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Mitochondrial DNA Damage: Role of Ogg1 and Aconitase

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1. Introduction

Mitochondria have a vital role in respiration-coupled energy production, amino acid and fatty acid metabolism, Fe^{2+}/Ca^{2+} homeostasis and the integration of apoptotic signals that regulate cellular life and death (Babcock et al., 1997; Loeb et al., 2005; Taylor & Turnbull, 2005; Kroemer et al., 2007). Given the importance of these cellular functions regulated by the mitochondria with implications for aging, degenerative diseases and carcinogenesis, it is not surprising that this organelle has been the subject of intensive investigation for decades and continues to challenge investigators. Mitochondria produce nearly 90% of all the energy made in the body by oxidative phosphorylation that occurs via the electron transport chain (ETC). Mitochondria are the major cellular site of reactive oxygen species (ROS) production. It is estimated that 1–5% of the oxygen consumed in the mitochondrial ETC is converted to ROS (Kroemer et al., 2007). Mammalian mitochondria have a covalently closed round mitochondrial DNA (mtDNA) that is replicated and expressed within the mitochondria in close proximity to the ETC and potentially damaging ROS (Clayton 1982; Clayton 1984; Kroemer et al., 2007). Mammalian mtDNA contains 37 genes that encode 13 proteins (all of which are involved in the ETC), 22 tRNAs, and 2 rRNAs (Anderson et al., 1981). The remaining mitochondrial ETC proteins, the metabolic enzymes, the DNA and RNA polymerases and the ribosomal proteins are all encoded by nuclear genome.

Oxidative stress-induced mtDNA damage is implicated in a wide range of pathologic processes including carcinogenesis, aging and degenerative diseases of various organs and tissues (Bohr et al., 2002; Van Houten et al., 2006; Kroemer et al., 2007; Gredilla et al., 2010). In this review, we summarize the evidence that mtDNA damage augments mitochondria-regulated (intrinsic) apoptosis; an event that underlies the pathophysiologic mechanisms of diverse diseases. We focus our attention on one form of oxidative stress, exposure to asbestos fibers, which are well known to cause pulmonary fibrosis (asbestosis) and malignancies (e.g. mesothelioma and lung cancer). Specifically, we examine the role of a mitochondrial oxidative DNA repair enzyme (8-oxoguanine DNA glycosylase; Ogg1) and a recently described novel mechanism whereby mitochondrial Ogg1 acts as a mitochondrial aconitase chaperone protein to prevent oxidant-induced alveolar epithelial cell (AEC) mitochondrial dysfunction and intrinsic apoptosis. We discuss studies showing that

mitochondrial aconitase, a crucial Kreb cycle enzyme, also functions in mtDNA maintenance and are a mitochondrial redox-sensor that is susceptible to oxidative degradation. Finally, we review accumulating evidence for important crosstalk between p53, which is a crucial DNA damage response protein, Ogg1, mtDNA damage and apoptosis.

2. MtDNA damage: Role of mitochondrial ROS

Individual cells contain several thousand copies of mtDNA, and in normal individuals, almost all of the mtDNA is similar. However, in some cases, especially in mitochondrial diseases, wild-type and variant mtDNAs coexist. The mutation rate of mtDNA is several folds higher in mtDNA than nuclear DNA (Bohr et al 2002; Van Houten et al 2006; Gredilla et al., 2010). There are three reasons for the high mutation rate in mtDNA. The first is that mtDNA, which is located along the mitochondrial inner membrane, is vulnerable to ROS-induced damage due to its close proximity to high levels of ROS produced from the ETC (Nass 1969; Albring et al., 1977; Chance et al., 1979; Shigenaga et al., 1994; Gredilla et al., 2010). The second reason is that mtDNA has no histone-containing protein shield as does the nuclear genome, so that mtDNA is uniquely susceptible to ROS-induced stress. Finally, mitochondria have a limited DNA repair systems as compared to what is present in the nucleus (see for review: Gredilla at al 2010). Collectively, these conditions cause mtDNA to accumulate various somatic mtDNA mutations in mitotic (Michikawa et al., 1999) and post-mitotic tissues (Soong et al., 1992; Corral-Debrinski et al., 1992; Liu et al., 1998). Mitochondrial DNA mutations and insertions/deletions have been observed in many types of human cancer (Bohr et al 2002). Mitochondrial functional defects have also been observed due to abnormal expression of mtDNA encoded proteins and defective oxidative phosphorylation (Kroemer et al 2007). Mitochondrial dysfunction and mtDNA mutations are also implicated in the development and complications of diabetic cardiomyopathy as well as directly associated with different types of neurodegenerative diseases (Medikayala et al., 2011). An emerging regulatory role for mitochondrial topoisomerases appears important for mtDNA integrity in the myocardium (Medikayala et al., 2011).

