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DNA REPAIR '99
Repair of mtDNA in Vertebrates

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The subject of this review is a process once thought by many to be nonexistent. Spurred by an early observation that pyrimidine dimers introduced into mtDNA were not repaired (Clayton et al. 1974), many people stampeded to the conclusion that mammalian mitochondria were incapable of repairing their DNA. Proponents of this view held that damaged mtDNA molecules might be either targeted for destruction or diluted out in the cell's pool of thousands of undamaged molecules. Perhaps wastage of an occasional damaged 16-kb DNA molecule would be a small price to pay to avoid duplication of the DNA-repair tool chest inside mitochondria. This careless disregard of DNA maintenance would be expected to contribute to the incidence of human diseases involving mtDNA mutations that compromise mitochondrial function.

Although these considerations may apply to some types of mtDNA damage, we now know that other types of damage occur too frequently to go unrepaired; these include spontaneous base loss, giving rise to abasic sites (also referred to as "AP sites" [for "apurinic/apyrimidinic sites"]), and certain key examples of endogenous damage to DNA bases. It is instructive to consider mtDNA damage and its potential repair in light of the repair pathways described for bacterial and eukaryotic nuclear DNA. In those genomes, most types of DNA damage are processed by one of three general mechanisms described in table 1. In each case, DNA repair consists of two coupled steps, involving (1) recognition of damage and (2) synthesis of a repair patch. Recognition and resection of a lesion from DNA are rate-limiting steps in repair. For the purposes of this review, it is appropriate to consider that the three repair processes highlighted in table 1 require distinct sets of proteins for lesion recognition—an oversimplification, since certain proteins may act in more than one repair pathway. This article will review the classes of DNA damage that are amenable to repair in mtDNA, the current understanding of the enzymatic machinery available for DNA repair in mitochondria, and the implications that human mtDNA-repair mechanisms have for aging and for mitochondrial disease. The emerging pattern is that mitochondria in higher organisms are reasonably well equipped to conduct base-excision repair (BER) but appear to be deficient in nucleotide-excision repair (NER) and mismatch repair (MMR).

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Mitochondria CAN Repair Some DNA Damage

The classical experiment to document DNA repair is to treat cells with DNA-damaging agents and monitor the kinetics with which DNA is repaired. If the damage does not introduce DNA breaks, samples can be treated with a damage-specific nuclease to monitor the persistence of endonuclease-sensitive sites. In the early days of DNA-repair research, such experiments used alkaline elution and alkaline sucrose gradient sedimentation to monitor the size of DNA fragments after DNA damage. These techniques were not widely applied to the study of mtDNA repair, because of the small quantities of mtDNA in somatic cells. The application of Southern blot hybridization methods to the study of repair of specific DNA sequences (Bohr et al. 1985) made it possible to study the repair of mtDNA in the presence of contaminating nuclear DNA. Work from several laboratories has shown that mtDNA damage caused by some oxidizing agents and alkylating agents can be repaired (Myers et al. 1988; Satoh et al. 1988; Pettepher et al. 1991; Driggers et al. 1993). In contrast, no repair has been reported for larger alkylating groups, such as N-7 butyl adducts or bulky adducts such as benz(a)pyrene diolepoxide, aflatoxin, or psoralen (Backer and Weinstein 1980; Niranjan et al. 1982; Cullinane and Bohr 1998). The situation is more complex for some agents that cause chemically heterogeneous lesions. It has been reported that some damage introduced into mtDNA by bleomycin and 4-nitroquinoline oxide can be repaired, whereas some lesions may be refractory to repair (Snyderwine and Bohr 1992; Shen et al. 1995). Similarly, only interstrand cross-links introduced by cis-platinum

Table 1

Simplified View of Nuclear DNA–Repair Pathways: Extent of Duplication in Mitochondria

