Biochimica et Biophysica Acta 1813 (2011) 186–200

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbamcr

Review

DNA repair in organelles: Pathways, organization, regulation, relevance in disease and aging

Pierre Boesch [a], Frédérique Weber-Lotfi [b], Noha Ibrahim [b], Vladislav Tarasenko [c], Anne Cosset [b], François Paulus [b], Robert N. Lightowlers [a], André Dietrich [b,*]

[a] Mitochondrial Research Group, Institute for Ageing and Health, Medical School, Newcastle University, Framlington Place, Newcastle upon Tyne, NE2 4HH, UK
[b] Institut de Biologie Moléculaire des Plantes, CNRS/Université de Strasbourg, 12 rue du Général Zimmer, 67084 Strasbourg, France
[c] Siberian Institute of Plant Physiology and Biochemistry, Russian Academy of Sciences, Ul. Lermontova 132, 664033 Irkutsk, Russia

ARTICLE INFO

Article history:
Received 30 June 2010
Received in revised form 1 October 2010
Accepted 5 October 2010
Available online 13 October 2010

Keywords:
Aging
Chloroplast
Disease
DNA damage
DNA repair
Mitochondrion

ABSTRACT

Both endogenous processes and exogenous physical and chemical sources generate deoxyribonucleic acid (DNA) damage in the nucleus and organelles of living cells. To prevent deleterious effects, damage is balanced by repair pathways. DNA repair was first documented for the nuclear compartment but evidence was subsequently extended to the organelles. Mitochondria and chloroplasts possess their own repair processes. These share a number of factors with the nucleus but also rely on original mechanisms. Base excision repair remains the best characterized. Repair is organized with the other DNA metabolism pathways in the organelle membrane-associated nucleoids. DNA repair in mitochondria is a regulated, stress-responsive process. Organelle genomes do not encode DNA repair enzymes and translocation of nuclear-encoded repair proteins from the cytosol seems to be a major control mechanism. Finally, changes in the fidelity and efficiency of mitochondrial DNA repair are likely to be involved in DNA damage accumulation, disease and aging. The present review successively addresses these different issues.

1. Introduction

The genetic material is a major target for reactive by-products or intermediates released from metabolic pathways, as well as for exogenous chemical or physical agents. These deleterious processes result in DNA modification or breakage, which in turn can impact gene expression and induce mutations. Damage affects both the nuclear DNA and the genomes retained in mitochondria and chloroplasts. Moreover, organelles are major sources for damaging by-products, as electrons leaking from the respiration and photosynthesis chains promote the production of strong oxidants. To maintain genome integrity, cells possess specific DNA repair pathways. These pathways were originally considered to be restricted to the nucleus. Organellar genomes are highly polyploid and their preservation was supposed to be ensured by the degradation of damaged molecules. Specific degradation of mitochondrial DNA may occur in some circumstances (reviewed in [1]), but there is now ample evidence that mitochondria and chloroplasts possess a counterpart of most of the nuclear DNA repair pathways (also recently reviewed in [1] for mammalian mitochondria). A number of factors and processes are shared between cell compartments, but DNA repair in organelles also shows specific and original aspects. Different mechanisms may cooperate and alternate pathways have been highlighted. Specific repair processes are membrane-localized and integrated with the other genetic mechanisms in the organelle nucleoids. Not only does DNA repair occur in mitochondria and chloroplasts but it also appears to be a major process which is specifically regulated. Dynamic relocalization of repair enzymes and modulating factors to mitochondria in response to genotoxic conditions is a characteristic feature of these control mechanisms. Accumulation of mitochondrial DNA (mtDNA) damage and mutation is associated with disease and aging, which makes the fidelity and efficiency of organelle DNA repair a predominant issue. The current experimental challenging of the mitochondrial theory of aging places organelle DNA repair in the center of the debate. The present review integrates all these aspects, including plant mitochondria and chloroplasts, in the light of the recent data.

2. DNA damage in organelles

2.1. UV-induced damage

UV light exposure promotes the formation of dimeric photoproducts between adjacent pyrimidines, yielding intrastrand cyclobutane

* Corresponding author. Tel.: +33 3 88 41 72 41; fax: +33 3 88 61 44 42.
E-mail address: andre.dietrich@ibmp-cnrs.unistra.fr (A. Dietrich).

0167-4889/$ – see front matter © 2010 Elsevier B.V. All rights reserved.
doi:10.1016/j.bbamcr.2010.10.002

pyrimidine dimers (CPDs) or (6–4) pyrimidine–pyrimidone photoproducts [(6–4)PPs]. The latter can photoisomerize into a third type of photoproduct called Dewar valence isomers [2]. UVA and UVB also trigger the formation of reactive oxygen species (ROS), which in turn damage the DNA [3]. Photoproducts occur in the nucleus, mitochondria and chloroplasts (*e.g.* [4–8]).

2.2. ROS and RNS

The most abundant ROS in living cells include superoxide and hydroxyl radicals ($O_2^{\bullet -}$, HO•), as well as hydrogen peroxide (H_2O_2). They can be generated by exogenous sources like UV light, ozone, ionizing radiations, metals, pesticides, air pollutants or pharmaceutical drugs (*e.g.* [9]). ROS are also produced endogenously by living organisms during normal metabolism. *In vitro*, mitochondrial respiration processes convert up to 2% of the consumed oxygen into superoxide anion $O_2^{\bullet -}$, which is the precursor of many other ROS [10]. Fortunately, the rate seems to be much lower *in vivo*, according to recent evaluations [11]. In light-exposed photosynthetic cells, the production of superoxide anion is particularly prominent in chloroplasts [12]. $O_2^{\bullet -}$ can be converted to H_2O_2, which in turn will yield HO•, the most toxic ROS [13]. As a first defense line, organelles possess antioxidant compounds and activities [10,14–16]. ROS that escape detoxification damage the DNA, leading to the formation of various modified bases (including thymine glycol, 5,6-dihydroxycytosine, 8-hydroxyguanine, 2,6-diamino-4-hydroxy-5-formamidopyrimidine), sugar break down products (for example 2-deoxypentose-4-ulose, 2-deoxypentonic acid lactone, erythrose), base-free sites and strand breaks [17,18].

Cells also contain reactive nitrogen species (RNS). The superoxide anion $O_2^{\bullet -}$ can react with nitric oxide (NO•) and produce peroxynitrite ($ONOO^-$). Peroxynitrite is able to oxidize DNA bases, especially guanine which leads to 8-nitroguanine [19,20]. On the other hand, $ONOO^-$ can promote sugar fragmentation, which generates strand breaks [19]. A further important reaction is the oxidation of nitric oxide by molecular oxygen to form the powerful nitrosating agent N_2O_3 (nitrous anhydride). The latter can deaminate primary amines on DNA bases, converting adenosine, cytosine, 5-methyl-cytosine and guanine to hypoxanthine, uracil, thymine and xanthine, respectively. Nitrous anhydride also produces abasic sites, which in turn induce strand breaks, and lead to the formation of DNA intrastrand, DNA interstrand and DNA/protein cross-links [19].

Among all these modifications, 8-hydroxyguanine (8-OHG or 8-oxoG) has been the most studied and serves as a biomarker of oxidative stress [21]. 8-oxoG formation occurs in mitochondria and chloroplasts under regular physiological conditions and the levels increase following various treatments or during aging (*e.g.* [22–26]).

Oxidized bases found in the DNA may also originate from the incorporation of oxidized nucleotides by DNA polymerase. Free oxidized nucleotides in the dNTP pool can be degraded by specific enzymes (reviewed in [1,27]). In human, hMTH1, the homologue of the bacterial MutT, localizes to both the nucleus and the mitochondrion and is responsible for the elimination of oxidized dGTP and dATP [28]. Still in human, different transcripts are produced by alternative splicing from the *DUT* gene encoding a dUTPase and one of the corresponding proteins is targeted to the mitochondria [29].

2.3. Alkylation and bulky adducts

Further DNA damage includes alkylation and formation of bulky adducts. DNA alkylation can be promoted by endogenous metabolic products [30] or occurs upon cell exposure to alkylating agents, affecting both nuclear and mitochondrial DNA (*e.g.* [31]). Reactive intermediates formed during metabolism of organic compounds by living cells can react with the DNA. Covalent binding of organic derivatives to the bases yields abnormal hypermodified nucleotides called “addition products” or “adducts” (*e.g.* [32]). Various types of adducts can be formed according to the organic compound and reactive intermediates involved. A number of studies detected bulky adducts in mitochondrial DNA, often with higher rates than in nuclear DNA (*e.g.* [33–36]). Adducts can also result from the reaction of the DNA with the products of endogenous fatty acid peroxidation, leading in particular to etheno derivatives. Etheno adducts have been detected in mitochondrial DNA [37].

3. Mitochondrial DNA repair mechanisms: the BER pathway

3.1. Modified base excision and strand incision

As a second defense line to maintain genome integrity, organelles possess detection and repair mechanisms matching different types of DNA lesions (*e.g.* [38,39]). The current data imply that most of the repair pathways originally characterized in the nucleus are also present in mitochondria and/or chloroplasts (Fig. 1). Due to the high levels of ROS produced in the organelles, the DNA in mitochondria and chloroplasts is primarily under oxidative threat. ROS-induced oxidative lesions are preferentially eliminated by base excision repair (BER). This pathway (Fig. 2) is the best established in organelles and appears to be ubiquitous. Previously characterized in animal and yeast mitochondria, it has now been extended to plant mitochondria and chloroplasts [40–42]. Mitochondrial BER enzymes were even detected in human cells depleted of mitochondrial DNA [43]. The first step in BER is the elimination of the damaged nucleotide. The abnormal base is removed by a DNA glycosylase and the remaining abasic nucleotide (AP site for apurinic and apyrimidinic site) is eliminated by a variety of lyase and AP endonuclease activities [44]. After removal of the damaged base and phosphodiester chain incision, the BER pathway requires DNA polymerase-mediated *de novo* insertion of either a single nucleotide (short-patch BER) or a short sequence (2 to 6 nucleotides) extending from the incision site (long-patch BER) [44]. It had first been believed that only short-patch BER occurs in mitochondria [42]. The case has recently been reopened and different groups have now detected long-patch BER activity in mammalian mitochondria [45–48]. By contrast, BER seems indeed to be restricted to short-patch in plant organelles [40]. Finally, as a last step in the BER mechanism, the newly synthesized DNA patch is ligated to the rest of the molecule [44].

The major oxidative lesion 8-oxoG is repaired by this BER pathway, starting with a specific 8-oxoG-DNA glycosylase/lyase activity. In human, the OGG1 protein, a functional homologue of bacterial MutM, provides such an activity. Alternative splicing of the transcripts from the *hOGG1* gene produces several mRNAs, one of which encodes a mitochondrial isoform of the enzyme [49]. Mitochondrial extracts from *ogg1*$^{-/-}$ homozygous mouse null mutants cannot excise 8-oxoG from a DNA substrate *in vitro*. Such mutants show a striking increase in the levels of 8-oxoG in the mitochondrial DNA, with limited effect on the nuclear DNA [50]. This implies that the nuclear compartment can use alternative pathways to deal with 8-oxoG, while the mitochondrion relies essentially on the product of the *OGG1* gene. MutY glycosylase provides a further level of repair, as it removes adenines or guanines misincorporated opposite 8-oxoG during DNA replication. A homologue of *Escherichia coli* MutY has been identified in mammals. A mitochondrial and a nuclear isoform of this enzyme (MYH) are provided by alternative splicing of the corresponding transcript [51,52]. Using *in vitro* incision of a double-stranded DNA oligonucleotide carrying an 8-oxoG paired with a C, we recently established that plant mitochondria and chloroplasts contain 8-oxoG-DNA glycosylase/lyase (unpublished results). The reaction products were as expected from removal of the single modified nucleotide, in agreement with a BER pathway.

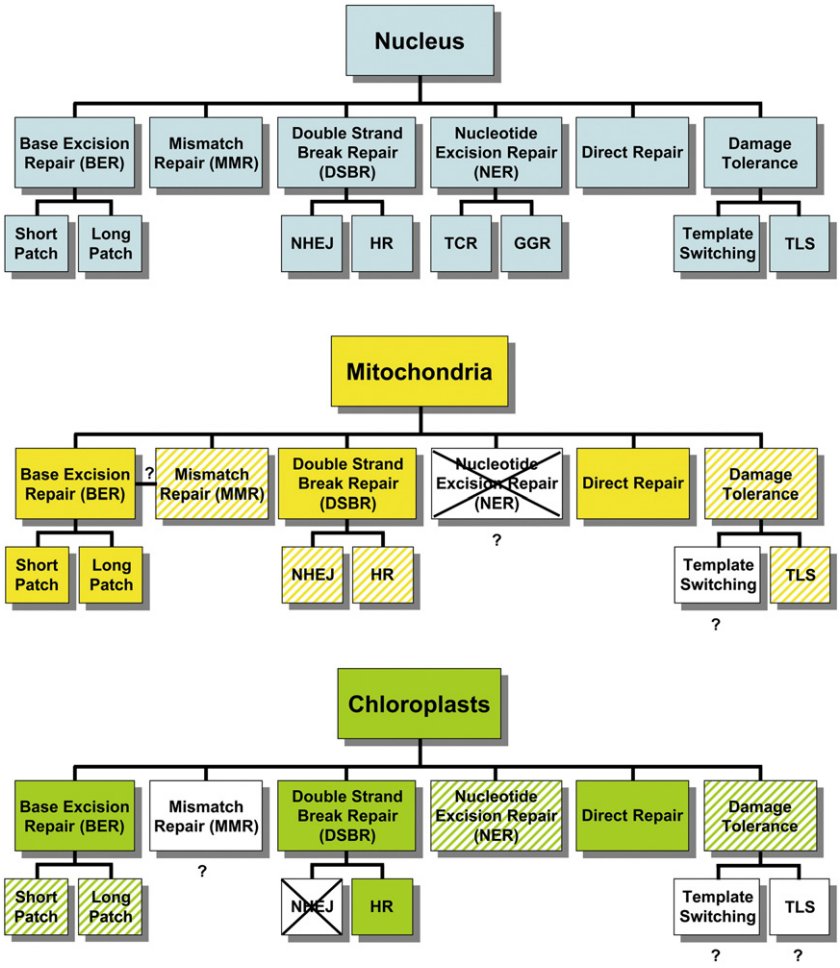

Fig. 1. DNA repair pathways in the nucleus, mitochondria and chloroplasts. Established pathways are shown with a full colour background, whereas documented pathways which need further confirmation are on a hatched background. It is considered that mitochondria have no NER pathway and chloroplasts no NHEJ. The figure displays the DNA repair pathways which can be found in organelles, but the presence or not of a given mechanism may depend on the organism considered. Abbreviations: NHEJ, non-homologous end joining; HR, homologous recombination; TCR, transcription-coupled repair; GGR, global genome repair; TLS, translesion synthesis.

To remove uracil produced upon cytosine deamination, mammalian cells possess a nuclear and a mitochondrial form of uracil-DNA glycosylase deriving from the same gene. These are generated through the use of two different promoters and alternative splicing processes [53]. Contrasting with such a mechanism, it has been proposed that *Saccharomyces cerevisiae* contains a single isoform of uracil-DNA glycosylase that possesses both a mitochondrial and a nuclear targeting sequence [54]. Plant mitochondrial uracil-DNA glycosylase activity was established *in situ* through *in organello* incision of double-stranded DNA oligonucleotides containing a single uracil [40]. These experiments were based on the competence of mitochondria for DNA import [55]. Further *in organello* assays with a long uracil-containing DNA substrate in turn validated a complete BER pathway for uracil repair in plant mitochondria [40]. Using *in vitro* incision reactions, we also demonstrated the presence of uracil-DNA glycosylase activity in chloroplasts (unpublished results), confirming the existence of a BER pathway in these organelles.

