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Review Article

DNA Damage and Base Excision Repair in Mitochondria and Their Role in Aging

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During the last decades, our knowledge about the processes involved in the aging process has exponentially increased. However, further investigation will be still required to globally understand the complexity of aging. Aging is a multifactorial phenomenon characterized by increased susceptibility to cellular loss and functional decline, where mitochondrial DNA mutations and mitochondrial DNA damage response are thought to play important roles. Due to the proximity of mitochondrial DNA to the main sites of mitochondrial-free radical generation, oxidative stress is a major source of mitochondrial DNA mutations. Mitochondrial DNA repair mechanisms, in particular the base excision repair pathway, constitute an important mechanism for maintenance of mitochondrial DNA integrity. The results reviewed here support that mitochondrial DNA damage plays an important role in aging.

1. Introduction

Our DNA, both nuclear and mitochondrial, is constantly exposed to endogenous and exogenous agents that induce DNA lesions and DNA instability, which includes blockage of DNA replication and transcription as well as chromosomal rearrangements [1]. In order to maintain genomic integrity, different DNA repair pathways have evolved in cells. Without efficient cellular DNA repair mechanisms, DNA stability and cellular survival are seriously compromised. DNA repair occurs both in prokaryotes and eukaryotes. In eukaryotes, DNA repair mechanisms have been described to take place not only in the nucleus, but in all cellular compartments containing DNA. Although these mechanisms have mostly been investigated in the nucleus, our knowledge regarding mitochondrial DNA repair pathways has significantly increased during the last decade. Because DNA repair pathways are important determinants of DNA stability, they are thought to play an important role in the aging process [2–4].

DNA repair mechanisms have been extensively investigated in the nucleus. Depending upon the type of DNA lesion that has been generated, a specific DNA repair pathway proceeds. Thus, bulky lesions, which are induced on DNA by UV light as well as by carcinogenic compounds, are removed by the nucleotide excision repair (NER) pathway, whereas DNA lesions such as oxidation products generated by ROS are repaired by the base excision repair (BER) pathway [5]; on the other hand, mismatches in DNA are removed by the mismatch repair pathway (MMR) and lesions such as interstrand cross-links are processed by recombinational DNA repair [1]. The relevance of the DNA repair pathways in the maintenance of the genome integrity and cellular survival is stressed by the critical consequences in the survival of the organisms when deficiencies in key enzymes of the DNA repair pathways occur [1, 2]. Moreover, several homologues between prokaryotes and eukaryotes have been reported among the different components of the DNA repair pathways [6], and proteins of the main pathways are highly conserved [3, 7–9].

Mitochondrial DNA (mtDNA) mutations and mitochondrial dysfunction are thought to play an important role in the aging process [10–13], and increased levels of mutations in DNA have been described to occur in brain and other tissues during normal aging leading to DNA instability [14–16]. According to the mitochondrial-free

radical theory of aging, the accumulation of reactive oxygen species-(ROS-)-induced mtDNA damage and mtDNA mutations over time are the main contributors to deleterious changes leading to cellular dysfunction and aging [17, 18].

In eukaryotic cells, the integrity of mtDNA is constantly challenged by the endogenous production of mitochondrial ROS, which are generated during mitochondrial respiration. ROS are particularly important genotoxic agents and can generate a large number of DNA lesions, including oxidized DNA bases, abasic sites, and single- and double-strand breaks. Because many of the ROS-induced DNA lesions show mutagenic or cytotoxic effects, mitochondrial-free radicals are thought to be an important source of DNA mutations and DNA instability, particularly in mitochondrial DNA. The proximity of mtDNA to the main sites of mitochondrial ROS generation, located within complexes I and III of the mitochondrial electron transport chain in the inner mitochondrial membrane, is the major reason for the higher steady-state levels of oxidative lesions and the higher instability observed in mtDNA when compared to nuclear DNA [19, 20]. For many years, such high level of oxidative lesions in mtDNA was considered to be a consequence, at least in part, of (i) the absence of efficient DNA repair mechanisms in mitochondria and (ii) the lack of protective histones in mtDNA. However, different studies have shown that mtDNA is organized into protein-DNA complexes called nucleoids, where DNA has been described to be associated with different proteins and anchored to the inner mitochondrial membrane [21–23]. These membrane-associated structures may provide more protection to the mtDNA against oxidative attack than was formerly thought. On the other hand, it is now well established that various DNA repair pathways actively take place in mitochondria. The initial studies on mitochondrial DNA repair capacity focused on UV light-induced DNA damage repair, and they provided the basis for the notion that mitochondria lacked functional DNA repair mechanisms [24]. Thirty years later, it is known that various DNA repair pathways do take place in mitochondria [25]. Most of the studies on mitochondrial DNA repair have focused on the BER mechanisms, which are the DNA repair pathway coping with oxidative lesions and it is the best-characterized DNA repair pathway in mitochondria [26, 27].