Repair Process	Lesions Processed	Proteins Acting in Nuclear DNA Repair	Genetic Correlations
BER	Spontaneous AP sites; glycosylase products	"Short patch" (AP endonuclease, DNA pol β, DNA ligase I/ III); "long patch" (AP endonuclease, DNA pol δ [or ϵ], FEN1, proliferating-cell nuclear antigen, replication factor C, DNA ligase I/ III)	Mouse knockouts of AP endonuclease, DNA pol β, and DNA ligase I embryonic lethal
NER	Pyrimidine dimers; bulky chemical adducts	16 proteins for excision (XPA, XPC [p125, p58], RPA [p70, p34, p11], TFIIH [XPB/ERCC3, XPD/ERCC2, p62, p44, cdk7/p41, cycH/p38, 34], XPF 9 [p112, p33], XPG); gap filling (DNA pol ϵ, proliferating-cell nuclear antigen, replication factor C [6 subunits], DNA ligase I/III)	Xeroderma pigmentosum (alleles XPA–XPG); Cockayne syndrome; trichothiodystrophy
MMR	Base mismatches; short insertions/deletions	Multiple *mut*-S and *mut*-H homologues; excision activities; proliferating-cell nuclear antigen; replication factor C; DNA pol δ	Hereditary nonpolyposis colon cancer

(cis-Pt) are repaired; but common intrastrand cross-links persist in mtDNA (Singh and Maniccia-Bozzo 1990; LeDoux et al. 1992). Some of the DNA-damaging agents used in these studies, such as bleomycin and cis-Pt, are administered to patients as cytotoxic chemotherapeutic agents, but the extent to which these treatments affect the structure of mtDNA in cancer survivors is largely unexplored.

Virtually all cases cited above in which mtDNA repair has been documented involve oxidative damage or alkylation, classes of DNA damage that also occur by endogenous mechanisms (Lindahl 1993). Oxidative damage is of particular relevance to mtDNA, since a large fraction of reactive oxygen species (ROS) in cells is thought to originate by leakage of electrons from the electron-transport system. The proximity of mtDNA to the ROS generator suggests that there may be a high rate of endogenous oxidative damage to mtDNA (Shigenaga et al. 1994). Some of the immediate products of ROS damage would include 8-oxo-guanine and thymine glycol as examples of base damage, as well as malondialdehyde and other products of oxidation of the deoxyribose backbone. However, it is difficult to measure these lesions with confidence, given the small amount of mtDNA available in cells. The incidence of base damage has generally been measured by high-performance liquid-chromatography analysis of hydrolyzed DNA; DNA-backbone damage can be assessed by PCR. An early study reported a significantly higher incidence of 8-oxo-dG in mtDNA than in nuclear DNA (Richter et al. 1988). 8-oxo-dG is of particular interest, since it has been well documented to lead to G→T transversions in DNA (Grollman and Moriya 1993). An initial report of high steady-state levels of 8-oxo-dG in the absence of oxidative stress has not been confirmed by other studies. The authors of the original report now acknowledge that contaminants may have caused them to overestimate the prevalence of this adduct (Helbock et al. 1998). If it is assumed that the lower steady-state incidence of these lesions is correct, then mitochondrial repair mechanisms would appear to be quite efficient at repairing the damage caused by ROS.

Enzymology of BER of mtDNA

As noted in table 1, the BER pathway processes abasic sites that have been generated either by spontaneous base loss or by enzymatic removal of bases by damage-specific glycosylases. The spectrum of base damage that can be repaired in mtDNA is sure to be limited by the collection of DNA glycosylases found in the organelle. Unfortunately, our present knowledge of the DNA glycosylase genes encoded in the human nuclear genome is still very incomplete, so it is uncertain how many genes encode either dedicated mitochondrial glycosylases or mitochondrially targeted isoforms of such enzymes. DNA glycosylases are relatively well understood in bacteria, where the recent sequencing of whole bacterial genomes is providing a wealth of information on these gene families. Table 2 provides a list of several well-characterized DNA glycosylases in *Escherichia coli* and the current understanding of their human homologues.

The prototypical DNA glycosylase, uracil DNA glycosylase (UDG), is directed to either nuclei or mitochondria by differential splicing (Slupphaug et al. 1993). Only during the past few years have other glycosylases have come under study in higher eukaryotes. Some progress has been made in following the UDG model by analysis of candidate genes that appear to encode DNA glycosylases with potential N-terminal mitochondrial localization signals (MLSs). This is done first by computer sequence analysis and subsequently by testing the ability of these N-terminal sequences to direct a reporter gene (such as green fluorescent protein [GFP]) to mitochondria. As shown in table 2, there is strong evidence to suggest that mitochondria contain 8-oxo-guanine glycosylase (OGG) (Nishioka et al., in press). The N-termini of other glycosylase genes—including hNTH1, hMYH,

Table 2

mtDNA Glycosylases: Relation to Nuclear Homologues of Bacterial Enzymes

E. coli Enzyme[a]	Human Homologue	Potential MLS?[b]	Protein Documented in Mitochondria?
UDG, *ung*	UDG	Yes (t)	Yes, by Slupphaug et al. (1993)
Thymine glycol glycosylase, endonuclease III, *nth*	hNTH	Yes (t)	Not determined
Formamidopyrimidine glycosylase, FAPY glycosylase, *mut*-m	OGG	Yes (t)	Yes, by Nishioka et al. (in press)
AG glycosylase, *mut*-Y	hMYH	Yes (t)	Not determined
Alkyl adenine glycosylase, *aag*	MAG, AAG	Yes (c)	Not determined

[a] Several glycosylases have been shown to act on more than one type of modified base.