Oxidative damage to the DNA also includes thymine glycol, which is usually eliminated by glycosylases of the endonuclease III (NTH) family. *S. cerevisiae* possesses two genes coding for a thymine glycol-DNA glycosylase, *NTG1* and *NTG2*. The former encodes an enzyme with a bipartite localization to both the mitochondrion and the nucleus, while the latter provides an exclusively nuclear isoform [56,57]. The 5′ to 3′ helicase PIF1 cooperates with NTG1 and the BER pathway to resist damaging of the mitochondrial genome in oxidative stress conditions [58]. Concomitant elimination of *NTG1*, *PIF1* and *SOD2*, the gene for the mitochondrial superoxide dismutase, led to the loss of the mitochondrial DNA, providing evidence that oxidative damage can be a major contributor to mitochondrial genomic instability in *S. cerevisiae* [58]. For mammalian mitochondria, contradictory results have been published. Localization of the human enzyme hNTHL1 to both the nucleus and the mitochondria was implied by Takao et al. [59], whereas Luna et al. found exclusive nuclear sorting [60]. A thymine glycol-DNA glycosylase/AP lyase was purified from rat mitochondria [61]. Karahalil et al. observed that thymine glycol incision activity was lost in mitochondria from *nth1*$^{-/-}$ mouse mutants [62], but Takao et al. reported the presence of another thymine glycol incision activity in mitochondrial extracts from NTH1-deficient mice [59]. Recent work in *Arabidopsis thaliana* showed a chloroplast localization for two endonuclease III homologues, AtNTH1 and AtNTH2 [41]. However, disruption of the corresponding genes suggested that these enzymes are not responsible for the major chloroplast thymine glycol-DNA glycosylase activity. As a consequence, there must be a third enzyme involved in thymine glycol excision from the chloroplast DNA, possibly a monofunctional glycosylase working together with an AP endonuclease [41].

Alkylated bases are usually excised by N-methylpurine-DNA glycosylase (MPG, also called AAG for alkyladenine-DNA glycosylase or 3-methyladenine DNA glycosylase). The presence of MPG in organelles has not been demonstrated so far but mammalian mitochondria repair DNA lesions which are regular substrates of MPG [31,63,64].

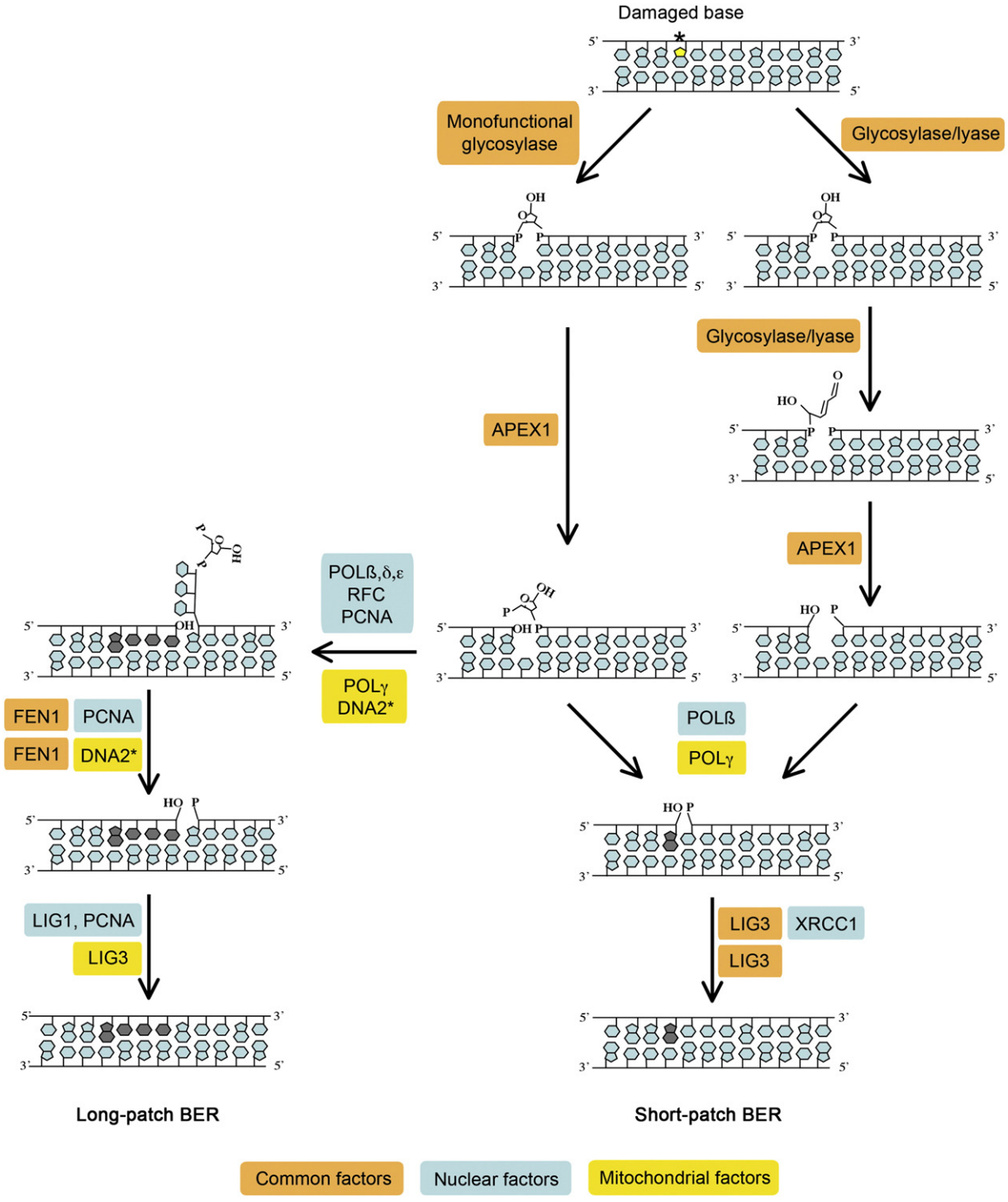

Fig. 2. Short-patch and long-patch base excision repair (BER) pathways in the nucleus and mitochondria of mammalian cells. The major factors involved are highlighted. Factors common to both compartments are displayed with an orange background, factors specific for the nucleus are on a blue background and factors specific for mitochondria are on a yellow background. *DNA2 is present in the nucleus but its putative role in nuclear BER is not clear so far. APEX1, AP endonuclease; POLβ, δ, ε, γ, DNA polymerase β, δ, ε, γ; RFC, replication factor C; PCNA, proliferating cell nuclear antigen; DNA2, endonuclease/helicase; FEN1, flap endonuclease 1; LIG1, LIG3, DNA ligase 1, 3; XRCC1, X-ray cross-complementing protein 1.

The mammalian major AP endonuclease, APEX1, localizes to both the nucleus and the mitochondria. The organelle form is a truncation product of the original APEX1 protein [65]. Mammalian cells have a second class II AP endonuclease, APE2, a subset of which is translocated into the mitochondria [66]. However, its catalytic activity is low and the actual function of this protein needs to be further studied. The *S. cerevisiae* major AP endonuclease, Apn1, harbours a mitochondrial targeting sequence at the N-terminus and a bipartite nuclear localization sequence in the C-terminal part, the latter acting in a dominant manner over the former. Apn1 can be targeted to the mitochondria through a particular mechanism mediated by Pir1, a yeast cell wall protein with internal repeats (Pir) [67]. Pir1 has the ability to compete with the nuclear import factors for binding to the nuclear localization sequence, allowing part of Apn1 to be imported

into mitochondria [68]. We recently characterized an AP site-cleaving activity in *A. thaliana* and *Solanum tuberosum* mitochondria [40] and in *A. thaliana* chloroplasts (unpublished results). The latter might correspond to the *ARP* gene (At2g41460)-encoded enzyme, which carries AP endonuclease activity and was recently shown to be targeted to the chloroplasts [41].

3.2. Re-synthesis and ligation

AP endonuclease releases a 3′-OH at the incised position but the mechanism of repair synthesis depends on the final status of the 5′-end of the incision. When AP endonuclease and the lyase activity of DNA polymerase manage to generate a ligatable 5′-phosphate end, repair synthesis proceeds through short-patch BER, *i.e.* incorporation of only one nucleotide. However, certain lesions or BER cleavage by-products are resistant to the lyase activity of DNA polymerase, like for instance 2-deoxyribonolactone [69]. In the nucleus, such situations lead to long-patch BER, with DNA synthesis extending from 2 to 6 nucleotides. In parallel, the original strand is displaced by the combined action of the PCNA (proliferating cell nuclear antigen) and FEN1 (flap endonuclease 1), leading to a "flap" structure which is subsequently cleaved to provide a ligatable 5′-phosphate [70]. In mitochondria, repair synthesis is carried out by DNA polymerase gamma (POLγ). As the nuclear enzyme, POLγ displays both polymerase and lyase activity but its lyase activity is weak [71,72]. On the other hand, derivatives resistant to the lyase activity of DNA polymerase are likely to be formed in organelles as well, especially due to constant oxidative pressure. As mentioned above, recent work established that long-patch BER, strand displacement and cleavage also occur in mammalian mitochondria, allowing to repair a broader range of lesions [45–48]. These processes are facilitated by the DNA2 helicase/nuclease and a flap endonuclease-like activity [45,73]. However, whether or not FEN1 is present in mammalian mitochondria is currently debated and the involvement of a still unidentified 5′-exo/endonuclease was also proposed [45,48]. The presence of FEN1 and DNA2 in mammalian mitochondria, as well as their roles in mitochondrial DNA repair and replication, are discussed in a recent review by Liu and Demple [1]. Whereas uracil repair was shown to occur through both short-patch and long-patch BER in mammalian organelles [45,46], we detected only short-patch repair of such lesions in plant mitochondria [40]. Whether both short-patch and long-patch BER occur in chloroplasts is not documented so far. Interestingly, earlier studies in wheat (*Triticum vulgare*) demonstrated that the chloroplast nuclease ChSI can cleave single-strand displaced structures [74], *i.e.* flap structures like those formed during long-patch BER.

POLγ is the only DNA polymerase found in mammalian mitochondria. It is a nuclear-encoded heterotrimer containing one copy of the POLGA catalytic subunit and two copies of the accessory factor POLGB [75]. Two duplicate genes, *POLγ1* and *POLγ2* (At3g20540 and At1g50840 loci, respectively), code for an organellar γ-type DNA polymerase in *A. thaliana*. Both proteins are dual-targeted to chloroplasts and mitochondria [76,77]. Especially striking, dual-targeting of POLγ2 appears to rely on a relaxed translation initiation control and the use of a non-AUG start codon [76]. The same genes were named *AtPolI-like A* and *AtPolI-like B* by another group which also characterized the organelle targeting of the corresponding proteins [78].

As the last step in the BER mechanism, the newly synthesized DNA patch is joined to the downstream sequence by a ligase. In human, a mitochondrial form of DNA ligase 3 (LIG3) is synthesized from an alternative translation initiation site and is likely to be the central DNA ligase in organelle repair processes [79]. Its antisense-mediated decrease results in a reduction in the mitochondrial DNA amount and an accumulation of single-strand nicks [80]. Only DNA ligase 1 (LIG1) has been found in the mitochondria of *S. cerevisiae* and this enzyme is considered to be the ligase involved in yeast organelle DNA repair [81]. DNA ligase 1 also seems to be the major DNA ligase in *A. thaliana* [82]. Production of three mRNA variants combined with the alternative use of the first two in-frame AUG codons results in a nuclear and mitochondrial form of *A. thaliana* DNA ligase 1 [83]. When present, the mitochondrial targeting sequence is dominant over the nuclear localization signal. Despite predictions and current database annotations, *A. thaliana* DNA ligase 1 does not appear to be targeted to the chloroplasts [83].

4. Mitochondrial DNA repair mechanisms: further pathways

4.1. Mismatch repair (MMR)

A mismatch repair (MMR) activity proficient in cleaving G:T and G:G mismatches is present in mammalian mitochondrial lysates but surprisingly it shows no bias in favour of the matrix strand and is thus prone to introducing mutations [84,85]. It has thus been suggested that this activity is involved in the repair of small loops rather than mismatches [84]. Recent data confirmed that human mitochondria possess a functional MMR pathway probably distinct from the corresponding nuclear pathway [86]. The YB-1 factor, previously reported to play a role in nuclear BER and repair of cross-linked DNA, seems to be a key component of human mitochondrial MMR and to be involved in mismatch recognition and binding. In *S. cerevisiae*, Msh1, a homologue of the *E. coli* mismatch repair component MutS, repairs G:A mispairs generated by replication past 8-oxodG, as well as other mismatches [87]. However, in addition to mitochondrial MMR, Msh1 may be involved in surveillance of mitochondrial DNA recombination [88]. Msh1-stimulated recombination might be involved in preventing oxidative lesion-induced instability of the mitochondrial genome [89]. Msh1 is also targeted to the organelles in *A. thaliana* but its role seems to be in mitochondrial DNA recombination control [90,91], so that in plants too the question of the mitochondrial MMR pathway remains open. BER would be a possible alternative mechanism to repair mismatches. Through *in vitro* incision reactions, we indeed revealed the activity of mismatch-cleaving, BER-type mitochondrial DNA glycosylases in *A. thaliana* (unpublished results). To our knowledge, mismatch repair in chloroplasts has yet to be investigated.

4.2. Double-strand break repair (DSBR)

Mitochondria repair double-strand breaks (DSBs), as shown in *Drosophila melanogaster* [92]. DSBs can be repaired by homologous recombination (HR) or non-homologous end joining (NHEJ). Evidence has been collected for both mechanisms in mammalian mitochondria [93–96] and recent results confirm both homology-dependent recombination and homology-independent repair [97,98]. Rad51, the central catalyst in eukaryotic nuclear HR, localizes also to mitochondria in human cells and could potentially be involved in organelle DSBR [99]. A number of proteins involved in recombination have been identified in *S. cerevisiae* mitochondria [38] and recombination activity has been demonstrated in plant mitochondria [100]. A RecA homologue is involved in the repair of mitochondrial DNA in the moss *Physcomitrella patens* [101]. In higher plant mitochondria, RecA homologues are involved in recombination surveillance [91]. Evidence for the presence of a RecA homologue in chloroplasts has been obtained in *Chlamydomonas reinhardtii* and in higher plants [102,103]. Chloroplasts can repair DSBs using short dispersed repeats located proximally, distally or on separate molecules and seem to carry out classical double-strand break repair (DSBR), single-strand annealing (SSA) as well as synthesis-dependent strand annealing (SDSA) [104]. Higher plant mitochondria and chloroplasts also have a capacity to repair DSBs by microhomology-mediated break-induced replication. This error-prone pathway may bypass accurate DNA repair in the case

of severe DNA damage and appears to be negatively regulated by the single-stranded DNA-binding proteins from the Whirly family [105]. Contrary to mitochondria, plastids seem to lack the possibility to repair DSBs by NHEJ [106].

