Curr Genet (2002) 41: 311–322
DOI 10.1007/s00294-002-0312-0

REVIEW ARTICLE

Dongchon Kang · Naotaka Hamasaki

Maintenance of mitochondrial DNA integrity: repair and degradation

Received: 4 December 2001 / Revised: 13 March 2002 / Accepted: 9 April 2002 / Published online: 11 July 2002

Abstract Mitochondria have their own genome, which is essential for proper oxidative phosphorylation and hence for a large part of ATP production in a cell. Although mitochondrial DNA-less (rho^0) cells can survive under certain conditions, the integrity of the mitochondrial genome is critical for the survival of multicellular organisms. Mitochondrial DNA (mtDNA) is damaged more than nuclear DNA because mitochondria produce a large amount of reactive oxygen species and tend to accumulate toxic xenobiotics. Therefore, there is keen interest in mechanisms that maintain the integrity of mtDNA. DNA repair may play an important role. The repair of mtDNA has been investigated less intensely than nuclear DNA repair because, for a long time, it was thought that mitochondria lacked DNA repair systems. In fact, DNA damage can be repaired in mitochondria. Base-excision repair in mitochondria is well established. The enzymes responsible for mtDNA repair have been identified and are encoded by the same genes as their nuclear counterparts. Mitochondrion-targeting sequences are generated through alternative splicing of mRNAs, alternative use of transcription initiation sites, or alternative use of translation initiation sites. In addition to DNA repair, the degradation of damaged mtDNA may be tolerated because there are multiple copies of mtDNA molecules in a cell.

Keywords DNA repair · DNA damage · Mitochondrial DNA · Reactive oxygen species

Communicated by S. Hohmann

D. Kang (✉) · N. Hamasaki
Department of Clinical Chemistry and
Laboratory Medicine,
Kyushu University Graduate School of Medical Sciences,
3-1-1 Maidashi, Higashi-ku,
Fukuoka 812-8582, Japan
E-mail: kang@biochem2.med.kyushu-u.ac.jp

Introduction

Mitochondria, which probably evolved from endosymbiotically incorporated organisms, have their own genome. Mitochondria replicate and transcribe their DNA semiautonomously. The circular, approximately 16-kbp and 80-kbp DNAs of human and yeast mitochondrial genomes, respectively, mainly encode subunits of the mitochondrial electron transport system and the rRNAs and tRNAs used for constructing the mitochondrial translational machinery. Each subunit encoded by mitochondrial DNA (mtDNA) is thought to be essential for normal oxidative phosphorylation. Thus, integrity of the mitochondrial genome is crucial for the survival of organisms.

Unlike nuclear DNA, mtDNA is continuously replicated, even in terminally differentiated cells, such as nerve cells and cardiomyocytes. Hence, somatic mtDNA damage (resulting in mtDNA mutation) potentially causes more adverse effects on cellular functions than does somatic nuclear DNA damage. Accordingly, DNA repair systems in mitochondria would actually be more important than those in nuclei, particularly for non-dividing cells. Mitochondria had long been considered to lack DNA repair systems, since pyrimidine dimers produced by UV-irradiation are not repaired in mitochondria (Clayton et al. 1974). The inability to repair pyrimidine dimers in mitochondria is further supported by the finding that there is no decrease in T4 endonuclease V (pyrimidine dimer-DNA glycosylase)-sensitive sites in UV-irradiated mtDNA (LeDoux et al. 1992). However, mitochondria indeed repair certain types of DNA damage. When nuclear DNA damage is too severe to be repaired, a cell commits suicide and undergoes the apoptotic program. In contrast, at least theoretically, a cell can abandon heavily damaged mtDNA molecules because there are multiple copies of mtDNA (Fig. 1).

This review article concerns DNA repair in mitochondria (Table 1) and attention is given to the biological significance of maintaining genetic integrity.

