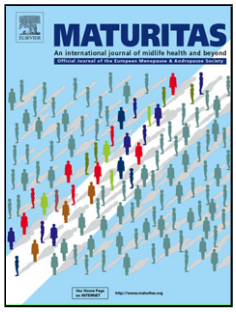

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Mitochondrial damage and ageing using skin as a model organ

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Highlights

- Several theories of ageing have been proposed since the late 19th century, including a large number of studies linking the mitochondria to ageing.
- Accumulation of oxidative damage over time as a result of elevated levels of reactive oxygen species, damage to mitochondrial DNA and mitochondrial dysfunction can lead to loss of cellular function and characteristic hallmarks of ageing.
- The skin is often used to study human ageing, due to its easy accessibility, and the observation that the ageing process is able to be accelerated in this organ via environmental insults, such as ultra violet radiation.
- A wide range of diseases are associated with ageing; therefore, understanding the cause of the ageing process as well as regulatory mechanisms involved could provide potentially advantageous therapeutic targets for the prevention or treatment of such diseases.

Abstract

Ageing describes the progressive functional decline of an organism over time, leading to an increase in susceptibility to age-related diseases and eventually to death, and it is a phenomenon observed across a wide range of organisms. Despite a vast repertoire of ageing studies performed over the past century, the exact causes of ageing remain unknown. For over 50 years it has been speculated that mitochondria play a key role in the ageing process, due mainly to correlative data showing an increase in mitochondrial dysfunction, mitochondrial DNA (mtDNA) damage, and reactive oxygen species (ROS) with age. However, the exact role of the mitochondria in the ageing process remains unknown.
The skin is often used to study human ageing, due to its easy accessibility, and the observation that the ageing process is able to be accelerated in this organ via environmental insults, such as ultra violet radiation (UVR). This provides a useful tool to investigate the

mechanisms regulating ageing and, in particular, the role of the mitochondria. Observations from dermatological and photoageing studies can provide useful insights into chronological ageing of the skin and other organs such as the brain and liver. Moreover, a wide range of diseases are associated with ageing; therefore, understanding the cause of the ageing process as well as regulatory mechanisms involved could provide potentially advantageous therapeutic targets for the prevention or treatment of such diseases.

Keywords – Mitochondria; Mitochondria DNA; ROS; Ageing; Skin

Introduction

Ageing describes the functional decline of an organism over time, which occurs across all tissues of the body, leading to an increase in susceptibility to age-related diseases including cancer, and eventually the death of the organism [1]. It is a phenomenon observed across different organisms, however the exact mechanism as to how and why we age remains largely unknown despite modern medicine, increased social awareness and advances in hygiene and diet which have dramatically increased the average human life expectancy over the last century [2]. It is important therefore to understand the mechanisms of ageing so that the ever-increasing elderly population can maintain their health for as long as possible, as well as providing mechanistic insight into diseases whereby age is a significant risk factor such as Alzheimer's disease (AD) and cancer [3]. Understanding the cause of the ageing process could provide potentially advantageous therapeutic targets for the prevention or treatment of such diseases. This review aims to explore the important role that mitochondria play in the ageing process, with particular emphasis on the use of skin as a highly advantageous model and surrogate for investigations into such mechanisms.

The Role of Mitochondria in Ageing

There are several theories of ageing that have been proposed since the late 19th century including the 'wear and tear theory of ageing', the 'antagonistic pleiotropy theory of ageing' and the 'disposable soma theory of ageing'. Strong evidence exists both in support and against these published theories which have been reviewed previously and therefore will not be discussed herein [4-6]. Of more interest is the large number of studies into how and why we age that involve the mitochondria. Mitochondria are dynamic organelles found within the cytoplasm of eukaryotic cells, and are responsible for the production of the majority of cellular energy via oxidative phosphorylation and the electron transport chain (ETC), in the form of adenosine triphosphate (ATP) [7]. A natural by-product of oxygen metabolism in the mitochondria is the formation of reactive oxygen species (ROS). ROS have important roles in cell signalling and homeostasis, however, in times of environmental stress, levels can increase dramatically which can result in significant damage to cell structures. Unlike nuclear DNA (nDNA), multiple copies of mitochondrial DNA (mtDNA) exist within each cell and are found in close proximity to the electron transport chain (ETC) making them extremely vulnerable to the effects of oxidative stress, exacerbated further by the fact that mtDNA has limited repair mechanisms [8]. As mtDNA encodes 13 subunits of the ETC plus the assembly machinery, ROS-induced damage has the potential to alter ETC function and decrease the efficiency of ATP production. An example of a theory of ageing involving the mitochondria is the 'rate of living theory of ageing' which was proposed in 1928 by Raymond Pearl [9], who presented the idea that the differing metabolic rates between animal species was a

