

# What is the role of mitochondrial dysfunction in skin photoaging?

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## Abstract

Skin ageing is a complex process involving both internal and external factors, which leads to a progressive loss of cutaneous function and structure. Solar radiation is the primary environmental factor implicated in the development of skin ageing, and the term photoaging describes the distinct clinical, histological and structural features of chronically sun-exposed skin. The changes that accompany photoaging are undesirable for aesthetic reasons and can compromise the skin and make it more susceptible to a number of dermatological disorders. As a result, skin ageing is a topic that is of growing interest and concern to the general population, illustrated by the increased demand for effective interventions that can prevent or ameliorate the clinical changes associated with aged skin. In this viewpoint essay, we explore the role that mitochondria play in the process of skin photoaging. There is continuing evidence supporting the proposal that mitochondrial dysfunction and oxidative stress are important contributing factors in the development of skin photoaging. Further skin-directed mitochondrial research is warranted to fully understand the impact of mitochondrial status and function in skin health. A greater understanding of the ageing process and the regulatory mechanisms involved could lead to the development of novel preventative interventions for skin ageing.

## KEYWORDS

mitochondrial dysfunction, oxidative stress, photoaging, skin ageing

## 1 | INTRODUCTION

Skin ageing is a complex process affected by both genetic and environmental factors, which leads to a progressive loss of cutaneous function and structure.<sup>[1]</sup> Intrinsic ageing is predominantly genetically determined and occurs as a natural consequence of physiological changes over time.<sup>[1]</sup> The clinical changes associated with chronological skin ageing include skin atrophy, loss of elasticity, fine wrinkles, dryness and prominence of vasculature.<sup>[2]</sup> Extrinsic ageing is related to the cumulative effects of environmental factors such as solar radiation, smoking, pollution, nutrition and lifestyle factors.<sup>[1]</sup> Extrinsic aged skin is characterised by deep wrinkles, rough texture, telangiectasia, lentiginos and irregular pigmentation.<sup>[2]</sup> The overall appearance of the

skin with age is related to the relative contribution of environmental factors superimposed on the degree of intrinsic ageing.<sup>[3]</sup>

Understanding the ageing process is important as advances in the medical field have led to an increase in life expectancy and rise in the ageing population.<sup>[4]</sup> Individuals are now exposed to environmental factors over a longer period of time, which increases the opportunity for cumulative damage to occur. The changes that accompany skin ageing are considered cosmetically undesirable and have associated psychological implications due to the societal emphasis placed on maintaining a youthful appearance.<sup>[5]</sup> Although there is focus on the aesthetic consequences of skin ageing, the process of ageing is also of clinical relevance. The structural and physiological deterioration that occurs with ageing can compromise the protective function of

the skin and make it more susceptible to a number of dermatological disorders.<sup>[6]</sup> In the elderly, age-related skin diseases are associated with morbidity and have a significant impact on quality of life.<sup>[6]</sup> There is now increased public awareness of skin diseases, and skin ageing is a topic that is of growing concern to the general population. This is highlighted by the increased demand for effective interventions that can prevent or delay the signs of skin ageing.

A better understanding of the molecular and cellular processes involved in the pathogenesis of skin ageing may facilitate the development of strategies to address the clinical and cosmetic sequelae of ageing skin. Despite the vast repertoire of studies which have attempted to elucidate the skin ageing process, the exact mechanism remains unknown. Accumulative damage to nuclear DNA (nDNA) has held precedence in ageing research, with numerous studies relating ageing phenotypes to cellular senescence and malfunction.<sup>[7]</sup> Nonetheless, for over 50 years it has been speculated that mitochondria play a key role in the ageing process, mainly due to correlative data showing an increase in mitochondrial dysfunction, mitochondrial DNA (mtDNA) damage and reactive oxygen species (ROS) with age.<sup>[8,9]</sup> However, the exact role of the mitochondria in ageing has not been determined. In this viewpoint essay, we aimed to explore the role that mitochondrial dysfunction and oxidative stress play in the process of skin photoaging.