The most frequently formed mitochondrial ROS are hydrogen peroxide (H_2O_2), superoxide anion ($O_2^{\bullet -}$), singlet oxygen, and hydroxyl radicals ($OH^{\bullet}$). Nearly 1-5% of the total molecular oxygen utilized by mammalian mitochondria is converted into ROS (Boveris & Chance 1977). Not surprisingly, mitochondria are one of the main cellular targets of oxidative damage resulting in relatively high levels of oxidized proteins, lipids and nucleic acids in mammalian mitochondria under normal metabolic conditions (see for reviews Raha & Robinson, 2000; Kroemer et al 2007). Generation of ROS produce a variety of lesions in cellular DNA, such as single or double strand breaks, intra- and inter-strand cross-linking and base damage (see for reviews Upadhyay & Kamp, 2003; Gredilla et al., 2010). Persistent DNA damage can cause cell cycle arrest, induction of transcription, induction of signal transduction pathways, replication errors, and genomic instability. Mitochondrial ROS can induce oxidative mitochondrial as well as nuclear DNA damage that results in apoptosis, if cells survive, promotes DNA mutations. For example, DNA damage is an early event in asbestos-exposed cells that can trigger apoptosis by inducing mitochondrial ROS production that may in part account for its malignant potential (see for reviews Kamp et al., 1992; Hardy & Aust, 1995; Jaurand 1997; Shukla et al., 2003; Liu et al., 2010).

Mitochondrial-associated gene expression, which is significantly different in cancer cells as compared to normal cells, identifies the changes in mitochondrial function emerging in

developing cancer cells (see for review Ralph et al., 2010). Cancer cell development is dependent on the interactions of key oncogenes and tumor suppressor genes and their encoded products (see for review Janicke et al., 2008; Ralph et al., 2010). Studies in yeast show that mtDNA mutations can either reduce or extend life span depending upon the severity, context, and developmental stage of mtDNA damage (Powell et al., 2000). Unexpectedly, complete absence of mtDNA in yeast is associated with increased life span (Powell et al., 2000). Mice with a homozygous mutation in the exonuclease domain of mtDNA polymerase gamma (POLG) have been used as a model of mitochondrial dysfunction and aging. These mice possess an mtDNA mutator phenotype, accumulating lot of deletions and point mutations in mtDNA. These mice do not display signs of elevated ROS generation, but instead exhibit increased apoptosis, a number of age-related phenotypes, and a shortened life span (Kujoth et al., 2005; Trifunovic et al., 2004). As recently reviewed elsewhere (Kamp et al., 2011), chronic inflammation can promote all stages of tumorigenesis including mtDNA damage important in regulating mitochondrial function that coordinates life and death signaling pathways. Lung mesothelial cell mtDNA damage is evident following exposure to a four-fold lower concentration of crocidolite asbestos than required for causing nuclear DNA damage (Shukla et al., 2003). Several lines of evidence implicate mtDNA oxidative injury as a key trigger of apoptosis that can result in inflammation-associated cancer including: (1) cell death is often associated with mtDNA oxidative lesions, (2) mtDNA damage result in ATP depletion and mitochondrial dysfunction, (3) enhancing mtDNA repair can prevent cell death, and (4) defective mtDNA repair enhances cell death (see for review Kamp et al., 2011).