determining factor in maximum lifespan potential. This theory was taken further by Denham Harman in 1956 [10], who proposed the 'free radical theory of ageing', which suggested that the rate of production of free radicals such as ROS, rather than the rate of metabolic activity directly, affected the ageing process of the animal. Highly reactive oxygen radicals were proposed to cause damage to biological structures which was thought to accumulate over time, eventually leading to a loss of cellular function and ageing [10]. In support of this theory, it has been observed that pigeons have approximately 9-fold longer maximal lifespans than rats, despite similar masses and metabolic rates; however, the rate of H_2O_2 production is significantly lower in pigeons [11-13]. This could imply that animals which generate fewer free radicals have longer lifespans. Additionally, both mice and rats have different metabolic rates, yet a similar level of H_2O_2 production, and their maximal lifespans are the same [13]. Further evidence for a role of free radicals in lifespan determination is based on the observation that the level of oxidative mtDNA damage in heart tissue is lower in longer-lived mammals [14, 15]. As mitochondria are responsible for the production of the majority of ROS within a cell [16] and the fact that not all oxidants are free radicals, the free radical theory of ageing was later refined to the 'mitochondrial theory of ageing' in 1972 and is currently one of the most widely accepted theories of ageing [17].

Accumulation of oxidative damage over time as a result of elevated ROS, mtDNA damage and mitochondrial dysfunction can lead to loss of cellular function and characteristic hallmarks of ageing further supporting a key role for mitochondria in the ageing process. The mitochondrial theory of ageing is based around the idea of a vicious cycle (figure 1) [18]. This theory suggests that ROS production from the ETC is able to cause damage to mtDNA, and because mtDNA encodes subunits of the ETC, this then leads to errors in gene expression and results in dysfunctional subunits. Dysfunctional mitochondria are then thought to contribute to further ROS leakage, in a continuous vicious cycle of damage accumulation [18, 19]. Whilst there is no definite proof that this model exists, evidence does exists in support of it and highlights an interesting concept in the understanding of the various mechanisms and components involved in mitochondrial-related ageing. The three stages of the vicious cycle (namely, increased ROS, mtDNA damage, and mitochondrial dysfunction) have been shown in previous studies to be able to occur independently and to be correlated with increased age. For example, Hayakawa *et al*., found that the level of mtDNA damage (8-oxo-dG lesions) was higher in the human heart muscle of older people compared to younger. In the study, mtDNA damage increased exponentially from 45 years and older [20]; this lends support to the exponential increase in damage which is thought to occur during the vicious cycle theory of ageing. Other studies have also shown an increase in oxidative mtDNA damage with age [21]. Higher levels of mtDNA mutations have also been shown to be causative in terms of ageing phenotypes; Trifunovic *et al*. and Kujoth *et al*. found that mice with accelerated mtDNA mutation levels (via a mutated mtDNA polymerase) showed increased mitochondrial dysfunction, as well as reduced longevity and an accelerated onset of ageing phenotypes [22, 23]. Additionally, mtDNA mutations and deletions have been shown to correlate with the ageing process; for example, the 4977 bp common deletion which may be used as a biomarker for general mtDNA damage, has been shown to accumulate in certain human tissues with age [24]. The T414G mtDNA point mutation has also been shown to be higher in the skin of older individuals [25].