2. DNA Repair and Mitochondria

As mentioned above, DNA repair research has focused mainly on the nuclear compartment; however, the investigations performed in the last two decades have confirmed that mitochondria do possess effective DNA repair mechanisms, and the understanding of how these mechanisms function has significantly increased in the last few years. The first DNA repair pathway that was described to actively take place in mammalian mitochondria was the BER pathway. Today, other DNA repair mechanisms that were thought to occur exclusively in the nucleus have been described to take place in mammalian mitochondria such as MMR [28, 29] and the long-patch BER [30–32]. Moreover, classical nuclear DNA repair enzymes have been identified in mitochondria [28, 31, 33–35], with similar function than the one observed in the nucleus [31, 35], or with novel functions according to its mitochondrial location [33].

However, and despite the increased knowledge in mtDNA repair, important questions still remain opened, such as the precise mechanisms for the repair of some specific lesions in mtDNA such as double-strand breaks or DNA adducts derived from lipid peroxidation. The latter are likely generated in mtDNA, since mitochondrial phospholipids are main targets of mitochondrial-free radicals [36] and mtDNA is associated with the inner mitochondrial membrane; DNA adducts derived from lipid peroxidation are known to be processed by NER [37, 38], but whether mitochondria possess the capacity to repair DNA lesions others than UV light-induced lesions via the NER pathway remains to be elucidated.

3. Mitochondrial Base Excision Repair

BER is the primary pathway known for repair of small DNA modifications caused by alkylation, deamination, or oxidation. BER takes place both in the nucleus and in mitochondria, and although the mechanisms are similar, mitochondria possess an independent BER machinery. Both nuclear BER and mtBER are based on a cascade of reactions starting with the recognition of the damage followed by enzymatic processing steps that aim to remove the lesion and restore genomic integrity. All the components of the mtBER pathway are nuclear encoded and imported into mitochondria [39]. The BER pathway includes 4 distinct steps: (i) recognition and removal of the modified base, (ii) processing of the generated apurinic/apyrimidinic (AP) site, (iii) incorporation of the correct nucleotide(s), and (iv) strand ligation.

3.1. Mitochondrial BER: Early Steps, Recognition, and AP Site Processing. The first step of BER is catalyzed by DNA glycosylases, which recognize the modified base and cleave the N-glycosidic bond, creating an abasic site. In addition to the cleavage activity towards the N-glycosidic bond, some DNA glycosylases also have AP lyase activity, which allows the cleavage of the DNA backbone. These DNA glycosylases are called bi-functional glycosylases while those possessing only cleavage activity are named monofunctional. Oxidized bases are generally removed by bifunctional DNA glycosylases. Among all the different DNA glycosylases that have been described to be present in the nucleus, only some of them have been detected in mitochondria [26, 40]. As the rest of enzymes involved in mtBER, nuclear genes encode mitochondrial DNA glycosylases. Mitochondrial and nuclear isoforms of the same DNA glycosylases are encoded by the same gene and are generated by alternative transcription initiation sites and alternative splicing [41]. That is the case of two of the main mitochondrial DNA glycosylases, 8-oxoguanine DNA glycosylase-1 (Ogg1) and Uracil-DNA glycosylase (UNG).