4.3. Nucleotide excision repair (NER)

Nucleotide excision repair (NER) involves removal and re-synthesis of a short fragment on the damaged strand. A bulge formed at the level of the lesion in the DNA is detected. The corresponding region is cut out by structure-specific endonucleases and the gap is re-filled (*e.g.* [107,108]). It is still considered that there is no NER pathway *per se* in mammalian and fungal mitochondria (*e.g.* [7]). In yeast, some classical NER substrates seem to be repaired by alternative mechanisms. For instance, cyclobutane pyrimidine dimers (CPDs) and (6–4) pyrimidine–pyrimidone photoproducts [(6–4)PPs] can be removed by UV-damaged DNA endonuclease-dependent excision repair (UVER) in *Schizosaccharomyces pombe* mitochondria [109]. In such a pathway, the UV-damaged DNA endonuclease (UVDE) cleaves the phosphodiester bond 5′-adjacent to the CPD or (6–4)PP and the repair is thought to be completed by a BER-like process [110]. Similarities of UVER to the BER pathway were documented by *in vitro* biochemical reconstitution assays [111]. The absence or presence of NER in plant mitochondria has not been documented so far. Homologues of Mfd, which mediates transcription-coupled NER in *E. coli*, and of UvrD/MutU/RecL, which plays essential roles in post-recognition and incision steps in bacterial NER, may be transported into the chloroplasts in *A. thaliana* [112]. Early work in *C. reinhardtii* showed that UV-induced pyrimidine dimers in the chloroplast DNA can be repaired in the dark, suggesting that plastids possess an excision repair pathway for UV photoproducts [113]. The mechanism seemed however to differ from nuclear NER. Although absent in other eukaryotes, homologues of bacterial $uvrB^+$ and $uvrC^+$, which are involved in the initial incision steps of NER, have been identified in the *C. reinhardtii* genome and a possible role of these genes in chloroplast-specific NER processes has been proposed for this organism [114].

4.4. Direct repair (DR)

As an alternative to the complex NER mechanism, photoreactivation driven by photolyase, a single enzyme, can repair UV-induced DNA damage without cleaving the phosphodiester chain [115]. Mammalian mitochondria contain a cryptochrome [116] but no photolyase activity has been reported to date. By contrast, in *S. cerevisiae*, a photolyase is targeted to mitochondria and reverts UV-induced damage to the DNA [117,118]. Similarly, mitochondria of *Xenopus laevis* possess photolyase activity and run photoreactivation [119]. Investigation of plant organelles led to contrasted observations. Photoproducts were removed from the mitochondrial and chloroplastic DNA in UV-irradiated *A. thaliana* detached leaves kept under blue light, suggesting efficient photorepair [120]. However, light-dependent repair of UV damage to the chloroplast DNA in soybean cells appeared to be considerably slower than expected for photolyase-mediated photoreactivation [121] and further analyses failed to detect photolyase activity in chloroplasts from spinach leaves [122]. Contrasting with the situation in higher plants, *C. reinhardtii* chloroplasts possess a CPD photolyase encoded by the *PHR2* gene and cooperating with the product of the *PHR1* gene for full activity [8]. The O^6-methylguanine-DNA methyltransferase (MGMT) is the key component for direct reversion of alkylated damage in the nuclear DNA. Data suggest that an MGMT variant is present in mammalian mitochondria, allowing direct repair of methylated or ethylated derivatives but not of more complex alkylations [123–125].

4.5. Damage tolerance

Lesions that cannot be repaired or which escape repair potentially block replication, hence the development of tolerance mechanisms which include translesion synthesis (TLS) and template switching (*e.g.* [126,127]). Translesion synthesis is mostly performed by specialized DNA polymerases able to copy defective templates [128]. The possibility of translesion synthesis in mitochondria is open, as DNA POLγ proved capable of mutagenic bypass through DNA lesions, introducing a dA opposite an AP site or an 8-oxodG [129] or inserting any of the four deoxynucleotides opposite bulky DNA adducts derived from benzo[a]pyrene diol epoxide [130].

5. Specific aspects and further factors of organelle DNA repair mechanisms

Interesting additional features of organelle DNA repair processes have been identified, some of them crossing the borders between established mechanisms. Mitochondria appear to lack a NER pathway but promitochondria of *S. cerevisiae* anaerobic cells showed excision repair of UV-induced pyrimidine dimers, based on a mechanism depending on the endonuclease Rad2 [117]. Interestingly, Rad2 is related to both NER and BER. As mentioned, fungal mitochondria carry out UV-damaged DNA endonuclease-dependent excision repair (UVER) of UV photoproducts [109]. Notably, UVER is partially dependent on Rad2. Recent work established that mutation of the Cockayne syndrome B (CSB) gene encoding a NER factor causes deficient removal of oxidative damage in the mitochondrial DNA [131,132]. The NER proteins CSA and CSB actually localize to mitochondria upon oxidative stress in mammalian cells (Fig. 3). They interact with the mitochondrial DNA and the organelle BER components, thus contributing to oxidative damage repair [133]. Whether this reflects a link between BER and an elusive mitochondrial NER remains to be established.

The yeast *THI4* gene and the *A. thaliana thi1* gene encode a protein with dual function in thiamine biosynthesis and in mitochondrial DNA maintenance [134]. These genes partially complement *E. coli* strains defective in both BER and NER, suggesting a general role in DNA damage tolerance rather than damage removal. The precise function of the THI4 and THI1 proteins in damage tolerance remains to be characterized but, remarkably, they contain sequences homologous to DNA-binding motifs and to bacterial DNA polymerases, as well as a dinucleotide binding domain. THI1 is targeted to both mitochondria and chloroplasts in *A. thaliana* [135], based on the existence of two isoforms generated through the use of two different translation initiation codons [136]. There is also evidence for mitochondrial targeting of the THI4 protein in *S. cerevisiae* [134].

Further factors are involved in organelle DNA maintenance and contribute to a complex network of interactions (Fig. 3). The PARP-1 protein is a key component in repair of single-strand breaks [137]. Such lesions can be BER by-products and PARP-1 is seen as a BER modulator. A fraction of PARP-1 actually localizes to mitochondria in a mitofilin-dependent process and intra-mitochondrial PARP-1 has been reported to play a role in maintaining the integrity of the organelle DNA [138]. PARP-1 is recruited into a complex which binds to the mitochondrial DNA and contains DNA ligase 3. The mammalian mitochondrial protein TFAM was originally identified as a transcription factor but turned out to have multiple roles in DNA metabolism [139]. It not only packages the DNA in the mitochondrial nucleoid (see below), controls the DNA copy number, and participates in transcription, but also appears to play a direct role in DNA repair. TFAM binds stronger to oxidatively damaged DNA than to intact DNA and shows higher affinity for 8-oxoG-containing base pairs than the relevant OGG1 and MYH DNA glycosylases [140]. It recognizes the adducts formed by cisplatin, an anticancer drug producing inter- and intrastrand cross-links in the DNA, as well as

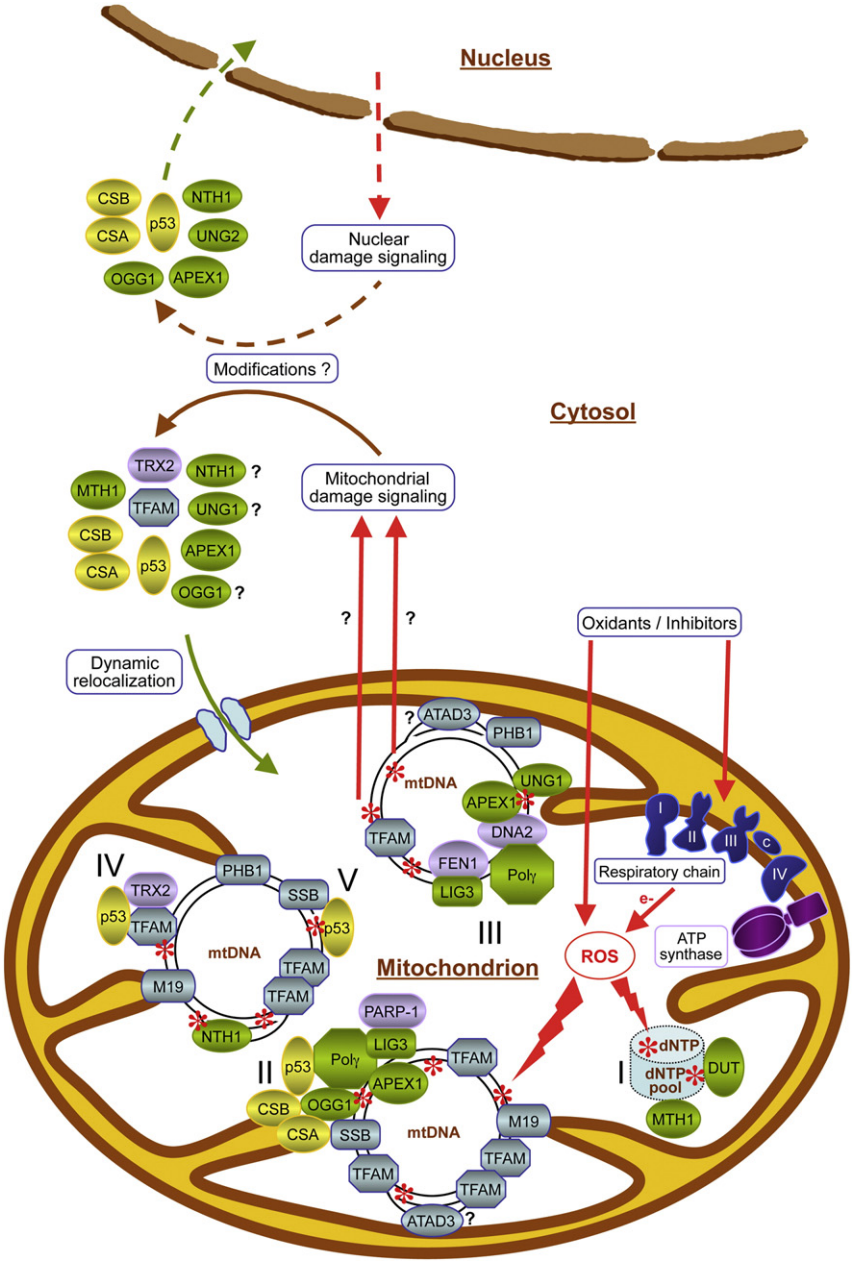

Fig. 3. Organization of oxidative DNA damage repair processes and factors in mammalian mitochondria, according to the literature data (see text for details and references). ROS generated by extra-mitochondrial oxidants or upon electrons leaking from the respiratory chain damage the organelle dNTP pool and the mitochondrial DNA (mtDNA). Damage signaling to the cytosol results in relocalization of repair proteins to the organelles, possibly upon post-translational modification. Mitochondrial damage signaling may compete with nuclear damage signaling for the recruitment of repair factors. Relocalization of OGG1, UNG1 and NTH1 is presented by analogy with yeast NTG1. Oxidized dNTPs can be eliminated by the DUT and MTH1 enzymes (I). The mitochondrial DNA is anchored to the membrane, possibly through PHB1, M19 or ATAD3. Most of the BER proteins are also membrane-bound. Short-patch BER (II) is mediated by a DNA glycosylase (for instance OGG1 for 8-oxoG repair), the AP endonuclease APEX1, the DNA polymerase POLγ and the DNA ligase LIG3; CSB recruits the BER proteins to the membrane; CSA and CSB interact with the single-stranded DNA-binding protein SSB and the glycosylase; the tumor suppressor p53 stimulates the glycosylase and POLγ; PARP-1 modulates BER. Long patch BER (III), in addition to the DNA glycosylase (for instance UNG1 for uracil repair), APEX1, POLγ and LIG3, requires the endonuclease/helicase DNA2 and the endonuclease FEN1. The transcription factor and packaging protein TFAM binds with high affinity to damaged DNA; TFAM binding is modulated by p53 and the thioredoxin TRX2 (IV). p53 itself can hydrolyse oxidized nucleotides at DNA 3′-ends and the reaction is enhanced by SSB (V). Main repair enzymes are in green; further factors are in yellow or purple; core DNA-interacting proteins are in blue.

the lesions induced by aminofluorene derivatives [141]. Interestingly, cisplatin-resistant cell lines seem to overexpress TFAM together with the mitochondrial thioredoxin 2 (TRX2) [142]. Both proteins interact directly, resulting in enhanced binding of TFAM to damaged DNA. TFAM also binds to p53, a tumor suppressor which localizes to mitochondria in response to death signals [143]. The complex has been biophysically characterized [144] and p53 in turn seems to modulate the binding of TFAM to damaged DNA, depending on the type of lesion considered [143]. Recent results suggest that TFAM indeed modulates the BER pathway in mitochondria by virtue of its DNA-binding activity and protein interactions [145]. On the other hand, the 3′–5′ exonuclease activity of p53 can hydrolyze oxidized nucleotides like 8-oxodG at DNA 3′-ends, a reaction which is enhanced upon interaction with the mitochondrial single-stranded DNA-binding protein (mtSSB) [146]. Further, p53 contributes to mitochondrial BER by stimulating both glycosylase-mediated removal of damaged bases and nucleotide incorporation by DNA POLγ [147–149].

6. Sub-organellar localization of DNA repair

DNA molecules in the organelles are not naked but are packed into nucleoprotein particles called nucleoids (*e.g.* [150–154]). Although their detailed composition is still a matter of discussion, these particles definitely contain a wide variety of proteins and factors for compaction and DNA metabolism (*e.g.* [155–157]). The structural organization of nucleoids involves TFAM in mammalian mitochondria [158] or histone-like proteins in chloroplasts [159]. Major DNA maintenance proteins are also core components of these dynamic particles which undergo remodeling in response to physiological conditions [160]. Factors proposed to control mammalian mitochondrial nucleoid organization include prohibitin 1 (PHB1) [161] and the AAA+ domain-containing protein ATAD3 [162]. Nucleoids are anchored to the organelle membranes through mechanisms which still need to be clarified [150,157,163–165]. The M19 mitochondrial protein has been suggested to be one of the membrane-tethering factors in mammalian organelles [166]. PHB1 itself is localized in the inner membrane and can be considered as a further candidate. Finally, ATAD3 is a mitochondrial membrane protein which has special binding properties for the displacement loop (D-loop) region of the mammalian organelle DNA [162]. It is thus tempting to speculate that it might play a major role in the association of the DNA and/or the nucleoids with the membranes. However, topological analyses of ATAD3 membrane insertion so far did not confirm the proposed interaction model [155,167].

Consistent with a membrane compartmentation of the organelle DNA, recent work has shown that most of the mitochondrial BER activities are membrane-bound in both mammalian [168] and plant [40] mitochondria. With the exception of AP endonuclease, the entire BER pathway interacts with the inner membrane in mammalian organelles and is supposed to associate with the nucleoids [168]. Interestingly, also p53 was recovered in a mitochondrial inner membrane subfraction containing BER components [148]. In plant mitochondria, uracil-DNA glycosylase and AP endonuclease are both membrane-associated [40], whereas surprisingly 8-oxoG-DNA glycosylase seemed to be soluble in our incision assays (unpublished results). In chloroplasts too, BER enzymes colocalize with the DNA in the nucleoids [41].

The functional organization of the BER machinery in the membranes has been further investigated in mammalian mitochondria (Fig. 3). Akbari et al. originally failed to detect stable repair complexes comprising uracil-DNA glycosylase [169]. This suggested that the different BER components would not stably interact with each other but that membrane co-localization would favour efficient substrate channeling [168–170]. A model has indeed been proposed in which the DNA would be mobile and would scroll through inner membrane complexes able to replicate, proofread and repair [168,171]. However, such a view has in turn to be reconciled with the idea that the mitochondrial DNA itself is anchored to the membrane in mammals [172]. Moreover, it has been implied that the NER proteins CSA and CSB interact with the mitochondrial single-stranded DNA-binding protein mtSSB and the BER enzyme OGG1 in a complex with the mitochondrial DNA [133]. Further, CSB seems to play a role in recruiting and/or retaining the BER proteins in complexes associated with the mitochondrial inner membrane [173]. Such complexes would connect the BER process to the nucleoids. Data from *in organello* repair experiments based on the natural competence of mitochondria for DNA import are in agreement with this model [46]. The experiments showed that mammalian mitochondria can carry out not only short-patch BER and long-patch BER but also generic nick-translation DNA synthesis. Coordinated BER synthesis occurs only at the membrane level on anchored DNA, whereas generic synthesis proceeds freely in the matrix.