Apoptosis, or programmed cell death, is an important mechanism by which cells with extensive DNA damage, including mtDNA damage, are eliminated without inciting an inflammatory response. Notably, cell-sorting experiments established that persistent mtDNA damage is necessary for triggering mitochondrial dysfunction and apoptosis (Santos et al., 2003). Although much is known about the complex molecular pathways regulating apoptosis, the precise mechanisms involved remain incompletely understood (see for reviews: Kroemer et al., 2007; Kim et al., 2008; Youle & Strasser, 2008; Franco et al., 2009). The two major pathways regulating apoptosis include the mitochondria (intrinsic) death pathway and the death receptor (extrinsic) pathway. The intrinsic death pathway is activated by various stimuli, such as ROS, DNA damage, and calcium, that result in permeabilization of the outer mitochondrial membrane (OMM), a reduction in mitochondrial membrane potential change ($\triangle\psi m$) and the release of apoptogenic proteins, including cytochrome c that activate caspase-9 and, ultimately caspase-3. Notably, mtDNA damage that occurs following oxidative stress or mutations in mitochondrial DNA polymerase are implicated in premature aging as well as tumor metastasis (Trifunovic et al., 2004; Ishikawa et al., 2008)

ROS and DNA damage, including that caused by asbestos, trigger intrinsic apoptosis that can be blocked by antioxidants and iron chelators (Kroemer et al., 2007; Youle & Strasser, 2008; Franco et al., 2009; Kamp et al., 1995; Aljandali 2001; Panduri 2003; Panduri 2004). Herein we focus on asbestos-induced apoptosis to lung cells. Accumulating evidence over the past decade convincingly demonstrate that all forms of asbestos fibers, as opposed to inert particulates (e.g. titanium dioxide [TiO_2]), cause apoptosis in AEC as well as mesothelial cells via the mitochondria-regulated death pathway (reviewed in Kamp et al., 2011). Our group used human A549 cell and rat primary cells isolated alveolar type II to

show that asbestos causes both a dose- and time-dependent reduction in △ψm that was associated with release of cytochrome c from the mitochondria to the cytoplasm as well as activation of caspase-9 (Panduri et al., 2003). In this study, both an iron chelator (phytic acid) and a free radical scavenger (sodium benzoate) blocked asbestos-induced reductions in △ψm and caspase-9, implying the importance of both iron-derived ROS and the mitochondrial death pathway. Furthermore, asbestos-induced apoptosis in A549 cells that stably overexpress Bcl-xl, an anti-apoptotic Bcl-2 family member, was significantly attenuated as compared to wild-type cells as evidenced by preservation of the OMM integrity and reduced DNA fragmentation (Panduri et al., 2003). Using confocal microscopy and Western blotting of mitochondrial proteins, we showed that asbestos stimulates mitochondrial translocation of pro-apoptotic Bax and that these effects are blocked by phytic acid (Panduri et al., 2006). Notably, using A549-ρ0 cells that lack mtDNA and a functional electron transport chain necessary for mitochondrial ROS generation, asbestos-induced ROS production, caspase-9 activation, and intrinsic apoptosis were all completely blocked (Panduri et al., 2006). These findings establish an important role for mitochondrial ROS in mediating asbestos-induced AEC apoptosis.

3. Ogg1 and mitochondrial base excision repair

Oxidative stress can induce many types of DNA base damage including two of the most abundant lesions, 8-hydroxyguanine (8-oxoG) and thymine glycol (TG) (Demple & Harrison, 1994; Dizdaroglu 1992; Bohr et al., 2002; Gredilla et al., 2010). Further, 8-oxoG is more susceptible to oxidative attack than guanine itself, resulting in the formation of oxidation products such as guanidinohydantoin and spiroiminodihydantoin (Bjelland & Seeberg, 2003; Hailer et al., 2005). The 8-oxoG residue exists predominantly in its keto form at physiological pH, resulting in the normal anti conformation around the *N*-glycosylic bond, and forming a common Watson-Crick base pair with cytosine. 8-oxoG adopts a *syn* conformation and base pairs with adenine leading to transversion mutations in replicating cells (Shibutani 1991), which may play a role in the development of cancer and the process of aging (Ames 1989; Lindahl 1993). In contrast, TG strongly blocks DNA replication (Ide et al., 1985; Clark & Beardsley, 1987) and transcription (Hatahet et al., 1994; Htun & Johnston, 1992) and must be efficiently removed and repaired to maintain genetic stability. Therefore, inefficient repair of oxidative mtDNA damage augments the accumulation of mtDNA damage and mutations that can lead to mitochondrial dysfunction and apoptosis. In this section we focus attention on repair of 8-oxoG by mitochondrial 8-oxoguanine DNA glycosylase 1 (mt-Ogg1) since it is among the best characterized mitochondrial base excision repair (BER) proteins.