In terms of a relationship between mitochondrial dysfunction and age, past work has shown that the individual complexes of the ETC decline with age in some tissues from different species [26, 27]. The mitochondrial membrane potential has also been shown to be decreased with age in specific tissues, as has the ATP-producing capability of mitochondria. However,

Lapointe *et al*., (2012) demonstrated that not all forms of mitochondrial dysfunction are detrimental in terms of lifespan, as mice with lower levels of ubiquinone showed mitochondrial dysfunction in the form of decreased respiratory activity, as well as increased oxidative stress, but these mice actually had increased longevity compared to wild-type mice [28]. The study suggested that mitochondrial dysfunction can result in ROS release, yet this ROS release may not necessarily contribute to a vicious cycle and a decrease in lifespan [28]. This has also been observed for *Caenorhabditis elegans* (*C. elegans*), for which ETC activity was lowered during development using RNA interference (RNAi), which resulted in increased lifespans [29]. These results suggest a complex relationship between mitochondrial function and age and so the vicious cycle theory remains disputed [19]. However, the mitochondria are still extremely likely to play a major role in the ageing process [30], even if not necessarily via a vicious cycle of damage.

More recently an interesting concept has been introduced in the field of mitochondria and ageing termed mitohormesis. This idea was developed based on observations that the relationship between ROS generation and ageing is not linear; low concentrations of ROS can induce a positive response whilst higher concentrations of ROS promotes damage (figure 1) [31]. This theory could provide an explanation for the observations discussed above, that an increase in ROS and/or mitochondrial dysfunction does not negatively impact lifespan and the ageing process [28]. In fact, evidence suggests that oxidative stress, induced by range of stressors, could delay the onset of age-related conditions and potentially extend lifespan [29]. There has been increasing appreciation for the beneficial role of ROS in cell signalling events such as signal transduction, gene regulation and redox regulation suggesting that low concentrations of ROS are physiologically vital to life and completely eliminating ROS may be detrimental [32]. This may explain the observation by Morley and Trainor that mice fed a life-long vitamin E supplemented diet showed no improvements in life span [33]. In support of this, Perez et al reviewed their extensive studies investigating the effect of over or under expressing eighteen genes regulating antioxidant enzymes and observed that only one (the deletion of sod1) had an effect on lifespan [34]. Although it is of note that other studies have found a beneficial effect on ageing with antioxidant supplementation [35] and it is likely that other factors are involved, such as localisation of dietary and endogenous antioxidants to the site of ROS generation in the mitochondria. Whilst it is unquestionably accepted that high levels of oxidative stress have a negative impact of cellular function and extensive evidence exists linking high levels of ROS to ageing, mitohormesis introduces an interesting concept that different levels of oxidative stress may have opposite biological outcomes [36]. Furthermore, this added complexity to the mitochondrial theories of ageing may significantly impact future research and treatment and/or prevention strategies for age-related diseases and ageing itself.

Several studies have linked a reduction in adult stem cells to age-related diseases and that increasing adult stem cells can delay ageing [37]. Gaining further insights into the mechanisms regulating mitochondrial activity during stem cell ageing and the effect of mtDNA damage on this will provide greater knowledge into the role mitochondria play in ageing and highlight potential therapeutic targets.

The term senescence describes the transformation of cells from a proliferating to a non-proliferating state, as a tumour suppressive mechanism to prevent cells with potentially cancerous DNA mutations from undergoing replication. During this process cells lose the ability to divide yet remain viable. This is in contrast to biological ageing which describes the

functional decline of a whole organism over time eventually leading to death, although the two processes are linked with senescence being thought to play a prominent role in ageing [38]. Senescent cells have been shown to be increased in an age-dependant manner in many tissues and organisms, including humans. Mitochondrial dysfunction is thought to play a role in the increased levels of senescent cells observed with age [39, 40]. Previous studies have shown that mice with knocked-down MnSOD have higher levels of mitochondrial ROS production, and an increased number of senescent cells, suggesting a causal role for mitochondrial ROS in senescence [27]. These mice also showed accelerated ageing phenotypes and a reduced lifespan, implicating a role for both senescence and mitochondria in ageing. Other studies suggesting a causal role of mitochondria in senescence have been performed in human lung fibroblasts, for which it was found that a decrease in superoxide production by the mitochondria (via uncoupling) resulted in a decreased number of senescent cells [39]. ROS production by inhibition of complex I has also been shown to lead to senescence in human skin fibroblasts, and mitochondrial complex III inhibition has been shown to induce senescence in a human lung fibroblast cell line.