7. Mitochondrial DNA damage, genetic processes and disease

Lesions in the DNA can block replication or transcription. Conversely, mispairing of modified bases and translesion synthesis lead to mutations. In 1988, two reports [174,175] showed that deletions and point mutations of the mitochondrial genome could be pathogenic. Since this date, there have been hundreds of associations of pathogenic mutations with mainly muscle and neurological disorders (although other tissues are commonly affected), which are often referred to as mitochondrial encephalomyopathies [176]. Although syndromes associated with specific mitochondrial DNA mutations are considered as rare, prevalence studies of known pathogenic mutations, or just of the m.3243A>G MELAS (*M*itochondrial *E*ncephalomyopathy, *L*actic *A*cidosis and *S*troke-like episodes) syndrome alone, report anything from 16 to 236 per 100,000 individuals of the Australian [177], British [178] or Finnish [179] community, making mitochondrial DNA disease the most common cause of hereditary neuromuscular disorder. More recently, a myriad of claims have been made to associate mitochondrial DNA mutations with more common disorders such as Parkinson's Disease [180], Alzheimer's Disease [181,182], male infertility [183] and cancer [184]. However, no causal link has been substantiated. Intriguingly, mitochondrial DNA repair itself may promote disease. DSB repair is thought to play a role in the generation of mitochondrial DNA deletions associated with human pathologies [185,186]. Some of these deletions seem to result from blunt end joining and are likely to be mediated by NHEJ [97,98]. Further, double-strand break repair may participate in chimeric gene formation and illegitimate recombination in plant mitochondria [90,91].

8. Mitochondrial DNA damage and aging

8.1. The aging theory

Many theories have been proposed to explain the phenomenon of aging (*e.g.* [187]). Among these, the free radical theory of aging [188] is a popular hypothesis and has been studied for almost half a century. It postulates that the production of ROS and the progressive accumulation of free radical damage is the cause of aging. As they are the main ROS producers in mammalian cells and the major target for their damaging effects, mitochondria were subsequently proposed to be the biological clock [189]. This postulate was refined to suggest that aging was due to the accumulation of damage to the mitochondrial DNA, yielding the mitochondrial theory of aging [189,190]. According to the latter, oxidative damage would result in increasing rates of mitochondrial DNA mutations. As the organelle genome encodes components of the respiratory chain and ATP synthase complexes, mutations could cause defects in oxidative phosphorylation, leading in turn to enhanced ROS production and further mitochondrial DNA damage. Such a vicious cycle would cause cellular dysfunction and ultimately death.

8.2. Challenging the ROS theory of aging

Numerous studies in a variety of species have tested different aspects of the mitochondrial theory of aging (*e.g.* [191–193]). However, perhaps the most celebrated is the production of a mouse model that concomitantly increases mitochondrial DNA mutation load and oxidative phosphorylation defects. Trifunovic et al. [194] and Kujoth et al. [195] introduced back into mice an error-prone form of mitochondrial POLγ (POLGA). The resultant increased mitochondrial DNA mutation rate correlated with decreased life expectancy and a phenotype consistent with premature aging. Although there is still some debate about whether the pathogenic molecules carry deletions or point mutations [196–199], both groups agreed that there is little evidence of increased ROS or oxidative stress as a consequence of the

mitochondrial DNA replication errors, arguing against any "vicious cycle".

In addition to the mouse studies with error-prone polymerase, reports from many authors using a variety of models now challenge the mitochondrial theory of aging (*e.g.* [200–209]). Oxidative damage of mitochondrial DNA indeed accumulates with age in mammals [210,211] and there is evidence that mitochondrial ROS production increases in aging *Drosophila*, although this does not regulate its lifespan [212]. One of the predictions the theory makes is that scavenging free radicals should increase life expectancy, while increasing ROS will lead to premature death. Several transgenic models have been established to address these questions. Overexpression of the mitochondrial Mn-superoxide dismutase (MnSOD) in *Drosophila* clearly extends lifespan [213], but in contrast, mice overexpressing a similar protein show no extension [214,215]. Overexpression of catalase, however, has been reported to increase life expectancy by almost 20% in mouse models [216]. Onset of age-related cardiac defects and cataracts were also delayed [217]. Increasing ROS levels by partially inactivating antioxidant activities does not appear to shorten lifespan. For example, transgenic mice expressing only one allele of mitochondrial thioredoxin TRX2, although exhibiting defects in oxidative phosphorylation and increased H_2O_2 production, did not show any decrease in life expectancy [215].

Thus, ROS production during normal metabolism is highly unlikely to be the single cause of aging and further models need to be explored. It has been hypothesized for instance that clustering of multiple genome copies in complex nucleoids may promote a progressive age-related accumulation of damage, deletions and point mutations in the DNA [218]. Mitochondrial nucleoids indeed appear to be remarkably stable. They do not freely exchange their DNA but rather tightly regulate their genetic content [219]. In any case, whether aging actually has a single cause remains by itself an open question.

8.3. Aging and DNA repair impairment

Evidence is still missing for a causative role of mitochondrial mutations in the development of aging phenotypes [191] but nevertheless damaged DNA accumulates in the organelles with age, raising the question of repair efficiency. Modifications in mitochondrial DNA repair may indeed contribute to the accumulation of DNA damage associated with aging, as illustrated for the BER pathway [220,221]. It is considered that 8-oxoG is one of the most abundant oxidative lesions and that it accumulates in mitochondrial DNA with age. This lesion is known to induce mutations due to the possibility of mispairing 8-oxoG with adenine during replication. Such an accumulation has been tentatively linked with neurodegenerative disorders and cancer [220]. The observation that, at the same time, the overall OGG1 8-oxoG-DNA glycosylase activity in mammalian cells increases with age was therefore quite puzzling [222]. It was first postulated that the continuous generation of ROS in mitochondria would eventually saturate the repair capability of the organelles, hence the need for an increasing amount of enzyme but with no avail. Szczesny et al. [223] later demonstrated that in aging mammalian cells the OGG1 protein actually accumulates in an unprocessed precursor form which remains in the intermembrane space, stuck to the outer membrane. Therefore, while the overall OGG1 content in the mitochondria increases with age, the amount of 8-oxoG-DNA glycosylase in the organelle inner compartment decreases, leading to the accumulation of 8-oxoG in the mitochondrial DNA. Similar observations were made for mitochondrial uracil-DNA glycosylase, which removes the mutagenic uracil in the DNA [223]. These data reveal an age-related decline in the mitochondrial import capacity for DNA repair factors. Such an impairment may become an important issue, as trafficking of repair proteins to the organelles might be a key process in the response to genotoxic stress (see below).

9. Regulation of mitochondrial DNA repair

9.1. Regulation through repair protein trafficking

Although functional BER activities were detected in mitochondrial lysates from human cells devoid of organelle DNA [43], mitochondrial DNA repair machineries are controlled and respond to genotoxic conditions. The mitochondrial isoforms of a number of repair proteins are generated through alternative splicing of primary transcripts, allowing for post-transcriptional control [170]. In this respect, it has been shown that the mammalian MYH DNA glycosylase has mitochondrial isoforms which are exclusive to the brain tissue [224]. Physiological regulation of BER protein expression has been partially documented at the cellular level but the relevance of these observations for mitochondrial processes remains to be established (reviewed in [39]). Notably, repair proteins are regularly mentioned to accumulate in the cytosol in unstressed conditions and to localize to mitochondria in response to DNA damaging conditions. Moving the pool of repair proteins to the damaged compartment is likely to be faster for the cells than inducing *de novo* gene expression and appears to be a major regulation mechanism of organelle DNA repair.

The most detailed study in this respect has been carried out for yeast *N*-glycosylases. Analysis of the subcellular distribution of the NTG1 and NTG2 DNA glycosylases in *S. cerevisiae* cells submitted to either nuclear or mitochondrial oxidative stress showed that NTG1 was dynamically relocalized to the compartment to which the stress was applied [225]. Generating organelle oxidative stress in yeast ρ0 cells (*i.e.* cells deprived of mitochondrial DNA) demonstrated that NTG1 localization to mitochondria was triggered by organelle DNA oxidative damage and not by the ROS level. This suggests that there is a sensing mechanism for organelle DNA damage which would be mediated by specific mitochondrial signals. Furthermore, nuclear and mitochondrial DNA damage signals would actually compete to recruit NTG1 [225,226]. The data also imply that lesions other than oxidized nucleotides can trigger relocalization of repair proteins. Sumoylation appeared to be involved in NTG1 nuclear trafficking, indicating a role of post-translational modification(s) in the relocalization process [225]. Whether protein modifications also determine mitochondrial targeting is not known but both the nuclear and the mitochondrial targeting sequence present in the protein were required for dynamic localization of NTG1 in response to oxidative stress [226]. Compromised NTG1 relocalization resulted in increased mutation rate and sensitivity to DNA damage.

As detailed in the previous sections, further repair proteins and modulating factors are targeted to both the nucleus and the mitochondria and some of them were shown to localize to the organelles in stress conditions. This is the case in particular for the AP endonuclease APEX1 [65,227] or the CSA and CSB proteins [133,173,228] in mammalian cells. Like *S. cerevisiae* NTG1, a number of these dual-targeted proteins have isoforms carrying both a nuclear and a mitochondrial localization sequence. Such a feature has been described for the human 8-oxoG-DNA glycosylase hOGG1-1a [229], the *S. cerevisiae* uracil-DNA glycosylase UNG1 [54], the mammalian thymine glycol-DNA glycosylase hNTHL1 [230] or the *S. cerevisiae* AP endonuclease APE1 [68]. It has thus been proposed that the dynamic localization process characterized with yeast NTG1 might be a general mechanism for BER regulation in response to DNA damage [226] (Fig. 3). Further data imply that the levels of BER enzymes in mammalian mitochondria are tightly controlled. Mitochondrial targeting of overexpressed methylpurine-DNA glycosylase (MPG) or bacterial exonuclease III (ExoIII) carrying a standard organelle import presequence imbalanced the BER pathway in human cancer cells and considerably enhanced sensitivity to oxidative damage [231,232]. This approach can be used to sensitize cancer cells to chemotherapeutic agents [233,234].

9.2. Repair regulation, disease and aging

In mammalian cells, oxidative damage to the mitochondrial DNA also correlates with the translocation of the tumor suppressor p53 to the organelles [235], which introduces a further regulation level, as p53 is thought to modulate DNA repair. As mentioned, p53 stimulates both removal of damaged bases and nucleotide re-insertion [147–149]. P53 is also likely to affect repair in mitochondria by altering the binding of TFAM to damaged DNA [143]. These mechanisms might in turn modulate p53-mediated apoptosis. Mitochondria actually regulate p53 in a number of ways, with likely consequences in the apoptosis processes [236]. In particular, the p53 pathway stimulates mitochondrial BER in colorectal cancer cells in reponse to damage and thus promotes mitochondrial genome stability [148]. Conversely, inhibition of mitochondrial DNA repair enhances apoptotic damage in carcinoma cells and may be useful in cancer treatment [237]. During apoptosis, monoubiquitination of the cytosolic form triggers translocation of p53 to the mitochondrial surface, where it is deubiquitinated and interacts with anti- and proapoptotic proteins [238]. Whether similar mechanisms allow a subfraction of p53 to localize to the inside of mitochondria upon oxidative/genotoxic stress remains to be documented.

Epileptic seizures are also associated with oxidative damage to the mitochondrial DNA. Animal model analyses established that the organelle DNA repair capacity is indeed altered during epileptogenesis and is severely impaired during the chronic phase of epilepsy [239]. Similarly, the mitochondrial BER pathway failed to respond to status epilepticus induced by pilocarpine, which is characterized by a high oxidative stress. Instead, BER enzyme levels in organelles decreased, an effect attributed to failure of mitochondrial import [240]. Nucleoside analogs like stavudine used as antiretroviral drugs, especially in the treatment of AIDS, may have severe side effects associated with mitochondrial toxicity. It turned out that, likely due to inhibition of POLγ, stavudine treatment actually reduces mitochondrial BER capacity and thus contributes to organelle DNA mutation [241].

Although aging is clearly associated with modifications in mitochondrial DNA repair capacity, the situation is contrasted [220,221]. Further studies in mammals and *Podospora anserina* showed that mitochondrial BER activities did not correlate, or even correlated negatively, with extended life span [221,242]. This may reflect a balance between DNA damage and repair, as mitochondrial DNA oxidative damage is inversely correlated with maximum life span in mammals. On the other hand, changes in mitochondrial BER play a role in DNA damage accumulation and age-related functional decline [221]. In *P. anserina*, aging is associated with a decrease in mitochondrial BER [242]. In mammals, variations in organelle BER capacity with age appear to be organ and tissue-specific [243], leading to increased BER enzyme activities in mitochondria from liver and heart [65,244,245] or gradual decline in brain [246–248]. Mitochondrial BER might be critical in the development and maintenance of the central nervous system during aging [249].

10. Conclusion

Originally believed to be absent, organelle DNA repair is now well established and has become an expanding field within a little more than a decade. BER remains the best documented and most studied pathway but almost all other standard mechanisms have been explored (*e.g.* Fig. 1). Only NER, the most complex DNA repair system involving a large number of protein factors, seems to be absent as such from mitochondria, at least in mammals and fungi. Nevertheless, some proteins considered as NER factors localize to the organelles and may cooperate with BER mechanisms, whereas fungi have developed mitochondrial UVER to handle some of the NER substrates. At the present stage, chloroplasts appear to lack NHEJ, but the existence of a plastid MMR has not been investigated to date.

DNA repair in organelles has also been established as a fundamental process, given the strong consequences observed upon its functional impairment. Inactivation of quite a number of genes encoding key repair proteins impacts mitochondrial DNA maintenance and causes an accumulation of DNA damage and mutations. Conversely, mobilization of the organelle repair machinery turned out to be very reactive to DNA damaging conditions. Considering the high extent of lesions and mutations in the mitochondrial DNA of older cells, one wonders what impairs or restricts this reactivity during aging. Decline of the mitochondrial import capacity for repair factors could be a first reason. Perhaps additive damage triggered by genotoxic conditions remaining below the threshold of repair induction also contributes. Nevertheless, understanding the regulation of organelle DNA repair in response to genotoxic pressure, its balance with the extent of DNA damage and its evolution with chronological age or disease is still a crucial goal for further investigations and should provide clues to control organelle DNA mutations and dysfunction.

Acknowledgements

Our work was supported by the French Centre National de la Recherche Scientifique (CNRS, UPR2357), the University of Strasbourg (UdS), the Wellcome Trust (Ref. 078900 to R.N.L.) and the Agence Nationale de la Recherche (ANR). P.B. was funded by a PhD fellowship from the French Ministry for Higher Education and Research. N.I. was funded by successive PhD fellowships provided by the Lebanese International University and the Lebanese Conseil National de la Recherche Scientifique. V.T. was funded by a post-doctoral fellowship provided by the French Ministry for Higher Education and Research.