The BER pathway accounts for the repair of the majority of spontaneously formed oxidized bases in mtDNA important for preserving the genome stability required for long-term cell survival (Barnes & Lindahl, 2004; Gredilla et al. 2010). All mitochondrial DNA repair enzymes, including those involved in BER, are encoded in the nucleus and imported into the mitochondria (Gredilla et al. 2010). The BER pathway removes small covalent modifications, which do not distort the DNA helix, such as the base modifications generated by ROS and single-strand breaks. The BER pathway in mitochondria and nucleus is highly conserved in all cellular organisms, from bacteria to man. BER is carried out in four sequential enzymatic steps catalyzed by the enzymes DNA glycosylase, AP-endonuclease, DNA polymerase and DNA ligase (Dianova et al., 2001; Gredilla et al., 2010). The initial

steps in the BER pathway are recognition and removal of the aberrant base by a DNA glycosylase. Most DNA glycosylases remove several structurally different damaged bases, and some of them have overlapping substrate specificities, which may indicate that they serve as back-up systems for each other (Dianovet al., 2001). The mammalian DNA glycosylase, Ogg1, recognizes and removes 8-oxoG that is base-paired with cytosine in DNA (Aburatani et al., 1997; Radicella et al., 1997). Ogg1 is a bifunctional DNA glycosylase, with an associated AP-lyase activity, cleaving DNA at abasic sites through a β-elimination mechanism (Bjoras et al., 1997). The human OGG1 gene is located on chromosome 3p26.2. Studies of mice that are deficient in Ogg1 demonstrate that this enzyme is responsible for most of the BER activity that is initiated at 8-oxoG in mammalian cells (Klungland et al., 1999). Interestingly, using fluorometric techniques to identify the site of Ogg1 DNA repair activity following exposure to oxidative stress, the mitochondria, rather than the nucleus, was primary site of Ogg1 DNA repair activity (Mirbahai et al., 2010). In Ogg1 knockout mice, the mitochondrial genome contains almost nine times more 8-oxoguanine than control animals, whereas in the nuclear DNA the level of 8-oxoguanine is increased only twofold (Souza-Pinto et al., 2001). OGG1 gene mutations or polymorphisms increase the risk of various malignancies including lung, kidney, gastric, and colorectal cancer, as well as leukemia (Chevillard et al., 1998; Shinmura et al., 1998; Audebert et al., 2000; Bohr et al., 2002; Elahi et al., 2002; Fortini et al., 2003; Russo et al., 2004; Mambo et al., 2005). Furthermore, reduced Ogg1 activity is a risk factor in lung and head and neck cancer (Paz-Elizur et al., 2008).

Several groups have demonstrated that overexpression of mitochondria-targeted Ogg1 prevents mtDNA damage and intrinsic apoptosis caused by ROS-exposed vascular endothelial and asbestos-exposed cells (Dobson et al., 2002; Ruchko et al., 2005; Rachek et al., 2006; Harrison et al., 2007; Panduri et al., 2009; Ruchko et al., 2010). This suggests a prominent role of mt-Ogg1 in regulating intrinsic apoptosis in diverse settings of oxidative stress. Alternative splicing of the OGG1 transcript results in two isoforms: α-Ogg1 and β-Ogg1 (Gredilla et al., 2010). β-Ogg1 levels in the mitochondria are 20-fold greater than α-Ogg1 levels yet, curiously, β-Ogg1 lacks 8-oxoG DNA glycosylase activity (Hashiguchi et al., 2004). This finding suggests a role for Ogg1 that is independent of DNA repair. Our group recently reported that overexpression of mitochondrial α-Ogg1 mutants lacking 8-oxoG DNA repair activity were as effective as wild type mt-Ogg1 in preventing oxidant-induced caspase-9 activation and intrinsic apoptosis. Mitochondria-targeted Ogg1 did not alter the levels of mitochondrial ROS produced but, interestingly, preserved mitochondrial aconitase suggesting a novel role for Ogg1 as discussed further below (Panduri et al., 2009).