[b] "(t)" denotes that the MLS has been tested for its ability to direct a reporter protein to mitochondria; "(c)" denotes that the signal has been identified only by computerized sequence analysis.

and AAG—appear to encode potential MLSs, and the first two of these have been shown to function to direct GFP to mitochondria (Takao et al. 1998). It is interesting to note that the human homologue of another enzyme (albeit not a glycosylase) involved in the response to oxidative damage—that is, human 8-oxo-dGTPase (a homologue of the bacterial mutT)—has also been identified in mitochondria (Kang et al. 1995). Thus, it seems likely that mitochondria contain all of the components of the so-called GO system of *E. coli,* which responds to oxidative damage to guanosine either as a free nucleotide or within DNA (Grollman and Moriya 1993). The data in table 2 are almost certainly incomplete; other enzyme activities are only now being investigated (Croteau et al. 1997), and many others remain to be explored.

The existence of DNA glycosylases and the unavoidable spontaneous formation of abasic sites in mtDNA suggests that the mitochondria should maintain a complete system for repair of abasic sites. Since my laboratory has been characterizing the mitochondrial replicative DNA pol γ, my colleagues and I undertook to purify other enzymes that might cooperate with this enzyme in the repair of abasic sites in mtDNA. By analogy to BER in bacterial and nuclear systems, this repair was expected to require at least three other enzymatic activities—those of an AP endonuclease, an AP lyase, and a DNA ligase (fig. 1). Although we succeeded in reconstituting BER with mitochondrial enzymes (Pinz and Bogenhagen 1998), a great deal remains to be learned concerning the enzymes that can act in this pathway, as discussed below.

AP Endonuclease

Despite the frequency and importance of abasic sites in mtDNA, we are still largely ignorant of AP endonucleases in mitochondria. From our work with *Xenopus* enzymes and from a previous study using mouse cells (Tomkinson et al. 1988), it appears that the mitochondrial AP endonuclease cleaves on the 5′ side of the AP site and behaves as a single chromatographic species. The mitochondrial enzymes have not yet been cloned, but Tomkinson et al. (1988) and Pinz and Bogenhagen (1998, and unpublished data) have found that antisera raised against the nuclear enzyme cross-react with proteins in preparations of mouse and *Xenopus* mitochondrial AP endonuclease.

DNA pol γ

DNA pol γ is capable of binding the 3′-OH group produced by AP endonuclease to fill a one-nucleotide gap. The *Xenopus* enzyme was found to contain an additional activity as an AP lyase (Pinz and Bogenhagen 1998), which was subsequently confirmed for the recombinant human DNA pol γ (Longley et al. 1998). Although this represents the second example of a DNA polymerase that can act as an AP lyase activity, the corresponding activity previously identified in DNA pol β has a much higher catalytic activity (Matsumoto and Kim 1995). DNA polymerases related to *E. coli* DNA polymerase I and T7 DNA polymerase also contain an AP lyase activity with a low turnover capacity (K. G. Pinz and D. F. Bogenhagen, unpublished data). DNA pol γ is a heterodimeric protein whose larger subunit contains the catalytic activities for the polymerase, 3′–5′ proofreading exonuclease, as well as for the newly discovered AP lyase activity. The smaller subunit acts as a processivity factor (Carrodeguas et al. 1999) but is not required for gap-filling synthesis in vitro (Longley et al. 1998; K. G. Pinz and D. F. Bogenhagen, unpublished data).

mtDNA Ligase

The final step in the BER pathway is the resealing of the DNA by DNA ligase. To date, all DNA ligases characterized in eukaryotes are ATP-dependent enzymes that act through an enzyme-adenylate intermediate to reseal single-strand breaks. mtDNA ligase has been purified from *Xenopus* oocyte mitochondria as an ~100-kD protein active in an adenylation assay (Pinz and Bogenhagen 1998). The enzyme has been shown to be clearly distinct from DNA ligase I, which is the predominant source of