References

[1] P. Liu, B. Demple, DNA repair in mammalian mitochondria: much more than we thought? Environ. Mol. Mutagen. 51 (2010) 417–426.
[2] L.F. Batista, B. Kaina, R. Meneghini, C.F. Menck, How DNA lesions are turned into powerful killing structures: insights from UV-induced apoptosis, Mutat. Res. 681 (2009) 197–208.
[3] J. Cadet, E. Sage, T. Douki, Ultraviolet radiation-mediated damage to cellular DNA, Mutat. Res. 571 (2005) 3–17.
[4] J.J. Chen, C.Z. Jiang, A.B. Britt, Little or no repair of cyclobutyl pyrimidine dimers is observed in the organellar genomes of the young *Arabidopsis* seedling, Plant Physiol. 111 (1996) 19–25.
[5] M. Hada, T. Hashimoto, O. Nikaido, M. Shin, UVB-induced DNA damage ans its photorepair in nuclei and chloroplasts of *Spinacea oleracea* L, Photochem. Photobiol. 68 (1998) 319–322.
[6] G.R. Harlow, M.E. Jenkins, T.S. Pittalwala, D.W. Mount, Isolation of uvh1, an *Arabidopsis* mutant hypersensitive to ultraviolet light and ionizing radiation, Plant Cell 6 (1994) 227–235.
[7] B. Pascucci, A. Versteegh, A. van Hoffen, A.A. van Zeeland, L.H. Mullenders, E. Dogliotti, DNA repair of UV photoproducts and mutagenesis in human mitochondrial DNA, J. Mol. Biol. 273 (1997) 417–427.
[8] J.L. Petersen, G.D. Small, A gene required for the novel activation of a class II DNA photolyase in *Chlamydomonas*, Nucleic Acids Res. 29 (2001) 4472–4481.
[9] J. Limon-Pacheco, M.E. Gonsebatt, The role of antioxidants and antioxidant-related enzymes in protective responses to environmentally induced oxidative stress, Mutat. Res. 674 (2009) 137–147.
[10] J.F. Turrens, Mitochondrial formation of reactive oxygen species, J. Physiol. 552 (2003) 335–344.
[11] M.P. Murphy, How mitochondria produce reactive oxygen species, Biochem. J. 417 (2009) 1–13.
[12] H. Foyer, G. Noctor, Redox sensing and signalling associated with reactive oxygen in chloroplasts, peroxisomes and mitochondria, Physiol. Plant. 119 (2003) 355–364.
[13] M.E. Goetz, A. Luch, Reactive species: a cell damaging rout assisting to chemical carcinogens, Cancer Lett. 266 (2008) 73–83.
[14] S. Kitajima, Hydrogen peroxide-mediated inactivation of two chloroplastic peroxidases, ascorbate peroxidase and 2-cys peroxiredoxin, Photochem. Photobiol. 84 (2008) 1404–1409.
[15] A. Krieger-Liszkay, A. Trebst, Tocopherol is the scavenger of singlet oxygen produced by the triplet states of chlorophyll in the PSII reaction centre, J. Exp. Bot. 57 (2006) 1677–1684.
[16] G. Noctor, R. De Paepe, C.H. Foyer, Mitochondrial redox biology and homeostasis in plants, Trends Plant Sci. 12 (2007) 125–134.

[17] M. Dizdaroglu, P. Jaruga, M. Birincioglu, H. Rodriguez, Free radical-induced damage to DNA: mechanisms and measurement, Free Radic. Biol. Med. 32 (2002) 1102–1115.
[18] M.D. Evans, M. Dizdaroglu, M.S. Cooke, Oxidative DNA damage and disease: induction, repair and significance, Mutat. Res. 567 (2004) 1–61.
[19] S. Burney, J.L. Caulfield, J.C. Niles, J.S. Wishnok, S.R. Tannenbaum, The chemistry of DNA damage from nitric oxide and peroxynitrite, Mutat. Res. 424 (1999) 37–49.
[20] S. Burney, J.C. Niles, P.C. Dedon, S.R. Tannenbaum, DNA damage in deoxynucleosides and oligonucleotides treated with peroxynitrite, Chem. Res. Toxicol. 12 (1999) 513–520.
[21] A. Valavanidis, T. Vlachogianni, C. Fiotakis, 8-Hydroxy-2′-deoxyguanosine (8-OHdG): a critical biomarker of oxidative stress and carcinogenesis, J. Environ. Sci. Health C Environ. Carcinog. Ecotoxicol. Rev. 27 (2009) 120–139.
[22] R.A. Floyd, M.S. West, W.E. Hogsett, D.T. Tingey, Increased 8-hydroxyguanine content of chloroplast DNA from ozone-treated plants, Plant Physiol. 91 (1989) 644–647.
[23] J. Ichikawa, D. Tsuchimoto, S. Oka, M. Ohno, M. Furuichi, K. Sakumi, Y. Nakabeppu, Oxidation of mitochondrial deoxynucleotide pools by exposure to sodium nitroprusside induces cell death, DNA Repair (Amst.) 7 (2008) 418–430.
[24] S.G. Jarrett, H. Lin, B.F. Godley, M.E. Boulton, Mitochondrial DNA damage and its potential role in retinal degeneration, Prog. Retin. Eye Res. 27 (2008) 596–607.
[25] M. Ohno, S. Oka, Y. Nakabeppu, Quantitative analysis of oxidized guanine, 8-oxoguanine, in mitochondrial DNA by immunofluorescence method, Meth. Mol. Biol. 554 (2009) 199–212.
[26] S. Xu, M. Zhong, L. Zhang, Z. Zhou, W. Zhang, Y. Wang, X. Wang, M. Li, Y. Chen, C. Chen, M. He, G. Zhang, Z. Yu, Exposure to 1800 MHz radiofrequency radiation induces oxidative damage to mitochondrial DNA in primary cultured neurons, Brain Res. 1311 (2010) 189–196.
[27] M.Y. Galperin, O.V. Moroz, K.S. Wilson, A.G. Murzin, House cleaning, a part of good housekeeping, Mol. Microbiol. 59 (2006) 5–19.
[28] K. Fujikawa, H. Kamiya, H. Yakushiji, Y. Fujii, Y. Nakabeppu, H. Kasai, The oxidized forms of dATP are substrates for the human MutT homologue, the hMTH1 protein, J. Biol. Chem. 274 (1999) 18201–18205.
[29] R.D. Ladner, S.J. Caradonna, The human dUTPase gene encodes both nuclear and mitochondrial isoforms. Differential expression of the isoforms and characterization of a cDNA encoding the mitochondrial species, J. Biol. Chem. 272 (1997) 19072–19080.
[30] W. Xiao, L. Samson, *In vivo* evidence for endogenous DNA alkylation damage as a source of spontaneous mutation in eukaryotic cells, Proc. Natl Acad. Sci. USA 90 (1993) 2117–2121.
[31] S.P. Ledoux, C.C. Shen, V.I. Grishko, P.A. Fields, A.L. Gard, G.L. Wilson, Glial cell-specific differences in response to alkylation damage, Glia 24 (1998) 304–312.
[32] H. Bartsch, DNA adducts in human carcinogenesis: etiological relevance and structure–activity relationship, Mutat. Res. 340 (1996) 67–79.
[33] R. Balansky, A. Izzotti, L. Scatolini, F. D'Agostini, S. De Flora, Induction by carcinogens and chemoprevention by N-acetylcysteine of adducts to mitochondrial DNA in rat organs, Cancer Res. 56 (1996) 1642–1647.
[34] D. Jung, Y. Cho, L.B. Collins, J.A. Swenberg, R.T. Di Giulio, Effects of benzo[a]pyrene on mitochondrial and nuclear DNA damage in Atlantic killifish (*Fundulus heteroclitus*) from a creosote-contaminated and reference site, Aquat. Toxicol. 95 (2009) 44–51.
[35] R.D. Thomas, D. Roy, Stilbene estrogen produces higher levels of mitochondrial DNA adducts than nuclear DNA adducts in the target organ of cancer (liver) of male Sprague Dawley rats, Oncol. Rep. 8 (2001) 1035–1038.
[36] Z. Yang, L.M. Schumaker, M.J. Egorin, E.G. Zuhowski, Z. Guo, K.J. Cullen, Cisplatin preferentially binds mitochondrial DNA and voltage-dependent anion channel protein in the mitochondrial membrane of head and neck squamous cell carcinoma: possible role in apoptosis, Clin. Cancer Res. 12 (2006) 5817–5825.
[37] J. Nair, S. Strand, N. Frank, J. Knauft, H. Wesch, P.R. Galle, H. Bartsch, Apoptosis and age-dependant induction of nuclear and mitochondrial etheno-DNA adducts in Long–Evans Cinnamon (LEC) rats: enhanced DNA damage by dietary curcumin upon copper accumulation, Carcinogenesis 26 (2005) 1307–1315.
[38] N.B. Larsen, M. Rasmussen, L.J. Rasmussen, Nuclear and mitochondrial DNA repair: similar pathways? Mitochondrion 5 (2005) 89–108.
[39] J.A. Stuart, M.F. Brown, Mitochondrial DNA maintenance and bioenergetics, Biochim. Biophys. Acta 1757 (2006) 79–89.
[40] P. Boesch, N. Ibrahim, F. Paulus, A. Cosset, V. Tarasenko, A. Dietrich, Plant mitochondria possess a short-patch base excision DNA repair pathway, Nucleic Acids Res. 37 (2009) 5690–5700.
[41] B.L. Gutman, K.K. Niyogi, Evidence for base excision repair of oxidative DNA damage in chloroplasts of *Arabidopsis thaliana*, J. Biol. Chem. 284 (2009) 17006–17012.
[42] R.H. Stierum, G.L. Dianov, V.A. Bohr, Single-nucleotide patch base excision repair of uracil in DNA by mitochondrial protein extracts, Nucleic Acids Res. 27 (1999) 3712–3719.
[43] J.A. Stuart, K. Hashiguchi, D.M. Wilson III, W.C. Copeland, N.C. Souza-Pinto, V.A. Bohr, DNA base excision repair activities and pathway function in mitochondrial and cellular lysates from cells lacking mitochondrial DNA, Nucleic Acids Res. 32 (2004) 2181–2192.
[44] J.S. Sung, B. Demple, Roles of base excision repair subpathways in correcting oxidized abasic sites in DNA, FEBS J. 273 (2006) 1620–1629.
[45] M. Akbari, T. Visnes, H.E. Krokan, M. Otterlei, Mitochondrial base excision repair of uracil and AP sites takes place by single-nucleotide insertion and long-patch DNA synthesis, DNA Repair (Amst.) 7 (2008) 605–616.
[46] P. Boesch, N. Ibrahim, A. Dietrich, R.N. Lightowlers, Membrane association of mitochondrial DNA facilitates base excision repair in mammalian mitochondria, Nucleic Acids Res. 38 (2010) 1478–1488.
[47] P. Liu, L. Qian, J.S. Sung, N.C. de Souza-Pinto, L. Zheng, D.F. Bogenhagen, V.A. Bohr, D.M. Wilson III, B. Shen, B. Demple, Removal of oxidative DNA damage via FEN1-dependent long-patch base excision repair in human cell mitochondria, Mol. Cell. Biol. 28 (2008) 4975–4987.
[48] B. Szczesny, A.W. Tann, M.J. Longley, W.C. Copeland, S. Mitra, Long patch base excision repair in mammalian mitochondrial genomes, J. Biol. Chem. 283 (2008) 26349–26356.
[49] D. Kang, N. Hamasaki, Maintenance of mitochondrial DNA integrity: repair and degradation, Curr. Genet. 41 (2002) 311–322.
[50] N.C. de Souza-Pinto, L. Eide, B.A. Hogue, T. Thybo, T. Stevnsner, E. Seeberg, A. Klungland, V.A. Bohr, Repair of 8-oxodeoxyguanosine lesions in mitochondrial DNA depends on the oxoguanine DNA glycosylase (OGG1) gene and 8-oxoguanine accumulates in the mitochondrial DNA of OGG1-defective mice, Cancer Res. 61 (2001) 5378–5381.
[51] A. Parker, Y. Gu, A.L. Lu, Purification and characterization of a mammalian homolog of *Escherichia coli* MutY mismatch repair protein from calf liver mitochondria, Nucleic Acids Res. 28 (2000) 3206–3215.
[52] M. Takao, Q.M. Zhang, S. Yonei, A. Yasui, Differential subcellular localization of human MutY homolog (hMYH) and the functional activity of adenine:8-oxoguanine DNA glycosylase, Nucleic Acids Res. 27 (1999) 3638–3644.
[53] H. Nilsen, M. Otterlei, T. Haug, K. Solum, T.A. Nagelhus, F. Skorpen, H.E. Krokan, Nuclear and mitochondrial uracil-DNA glycosylases are generated by alternative splicing and transcription from different positions in the UNG gene, Nucleic Acids Res. 25 (1997) 750–755.
[54] A. Chatterjee, K.K. Singh, Uracil-DNA glycosylase-deficient yeast exhibit a mitochondrial mutator phenotype, Nucleic Acids Res. 29 (2001) 4935–4940.
[55] M. Koulintchenko, Y. Konstantinov, A. Dietrich, Plant mitochondria actively import DNA *via* the permeability transition pore complex, EMBO J. 22 (2003) 1245–1254.
[56] I. Alseth, L. Eide, M. Pirovano, T. Rognes, E. Seeberg, M. Bjoras, The *Saccharomyces cerevisiae* homologues of endonuclease III from *Escherichia coli*, Ntg1 and Ntg2, are both required for efficient repair of spontaneous and induced oxidative DNA damage in yeast, Mol. Cell. Biol. 19 (1999) 3779–3787.
[57] H.J. You, R.L. Swanson, C. Harrington, A.H. Corbett, S. Jinks-Robertson, S. Senturker, S.S. Wallace, S. Boiteux, M. Dizdaroglu, P.W. Doetsch, *Saccharomyces cerevisiae* Ntg1p and Ntg2p: broad specificity N-glycosylases for the repair of oxidative DNA damage in the nucleus and mitochondria, Biochemistry 38 (1999) 11298–11306.
[58] N.A. Doudican, B. Song, G.S. Shadel, P.W. Doetsch, Oxidative DNA damage causes mitochondrial genomic instability in *Saccharomyces cerevisiae*, Mol. Cell. Biol. 25 (2005) 5196–5204.
[59] M. Takao, S. Kanno, T. Shiromoto, R. Hasegawa, H. Ide, S. Ikeda, A.H. Sarker, S. Seki, J.Z. Xing, X.C. Le, M. Weinfeld, K. Kobayashi, J. Miyazaki, M. Muijtjens, J.H. Hoeijmakers, G. van der Horst, A. Yasui, Novel nuclear and mitochondrial glycosylases revealed by disruption of the mouse Nth1 gene encoding an endonuclease III homolog for repair of thymine glycols, EMBO J. 21 (2002) 3486–3493.
[60] L. Luna, M. Bjoras, E. Hoff, T. Rognes, E. Seeberg, Cell-cycle regulation, intracellular sorting and induced overexpression of the human NTH1 DNA glycosylase involved in removal of formamidopyrimidine residues from DNA, Mutat. Res. 460 (2000) 95–104.
[61] R.H. Stierum, D.L. Croteau, V.A. Bohr, Purification and characterization of a mitochondrial thymine glycol endonuclease from rat liver, J. Biol. Chem. 274 (1999) 7128–7136.
[62] B. Karahalil, N.C. de Souza-Pinto, J.L. Parsons, R.H. Elder, V.A. Bohr, Compromised incision of oxidized pyrimidines in liver mitochondria of mice deficient in NTH1 and OGG1 glycosylases, J. Biol. Chem. 278 (2003) 33701–33707.
[63] C.C. Pettepher, S.P. LeDoux, V.A. Bohr, G.L. Wilson, Repair of alkali-labile sites within the mitochondrial DNA of RINr 38 cells after exposure to the nitrosourea streptozotocin, J. Biol. Chem. 266 (1991) 3113–3117.
[64] M. Pirsel, V.A. Bohr, Methyl methanesulfonate adduct formation and repair in the DHFR gene and in mitochondrial DNA in hamster cells, Carcinogenesis 14 (1993) 2105–2108.
[65] S. Mitra, T. Izumi, I. Boldogh, K.K. Bhakat, R. Chattopadhyay, B. Szczesny, Intracellular trafficking and regulation of mammalian AP-endonuclease 1 (APE1), an essential DNA repair protein, DNA Repair (Amst.) 6 (2007) 461–469.
[66] D. Tsuchimoto, Y. Sakai, K. Sakumi, K. Nishioka, M. Sasaki, T. Fujiwara, Y. Nakabeppu, Human APE2 protein is mostly localized in the nuclei and to some extent in the mitochondria, while nuclear APE2 is partly associated with proliferating cell nuclear antigen, Nucleic Acids Res. 29 (2001) 2349–2360.
[67] M. Mazan, K. Mazanova, V. Farkas, Phenotype analysis of *Saccharomyces cerevisiae* mutants with deletions in Pir cell wall glycoproteins, Antonie Leeuwenhoek 94 (2008) 335–342.
[68] R. Vongsamphanh, P.K. Fortier, D. Ramotar, Pir1p mediates translocation of the yeast Apn1p endonuclease into the mitochondria to maintain genomic stability, Mol. Cell. Biol. 21 (2001) 1647–1655.
[69] K.M. Kroeger, M. Hashimoto, Y.W. Kow, M.M. Greenberg, Cross-linking of 2-deoxyribonolactone and its beta-elimination product by base excision repair enzymes, Biochemistry 42 (2003) 2449–2455.
[70] V.A. Dianova II, G.L. Bohr, Dianov, Interaction of human AP endonuclease 1 with flap endonuclease 1 and proliferating cell nuclear antigen involved in long-patch base excision repair, Biochemistry 40 (2001) 12639–12644.
[71] L.S. Kaguni, DNA polymerase gamma, the mitochondrial replicase, Annu. Rev. Biochem. 73 (2004) 293–320.