4. Aconitase and mitochondrial DNA

Aconitase, an enzyme that is vital for carbohydrate and energy metabolism, is responsible for the interconversion of citrate and isocitrate in the tricarboxcylic acid (TCA) cycle (Emptage et al., 1983). The importance of mitochondrial aconitase is suggested by the observation that citrate levels in the human prostate appear important for promoting oncogenic conditions. Normal citrate-producing prostate epithelial cells can develop into citrate-oxidizing malignant cells that result in a net increase of 22 ATP/mol glucose that affords energy for malignant-associated activities (Costello & Franklin, 1994). It has been suggested that mitochondrial aconitase is a key enzyme associated with this bioenergy transformation since loss of its activity reduces cellular survival (Singh et al., 2006).

Mitochondrial aconitase is an iron-sulfur protein that is vulnerable to oxidative inactivation and is implicated as a mitochondrial redox-sensor (Gardner et al., 1994; Bulteau et al., 2003). Aconitase inactivation can further promote oxidant generation by releasing redox-active Fe from the $(4Fe–4S)^{2+}$ center following exposure to oxidants such as $O_2^{\bullet -}$ (Gardner et al., 2000) or deficiency of mitochondrial manganese superoxide dismutase (MnSOD) (Williams et al., 1998). Oxidative-inactivation of aconitase is associated with decreased Drosophila lifespan (Yan et al., 1997). Reduced aconitase activity has also been described in a number of neurodegenerative diseases, including progressive supranuclear palsy (Park 2001), Friedreich's ataxia (Bradley 2000), and Huntington's disease (Tabrizi 1999).

Collectively, the above findings suggested a key role for mitochondrial aconitase beyond the TCA cycle. In this regard, a provocative finding in yeast showed that mitochondrial aconitase preserves mtDNA independent of aconitase's catalytic activity (Chen et al., 2005). This was the first suggestion of a dual role for aconitase as a mitochondrial TCA enzyme as well as in mtDNA maintenance, mitochondrial aconitase co-precipitates with frataxin, which is an iron chaperone protein that prevents aconitase oxidative inactivation and/or augments aconitase reactivation (Bulteau et al., 2004). This study suggested that prevention of oxidative inactivation of mitochondrial aconitase may be important for the pathogenesis of a degenerative disease (e.g. Friedrich's ataxia). Further evidence for this possibility was our recent finding that mt-Ogg1 overexpression completely blocks oxidant induced decreases in AEC mitochondrial aconitase activity and protein expression (Panduri et al., 2009). Moreover, using immunoprecipitation to explore the possible interactive effects between mitochondrial Ogg1 and aconitase, mitochondrial aconitase coprecipitated with both wild-type and mutant mt-Ogg1. Notably, overexpression of mitochondrial aconitase eliminated oxidant induced AEC apoptosis whereas Ogg1 underexpression using shRNA techniques reduced basal mitochondrial aconitase levels and augmented oxidant-induced AEC apoptosis (Panduri et al., 2009). These latter findings are in accord with several recent studies showing that Ogg1 deficiency increases oxidant-induced apoptosis (Youn et al., 2007; Bacsi et al., 2007; Xie et al., 2008). Collectively, these results suggest a novel interaction between an mtDNA repair enzyme (mt-Ogg1) and aconitase in preventing intrinsic AEC apoptosis following exposure to oxidative stress (e.g. asbestos or H_2O_2).