In human lung fibroblast cells, it was found that p21 activation (which induces senescence) is able to induce mitochondrial dysfunction (decreased mitochondrial membrane potential) and increase ROS production [41]. This ROS production by the mitochondria following senescence was shown to be necessary for maintaining the senescent phenotype, by maintaining DNA damage and the DNA damage response [41]. This could potentially imply that an increase in mitochondrial dysfunction and ROS production with age are both a cause and a consequence of increased senescence levels with age. This could extend the vicious cycle theory of ageing further by introducing an additional interacting factor to contribute to mitochondrial dysfunction and ROS, whilst also itself being affected by ROS. The role of mtDNA damage in senescence remains unclear, however it has been suggested that mtDNA damage contributes to the senescent phenotype by increasing mitochondrial dysfunction and ROS, which ties-in with the vicious cycle theory of ageing. MtDNA damage has also been shown to be higher in senescent cells, by measuring the level of damage via qPCR within an 11 kb section of the mitochondrial genome [39]. However, not all cells in older organisms become senescent, as the induction of senescence is a stress response which only occurs in a minority of cells exposed to unfavourable conditions, or with mutations leading to oncogenic activation. More recently complex II has been shown to be implicated in human dermal fibroblast senescence and ageing [8, 38, 42]. Bowman et al demonstrated that complex II activity, transcript and protein levels decrease with age. Moreover, these effects are only seen in senescent cell populations. This result was shown to be specific to complex II as no change with complex IV was observed. The authors further speculate that this decrease in complex II activity could result in an increase in ROS resulting in mtDNA damage and oxidative stress which are known to contribute to the ageing process [38].

Whilst vast evidence exists implicating mitochondria in the ageing process, until recently there was no conclusive proof that mitochondria are major triggers of cell ageing. Correia-Melo *et al.* induced mitochondrial degradation to completely eliminate all mitochondria and demonstrated that these cells did not undergo hallmark changes of cellular senescence in terms of inflammatory molecules, oxygen free radicals and gene expression. However, cell cycle arrest still occurred, thereby maintaining the tumour suppressive properties of the cells. This study demonstrates for the first time that mitochondria are pivotal in the ability of a cell to senesce and the ageing process [43].

Skin: a model organ for investigating the role of mitochondria in ageing

The skin can undergo two distinct types of ageing; intrinsic (chronological) and extrinsic ageing (photoageing). The skin is often used to study human ageing, due to its easy accessibility, and the observation that the ageing process is able to be accelerated in this organ via environmental insults, such as ultra violet radiation (UVR) [25, 44]. The exposed nature of the skin means it is at more risk of environmental insults than most organs [45], and the characteristics of aged skin such as wrinkles, laxity, uneven pigmentation, brown spots and a leathery appearance are most prominent in areas of the body which are most exposed to UVR such as the face and the hands. This suggests that these characteristics of ageing can be accelerated by UVR, an occurrence known as photoageing [25].

Solar radiation is comprised of UVR (UVA and UVB), visible light and infrared (IR) [44] with a relative contribution of approximately 6%, 40% and 54% respectively. UVR from the sun is the main extrinsic influence of skin ageing; excessive exposure to UVR can lead to cellular, molecular, and genetic changes in the skin, which if unrepaired can have deleterious effects on cellular function [19, 46]. Sunburn is generally observed a few hours after acute exposure to UVR; however, more serious effects of chronic UVR exposure include immunosuppression, increased risk of skin cancer due to DNA mutations, and accelerated skin ageing [46]. UVR is able to cause damage to cells either by the production of ROS or via direct DNA damage. In terms of UVR-induced ageing, both UVA and UVB have been shown to contribute, however alterations within the dermis appear to be the fundamental cause of the aforementioned visual signs of ageing. Due to its ability to penetrate to the deeper layers of skin, UVA has been identified as a major contributor to photoaged skin [46]. UVR can induce the expression of matrix metalloproteinases (MMPs) which can degrade the collagen and elastin components of the dermis leading to increased formation of wrinkles.