[72] K.G. Pinz, D.F. Bogenhagen, Characterization of a catalytically slow AP lyase activity in DNA polymerase gamma and other family A DNA polymerases, J. Biol. Chem. 275 (2000) 12509–12514.
[73] L. Zheng, M. Zhou, Z. Guo, H. Lu, L. Qian, H. Dai, J. Qiu, E. Yakubovskaya, D.F. Bogenhagen, B. Demple, B. Shen, Human DNA2 is a mitochondrial nuclease/helicase for efficient processing of DNA replication and repair intermediates, Mol. Cell 32 (2008) 325–336.
[74] A. Przykorska, K. Solecka, K. Olszak, G. Keith, B. Nawrot, E. Kuligowska, Wheat (*Triticum vulgare*) chloroplast nuclease ChSI exhibits 5′ flap structure-specific endonuclease activity, Biochemistry 43 (2004) 11283–11294.
[75] E. Yakubovskaya, M. Lukin, Z. Chen, J. Berriman, J.S. Wall, R. Kobayashi, C. Kisker, D.F. Bogenhagen, The EM structure of human DNA polymerase gamma reveals a localized contact between the catalytic and accessory subunits, EMBO J. 26 (2007) 4283–4291.
[76] A.C. Christensen, A. Lyznik, S. Mohammed, C.G. Elowsky, A. Elo, R. Yule, S.A. Mackenzie, Dual-domain, dual-targeting organellar protein presequences in *Arabidopsis* can use non-AUG start codons, Plant Cell 17 (2005) 2805–2816.
[77] A. Elo, A. Lyznik, D.O. Gonzalez, S.D. Kachman, S.A. Mackenzie, Nuclear genes that encode mitochondrial proteins for DNA and RNA metabolism are clustered in the *Arabidopsis* genome, Plant Cell 15 (2003) 1619–1631.
[78] Y. Mori, S. Kimura, A. Saotome, N. Kasai, N. Sakaguchi, Y. Uchiyama, T. Ishibashi, T. Yamamoto, H. Chiku, K. Sakaguchi, Plastid DNA polymerases from higher plants, *Arabidopsis thaliana*, Biochem. Biophys. Res. Commun. 334 (2005) 43–50.
[79] U. Lakshmipathy, C. Campbell, The human DNA ligase III gene encodes nuclear and mitochondrial proteins, Mol. Cell. Biol. 19 (1999) 3869–3876.
[80] U. Lakshmipathy, C. Campbell, Antisense-mediated decrease in DNA ligase III expression results in reduced mitochondrial DNA integrity, Nucleic Acids Res. 29 (2001) 668–676.
[81] S.L. Donahue, B.E. Corner, L. Bordone, C. Campbell, Mitochondrial DNA ligase function in *Saccharomyces cerevisiae*, Nucleic Acids Res. 29 (2001) 1582–1589.
[82] R.M. Taylor, M.J. Hamer, J. Rosamond, C.M. Bray, Molecular cloning and functional analysis of the *Arabidopsis thaliana* DNA ligase I homologue, Plant J. 14 (1998) 75–81.
[83] P.A. Sunderland, C.E. West, W.M. Waterworth, C.M. Bray, An evolutionarily conserved translation initiation mechanism regulates nuclear or mitochondrial targeting of DNA ligase 1 in *Arabidopsis thaliana*, Plant J. 47 (2006) 356–367.
[84] P.A. Mason, R.N. Lightowlers, Why do mammalian mitochondria possess a mismatch repair activity? FEBS Lett. 554 (2003) 6–9.
[85] P.A. Mason, E.C. Matheson, A.G. Hall, R.N. Lightowlers, Mismatch repair activity in mammalian mitochondria, Nucleic Acids Res. 31 (2003) 1052–1058.
[86] N.C. de Souza-Pinto, P.A. Mason, K. Hashiguchi, L. Weissman, J. Tian, D. Guay, M. Lebel, T.V. Stevnsner, L.J. Rasmussen, V.A. Bohr, Novel DNA mismatch-repair activity involving YB-1 in human mitochondria, DNA Repair (Amst.) 8 (2009) 704–719.
[87] P. Dzierzbicki, P. Koprowski, M.U. Fikus, E. Malc, Z. Ciesla, Repair of oxidative damage in mitochondrial DNA of *Saccharomyces cerevisiae*: involvement of the MSH1-dependent pathway, DNA Repair (Amst.) 3 (2004) 403–411.
[88] S.A. Mookerjee, E.A. Sia, Overlapping contributions of Msh1p and putative recombination proteins Cce1p, Din7p, and Mhr1p in large-scale recombination and genome sorting events in the mitochondrial genome of *Saccharomyces cerevisiae*, Mutat. Res. 595 (2006) 91–106.
[89] A. Kaniak, P. Dzierzbicki, A.T. Rogowska, E. Malc, M. Fikus, Z. Ciesla, Msh1p counteracts oxidative lesion-induced instability of mtDNA and stimulates mitochondrial recombination in *Saccharomyces cerevisiae*, DNA Repair (Amst.) 8 (2009) 318–329.
[90] M.P. Arrieta-Montiel, V. Shedge, J. Davila, A.C. Christensen, S.A. Mackenzie, Diversity of the *Arabidopsis* mitochondrial genome occurs *via* nuclear-controlled recombination activity, Genetics 183 (2009) 1261–1268.
[91] V. Shedge, M. Arrieta-Montiel, A.C. Christensen, S.A. Mackenzie, Plant mitochondrial recombination surveillance requires unusual RecA and MutS homologs, Plant Cell 19 (2007) 1251–1264.
[92] F. Morel, M. Renoux, P. Lachaume, S. Alziari, Bleomycin-induced double-strand breaks in mitochondrial DNA of *Drosophila* cells are repaired, Mutat. Res. 637 (2008) 111–117.
[93] G. Coffey, U. Lakshmipathy, C. Campbell, Mammalian mitochondrial extracts possess DNA end-binding activity, Nucleic Acids Res. 27 (1999) 3348–3354.
[94] O.A. Kajander, P.J. Karhunen, I.J. Holt, H.T. Jacobs, Prominent mitochondrial DNA recombination intermediates in human heart muscle, EMBO Rep. 2 (2001) 1007–1012.
[95] U. Lakshmipathy, C. Campbell, Double strand break rejoining by mammalian mitochondrial extracts, Nucleic Acids Res. 27 (1999) 1198–1204.
[96] B. Thyagarajan, R.A. Padua, C. Campbell, Mammalian mitochondria possess homologous DNA recombination activity, J. Biol. Chem. 271 (1996) 27536–27543.
[97] S.R. Bacman, S.L. Williams, C.T. Moraes, Intra- and inter-molecular recombination of mitochondrial DNA after *in vivo* induction of multiple double-strand breaks, Nucleic Acids Res. 37 (2009) 4218–4226.
[98] H. Fukui, C.T. Moraes, Mechanisms of formation and accumulation of mitochondrial DNA deletions in aging neurons, Hum. Mol. Genet. 18 (2009) 1028–1036.
[99] J.M. Sage, O.S. Gildemeister, K.L. Knight, Discovery of a novel function for human Rad51: maintenance of the mitochondrial genome, J. Biol. Chem. 285 (2010) 18984–18990.
[100] M. Manchekar, K. Scissum-Gunn, D. Song, F. Khazi, S.L. McLean, B.L. Nielsen, DNA recombination activity in soybean mitochondria, J. Mol. Biol. 356 (2006) 288–299.
[101] M. Odahara, T. Inouye, T. Fujita, M. Hasebe, Y. Sekine, Involvement of mitochondrial-targeted RecA in the repair of mitochondrial DNA in the moss, *Physcomitrella patens*, Genes Genet. Syst. 82 (2007) 43–51.
[102] E. Nakazato, H. Fukuzawa, S. Tabata, H. Takahashi, K. Tanaka, Identification and expression analysis of cDNA encoding a chloroplast recombination protein REC1, the chloroplast RecA homologue in *Chlamydomonas reinhardtii*, Biosci. Biotechnol. Biochem. 67 (2003) 2608–2613.
[103] H. Cerutti, A.M. Johnson, J.E. Boynton, N.W. Gillham, Inhibition of chloroplast DNA recombination and repair by dominant negative mutants of *Escherichia coli* RecA, Mol. Cell. Biol. 15 (1995) 3003–3011.
[104] O.W. Odom, K.H. Baek, R.N. Dani, D.L. Herrin, *Chlamydomonas* chloroplasts can use short dispersed repeats and multiple pathways to repair a double-strand break in the genome, Plant J. 53 (2008) 842–853.
[105] L. Cappadocia, A. Marechal, J.S. Parent, E. Lepage, J. Sygusch, N. Brisson, Crystal structures of DNA–Whirly complexes and their role in *Arabidopsis* organelle genome repair, Plant Cell 22 (2010) 1849–1867.
[106] S. Kohl, R. Bock, Transposition of a bacterial insertion sequence in chloroplasts, Plant J. 58 (2009) 423–436.
[107] R. Dip, U. Camenisch, H. Naegeli, Mechanisms of DNA damage recognition and strand discrimination in human nucleotide excision repair, DNA Repair (Amst.) 3 (2004) 1409–1423.
[108] S. Kimura, K. Sakaguchi, DNA repair in plants, Chem. Rev. 106 (2006) 753–766.
[109] S. Yasuhira, A. Yasui, Alternative excision repair pathway of UV-damaged DNA in *Schizosaccharomyces pombe* operates both in nucleus and in mitochondria, J. Biol. Chem. 275 (2000) 11824–11828.
[110] R. Yonemasu, S.J. McCready, J.M. Murray, F. Osman, M. Takao, K. Yamamoto, A.R. Lehmann, A. Yasui, Characterization of the alternative excision repair pathway of UV-damaged DNA in *Schizosaccharomyces pombe*, Nucleic Acids Res. 25 (1997) 1553–1558.
[111] J.L. Alleva, S. Zuo, J. Hurwitz, P.W. Doetsch, *In vitro* reconstitution of the *Schizosaccharomyces pombe* alternative excision repair pathway, Biochemistry 39 (2000) 2659–2666.
[112] J.B. Hays, *Arabidopsis thaliana*, a versatile model system for study of eukaryotic genome-maintenance functions, DNA Repair (Amst.) 1 (2002) 579–600.
[113] G.D. Small, C.S. Greimann, Photoreactivation and dark repair of ultraviolet light-induced pyrimidine dimers in chloroplast DNA, Nucleic Acids Res. 4 (1977) 2893–2902.
[114] D. Vlcek, A. Sevcovicova, B. Sviezena, E. Galova, E. Miadokova, *Chlamydomonas reinhardtii*: a convenient model system for the study of DNA repair in photoautotrophic eukaryotes, Curr. Genet. 53 (2008) 1–22.
[115] A. Sancar, Structure and function of photolyase and *in vivo* enzymology: 50th anniversary, J. Biol. Chem. 283 (2008) 32153–32157.
[116] K. Kobayashi, S. Kanno, B. Smit, G.T. van der Horst, M. Takao, A. Yasui, Characterization of photolyase/blue-light receptor homologs in mouse and human cells, Nucleic Acids Res. 26 (1998) 5086–5092.
[117] K. Pasupathy, D.S. Pradhan, Evidence for excision repair in promitochondrial DNA of anaerobic cells of *Saccharomyces cerevisiae*, Mutat. Res. 273 (1992) 281–288.
[118] A. Yasui, H. Yajima, T. Kobayashi, A.P. Eker, A. Oikawa, Mitochondrial DNA repair by photolyase, Mutat. Res. 273 (1992) 231–236.
[119] M. Ryoji, H. Katayama, H. Fusamae, A. Matsuda, F. Sakai, H. Utano, Repair of DNA damage in a mitochondrial lysate of *Xenopus laevis* oocytes, Nucleic Acids Res. 24 (1996) 4057–4062.
[120] C.K. Draper, J.B. Hays, Replication of chloroplast, mitochondrial and nuclear DNA during growth of unirradiated and UVB-irradiated *Arabidopsis* leaves, Plant J. 23 (2000) 255–265.
[121] G.C. Cannon, L.A. Hedrick, S. Heinhorst, Repair mechanisms of UV-induced DNA damage in soybean chloroplasts, Plant Mol. Biol. 29 (1995) 1267–1277.
[122] M. Hada, K. Hino, G. Buchholz, J. Goss, E. Wellmann, M. Shin, Assay of DNA photolyase activity in spinach leaves in relation to cell compartmentation—evidence for lack of DNA photolyase in chloroplasts, Biosci. Biotechnol. Biochem. 64 (2000) 1288–1291.
[123] S.P. LeDoux, G.L. Wilson, E.J. Beecham, T. Stevnsner, K. Wassermann, V.A. Bohr, Repair of mitochondrial DNA after various types of DNA damage in Chinese hamster ovary cells, Carcinogenesis 13 (1992) 1967–1973.
[124] K.A. Myers, R. Saffhill, P.J. O'Connor, Repair of alkylated purines in the hepatic DNA of mitochondria and nuclei in the rat, Carcinogenesis 9 (1988) 285–292.
[125] M.S. Satoh, N. Huh, M.F. Rajewsky, T. Kuroki, Enzymatic removal of O6-ethylguanine from mitochondrial DNA in rat tissues exposed to N-ethyl-N-nitrosourea *in vivo*, J. Biol. Chem. 263 (1988) 6854–6856.
[126] E.C. Friedberg, Suffering in silence: the tolerance of DNA damage, Nat. Rev. Mol. Cell Biol. 6 (2005) 943–953.
[127] T. Roldan-Arjona, R.R. Ariza, Repair and tolerance of oxidative DNA damage in plants, Mutat. Res. 681 (2009) 169–179.
[128] S. Prakash, R.E. Johnson, L. Prakash, Eukaryotic translesion synthesis DNA polymerases: specificity of structure and function, Annu. Rev. Biochem. 74 (2005) 317–353.
[129] K.G. Pinz, S. Shibutani, D.F. Bogenhagen, Action of mitochondrial DNA polymerase gamma at sites of base loss or oxidative damage, J. Biol. Chem. 270 (1995) 9202–9206.
[130] M.A. Graziewicz, J.M. Sayer, D.M. Jerina, W.C. Copeland, Nucleotide incorporation by human DNA polymerase gamma opposite benzo[a]pyrene and benzo[c] phenanthrene diol epoxide adducts of deoxyguanosine and deoxyadenosine, Nucleic Acids Res. 32 (2004) 397–405.
[131] T. Stevnsner, S. Nyaga, N.C. de Souza-Pinto, G.T. van der Horst, T.G. Gorgels, B.A. Hogue, T. Thorslund, V.A. Bohr, Mitochondrial repair of 8-oxoguanine is deficient in Cockayne syndrome group B, Oncogene 21 (2002) 8675–8682.
[132] M. Muftuoglu, N.C. de Souza-Pinto, A. Dogan, M. Aamann, T. Stevnsner, I. Rybanska, G. Kirkali, M. Dizdaroglu, V.A. Bohr, Cockayne syndrome group B