## 2 | MITOCHONDRIA AND AGEING

A number of theories have been proposed to explain the process of ageing. The “free radical theory of ageing” proposed by Harman<sup>[8]</sup> suggested that highly ROS cause accumulative damage to biological structures over time, leading to loss of cellular function and ageing. Mitochondria are dynamic organelles found within the cytoplasm of eukaryotic cells, which are responsible for the production of cellular energy through oxidative phosphorylation.<sup>[9]</sup> Mitochondria are considered to be the predominant source of intracellular ROS, which are formed as a natural by-product of oxygen metabolism.<sup>[10]</sup> Although ROS have integral physiological roles in cell signalling and oxygen homeostasis, in times of environmental stress, ROS levels can dramatically increase leading to an imbalance in tissue homeostasis and oxidative stress.<sup>[11]</sup> Excess formation of ROS can cause significant damage to biological structures through a variety of mechanisms including DNA damage and lipid peroxidation.<sup>[12]</sup> The mtDNA are located in close proximity to the site of ROS production, and multiple copies exist within each cell. These factors make mtDNA particularly vulnerable to the effects of oxidative stress, exacerbated further by the fact that mtDNA has limited repair mechanisms and lacks protective histones.<sup>[13]</sup> The mutation frequency of mtDNA is approximately 50-fold higher than that of nDNA.<sup>[14]</sup> As the integrity of mtDNA is essential for mitochondrial function, the accumulation of mutations can result in dysfunctional mitochondrial subunits.<sup>[15]</sup> The dysfunctional mitochondria are thought to contribute to increased ROS production, leading to further oxidative damage to mitochondria in a continuous cycle.<sup>[16]</sup> This forms the basis of the later “mitochondrial theory of

ageing” which is based around the idea of a vicious cycle whereby accumulation of oxidative damage over time as a result of elevated ROS, mtDNA damage and mitochondrial dysfunction leads to the decline of cellular function and the characteristic hallmarks of ageing.<sup>[17]</sup>

Although there is no direct proof that this model is valid, there is evidence that provides support for various mechanisms and components involved in mitochondrial-related ageing. Studies have demonstrated that mtDNA damage increases with age and is accompanied by a decline in mitochondrial function.<sup>[18,19]</sup> For example, 1 study found that the level of mtDNA damage was higher in the heart muscle of older people, and the level of mtDNA damage increased exponentially after the age of 45 years.<sup>[19]</sup> Higher levels of mtDNA mutations have also been shown to be associated with premature ageing. Studies have demonstrated that mice with increased levels of mutated mtDNA show increased levels of mitochondrial dysfunction, reduced lifespan and a premature ageing phenotype.<sup>[20,21]</sup> Interestingly and controversially, the initial descriptions of the “mutator” mouse suggested that ROS was not increased. However, further work in 2012 informs us that the mouse exhibits stem cell ageing which may be driven by an early increase in ROS within the stem cells which precedes any of the measurable mitochondrial defects. Interestingly in this respect is that antioxidant treatment helped to restore the stem cell defect.<sup>[22]</sup>

Cellular senescence refers to the irreversible arrest of proliferation, which acts as a tumor-suppressive mechanism which inhibits cells with DNA mutations from undergoing replication.<sup>[23]</sup> Senescent cells have been shown to accumulate with increasing age and are implicated in the pathogenesis of age-related diseases.<sup>[23]</sup> Oxidative stress and mitochondrial dysfunction are thought to play a role in cellular senescence.<sup>[24]</sup> Most studies until recently have focussed on the role of complexes I and III as they are typically associated with the generation of ROS within the mitochondria. However, recent work has controversially shown that the role of complex II in the generation of ROS is more important than previously thought.<sup>[16]</sup> Interestingly in this respect, mitochondrial complex II activity has been shown to be implicated in senescence and ageing. Bowman and Birch-Machin<sup>[25]</sup> demonstrated that complex II activity decreases with age in human skin fibroblasts, an effect only seen in senescent cell populations. This decrease in complex II activity could increase ROS levels resulting in mtDNA damage and dysfunction. A recent study demonstrated that elimination of mitochondria through induction of mitochondrial degradation prevented cells from undergoing the hallmark changes associated with senescence.<sup>[26]</sup>

In addition to ageing, aberrant mitochondrial function can result in cellular dysfunction and pathogenesis of human disease. Cells contain many copies of the mitochondrial genome and may contain a mixture of undamaged wild-type DNA and damaged mutant mtDNA, a phenomenon known as heteroplasmy.<sup>[13]</sup> Cellular dysfunction occurs when the threshold of tolerable accumulated damage is breached, leading to the manifestation of disease.<sup>[27]</sup> However, there is a wide variation in the energetic threshold of particular tissues whereby the mutational load can lead to a functional effect.<sup>[8,10,14]</sup> In this respect, there is little information regarding skin. Mitochondria diseases are a diverse group of disorders that exhibit a wide spectrum of clinical

presentations.<sup>[28]</sup> Mutations of mtDNA have been associated with the pathogenesis of a number of these conditions.<sup>[28]</sup> Emerging evidence has linked mitochondrial dysfunction and oxidative stress to a broad spectrum of age-related diseases, including neurodegenerative disease and cancer.<sup>[28]</sup> There is also increasing evidence that alterations in mitochondrial function can adversely impact skin health and lead to skin disease. Approximately 10% of patients with primary mitochondrial disorders present with skin manifestations.<sup>[29]</sup> Feichtinger et al.<sup>[29]</sup> have previously compiled an extensive review examining the relationship between mitochondrial pathology and skin disease. They highlighted a wide range of skin conditions, both common and rare, which are associated with mitochondrial dysfunction. Recent evidence indicates that mitochondrial dysfunction not only plays a role in skin disease but may also be involved in the process of skin ageing.