A possible mechanism as to how UVR is able to accelerate the ageing process could be via its interaction with mitochondria, where it may contribute to a vicious cycle of increasing damage, which has been strongly linked to the ageing process [19, 45]. In this scenario, UVR may increase ROS levels, or cause mtDNA damage directly, which could result in an increase in mitochondrial dysfunction and a further production of ROS in a continuing vicious cycle. Even if this vicious cycle is not occurring, any damage to mtDNA or mitochondria directly by UVR could still result in an increase in photoageing, as mitochondria are thought to play a prominent role in the ageing process [19]. This has led to the development of mtDNA as an established biomarker of UVR-induced damage [47]. Furthermore, there is a strong positive correlation between many of the same symptoms and mtDNA mutations found in photo-aged skin compared to chronologically aged skin; therefore, excessively UV-exposed skin may be used as a model for skin from older individuals [47]. For example, the mtDNA 3895 bp and 4977 bp deletions, as well as the T414G mutation, are correlated more strongly with skin from sun-exposed regions and also in the skin of older individuals [25, 47].

Whilst the role UVR plays in mitochondria damage induced photoageing has been explored, relatively little is known about the role of IRR in photoageing and/or mitochondria damage. IRR makes up 54% of solar light and evidence exists that it has a detrimental effect on human skin. Investigations to date have observed an increase in intracellular ROS following irradiation with IR, which is known to have a strong correlation to mitochondria damage, as discussed previously [48]. Additionally, IRR has been shown to effect gene expression of MMPs which break down collagen and lead to characteristic photoaged skin. However, in contrast to UVR, the low energy level of IRR means it is poorly absorbed by chromophores such as melanin or directly affect DNA, therefore another mechanism must explain these

damaging effects [44]. Interestingly, the mitochondria is believed to be a key cellular target involved in the pathogenesis of IRR induced premature ageing in the skin via the enzyme cytochrome C Oxidase (also known as complex IV of the ETC) acting as a chromophore for IRA leading to disruptions within the ETC and defective energy production. Consequently, cellular signalling cascades are initiated which alter gene expression of key proteins involved in photoageing e.g. MMPs leading to the visual appearance of photoageing skin [44].

Less attention has been given to the role of environmental pollutants in skin ageing [49], for example air pollution is a growing concern with established links between chronic exposure to environmental pollutants and respiratory, cardiovascular, and more recently skin diseases [19]. Pollutants have been shown to have a negative effect on skin function, however what is less clear is the mechanistic regulation of such effects. Recent investigations have demonstrated the potential of various pollutants to form free radicals in the skin and linked this to classical visible signs of skin ageing such as wrinkles. Furthermore, environmental contaminants have been observed to target the mitochondria suggesting a relationship between environmental insult and mitochondrial-induced skin ageing in a similar manner to that induced by solar radiation. For example, pollutants such as polycyclic aromatic hydrocarbons which are formed from the incomplete combustion of organic material such as oil and coal, have been shown to cause more mtDNA damage than nDNA damage [50]. Particulate matter (PM) and cigarette smoke have also been reported to cause their damaging effects through mitochondrial toxicity, although it has not been established whether these effects are the primary or secondary to effects elsewhere [50]. Hou *et al.* showed for the first time in 2010 a direct link between PM exposure and mtDNA damage. This study analysed the blood of 63 male steel workers and correlated mtDNA copy number, an established marker of mitochondria damage to individual PM exposure. These findings support in vitro data demonstrating that PM can cause ROS-induced disruption to the mitochondrion [51]. Whilst further work is required to support the relationship between pollution and premature ageing via mitochondria-mediated mechanisms, it provides important evidence to enhance knowledge on the role mitochondria play in the ageing process in both skin and other organs exposed to environmental pollutants such as lungs.