UNG was the first DNA-glycosylase to be identified [42]. Uracil in DNA is generated by deamination of cytosine or by misincorporation of dUMP. The removal of uracil

from DNA is crucial due to its ability to pair with adenine, causing GC to AT transition mutations upon replication. Despite UNG was the first DNA-glycosylase investigated, it is Ogg1 the one that has been investigated most extensively. Ogg1 is a bifunctional DNA glycosylase that recognizes and cleaves 8-hydroxi-guanine (8-oxoG) from double-strand DNA. For many years, this DNA lesion has been the most broadly used as DNA damage marker, both in nuclear and mitochondrial DNA, mainly because 8-oxoG is relatively easy to detect and measure. However, it does not necessarily mean that 8-oxoG is the most frequent and biologically relevant DNA lesion. Actually, oxidative DNA lesions such as 2,6-diamino-4-hydroxy-5-formamidopyrimidine (FapyG) and 4,6-diamino-5-formamidopyrimidine (FapyA) have been detected in genomic DNA at similar or even higher levels than 8-oxoG. Recently a new group of DNA glycosylases, NEIL glycosylases, has been identified in mammalian tissues primarily excising FapyG and FapyA. These glycosylases are homologous of the *Escherichia coli* DNA glycosylases Fpg/Nei and three main isoforms, NEIL1, NEL2, and NEIL3, have been described [43, 44], being present both in nucleus and mitochondria [34, 44, 45]. Moreover, some of them have been involved in repair mechanisms of oxidative lesions in transcribed or replicating DNA [46]. The identification of this group of DNA glycosylases in mammals was of great interest, particularly when the knock-out (KO) mouse for NEIL1 was developed [47]. Due to the partial redundancy in the activity of DNA glycosylases, KO mice for most of them do not exhibit a significant phenotype. However, KO mice for NEIL1 accumulate mtDNA deletions to a higher extent than wild-type mice and develop symptoms associated with the metabolic syndrome [47].

After recognition and cleavage of the modified or erroneous base by the specific DNA glycosylase, an abasic site is generated. Repair of these lesions shares common steps with that of ROS-induced DNA single-strand breaks and spontaneously generated AP sites. These DNA lesions are continuously generated and various enzymatic processes have evolved to repair them. Among those processes, AP endonuclease (APE) is the most important and ubiquitous [48]. Although two isoforms of APE, APE1 and APE2, have been described in mammalian tissues, APE1 is the main AP endonuclease in mammalian cells taking part of the BER processes both in nucleus and mitochondria [49]. The absence of significant APE-specific activity of the recombinant APE2 has suggested that it functions in other cellular processes different than BER [50]. Together with its activity in DNA repair processes, APE1 also has a redox activity that is involved in signal transduction. APE1 participates in several important cellular mechanisms such as apoptosis, proliferation, and differentiation functioning as a transcriptional coactivator [51–53]. Unlike most of the known enzymes taking part in the BER process in mitochondria, mitochondrial APE nature remains unclear. It is still discussed whether the mitochondrial APE is an N-terminal truncated product of APE1 [54]. The deletion of the N-terminal residues containing the nuclear localization signal has been described to induce a 3-fold increase in the specific activity of APE1 [55], and APE activity is higher in mitochondrial fractions than in nuclear fractions. However, the presence of this truncated isoform of APE1 has only been reported in bovine liver mitochondria, while no truncated product has been observed in mitochondrial extracts of different human cell lines [55]. The relevance of APE1 in mammalian cells is stressed by the reports showing a significant increase in single-strand breaks as well as AP sites when APE1 is inactivated [56, 57]. Moreover, and in contrast to DNA glycosylase KO mice, cellular survival is critically compromised in the absence of APE1, and KO mice for APE1 show embryonic lethality [58].