The underlying mechanisms that account for the interactive protective effect of mt-Ogg1 and aconitase require further study but there are at least two possibilities, which are not mutually exclusive. First, mt-Ogg1 may block key oxidative modification sites on mitochondrial aconitase responsible for triggering degradation by mitochondrial Lon protease (Bota & Davies, 2002; Bota et al., 2005). Lon protease selectively degrades oxidatively modified aconitase at a much higher rate than unexposed aconitase; a finding that may be important in defending the mitochondria against the accumulation of oxidized proteins as well as ensuring that such cells will undergo intrinsic apoptosis (Wallace, 1999; Bota et al., 2005; Bota & Davies, 2002; Panduri et al. 2009). Support for this possibility is our finding that MG132, a protease inhibitor that blocks mitochondrial Lon protease (Granot et al., 2007), attenuates asbestos-induced reductions in mitochondrial aconitase activity (Panduri et al., 2009). Second, overexpression of mt-Ogg1 or aconitase may preserve mtDNA levels necessary to prevent activation of intrinsic apoptosis. Future studies are required to clarify these possibilities as well as to determine precisely how mt-hOgg1 interacts with aconitase and whether other mtDNA repair proteins act similarly.

5. p53 and mitochondrial DNA repair

p53 functions as the ″gatekeeper″ of the genome by integrating various signals and initiating appropriate biological responses including cell cycle arrest, differentiation, apoptosis, senescence, and anti-angiogenesis (see for reviews Levine 1997; Vogelstein et al., 2000; Vousden et al., 2009). Previous studies have shown that the functions of p53 are mediated by transcriptional activation that regulates expression of downstream target genes (El-Deiry 1998). Expression of some cellular genes, including WAF1, CIP1, p21, IGF-BP3, mdm2, cyclin G, PCNA, and GADD45, are directly regulated by p53-mediated transactivation (Ko & Prives, 1996). p53 is also a redox-sensitive transcription factor whose function is integrally connected to ROS production as well as mediating the down-stream cellular effects following oxidative stress including the induction of apoptotic cell death (reviewed in Sablina et al., 2005; Janicke et al., 2008; Vaseva et al., 2009; Liu et al., 2010). ROS can induce p53 expression whereas p53 stabilization can augment further ROS production, often via effects on the mitochondria (Janicke et al., 2008; Liu et al., 2010). The mitochondria are an important target of transcription-dependent and -independent actions of p53 required to trigger apoptosis. By regulating thousands of genes, either directly or indirectly, p53 is implicated in numerous key cellular roles, including a recently described role for mtDNA maintenance (El-Deiry et al., 1992; Janicke et al., 2008, Bakhanashvili et al., 2008; Lebedeva et al., 2009).

The mechanism by which p53 regulates cellular responses following exposure to oxidative stress generally depends on the levels of ROS. A biphasic response is seen in which low basal p53 expression promotes ROS homeostasis and cell survival by augmenting anti-oxidant defenses as one of its tumor-suppressing mechanisms while higher levels of ROS induce persistent p53 expression that blocks the cell cycle enabling time for DNA repair and, if repair is insufficient, triggers apoptosis (Bensaad et al., 2005; Janicke et al., 2008; Vousden et al., 2009). Notably, p53 also enhances Ogg1 activity for 8-oxoG removal suggesting a link between Ogg1, p53 and mtDNA (Achanta & Huang , 2004). A recently described role for p53 in mtDNA maintenance following exposure to mitochondrial ROS is evidenced by its involvement in maintaining mtDNA copy number and mtDNA synthesis (Bakhanashvili et al., 2008; Lebedeva et al., 2009). Cells that are p53-depleted exhibit significant disruption of cellular ROS homeostasis that are characterized by reduced mitochondrial biogenesis and increased H_2O_2 production (Lebedeva et al., 2009). In contrast, thymic lymphomas derived from the $p53^{-/-}$ mouse (a common model of carcinogenesis) have highly significant upregulation of mitochondrial biogenesis, mitochondrial protein translation, mtDNA copy number, ROS levels, anti-oxidant defenses, proton transport, ATP synthesis, hypoxia response, and glycolysis, indicating important mitochondrial bioenergetic profile changes of cells occurs during the process of malignant transformation (Samper et al., 2009). Hypoxia stimulates mitochondrial ROS production, which activates p53 stabilization and localization to the mitochondria where p53 has many effects including inhibiting MnSOD thereby promoting $O_2^{\bullet -}$ formation and greater oxidative damage (Ralph et al., 2010) as well as regulating mtDNA repair and replication as noted above. Taken together, the emerging evidence strongly implicate that p53 is a key regulator of mitochondrial function, including ROS production and associated mtDNA repair following oxidative damage, as well as mtDNA replication and mitochondrial biogenesis (Ralph et al., 2010).