An interesting theory has recently been put forward which suggests that mtDNA damage is not the cause of the cellular, molecular and functional changes associated with ageing rather that ageing precedes mtDNA damage [52]. A hallmark characteristic of dermal fibroblasts in aged skin is reduced spreading and contact with collagen fibrils. This results in a change in cellular morphology and the normally elongated spindle-like cells become short and circular. The authors suggest that an age-induced reduction in fibroblast spreading causes an increase in ROS which consequently damages mtDNA [52]. This is in contrast to general consensus that mtDNA damage and elevated ROS levels causes age-associated changes. This investigation introduces an interesting concept that ageing is a cycling and dynamic process of positive feedback mechanisms whereby age-related changes in cells results in mtDNA damage and oxidative stress, which in turn lead to further age-related changes in cells and so on.

Sunscreens in protecting mitochondrial induced ageing

The advantageous properties of the skin as a model to investigate mechanisms regulating

ageing can be extended to include its use in assessing the protective abilities of topical treatments. It is well established that UVR can result in elevated ROS and damage to mtDNA which can damage the skin leading to premature skin ageing. Therefore, in order to prevent photoageing from occurring, as well as minimising the risk of other damaging effects of solar radiation such as skin cancer, it is advised to regularly apply sunscreen as part of a recommended sun protection regime. The active ingredients found in sunscreen formulations are categorised as being either physical (mineral) or chemical (organic) compounds. Physical sunscreens such as titanium dioxide (TiO_2) and zinc oxide (ZnO) are thought to shield the skin by absorbing, reflecting and scattering UVA and UVB whilst chemical sunscreens protect by absorbing UVA and or UVB. Older generation sunscreens provided protection against UVB whilst allowing for UVA to pass through the skin. UVA was later recognised as being a contributing factor to skin cancer in the 1980s as well as being the primary cause of photo ageing [53]. This led to the development of broad spectrum formulations containing both UVA and UVB filters which are now regulated by strict European guidelines.

Studies investigating the protective effects of UVA filters in sunscreens on UVR-induced molecular damage are limited. However, Bruge *et al*. recently demonstrated that BMDM (Butyl Methoxydibenzoylmethane), a widely used chemical UVA filter has the ability to reduce UVA induced ROS generation, decrease the level of DNA damage, reduce expression of the enzyme MMP1 and maintain mitochondrial membrane potential [54]. The ability of commercially available sunscreens to reduce UV induced free radical production has also been investigated. When applied at the recommended dose of $2mg/cm^2$ the sunscreens assessed reduced free radical production by 55%. Lower amounts of sunscreen (0.5-$1.5mg/cm^2$) simulating the average amount applied by consumers reduced free radical production by 46% [55]. These studies provide evidence that the use of sunscreens, in particular those containing UVA filters, provide protection against UVR-induced mitochondrial damage and consequently may delay the ageing process in skin and highlighting an important 'proof of concept' that mitochondria-related ageing can be regulated topically.

Based on the evidence that UVR-induced ROS generation within a cell is detrimental to mitochondrial function and may lead to photoageing, it has been speculated that sunscreen supplementation with antioxidants such as vitamin C, vitamin E and polyphenols may offer further protection in addition to the primary chemical and physical active ingredients [56]. Matsui et al. assessed the ability of topical antioxidants to reduce UV induced skin damage. The application of sunscreen alone showed a 43% decrease in MMP1 expression compared to the UV control. The sunscreens supplemented with antioxidants showed a higher level of protection with a 60% decrease in MMP1 expression [57]. Furthermore, Tiron, an antioxidant which is preferentially localized to the mitochondria, exhibits complete (100%) protection against UVA and H_2O_2 induced mitochondrial DNA damage in human dermal fibroblasts [46].

Ageing in other organs

Whilst skin is an advantageous model for investigating the role of mitochondria in ageing, other organs show similar patterns regarding a decline in mitochondrial function, increase in mtDNA damage and elevated ROS with ageing [20]. This relationship is particularly strong in organs with high metabolic activity for example the brain and liver [58]. The brain has high energy demands and a gradual decrease in energy metabolism as well as elevated ROS