3.2. Mitochondrial BER: Final Steps, Short- and Long-Patch BER. Once the AP site has been processed by APE1, the following step in the BER pathway is catalyzed by a DNA polymerase, which inserts the correct nucleotide(s) in the generated gap. There is only one known DNA polymerase in mammalian mitochondria, the DNA polymerase gamma (polγ), which is involved in all replication and repair of mtDNA. Two different BER subpathways exist depending on whether polγ inserts one nucleotide or more: short-patch (SP) or long-patch (LP) BER [26]. During the SP-BER, one single nucleotide is incorporated into the gap by polγ, while the LP-BER involves the incorporation of several nucleotides, typically 2 to 7. Long-patch BER processing of a DNA lesion is more complex than SP-BER, since the incorporation of various nucleotides results in the exposure of the original DNA strand as part of a single-strand overhang or flap structure. Additional enzymatic activities are required in order to process such structure [27]. In the nucleus, the flap structure is recognized and cleaved by the flap endonuclease 1 (FEN-1), which is an essential enzyme for LP-BER [59]. Why BER proceeds through the short- or long-patch is not completely understood. It seems to depend, at least in part, on the type of lesion and on the intermediates that are generated during the process. For instance, AP sites can be further oxidized, and this sort of DNA lesion requires to be processed by LP-BER [60].

Until recently it was believed that SP-BER occurred both in nucleus and mitochondria, whereas LP-BER only took place in the nucleus. However, considering the constant exposure of mtDNA to mitochondrial-free radicals, it was likely that certain types of lesions, such as oxidized AP sites, were generated at a significant rate in mtDNA [60]. Therefore, SP-BER would be insufficient to cope with all the collection of lesions inflicted in mtDNA. Various investigations have recently shown that, likewise nuclear BER, mitochondrial BER can also progress in a long-patch manner [30–32, 61]. Furthermore, and similarly to nuclear long-patch BER, different studies support that FEN-1 plays an important role in mitochondrial LP-BER [31, 61]. Besides, during the processing of the 5′ flap structure FEN-1 interacts with Dna2, a helicase/nuclease protein, in human HeLa cell mitochondria [35].

The final step of the mitochondrial BER pathway, the nick sealing, is catalyzed by a DNA ligase. While two DNA ligases are described in the nucleus (I and III), in mammalian mitochondria only DNA ligase III has been detected, acting both in replication and repair. DNA ligase

III is a splice variant from the LIG3 gene encoding for both the nuclear and mitochondrial enzymes. The mechanism of action as well as the interaction with other proteins of the mitochondrial variant of DNA ligase III is still unclear.

3.3. Mitochondrial BER Proteins, Organization, and Interactions. Some of the proteins involved in mtDNA repair have been described to be components of the nucleoids [62, 63]. One of the essential components of the nucleoids is the mitochondrial transcription factor A (TFAM) that plays a significant role in the organization and structure of the mitochondrial nucleoids [64, 65]. TFAM has recently been associated with mtBER activity, modulating DNA repair efficiency in mitochondria [66]. Likewise, essential proteins of the mtBER like polγ, in particular its accessory subunit polGβ, have also been described to be key factors in the organization of these nucleoprotein complexes [67]. Investigations on how the organization of mtDNA in mitochondria affects and modulates BER is increasing, and recent studies have suggested that mtDNA association to the inner membrane is critical for proper base excision repair [68]. Moreover, the cockayne syndrome group B (CSB) protein, which was thought to be present exclusively in the nucleus, has been recently localized to mitochondria [33]. Mutations in the CSB gene are responsible for the Cockayne syndrome, a segmental premature aging syndrome [69]. The Cockayne syndrome is associated with severe development deficiencies and neurodegeneration. The CSB protein plays a role in genomic maintenance and transcription regulation in the nucleus, and it had also been suggested to play a role in mtBER, although the mechanism was obscure [4]. Recent studies have indicated that CSB may play a role in general mitochondrial maintenance [70]. Interestingly, the investigation on CSB protein and its location in mitochondria have suggested that CSB protein could play a direct role in mtBER by interacting and stabilizing BER proteins in the protein-DNA complexes associated with the inner mitochondrial membrane when mtDNA repair takes place [33].