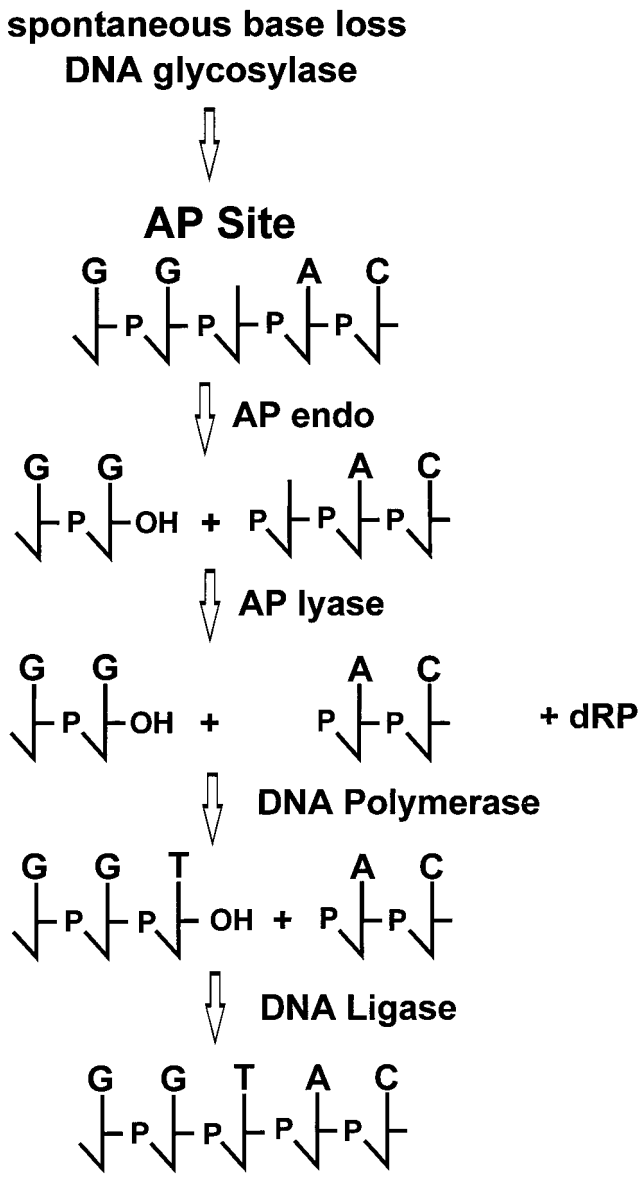

Figure 1 Common pathway for BER. The sequence context shown is appropriate for repair of a uracil residue in DNA, initiated by action of UDG. A single BER pathway has been documented for repair of bacterial DNA, for the nuclear pol β–dependent pathway and for mtDNA repair. An alternative "long patch" repair pathway, dependent on proliferating-cell nuclear antigen, also exists for eukaryotic nuclear DNA "dRP" denotes the deoxyribose phosphate group excised from the DNA. The complementary strand of the DNA duplex is not shown. (For other details, see the text.)

ligase activity in *Xenopus* oocytes. My colleagues and I have noted that, in published cDNA sequences of human DNA ligase III and IV (Wei et al. 1995), each of these gene products could be translated from in-frame initiation codons that were upstream of those indicated in the initial reports. Remarkably, in each case, the upstream sequences revealed a potential N-terminal MLS, suggesting that alternative translational initiation could generate both a mitochondrial and a nuclear isoform of each of these enzymes. Indeed, when we cloned cDNAs encoding *Xenopus* DNA ligase III and IV, we found that the putative MLS regions were conserved in these genes and that the putative MLS regions of DNA ligase III can direct GFP to mitochondria (R. M. Perez-Jannotti, S. M. Klein, and D. F. Bogenhagen, unpublished data). Moreover, an antiserum raised against a DNA ligase III–specific epitope was found to cross-react with the mtDNA ligase. Although protein sequence data or other definitive proof that mtDNA ligase is a product of the DNA ligase III gene is lacking, it is likely that the DNA ligase III gene will join the collection of DNA glycosylase genes described above, as a dual-function gene capable of providing enzyme to both the mitochondrion and the nucleus. When DNA ligase III resides in the nucleus, it acts in association with the XRCC1 gene product that has not yet been shown to enter mitochondria. It is unknown whether the mitochondrial isoform acts on its own or has a molecular partner in place of XRCC1. It is also uncertain whether DNA ligase IV may enter mitochondria in some cells. Since mtDNA ligase was purified by use of an adenylation assay, and since DNA ligase IV has been reported to purify in an adenylated form that is not efficiently labeled in vitro, it is possible that a mitochondrial form of DNA ligase IV may have been overlooked because of the use of the adenylation assay. In the mouse, DNA ligase IV is an essential gene (Frank et al. 1998); whether mitochondrial abnormalities contribute to the demise of DNA ligase IV knockout-mouse embryos is unknown.