Somatic mutation with ageing

MtDNA is much more vulnerable than nuclear DNA. First, mtDNA is under much stronger oxidative stress than nuclear DNA (Beckman and Ames 1996). Mammalian mitochondria account for over 90% of cellular oxygen consumption; and 1–5% of the mitochondrially consumed oxygen is converted to reactive oxygen species (ROS) in the mitochondrial respiratory chain (Papa 1996). MtDNA is obviously in proximity to the ROS-generating respiratory chain. Also, mtDNA is much more strongly subject to chemical damage than nuclear DNA (Bandy and Davison 1990). Mitochondria maintain a matrix-side negative membrane potential for oxidative phosphorylation. This membrane potential facilitates the accumulation of lipophilic cations in mitochondria. Mitochondria can take up lipophilic cations from the cytosol and concentrate these cations inside, up to 1,000-fold. For this reason, one can see a clear mitochondrial structure with fluorescent dyes such as Mitotracker. However, many biologically toxic chemicals are also lipophilic and have positive charges.

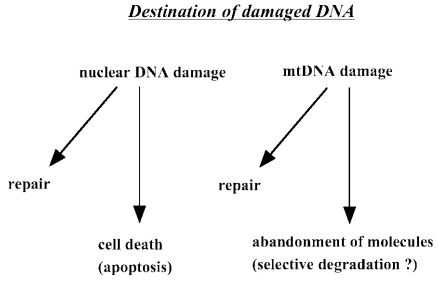

Fig. 1. Destination of damaged DNA

The vulnerability of mtDNA is illustrated, for example, by the fact that 8-oxoguanine (8-oxoG), an oxidatively modified guanine base, accumulates more and increases more rapidly in mtDNA than in nuclear DNA (Beckman and Ames 1996). Thus, higher mutation rates in mtDNA are expected. Mutation rates of human mtDNA are indeed several hundred-fold higher than nuclear gene mutation rates (Khrapko et al. 1997). Most of them are A to G or G to A transition mutations. The appearance of the same kind and position of hot spot mutations in different tissues and cultured cells suggests that the mutations are spontaneous in origin. The mutations most likely arise from DNA replication and/or replicative bypass of DNA adducts created by endogenous factors, such as ROS. Point mutations in the control/D-loop region of human mtDNA accumulate in an ageing-dependent manner (Michikawa et al. 1999). Age-related large rearrangements of mtDNA have been reported (Hayakawa et al. 1996; Kajander et al. 2000). The somatically occurring variant mtDNA molecules can become amplified, depending on conditions and leading to cellular dysfunction with age. DNA polymerase gamma, which is the only DNA polymerase identified in mammalian mitochondria and supposed to be a replicase for mtDNA, has an 3′–5′ exonuclease activity for proof reading (Longley et al. 1998a, b). DNA polymerase gamma synthesizes DNA as faithfully as DNA polymerases for nuclear DNA replication. Therefore, the higher mutation rates in mtDNA are due to stronger damage and/or poorer repair.

The apparent existence of hot spots of mutations in mtDNA has to be interpreted cautiously. The A3243G mutation, which causes mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes, is found in healthy subjects and increases with age (Kadenbach et al. 1995). The accumulation of A3243G is thought to

Table 1. Mitochondrial DNA repair proteins listed in this review article. Genes expressed in bold are common to their nuclear counterparts. *AP* Apurinic

Enzyme	Gene		
	Saccharomyces cerevisiae	Human	
Uracil DNA glycosylase	?[a]	**UNG1**	AP lyase – no
8-Oxoguanine DNA glycosylase	*OGG1*	**OGG1**	AP lyase – yes
Adenine DNA glycosylase		**MYH**	AP lyase – yes
Thymine glycol DNA glycosylase	*NTG1*	**NTH1**	AP lyase – yes
3-Methyladenine DNA glycosylase	*MAG* (?)[b]	**MPG**[c]	AP lyase – no
AP endonuclease	*APN1*	**APE1/Ref-1**	
		APE2	
DNA polymerase	*MIP1*	POLG	
DNA ligase	***CDC9***	**LIG3**	
DNA helicase	*PIF1*	?[a]	
Single-stranded DNA-binding protein	*RIM1*	SSB	
Non-specific DNA-binding protein	*ABF2*	TFAM	
Junction-specific endonuclease	*CCE1*/*MGT11*		
Mismatch binding protein	*MSH1*		
8-OxodGTPase		**MTH1**	
dUTPase		**UTP1**	

[a] Activity is present but the gene has yet to be determined
[b] Mitochondrial localization was not examined
[c] Exon 1a contains a putative mitochondrion-targeting sequence, but mitochondrial localization is not shown