It is known well that most human tumors contain mutations in one or more p53 gene family members (see for reviews Janicke et al., 2008; Vousden & Prives, 2009). In this section we

focus on the role of p53 in the lungs exposed to asbestos fibers. Altered p53 expression has been implicated in the pathophysiology of pulmonary fibrosis, including that due to asbestos, as well as asbestos-associated malignancies, especially bronchogenic lung cancer (Nelson et al., 2001; Mishra et al., 1997; Burmeister et al., 2004; Plataki et al., 2005). Asbestos activates p53 and p21 expression in lung epithelial and mesothelial cells that result in cell cycle arrest (Levresse et al., 1997; Matsuoka et al., 2003; Kopnin et al., 2004). Furthermore, increased p53 levels are detected in lung cancers of patients with asbestosis (Nuorva et al., 1994) and p53 point mutations are present in the lung epithelium of smokers and asbestos-exposed individuals (Husgafvel-Pursiainen et al., 1997). Crocidolite asbestos promotes p53 gene mutations predominantly in axons 9 through 11 in BALB/c-3 T3 cells (Lin et al., 2000). Finally, studies in lung epithelial and mesothelial cells using gene expression microarray techniques have established that induction of p53 gene expression following asbestos fiber exposure is an important event (Nymark et al., 2007; Hevel et al., 2008). Thus, p53 has a crucial role regulating lung cellular DNA damage response following exposure to oxidative stress as occurs with asbestos and tobacco smoke.

The mechanisms by which p53 regulate apoptosis are complex and incompletely understood. One established pathway involves intrinsic apoptosis via p53 crosstalk with the mitochondria by increasing transcription of pro-apoptotic stimuli (e.g. Bax and BH3-only proteins) while inhibiting gene expression of anti-apoptotic Bcl-2 family members (Miyashita et al., 1995; Oda et al., 2000; Nakano et al., 2001; Janicke et al., 2008; Vousden & Prives, 2009). There is considerable evidence that p53 phosphorylation at the Ser15 position following exposure to DNA damaging agents, including asbestos, is in part responsible for p53 stabilization and its subsequent mitochondrial translocation. Several different proteins have been implicated in the phosphorylation of p53 at Ser15, including members of the phosphatidylinostitol 3-kinase-related kinase (PI3K) family such as DNA-activated protein kinase (DNA-PK) and ataxia-telangiectasia mutated (ATM) kinase, as well as members of the mitogen-activated protein kinase (MAPK). In one study, suppression of DNA-PK coupled with a mutated form of ATM inhibited asbestos-induced Ser15 phosphorylation and accumulation of p53 (Matsuoka et al., 2003). Considerable evidence has established that p53 is a crucial regulator of mitochondrial function, including ROS generation and mtDNA repair following oxidative damage as well as mitochondrial biogenesis and mtDNA replication (see for review Liu et al., 2010). For example, p53 mediates asbestos-induced mitochondria-regulated apoptosis in lung epithelial cells and this is blocked in cells incapable of producing mitochondrial ROS (Panduri et al., 2006). Notably, loss of p53 results in mtDNA depletion, altered mitochondrial function and increased H_2O_2 production (Lebedeva et al., 2009).

The above data are providing insights into the molecular mechanisms by which p53 regulates the cellular response to DNA damage caused by exposure to oxidative stress that is likely important in the pathogenesis of inflammation-associated cancer (see for review: Kamp et al., 2011). An important link between p53 and Ogg1 is suggested by the finding that Ogg1 is under transcriptional regulation by p53 in colon and renal epithelial cells (Youn et al., 2007). In this study, the expression and activity of Ogg1 were decreased in HCT116p53$^{-/-}$ cells. Further, gel-shift assays showed that p53 binds to the putative cis-elements within the OGG1 promoter while supplementing p53 in HCT116p53$^{-/-}$ cells enhanced OGG1 transcription. In renal epithelial cells, tuberin also regulates OGG1 expression since transcriptional activity of the OGG1 promoter is decreased in tuberin-null cells; an effect that in part is mediated by the transcription factor NF-YA (Habib et al., 2008).