### 3 | MITOCHONDRIA AND PHOTOAGING

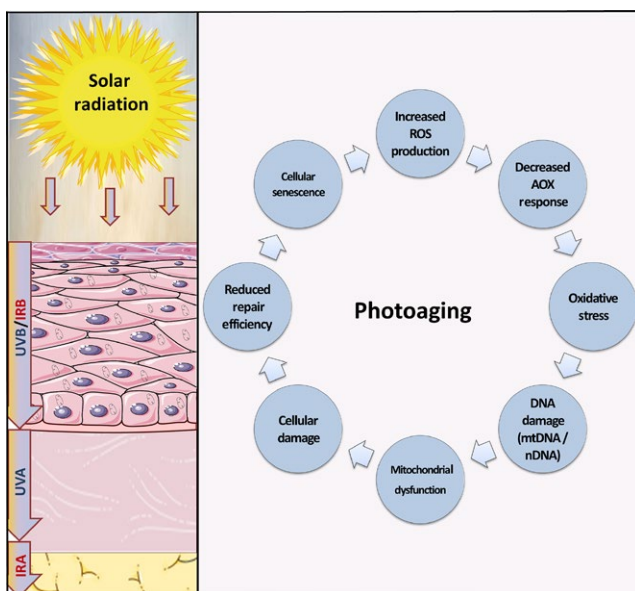
The skin serves as an interface between the body and the environment and is chronically exposed to external stress factors such as solar radiation and pollution.<sup>[30]</sup> A major mechanism by which these environmental insults exert a detrimental effect on the skin is through oxidative stress (Figure 1). Exposure to these exogenous factors has been shown to be a major contributing factor to the production of ROS and oxidative damage.<sup>[31]</sup> Although the skin possesses an antioxidant defense system to obviate the harmful effects of ROS, excess ROS levels can overwhelm the cutaneous endogenous antioxidant capacity leading to an imbalance in tissue oxygen homeostasis. The resultant ROS-mediated damage from these sources can impair skin structure and function, leading to the phenotypic features of extrinsic skin ageing.

Exposure to solar radiation is considered as the primary environmental factor in the development of extrinsic skin ageing.<sup>[32]</sup> The

distinct clinical and histological features of chronically sun-exposed skin are termed photoaging.<sup>[14]</sup> Sunlight is composed of electromagnetic rays of varying wavelengths and includes visible light, ultraviolet radiation (UVR) and infrared radiation (IRR).<sup>[32]</sup> UVR accounts for 5% of the solar spectrum and can be divided into 3 categories according to wavelength: UVA (320–400 nm), UVB (280–320 nm) and UVC (100–280 nm).<sup>[32,33]</sup> UVC is filtered by atmospheric ozone and consequently does not reach the skin.<sup>[34]</sup> UVR-induced changes at the dermal level are largely responsible for the phenotype of photoaged skin.<sup>[35]</sup> The phenotypic appearance of photoaged skin is largely due to UVR-induced changes in the dermis.<sup>[36]</sup> The shorter wavelengths of UVB penetrate the epidermis and have been shown to induce the production of matrix metalloproteinases (MMPs), resulting in dermal collagen degradation.<sup>[37]</sup> As shown in Figure 1, the longer wavelengths of UVA penetrate more deeply into the skin and act by exerting a direct effect on the dermis.

Excessive exposure to UVR can lead to cellular, genetic and molecular changes in the skin, which if unrepaired can have deleterious effects on cellular function. UV rays penetrating the skin are absorbed by protein, lipids and nuclear and mtDNA within skin cells.<sup>[38]</sup> This initiates a cascade of events leading to progressive deterioration of cell structure and function and accelerated skin ageing.<sup>[31]</sup> UVR causes damage to cells by both direct and indirect means, either by potent stimulation of ROS or by direct damage to nuclear and mtDNA.<sup>[11]</sup>

