can prevent the formation of oxidation products, thus attenuating environmentally induced oxidative damage to the skin [36]. A recent study showed that the application of antioxidant mixtures significantly reduced ozone-induced oxidative stress in human keratinocytes [37]. These findings contribute to the growing evidence demonstrating that environmental pollution has a detrimental impact on skin health and can lead to skin ageing [28].

2.3. Diet

Recently there has been considerable interest in the effects of diet on oxidative stress due to the diet being an important source of exogenously derived antioxidants [8]. Strategies such as diet and exogenous antioxidant supplementation may have a potential role in combating oxidative stress caused as a result of environmental factors. The highly antioxidant Mediterranean diet, characterised by high fruit and vegetable intake, has been shown to be associated with increased longevity and reduced risk of age-related diseases [38–40]. Studies have demonstrated that adherence to the Mediterranean diet is significantly associated with lower levels of oxidative stress [41,42]. Furthermore, it has been shown that consumption of the Mediterranean diet is able to prevent cellular senescence in human epithelial cells [42]. In contrast, a high-fat diet has been shown to be associated with mitochondrial dysfunction, increased levels of oxidative stress and accelerated cellular senescence [43]. A recent study showed that insulin resistance secondary to a high-fat diet leads to increased levels of oxidative stress, which contributes to neurodegeneration in AD [44]. Carotenoid substances, found in fruit and vegetables, as well as vitamins A, C and E, are said to be the most protective and correlate negatively with levels of oxidative stress [45]. A study examining the influence of lifestyle factors on the level of carotenoid antioxidants beta-carotene and lycopene found that antioxidant levels in the skin significantly increased with dietary consumption of carotenoid-rich food [46]. The results indicated that dietary supplementation of antioxidants may provide efficient protection against extrinsic skin ageing. Environmental inducers of ROS, such as UVR exposure, can lead to a reduction in antioxidants and an increase in levels of oxidative stress [46]. There is emerging evidence that antioxidant

supplementation may be able to protect human skin against UVR damage. A study comparing the effects of mitochondria-localised antioxidants with cellular antioxidants found that tiron, an antioxidant preferentially localised to the mitochondria, was able to confer complete protection against UVA- and H₂O₂-induced mitochondrial damage [47]. Interestingly, the protective effect of tiron was found to be greater than a range of cellular antioxidants investigated, which included resveratrol and curcumin. One study showed that lycopene, a carotenoid antioxidant found in red fruit and vegetables, is able to protect human skin against UVR-induced effects partially mediated by oxidative stress such as dermal erythema and mitochondrial DNA damage [48]. Furthermore, supplementation was associated with a reduction in UV-induced matrix metalloprotein 1 (MMP-1) expression, a collagenolytic enzyme which acts as a key regulator in photoageing [48]. A recent study demonstrated that oral supplements containing lycopene-rich tomato nutrient complex and lutein were able to protect human skin against UVB/A and UVA1 radiation by inhibiting the expression of genes involved in UVR-induced skin damage [49]. Intake of lycopene and lutein was associated with significantly reduced expression of MMP-1 and heme oxygenase-1, a sensitive marker of oxidative stress [49]. Data from these studies demonstrates that dietary supplementation with carotenoid antioxidants could potentially protect against the acute and potentially longer-term aspects of photoageing. Despite these scientific studies providing evidence that antioxidant supplementation could confer significant benefits, some studies have demonstrated conflicting observations. One study examining life-long supplementation of vitamin E in mice showed no overall improvement in life span [50]. In support of this, a study by Perez et al. investigated the effect of over- or under-expression of a wide number of genes regulating antioxidant enzymes and found that only one had an effect on lifespan [51]. In addition, clinical data have failed to demonstrate a beneficial effect with a trial comparing regular sunscreen use with carotenoid supplementation, showing that beta-carotene had no overall effect on skin ageing [52]. A Cochrane review examining the effect of antioxidant supplementation on mortality found that supplementation with beta-carotene, vitamin E and vitamin A may increase mortality [53]. It is clear from these studies that the link between antioxidant supplementation and ageing is complex and incompletely understood. Mitohormesis could provide one potential explanation for the observations discussed above, as according to this hypothesis, moderate amounts of ROS may be physiologically beneficial whilst excess amounts may have a detrimental effect [19,54]. Therefore, attempting to eliminate ROS with antioxidant supplementation might disrupt ROS homeostasis with potentially harmful side effects. Further studies and trials are required to fully elucidate the balance between ROS and antioxidants, and how diet and antioxidant supplementation may impact this balance.

3. Conclusions

Extensive evidence indicates that oxidative stress induced by ROS plays an important role in the process of human skin ageing. Extrinsic skin ageing is driven to a large extent by environmental factors and external stressors such as UVR environmental pollution, and lifestyle factors have been shown to stimulate the production of ROS and generate oxidative stress [24]. The oxidative damage from these exogenous sources can impair skin structure and function, leading to the phenotypic features of extrinsic skin ageing. Many studies have been conducted to elucidate the mechanism of ageing and from this there is continuing evidence that supports the proposal that mitochondria are widely implicated in both ageing and senescence. However, the ageing process is not fully understood and further work is required to understand the molecular processes involved in cutaneous ageing. This could potentially lead to the development of preventative and therapeutic interventions for skin ageing.

Author Contributions: Both authors contributed to writing the paper.

Conflicts of Interest: The authors declare no conflict of interest.

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