4. Mitochondrial DNA Damage, DNA Repair, and Aging

The increased susceptibility to cellular loss and the progressive functional decline observed during aging has been associated with accumulation of damage to macromolecules, particularly to mtDNA [10, 13]. According to the mitochondrial-free radical theory of aging free radicals generated by mitochondria are the main contributors to the accumulation of damage. Over the years, several investigations have linked mitochondrial ROS production and accumulation of mtDNA mutations to the aging process, and because mtDNA repair mechanisms are essential in order to avoid increased accumulation of mtDNA mutations, they are thought to play an important role in the aging process [2]. Although mitochondrial ROS and mtDNA mutations were supported as main contributors of aging mainly by descriptive data and correlative studies, the generation of a knock-in mouse expressing proof-reading deficient polγ, but conserving its replicative function, is considered by some authors as an important support of accelerated mtDNA mutation rate resulting in increased aging rate [12, 71]. This mouse model, the mutator mouse, appears as an interesting model in which to investigate the causative link between mtDNA mutation accumulation and aging, and the role that mtBER may play in the process [72, 73]. In various tissues of this mouse model, mtDNA point mutations as well as mtDNA deletions have been described to accumulate at a much higher rate than in the wild-type mice [12, 71, 74]. However, how the accumulation of mtDNA mutations lead to the loss of mitochondrial function and aging is still discussed [74]. Investigations on brain and heart samples have suggested that it is the accumulation of large mtDNA deletions and clonal expansion, instead of mtDNA point mutations, that drive the premature aging phenotype [16, 75]. However, after performing research on hepatic and cardiac tissues, Edgar et al., recently reported that circular mtDNA molecules with large deletions represent only a minor proportion of the total mtDNA in this mouse model and suggested that random point mutations occurring in mtDNA are the driving force behind the premature aging phenotype [76]. Discrepancies could be due, at least in part, to the different mechanisms that have been suggested to be responsible of the generation of mtDNA mutations in postmitotic and mitotic tissues [77]. It has been proposed that in postmitotic cells, such as neurons, mtDNA deletions occur primary during repair of damaged DNA, whereas in mitotic tissues mtDNA point mutations are more likely to be caused during replication [78]. This could lead to significant differences in the type of mtDNA mutations being detected in postmitotic and mitotic cells during normal aging. Thus, for substantia nigra neurons from aged individuals and Parkinson's disease patients, direct evidence exists of mitochondrial dysfunction due to accumulation of mtDNA deletions [79, 80], while mtDNA point mutations have been reported to occur rarely in these neurons during aging [77]. If mtDNA deletions are actually generated during repair of damage mtDNA, alteration in mtBER fidelity with age would play an important role in mtDNA deletion accumulation and aging. A recent study has reported the presence of large linear mtDNA fragments in liver mitochondria in the mutator mouse model [81]. The authors suggest that due to the increased errors inserted during DNA synthesis, replication arrest would occur as a result of an effort to execute DNA repair. In a scenario of a high mutant load, replication pausing would be extended and strand breakage would likely occur at pause sites, leading to formation of mtDNA linear fragments. Although the level of these mtDNA fragments does not increase with age in the mutator mice, Bailey et al. [81] suggest that the long-term impact of aberrant mitochondrial DNA replication might contribute to the premature aging phenotype of these mutator mice. Moreover, they suggest that as a result of aberrant mitochondrial replication, essential factors involved in DNA metabolism would be mobilized to mitochondria and eventually would become exhausted. Because nuclear and mitochondrial DNA metabolism share several of those essential factors, the collapse of DNA factors in mitochondria could probably have an impact on nuclear DNA metabolism, contributing to the premature aging phenotype.

The impact of mtDNA deletions on nuclear DNA has also been suggested as a potential determinant of aging in different organisms. Various studies have investigated whether the migration of mtDNA sequences from mitochondria to the nucleus could be relevant in the aging process. Gene transfer from organelles to the nucleus has occurred repeatedly during eukaryote evolution [82], but inappropriate *de novo* insertion of mtDNA fragments into human chromosomal DNA has been reported to result in rare severe genetic diseases [83].