protein stimulates repair of formamidopyrimidines by NEIL1 DNA glycosylase, J. Biol. Chem. 284 (2009) 9270–9279.
[133] Y. Kamenisch, M. Fousteri, J. Knoch, A.K. von Thaler, B. Fehrenbacher, H. Kato, T. Becker, M.E. Dolle, R. Kuiper, M. Majora, M. Schaller, G.T. van der Horst, H. van Steeg, M. Rocken, D. Rapaport, J. Krutmann, L.H. Mullenders, M. Berneburg, Proteins of nucleotide and base excision repair pathways interact in mitochondria to protect from loss of subcutaneous fat, a hallmark of aging, J. Exp. Med. 207 (2010) 379–390.
[134] C.R. Machado, U.M. Praekelt, R.C. de Oliveira, A.C. Barbosa, K.L. Byrne, P.A. Meacock, C.F. Menck, Dual role for the yeast *THI4* gene in thiamine biosynthesis and DNA damage tolerance, J. Mol. Biol. 273 (1997) 114–121.
[135] S.M. Chabregas, D.D. Luche, L.P. Farias, A.F. Ribeiro, M.A. van Sluys, C.F. Menck, M.C. Silva-Filho, Dual targeting properties of the N-terminal signal sequence of *Arabidopsis thaliana* THI1 protein to mitochondria and chloroplasts, Plant Mol. Biol. 46 (2001) 639–650.
[136] S.M. Chabregas, D.D. Luche, M.A. Van Sluys, C.F. Menck, M.C. Silva-Filho, Differential usage of two in-frame translational start codons regulates subcellular localization of *Arabidopsis thaliana* THI1, J. Cell Sci. 116 (2003) 285–291.
[137] B.F. Pachkowski, K. Tano, V. Afonin, R.H. Elder, S. Takeda, M. Watanabe, J.A. Swenberg, J. Nakamura, Cells deficient in PARP-1 show an accelerated accumulation of DNA single strand breaks, but not AP sites, over the PARP-1-proficient cells exposed to MMS, Mutat. Res. 671 (2009) 93–99.
[138] M.N. Rossi, M. Carbone, C. Mostocotto, C. Mancone, M. Tripodi, R. Maione, P. Amati, Mitochondrial localization of PARP-1 requires interaction with mitofilin and is involved in the maintenance of mitochondrial DNA integrity, J. Biol. Chem. 284 (2009) 31616–31624.
[139] D. Kang, N. Hamasaki, Mitochondrial transcription factor A in the maintenance of mitochondrial DNA: overview of its multiple roles, Ann. NY Acad. Sci. 1042 (2005) 101–108.
[140] Y. Yoshida, H. Izumi, T. Ise, H. Uramoto, T. Torigoe, H. Ishiguchi, T. Murakami, M. Tanabe, Y. Nakayama, H. Itoh, H. Kasai, K. Kohno, Human mitochondrial transcription factor A binds preferentially to oxidatively damaged DNA, Biochem. Biophys. Res. Commun. 295 (2002) 945–951.
[141] M. Pietrowska, I. Kolodziejczyk, P. Widlak, Mitochondrial transcription factor A is the major protein in rodent hepatocytes that recognizes DNA lesions induced by N-acetoxy-acetylaminofluorene, Acta Biochim. Pol. 53 (2006) 777–782.
[142] A. Kidani, H. Izumi, Y. Yoshida, E. Kashiwagi, H. Ohmori, T. Tanaka, M. Kuwano, K. Kohno, Thioredoxin2 enhances the damaged DNA binding activity of mtTFA through direct interaction, Int. J. Oncol. 35 (2009) 1435–1440.
[143] Y. Yoshida, H. Izumi, T. Torigoe, H. Ishiguchi, H. Itoh, D. Kang, K. Kohno, P53 physically interacts with mitochondrial transcription factor A and differentially regulates binding to damaged DNA, Cancer Res. 63 (2003) 3729–3734.
[144] T.S. Wong, S. Rajagopalan, S.M. Freund, T.J. Rutherford, A. Andreeva, F.M. Townsley, M. Petrovich, A.R. Fersht, Biophysical characterizations of human mitochondrial transcription factor A and its binding to tumor suppressor p53, Nucleic Acids Res. 37 (2009) 6765–6783.
[145] C. Canugovi, S. Maynard, A.C. Bayne, P. Sykora, J. Tian, N.C. de Souza-Pinto, D.L. Croteau, V.A. Bohr, The mitochondrial transcription factor A functions in mitochondrial base excision repair, DNA Repair (Amst.) (2010), doi:10.1016/j.dnarep.2010.1007.1009.
[146] T.S. Wong, S. Rajagopalan, F.M. Townsley, S.M. Freund, M. Petrovich, D. Loakes, A.R. Fersht, Physical and functional interactions between human mitochondrial single-stranded DNA-binding protein and tumour suppressor p53, Nucleic Acids Res. 37 (2009) 568–581.
[147] G. Achanta, R. Sasaki, L. Feng, J.S. Carew, W. Lu, H. Pelicano, M.J. Keating, P. Huang, Novel role of p53 in maintaining mitochondrial genetic stability through interaction with DNA Pol gamma, EMBO J. 24 (2005) 3482–3492.
[148] D. Chen, Z. Yu, Z. Zhu, C.D. Lopez, The p53 pathway promotes efficient mitochondrial DNA base excision repair in colorectal cancer cells, Cancer Res. 66 (2006) 3485–3494.
[149] N.C. de Souza-Pinto, C.C. Harris, V.A. Bohr, p53 functions in the incorporation step in DNA base excision repair in mouse liver mitochondria, Oncogene 23 (2004) 6559–6568.
[150] H. Dai, Y.S. Lo, A. Litvinchuk, Y.T. Wang, W.N. Jane, L.J. Hsiao, K.S. Chiang, Structural and functional characterizations of mung bean mitochondrial nucleoids, Nucleic Acids Res. 33 (2005) 4725–4739.
[151] M. Kucej, R.A. Butow, Evolutionary tinkering with mitochondrial nucleoids, Trends Cell Biol. 17 (2007) 586–592.
[152] F. Malka, A. Lombes, M. Rojo, Organization, dynamics and transmission of mitochondrial DNA: focus on vertebrate nucleoids, Biochim. Biophys. Acta 1763 (2006) 463–472.
[153] S. Park, T. Hanekamp, M.K. Thorsness, P.E. Thorsness, Yme2p is a mediator of nucleoid structure and number in mitochondria of the yeast *Saccharomyces cerevisiae*, Curr. Genet. 50 (2006) 173–182.
[154] N. Sato, K. Terasawa, K. Miyajima, Y. Kabeya, Organization, developmental dynamics, and evolution of plastid nucleoids, Int. Rev. Cytol. 232 (2003) 217–262.
[155] D.F. Bogenhagen, D. Rousseau, S. Burke, The layered structure of human mitochondrial DNA nucleoids, J. Biol. Chem. 283 (2008) 3665–3675.
[156] A. Sakai, H. Takano, T. Kuroiwa, Organelle nuclei in higher plants: structure, composition, function, and evolution, Int. Rev. Cytol. 238 (2004) 59–118.
[157] J.N. Spelbrink, Functional organization of mammalian mitochondrial DNA in nucleoids: history, recent developments, and future challenges, IUBMB Life 62 (2010) 19–32.
[158] D. Kang, S.H. Kim, N. Hamasaki, Mitochondrial transcription factor A (TFAM): roles in maintenance of mtDNA and cellular functions, Mitochondrion 7 (2007) 39–44.
[159] D. Karcher, D. Koster, A. Schadach, A. Klevesath, R. Bock, The *Chlamydomonas* chloroplast HLP protein is required for nucleoid organization and genome maintenance, Mol. Plant 2 (2009) 1223–1232.
[160] M. Kucej, B. Kucejova, R. Subramanian, X.J. Chen, R.A. Butow, Mitochondrial nucleoids undergo remodeling in response to metabolic cues, J. Cell Sci. 121 (2008) 1861–1868.
[161] K. Kasashima, M. Sumitani, M. Satoh, H. Endo, Human prohibitin 1 maintains the organization and stability of the mitochondrial nucleoids, Exp. Cell Res. 314 (2008) 988–996.
[162] J. He, C.C. Mao, A. Reyes, H. Sembongi, M. Di Re, C. Granycome, A.B. Clippingdale, I.M. Fearnley, M. Harbour, A.J. Robinson, S. Reichelt, J.N. Spelbrink, J.E. Walker, I.J. Holt, The AAA+ protein ATAD3 has displacement loop binding properties and is involved in mitochondrial nucleoid organization, J. Cell Biol. 176 (2007) 141–146.
[163] S. Meeusen, J. Nunnari, Evidence for a two membrane-spanning autonomous mitochondrial DNA replisome, J. Cell Biol. 163 (2003) 503–510.
[164] K. Terasawa, N. Sato, Visualization of plastid nucleoids *in situ* using the PEND–GFP fusion protein, Plant Cell Physiol. 46 (2005) 649–660.
[165] Y. Wang, D.F. Bogenhagen, Human mitochondrial DNA nucleoids are linked to protein folding machinery and metabolic enzymes at the mitochondrial inner membrane, J. Biol. Chem. 281 (2006) 25791–25802.
[166] M. Sumitani, K. Kasashima, E. Ohta, D. Kang, H. Endo, Association of a novel mitochondrial protein M19 with mitochondrial nucleoids, J. Biochem. 146 (2009) 725–732.
[167] A. Hubstenberger, N. Merle, R. Charton, G. Brandolin, D. Rousseau, Topological analysis of ATAD3A insertion in purified human mitochondria, J. Bioenerg. Biomembr. 42 (2010) 143–150.
[168] J.A. Stuart, S. Mayard, K. Hashiguchi, N.C. Souza-Pinto, V.A. Bohr, Localization of mitochondrial DNA base excision repair to an inner membrane-associated particulate fraction, Nucleic Acids Res. 33 (2005) 3722–3732.
[169] M. Akbari, M. Otterlei, J. Pena-Diaz, H.E. Krokan, Different organization of base excision repair of uracil in DNA in nuclei and mitochondria and selective upregulation of mitochondrial uracil-DNA glycosylase after oxidative stress, Neuroscience 145 (2007) 1201–1212.
[170] Y. Nakabeppu, Regulation of intracellular localization of human MTH1, OGG1, and MYH proteins for repair of oxidative DNA damage, Prog. Nucleic Acid Res. Mol. Biol. 68 (2001) 75–94.
[171] R.K. Naviaux, Assay of mtDNA polymerase gamma from human tissues, Meth. Mol. Biol. 197 (2002) 259–271.
[172] D.A. Jackson, J. Bartlett, P.R. Cook, Sequences attaching loops of nuclear and mitochondrial DNA to underlying structures in human cells: the role of transcription units, Nucleic Acids Res. 24 (1996) 1212–1219.
[173] M.D. Aamann, M.M. Sorensen, C. Hvitby, B.R. Berquist, M. Muftuoglu, J. Tian, N.C. de Souza-Pinto, M. Scheibye-Knudsen, D.M. Wilson Iii, T. Stevnsner, V.A. Bohr, Cockayne syndrome group B protein promotes mitochondrial DNA stability by supporting the DNA repair association with the mitochondrial membrane, FASEB J. 24 (2010) 2334–2346.
[174] I.J. Holt, A.E. Harding, J.A. Morgan-Hughes, Deletions of muscle mitochondrial DNA in patients with mitochondrial myopathies, Nature 331 (1988) 717–719.
[175] D.C. Wallace, G. Singh, M.T. Lott, J.A. Hodge, T.G. Schurr, A.M. Lezza, L.J. Elsas II, E.K. Nikoskelainen, Mitochondrial DNA mutation associated with Leber's hereditary optic neuropathy, Science 242 (1988) 1427–1430.
[176] H.A. Tuppen, E.L. Blakely, D.M. Turnbull, R.W. Taylor, Mitochondrial DNA mutations and human disease, Biochim. Biophys. Acta 1797 (2010) 113–128.
[177] N. Manwaring, M.M. Jones, J.J. Wang, E. Rochtchina, C. Howard, P. Mitchell, C.M. Sue, Population prevalence of the MELAS A3243G mutation, Mitochondrion 7 (2007) 230–233.
[178] A.M. Schaefer, R. McFarland, E.L. Blakely, L. He, R.G. Whittaker, R.W. Taylor, P.F. Chinnery, D.M. Turnbull, Prevalence of mitochondrial DNA disease in adults, Ann. Neurol. 63 (2008) 35–39.
[179] K. Majamaa, J.S. Moilanen, S. Uimonen, A.M. Remes, P.I. Salmela, M. Karppa, K.A. Majamaa-Voltti, H. Rusanen, M. Sorri, K.J. Peuhkurinen, I.E. Hassinen, Epidemiology of A3243G, the mutation for mitochondrial encephalomyopathy, lactic acidosis, and strokelike episodes: prevalence of the mutation in an adult population, Am. J. Hum. Genet. 63 (1998) 447–454.
[180] M. Gu, J.M. Cooper, J.W. Taanman, A.H. Schapira, Mitochondrial DNA transmission of the mitochondrial defect in Parkinson's disease, Ann. Neurol. 44 (1998) 177–186.
[181] I. Onyango, S. Khan, B. Miller, R. Swerdlow, P. Trimmer, P. Bennett Jr., Mitochondrial genomic contribution to mitochondrial dysfunction in Alzheimer's disease, J. Alzheimers Dis. 9 (2006) 183–193.
[182] R.H. Swerdlow, S.M. Khan, The Alzheimer's disease mitochondrial cascade hypothesis: an update, Exp. Neurol. 218 (2009) 308–315.
[183] J.C. St John, R.P. Jokhi, C.L. Barratt, The impact of mitochondrial genetics on male infertility, Int. J. Androl. 28 (2005) 65–73.
[184] M. Brandon, P. Baldi, D.C. Wallace, Mitochondrial mutations in cancer, Oncogene 25 (2006) 4647–4662.
[185] K.J. Krishnan, A.K. Reeve, D.C. Samuels, P.F. Chinnery, J.K. Blackwood, R.W. Taylor, S. Wanrooij, J.N. Spelbrink, R.N. Lightowlers, D.M. Turnbull, What causes mitochondrial DNA deletions in human cells? Nat. Genet. 40 (2008) 275–279.
[186] S. Srivastava, C.T. Moraes, Double-strand breaks of mouse muscle mtDNA promote large deletions similar to multiple mtDNA deletions in humans, Hum. Mol. Genet. 14 (2005) 893–902.