p53 modulates cellular metabolism by enhancing aerobic respiration and blocking glycolysis in most cell types; findings that are likely important in cellular malignant transformation (Bensaad et al., 2006; Bensaad et al., 2007). Interestingly, there is some evidence that p53 impacts mitochondrial aconitase levels since thymoquinone, a p53-dependent antineoplastic drug, reduces aconitase enzyme activity in isolated rat liver mitochondria (Roepke et al., 2007). Also, mitochondrial aconitase gene expression in prostate carcinoma cells is inhibited by both endogenous p53 induction by camptothecin treatment and exogenous p53 induction by transient overexpression of p53 (Tsui et al., 2011). Further, these investigators showed that mitochondrial aconitase is a p53-downregulated gene. Camptothecin did not affect mitochondrial aconitase reporter activity in p53-null PC-3 cells suggesting that the decrease in mitochondrial aconitase gene expression by camptothecin occurs via p53 activation. The relevance of these findings to other cell types as well as the *in vivo* significance requires further study.

6. Conclusion

In this review we have summarized emerging evidence demonstrating an important interactive effect between mitochondrial Ogg1, mitochondrial aconitase, and p53 in mtDNA repair and oxidant-induced intrinsic apoptosis. Although we focused on the role of oxidative stress caused by exposure to asbestos fibers, it is likely that many of the described interactive effects between mt-Ogg1, aconitase, p53 and intrinsic apoptosis will have broader implications but this awaits future investigations. Additional studies are necessary to further characterize the role of mitochondrial Ogg1 and aconitase in preventing mtDNA damaging (including following asbestos exposure), p53 activation and intrinsic apoptosis. It will also be of considerable interest to better understand the molecular mechanisms by which mitochondrial Ogg1 binds aconitase. Finally, and perhaps most importantly, we reason that the asbestos paradigm will continue to provide insights into the molecular mechanisms underlying the interactive effects between mt-Ogg1, aconitase, p53 and intrinsic apoptosis that should shed light into the pathogenesis of other more common diseases, such as lung cancer and idiopathic pulmonary fibrosis, for which more effective management regimens are urgently required. Strategies aimed at augmenting mtDNA integrity by increasing mt-Ogg1 and/or aconitase levels to mitigate the deleterious effects of oxidative stress may prove useful for developing novel therapeutic treatments for tumors and degenerative diseases as well as modulating the effects of aging.

7. Abbreviations

Electron transport chain (ETC)
outer mitochondrial membrane (OMM)
alveolar epithelial cell (AEC)
reactive oxygen species (ROS)
mitochondrial human 8-oxoguanine-DNA glycosylase 1 (mt-hOgg1)
alveolar type II (AT2) cells
hydrogen peroxide (H_2O_2),
superoxide anion (O_2-)
hydroxyl radical (HO•)
8-hydroxydeoxyguanosine (8OHdG)

mitochondrial DNA (mtDNA)
tricarboxcylic acid (TCA)
mitochondrial membrane potential (△ψm)
titanium dioxide (TiO_2)
thymine glycol (TG)
base excision repair (BER)
8-hydroxyguanine (8-oxoG)
manganese superoxide dismutase (MnSOD)

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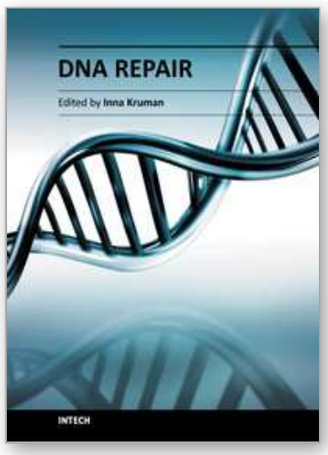

DNA Repair

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The book consists of 31 chapters, divided into six parts. Each chapter is written by one or several experts in the corresponding area. The scope of the book varies from the DNA damage response and DNA repair mechanisms to evolutionary aspects of DNA repair, providing a snapshot of current understanding of the DNA repair processes. A collection of articles presented by active and laboratory-based investigators provides a clear understanding of the recent advances in the field of DNA repair.

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