In the filamentous ascomycete fungus *Podospora anserina*, mtDNA instability is thought to play an important role in the aging process [84] and rearrangements of the mtDNA are considered as a hallmark of senescence in wild-type strains. These rearrangements include the systematic amplification of the first intron of the cytochrome c oxidase subunit-I gene as circular DNA molecules [85]. Twenty years ago, integration of these mtDNA plasmids within the nuclear genome was reported to take place during senescence in *P. anserina* [86]. In the last few years the hypothesis of insertion of mitochondrial DNA fragments into nuclear DNA as aging factor [87] has been tested by different research groups. It has been reported that migration of mitochondrial DNA fragments into the nucleus affects the survival rates in *Saccharomyces cerevisiae* [88]. In *S. cerevisiae* mtDNA fragments are initially present as circular molecules in the nucleus, and the frequency of integration events into chromosomal DNA increases during lifespan [88]. Cheng and Ivessa have reported that in *S. cerevisiae* mutants with a higher translocation rate of mtDNA fragments into the nucleus than in wild-type strains, chronological lifespan is reduced, while in mutants showing a reduced translocation rate of mtDNA fragments in the nucleus, the chronological lifespan is extended. Moreover, Caro et al. [89] have reported that mitochondrial DNA sequences into nuclear DNA accumulate with aging in rat liver and brain. Furthermore, the integration of the mitochondrial sequences seems to occur at specific sites of the chromosomes instead of randomly.

Taken together, it appears likely that mtBER has an important role in the aging process due to its role avoiding mtDNA mutations. Caloric restriction (CR) is a well-known experimental manipulation that reduces the accumulation rate of mtDNA mutations [90, 91] and increases maximum life span in several species [92]. Various investigations have studied the role of DNA repair mechanisms on the beneficial effects of CR. Caloric restriction has been reported to promote genomic stability, at least in part, by a general enhancement of nuclear DNA repair mechanisms [93]. However, although total [94] and nuclear [95, 96] BER capacity in different rat brain regions and tissues have been shown to be increased in CR animals when compared to *ad libitum* fed animals [94], investigation of the BER activities in the mitochondrial compartments has shown that mtBER capacity did not change in liver and even decreased in the brain and kidney of caloric restricted rats. [96]. The lower mtBER capacity observed in restricted rats would be in agreement with the fact that mitochondria from caloric restricted rodents have been shown to generate ROS and accumulate oxidative damage to mtDNA at lower rates than *ad libitum* fed animals [92]. Hence, when the generation of mitochondrial ROS and the levels of mtDNA damage are significantly reduced, it may be possible for the organism to invest less energy in mtDNA repair capacity without negative consequences.

On the other hand, different studies have reported that deficiencies and changes in mitochondrial BER fidelity occur during aging, particularly in postmitotic tissues. In vertebrates, the most important postmitotic tissue is probably the brain, due to its main role in homeostasis of the organism. Mitochondrial BER capacity has been described to be organ-specific, with the brain being one of the tissues with the lowest capacity [97]. Various studies have reported an age-related decline in DNA glycosylase activities brain cortical mitochondria in rats [98] and mice [45, 99], suggesting that mtBER may play a critical role in the maintenance of the central nervous system during aging [100]. In addition, important differences in mtBER have been observed among various brain regions during aging [45]. The cortical region and the cerebellum have been described to accumulate less mtDNA lesions with aging and to be more resistant to oxidative stress conditions [101]. Interestingly, those regions showed higher BER capacity than hippocampus, which has been described to be a much more vulnerable region in the brain [101, 102].

A recent investigations has reported that the age-related decline in brain mtBER occurs specifically at the synapses [103], stressing the relevance of the central nervous system heterogeneity in these processes. Moreover, deficiencies in mtBER in skeletal muscles during aging have been suggested to contribute to age-related sarcopenia [104]. Finally, potential age-related changes in mtBER have been investigated in other aging models such as *P. anserina* as well; again, aging was associated with a decrease in mitochondrial BER [7], probably contributing to the observed mtDNA instability in the aged fungi [105].

In conclusion, several investigation support that age-related mtBER impairment and increased mtDNA instability contribute to aging. Further investigations are required to clarify the precise mechanisms and whether other DNA repair mechanisms mitochondrial and/or nuclear are also involved in the aging process. Moreover, better knowledge of how mitochondrial DNA repair mechanisms function will help to find strategies to potentially retard mtDNA mutation generation and hence cellular dysfunction observed during aging.

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