One possible mechanism by which UVR is able to accelerate the ageing process could be via its mitochondrial interaction. UVR-mediated mtDNA damage can lead to mitochondrial dysfunction and increased production of ROS in a vicious cycle of increasing damage, leading to a putative increase in photoaging (Figure 1).<sup>[16]</sup> A study looking at the action spectrum of UVR-induced mitochondrial damage showed that mtDNA in primary dermal fibroblasts are more vulnerable to damage at UVR wavelengths >320 nm in comparison with nDNA.<sup>[39]</sup> As mtDNA has limited repair mechanisms, exposure to UVR results in an accumulation of damage, which may accelerate skin ageing. This has led to the development of mtDNA as a reliable and sensitive marker of UVR-induced skin damage.<sup>[34]</sup> Photoaged skin is characterised by increased numbers of large-scale deletions of mtDNA, which can act as useful markers of photoaging rather than chronological skin ageing.<sup>[34]</sup> Studies have found an increase in incidence of specific deletions of mtDNA in photoaged skin compared with sun-protected skin.<sup>[40]</sup> The most frequently reported mtDNA mutation in human skin is a large 4977-base pair deletion known as the “common deletion,” which is increased by up to 10-fold in photoaged skin compared with sun-protected skin in the same individuals.<sup>[14]</sup> Studies by our group have shown that the 3895-base pair deletion and the T414G mutation are found with increased frequency in sun-exposed skin when compared to sun-protected skin.<sup>[40,41]</sup> This provides evidence that chronic exposure to UVR results in an increase in the number of mtDNA deletions in human skin. These mtDNA deletions remove portions of the genome that encode complex I (eg, common deletion and 3895 bp) but also complex IV (common deletion) which potentially may affect ATP production dependent upon the degree of heteroplasmy.<sup>[10,14,34]</sup> Given the importance of mtDNA integrity in mitochondrial health, we



**FIGURE 1** The cycle of oxidative stress and mitochondrial dysfunction in skin photoaging

can speculate that the presence of these mtDNA deletions in human skin has structural and functional consequences, resulting in the phenotypic changes of photoaged skin. An additional scenario to consider in this respect is the degree of influence of fission and fusion of mitochondria to limit mtDNA damage. Mitochondria do not exist as isolated organelles, but they are a complex dynamic network within cells which undergoes fusion and fission. The balance of this process may play an important role in controlling the expression of mtDNA damage within cells as mitochondrial fusion will dilute a mutant mtDNA species in the background of the wild-type pool but fission may allow segregation of abnormal mitochondria followed by selective mitophagy.<sup>[42]</sup>

Whilst the role of UVR is well established, relatively little is known about the role of IRR in photoaging. IRR is divided into 3 categories according to wavelength: IRA (740–1400 nm), IRB (1400–3000 nm) and IRC (3000 nm–1 mm). IRR accounts for over 50% of the solar spectrum and is able to deeply penetrate the skin, reaching both the dermis and hypodermis (Figure 1).<sup>[43]</sup> There is evidence that irradiation with IRR has a detrimental effect on skin.<sup>[35]</sup> Mitochondria are believed to be a key cellular target in the pathogenesis of IRR-induced photoaging. Complex IV acts as chromophore for IRA, leading to disruptions in the electron transport chain and defective energy production. This initiates cellular signalling pathways which result in alteration of gene expression of key proteins involved in photoaging such as MMPs, which result in collagen breakdown and the characteristic features of photoaged skin.<sup>[18,35]</sup> Studies have shown that irradiation with IRR results in an increase in intracellular ROS. We can postulate that this increase in ROS may initiate damage to mtDNA and lead to mitochondrial dysfunction, implicating IRR in the photoaging process.

## 4 | CONCLUSIONS

In this viewpoint essay, we discuss the role of oxidative stress and mitochondrial dysfunction in the process of skin ageing. Many studies have been conducted to elucidate the mechanism of ageing, and there is continuing evidence that supports the proposal that mitochondria are implicated in both normal ageing and skin photoaging. However, skin ageing is a complex process involving a multitude of factors and further work is warranted to understand the exact role of mitochondria in cutaneous ageing. A greater understanding of the ageing process and the regulatory mechanisms involved could potentially lead to the development of new preventative interventions for skin ageing.

## CONFLICT OF INTERESTS

The authors have declared no conflicting interests.

## AUTHOR CONTRIBUTION

All authors have read and contributed to the final manuscript. KN wrote the original manuscript. RH created the figure. RH and MBM responded to reviewer's comments and completed revisions to the text and figure.

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**How to cite this article:** Naidoo K, Hanna R, Birch-Machin MA. What is the role of mitochondrial dysfunction in skin photoaging? *Exp Dermatol.* 2017;00:1–5.  
<https://doi.org/10.1111/exd.13476>