[187] T.B. Kirkwood, Understanding the odd science of aging, Cell 120 (2005) 437–447.
[188] D. Harman, Aging: a theory based on free radical and radiation chemistry, J. Gerontol. 11 (1956) 298–300.
[189] D. Harman, The biologic clock: the mitochondria? J. Am. Geriatr. Soc. 20 (1972) 145–147.
[190] J. Miquel, A.C. Economos, J. Fleming, J.E. Johnson Jr., Mitochondrial role in cell aging, Exp. Gerontol. 15 (1980) 575–591.
[191] L.C. Greaves, D.M. Turnbull, Mitochondrial DNA mutations and ageing, Biochim. Biophys. Acta 1790 (2009) 1015–1020.
[192] J. Gruber, S. Schaffer, B. Halliwell, The mitochondrial free radical theory of ageing—where do we stand? Front. Biosci. 13 (2008) 6554–6579.
[193] F.L. Muller, M.S. Lustgarten, Y. Jang, A. Richardson, H. Van Remmen, Trends in oxidative aging theories, Free Radic. Biol. Med. 43 (2007) 477–503.
[194] A. Trifunovic, A. Wredenberg, M. Falkenberg, J.N. Spelbrink, A.T. Rovio, C.E. Bruder, Y.M. Bohlooly, S. Gidlof, A. Oldfors, R. Wibom, J. Tornell, H.T. Jacobs, N.G. Larsson, Premature ageing in mice expressing defective mitochondrial DNA polymerase, Nature 429 (2004) 417–423.
[195] G.C. Kujoth, A. Hiona, T.D. Pugh, S. Someya, K. Panzer, S.E. Wohlgemuth, T. Hofer, A.Y. Seo, R. Sullivan, W.A. Jobling, J.D. Morrow, H. Van Remmen, J.M. Sedivy, T. Yamasoba, M. Tanokura, R. Weindruch, C. Leeuwenburgh, T.A. Prolla, Mitochondrial DNA mutations, oxidative stress, and apoptosis in mammalian aging, Science 309 (2005) 481–484.
[196] D. Edgar, I. Shabalina, Y. Camara, A. Wredenberg, M.A. Calvaruso, L. Nijtmans, J. Nedergaard, B. Cannon, N.G. Larsson, A. Trifunovic, Random point mutations with major effects on protein-coding genes are the driving force behind premature aging in mtDNA mutator mice, Cell Metab. 10 (2009) 131–138.
[197] D. Edgar, A. Trifunovic, The mtDNA mutator mouse: dissecting mitochondrial involvement in aging, Aging (Albany NY) 1 (2009) 1028–1032.
[198] M. Vermulst, J. Wanagat, L.A. Loeb, On mitochondria, mutations, and methodology, Cell Metab. 10 (2009) 437.
[199] D. Edgar, N.G. Larsson, A. Trifunovic, Point mutations are causing progeroid phenotypes in the mtDNA mutator mouse, Cell Metab. 11 (2010) 1.
[200] M.F. Alexeyev, Is there more to aging than mitochondrial DNA and reactive oxygen species? FEBS J. 276 (2009) 5768–5787.
[201] M.V. Blagosklonny, Aging: ROS or TOR, Cell Cycle 7 (2008) 3344–3354.
[202] N.D. Bonawitz, G.S. Shadel, Rethinking the mitochondrial theory of aging: the role of mitochondrial gene expression in lifespan determination, Cell Cycle 6 (2007) 1574–1578.
[203] R. Buffenstein, Y.H. Edrey, T. Yang, J. Mele, The oxidative stress theory of aging: embattled or invincible? Insights from non-traditional model organisms, Age (Dordr.) 30 (2008) 99–109.
[204] J.P. de Magalhaes, G.M. Church, Cells discover fire: employing reactive oxygen species in development and consequences for aging, Exp. Gerontol. 41 (2006) 1–10.
[205] H. Fukui, C.T. Moraes, The mitochondrial impairment, oxidative stress and neurodegeneration connection: reality or just an attractive hypothesis? Trends Neurosci. 31 (2008) 251–256.
[206] D. Gems, R. Doonan, Antioxidant defense and aging in *C. elegans*: is the oxidative damage theory of aging wrong? Cell Cycle 8 (2009) 1681–1687.
[207] Y.C. Jang, H. Van Remmen, The mitochondrial theory of aging: insight from transgenic and knockout mouse models, Exp. Gerontol. 44 (2009) 256–260.
[208] V.I. Perez, A. Bokov, H. Van Remmen, J. Mele, Q. Ran, Y. Ikeno, A. Richardson, Is the oxidative stress theory of aging dead? Biochim. Biophys. Acta 1790 (2009) 1005–1014.
[209] J. Lapointe, S. Hekimi, When a theory of aging ages badly, Cell. Mol. Life Sci. 67 (2010) 1–8.
[210] N. Arnheim, G. Cortopassi, Deleterious mitochondrial DNA mutations accumulate in aging human tissues, Mutat. Res. 275 (1992) 157–167.
[211] G. Barja, A. Herrero, Oxidative damage to mitochondrial DNA is inversely related to maximum life span in the heart and brain of mammals, FASEB J. 14 (2000) 312–318.
[212] A. Sanz, D.J. Fernandez-Ayala, R.K. Stefanatos, H.T. Jacobs, Mitochondrial ROS production correlates with, but does not directly regulate lifespan in *Drosophila*, Aging (Albany NY) 2 (2010) 220–223.
[213] J. Sun, D. Folk, T.J. Bradley, J. Tower, Induced overexpression of mitochondrial Mn-superoxide dismutase extends the life span of adult *Drosophila melanogaster*, Genetics 161 (2002) 661–672.
[214] Y.C. Jang, V.I. Perez, W. Song, M.S. Lustgarten, A.B. Salmon, J. Mele, W. Qi, Y. Liu, H. Liang, A. Chaudhuri, Y. Ikeno, C.J. Epstein, H. Van Remmen, A. Richardson, Overexpression of Mn superoxide dismutase does not increase life span in mice, J. Gerontol. A Biol. Sci. Med. Sci. 64 (2009) 1114–1125.
[215] V.I. Perez, H. Van Remmen, A. Bokov, C.J. Epstein, J. Vijg, A. Richardson, The overexpression of major antioxidant enzymes does not extend the lifespan of mice, Aging Cell 8 (2009) 73–75.
[216] S.E. Schriner, N.J. Linford, G.M. Martin, P. Treuting, C.E. Ogburn, M. Emond, P.E. Coskun, W. Ladiges, N. Wolf, H. Van Remmen, D.C. Wallace, P.S. Rabinovitch, Extension of murine life span by overexpression of catalase targeted to mitochondria, Science 308 (2005) 1909–1911.
[217] D.F. Dai, T. Chen, J. Wanagat, M. Laflamme, D.J. Marcinek, M.J. Emond, C.P. Ngo, T.A. Prolla, P.S. Rabinovitch, Age-dependent cardiomyopathy in mitochondrial mutator mice is attenuated by overexpression of catalase targeted to mitochondria, Aging Cell 9 (2010) 536–544.
[218] D.F. Bogenhagen, Does mtDNA nucleoid organization impact aging? Exp. Gerontol. 45 (2010) 473–477.
[219] R.W. Gilkerson, E.A. Schon, E. Hernandez, M.M. Davidson, Mitochondrial nucleoids maintain genetic autonomy but allow for functional complementation, J. Cell Biol. 181 (2008) 1117–1128.
[220] N.M. Druzhyna, G.L. Wilson, S.P. LeDoux, Mitochondrial DNA repair in aging and disease, Mech. Ageing Dev. 129 (2008) 383–390.
[221] R. Gredilla, V.A. Bohr, T. Stevnsner, Mitochondrial DNA repair and association with aging—an update, Exp. Gerontol. 45 (2010) 478–488.
[222] T. Stevnsner, T. Thorslund, N.C. de Souza-Pinto, V.A. Bohr, Mitochondrial repair of 8-oxoguanine and changes with aging, Exp. Gerontol. 37 (2002) 1189–1196.
[223] B. Szczesny, T.K. Hazra, J. Papaconstantinou, S. Mitra, I. Boldogh, Age-dependent deficiency in import of mitochondrial DNA glycosylases required for repair of oxidatively damaged bases, Proc. Natl Acad. Sci. USA 100 (2003) 10670–10675.
[224] E.W. Englander, Z. Hu, A. Sharma, H.M. Lee, Z.H. Wu, G.H. Greeley, Rat MYH, a glycosylase for repair of oxidatively damaged DNA, has brain-specific isoforms that localize to neuronal mitochondria, J. Neurochem. 83 (2002) 1471–1480.
[225] L.M. Griffiths, D. Swartzlander, K.L. Meadows, K.D. Wilkinson, A.H. Corbett, P.W. Doetsch, Dynamic compartmentalization of base excision repair proteins in response to nuclear and mitochondrial oxidative stress, Mol. Cell. Biol. 29 (2009) 794–807.
[226] D.B. Swartzlander, L.M. Griffiths, J. Lee, N.P. Degtyareva, P.W. Doetsch, A.H. Corbett, Regulation of base excision repair: Ntg1 nuclear and mitochondrial dynamic localization in response to genotoxic stress, Nucleic Acids Res. 38 (2010) 3963–3974.
[227] B. Frossi, G. Tell, P. Spessotto, A. Colombatti, G. Vitale, C. Pucillo, H(2)O(2) induces translocation of APE/Ref-1 to mitochondria in the Raji B-cell line, J. Cell. Physiol. 193 (2002) 180–186.
[228] T. Stevnsner, M. Muftuoglu, M.D. Aamann, V.A. Bohr, The role of Cockayne Syndrome group B (CSB) protein in base excision repair and aging, Mech. Ageing Dev. 129 (2008) 441–448.
[229] K. Shinmura, J. Yokota, The OGG1 gene encodes a repair enzyme for oxidatively damaged DNA and is involved in human carcinogenesis, Antioxid. Redox Signal. 3 (2001) 597–609.
[230] S. Ikeda, T. Kohmoto, R. Tabata, Y. Seki, Differential intracellular localization of the human and mouse endonuclease III homologs and analysis of the sorting signals, DNA Repair (Amst.) 1 (2002) 847–854.
[231] M.L. Fishel, Y.R. Seo, M.L. Smith, M.R. Kelley, Imbalancing the DNA base excision repair pathway in the mitochondria; targeting and overexpressing N-methylpurine DNA glycosylase in mitochondria leads to enhanced cell killing, Cancer Res. 63 (2003) 608–615.
[232] I.N. Shokolenko, M.F. Alexeyev, F.M. Robertson, S.P. LeDoux, G.L. Wilson, The expression of exonuclease III from *E. coli* in mitochondria of breast cancer cells diminishes mitochondrial DNA repair capacity and cell survival after oxidative stress, DNA Repair (Amst.) 2 (2003) 471–482.
[233] J.F. Harrison, M.L. Rinne, M.R. Kelley, N.M. Druzhyna, G.L. Wilson, S.P. Ledoux, Altering DNA base excision repair: use of nuclear and mitochondrial-targeted N-methylpurine DNA glycosylase to sensitize astroglia to chemotherapeutic agents, Glia 55 (2007) 1416–1425.
[234] H. Zhang, T. Mizumachi, J. Carcel-Trullols, L. Li, A. Naito, H.J. Spencer, P.M. Spring, B.R. Smoller, A.J. Watson, G.P. Margison, M. Higuchi, C.Y. Fan, Targeting human 8-oxoguanine DNA glycosylase (hOGG1) to mitochondria enhances cisplatin cytotoxicity in hepatoma cells, Carcinogenesis 28 (2007) 1629–1637.
[235] R. Nithipongvanitch, W. Ittarat, J.M. Velez, R. Zhao, D.K. St Clair, T.D. Oberley, Evidence for p53 as guardian of the cardiomyocyte mitochondrial genome following acute adriamycin treatment, J. Histochem. Cytochem. 55 (2007) 629–639.
[236] A.K. Holley, D.K. St Clair, Watching the watcher: regulation of p53 by mitochondria, Future Oncol. 5 (2009) 117–130.
[237] E. Ueta, E. Sasabe, Z. Yang, T. Osaki, T. Yamamoto, Enhancement of apoptotic damage of squamous cell carcinoma cells by inhibition of the mitochondrial DNA repairing system, Cancer Sci. 99 (2008) 2230–2237.
[238] A.V. Vaseva, U.M. Moll, The mitochondrial p53 pathway, Biochim. Biophys. Acta 1787 (2009) 414–420.
[239] S.G. Jarrett, L.P. Liang, J.L. Hellier, K.J. Staley, M. Patel, Mitochondrial DNA damage and impaired base excision repair during epileptogenesis, Neurobiol. Dis. 30 (2008) 130–138.
[240] Y. Lin, J. Xu, L. Cao, Y. Han, J. Gao, N. Xie, X. Zhao, H. Jiang, Z. Chi, Mitochondrial base excision repair pathway failed to respond to status epilepticus induced by pilocarpine, Neurosci. Lett. 474 (2010) 22–25.
[241] Y. Wu, N. Li, T. Zhang, H. Wu, C. Huang, D. Chen, Mitochondrial DNA base excision repair and mitochondrial DNA mutation in human hepatic HuH-7 cells exposed to stavudine, Mutat. Res. 664 (2009) 28–38.
[242] M. Soerensen, R. Gredilla, M. Muller-Ohldach, A. Werner, V.A. Bohr, H.D. Osiewacz, T. Stevnsner, A potential impact of DNA repair on ageing and lifespan in the ageing model organism *Podospora anserina*: decrease in mitochondrial DNA repair activity during ageing, Mech. Ageing Dev. 130 (2009) 487–496.
[243] B. Karahalil, B.A. Hogue, N.C. de Souza-Pinto, V.A. Bohr, Base excision repair capacity in mitochondria and nuclei: tissue-specific variations, FASEB J. 16 (2002) 1895–1902.
[244] N.C. de Souza-Pinto, D.L. Croteau, E.K. Hudson, R.G. Hansford, V.A. Bohr, Age-associated increase in 8-oxo-deoxyguanosine glycosylase/AP lyase activity in rat mitochondria, Nucleic Acids Res. 27 (1999) 1935–1942.
[245] N.C. de Souza-Pinto, B.A. Hogue, V.A. Bohr, DNA repair and aging in mouse liver: 8-oxodG glycosylase activity increase in mitochondrial but not in nuclear extracts, Free Radic. Biol. Med. 30 (2001) 916–923.

[246] D. Chen, G. Cao, T. Hastings, Y. Feng, W. Pei, C. O'Horo, J. Chen, Age-dependent decline of DNA repair activity for oxidative lesions in rat brain mitochondria, J. Neurochem. 81 (2002) 1273–1284.
[247] R. Gredilla, C. Garm, R. Holm, V.A. Bohr, T. Stevnsner, Differential age-related changes in mitochondrial DNA repair activities in mouse brain regions, Neurobiol. Aging 31 (2008) 993–1002.
[248] S.Z. Imam, B. Karahalil, B.A. Hogue, N.C. Souza-Pinto, V.A. Bohr, Mitochondrial and nuclear DNA-repair capacity of various brain regions in mouse is altered in an age-dependent manner, Neurobiol. Aging 27 (2006) 1129–1136.
[249] L. Weissman, D.G. Jo, M.M. Sorensen, N.C. de Souza-Pinto, W.R. Markesbery, M.P. Mattson, V. A. Bohr, Defective DNA base excision repair in brain from individuals with Alzheimer's disease and amnestic mild cognitive impairment, Nucleic Acids Res. 35 (2007) 5545–5555.