mtDNA Repair as a Problem in Cell Biology

Although many proteins involved in repair and maintenance of mtDNA remain to be discovered, several examples of repair proteins that are produced from dual-function genes that contribute products to both the nucleus and mitochondria have already been identified. This type of organization is not unprecedented, since a number of proteins involved in tRNA processing have been shown to be products of dual-function genes (Martin and Hopper 1994). It is appropriate to ask both how the expression of proteins such as UDG, OGG1, and DNA ligase III is controlled to suit the needs of both organelles and how this regulation varies in different cell types. One can envision circumstances in which the supply of repair proteins to mitochondria may be either excessive or insufficient. In the case of UDG, ~25% of the total activity in a cell is directed to mitochondria, which contain only 0.1% of the cell's DNA. Thus, relative to the nucleus, mitochondria contain a large excess of this enzyme scanning DNA for misincorporated U residues. Because some glycosylases have a propensity

to remove normal bases at a measurable efficiency, and because the overexpression of at least one member of these enzymes is mutagenic (Berdal et al. 1998), it is possible that delivering too much of a repair glycosylase to mitochondria may be detrimental. Conversely, it is possible that, in postreplicative cells, which may be expected to reduce their expression of repair and replication factors, mitochondria could become depleted of these factors. This could contribute to problems in mtDNA maintenance during aging, since muscle- and nerve-cell mitochondria continue to require nuclear-gene products to repair and replace their DNA.

Does Deficiency in Mitochondrial NER or MMR Contribute to Human Mitochondrial Disease?

This review has concentrated on BER of mtDNA as the one example of a repair pathway that does seem to function in mitochondria. As summarized above, there is little evidence that NER functions in mitochondria to remove bulky DNA adducts. NER of nuclear DNA requires a large collection of proteins (including the alphabet soup of XP and ERCC genes; see table 1), most of which probably have no access to mtDNA. This deficiency in NER is striking, in the face of extensive evidence that many chemical carcinogens form adducts with mtDNA, at frequencies often 10–50-fold higher than they do with nuclear DNA. In the case of chemical damage to mtDNA, the rate of accumulation of damaged bases and the fate of damaged DNA molecules have not been studied in detail. If these lesions are not removed, they will be encountered by DNA pol γ and mtRNA polymerase in the course of replication and transcription and will likely block both processes. Deletions or rearrangements may result when a DNA pol γ molecule is stalled at a bulky lesion. This model represents a plausible, if speculative, mechanism whereby unrepaired bulky damage to mtDNA may contribute to mitochondrial mutagenesis. However, damage to mtDNA by exogenous chemicals does not appear to cause a high rate of fixation of mutations (Mita et al. 1988). It may be that most mtDNA molecules bearing bulky damage are indeed targeted for destruction, perhaps by a turnover mechanism that uses an arrested polymerase as a signal to promote degradation. More research on the fate of damaged mtDNA molecules is required for resolution of these issues.

The suggestion in this review—that is, that mitochondria in higher organisms are deficient in mismatch repair—is also largely speculative. *Saccharomyces cerevisiae* maintains a *mut*-S homologue, *msh*-1, and mutations in *msh*-1 induce a high rate of mtDNA mutations (Reenan and Kolodner 1992; Vanderstraeten et al. 1998). However, a complete MMR pathway in yeast mitochondria has not yet been described. The presence of an active MMR system in yeast may help explain the lower rate of evolutionary change in yeast mtDNA genomes as compared with those in higher eukaryotes. A mitochondrial *mut*-S gene is retained in a coral mtDNA genome (Pont-Kingdon et al. 1995) but not in other metazoans. No available evidence indicates that the *mut*-S or *mut*-L homologues of higher eukaryotes have access to mitochondria, but this lack of data may be seen as a challenge—to nucleic-acid biochemists, cell biologists, and geneticists—to show that MMR does indeed occur in mitochondria in higher organisms.

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