levels have been reported in the ageing brain and some neurodegenerative disorders resulting in a hypometabolic state. Mitochondria play a key role in energy production and therefore, a reduction in expression and activity of respiratory chain complexes as well as increases in mtDNA mutations have been shown to further contribute to this dysfunctional state [59]. Moreover, mitochondrial defects associated with elevated ROS are hallmarks of both the ageing and Alzheimer's disease (AD) brain [3, 59]. Indeed, it has been shown that mitochondrial dysfunction precedes Aβ plaques and neurofibrillary tangles; the established markers of AD, furthermore alterations to mitochondrial morphology and ETC complexes were noted in autopsy samples from Alzheimer's patients and a higher number of mtDNA mutations were observed in AD patients compared to age-matched controls [3]. Antioxidant supplementation has been shown, with variable success, to reduce age-related mitochondrial dysfunction in the brain and therefore highlights an interesting therapeutic option for the treatment of age-related neurological diseases such as AD [58]. Additionally, age related changes in digestion, metabolism and clearance of drugs have been attributed to declining function of the liver with age. Mitochondria have also been implicated in the aging liver with a decrease in mitochondria number and a reduction in respiratory chain enzymes. Indeed, a study found that 87% of those above 50 years had defects in the respiratory chain caused by loss of mitochondrial coded subunits [58].

Conclusion

A wide range of diseases are associated with ageing, therefore, understanding the cause of the ageing process as well as regulatory mechanisms involved could provide potentially advantageous therapeutic targets for the prevention or treatment of such diseases. Attempts to elucidate the mechanisms of ageing have been performed and many interesting theories have been suggested, in particular those implicating the mitochondria. However, the ageing process is still not fully understood, and therefore more work is required before attempts to slow the ageing process can be carried out. More recent developments in the field of mitohormesis provides an interesting concept for the varying roles oxidative stress plays in ageing. Whilst more research into the specific molecular effects and biological outcomes are required, it supports evidence that mitochondria are heavily implicated in the ageing process, although the exact role it plays appears to be more complex than originally postulated.

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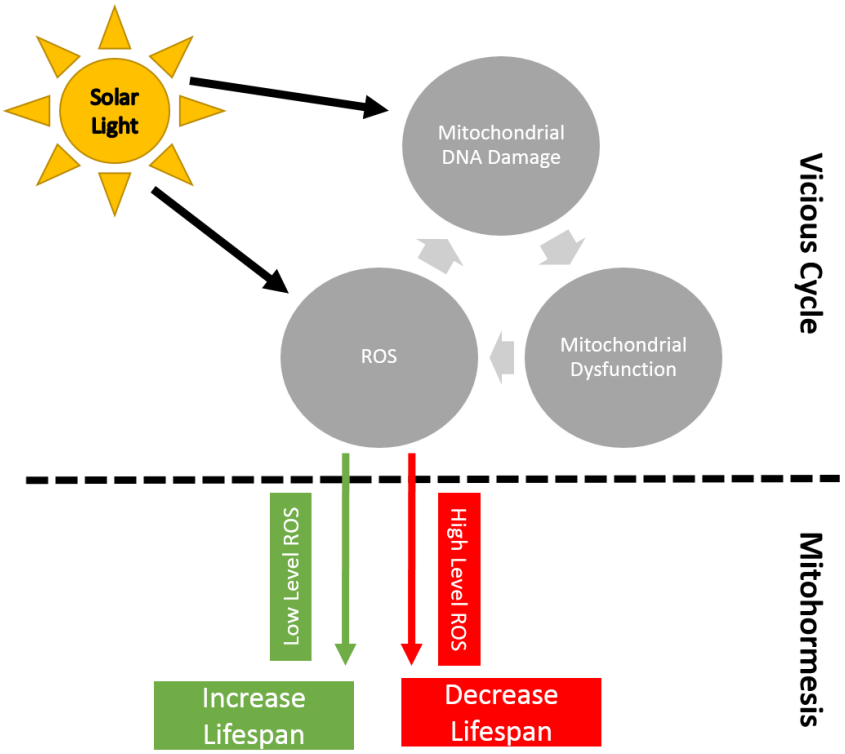

Figure 1. How solar light may interact with the vicious cycle theory of ageing.
Solar light is able to interact with and cause damage to mitochondria, either by causing direct mtDNA damage, or via an increase in ROS production. MtDNA damage may then cause an increase in mitochondrial dysfunction, and possibly a further increase of ROS. ROS generated may have a positive or negative effect on age-related processes and lifespan, depending on the levels, a term known as Mitohormesis.