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Mitochondrial Toxicity of Tobacco Smoke and Air Pollution

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1. INTRODUCTION

Increases in smoking, urbanization and the persistence of burning unrefined fuel indoors in low-and middle-income countries (more than 80% of the world's population) have led to a substantial increase in exposure to environmental pollutants [1–4]. Tobacco cigarette smoking contributes to nearly half a million deaths in the U.S. and 5 million deaths worldwide every year [5, 6]. Compared to never smokers, tobacco cigarette smokers have an average loss of 13.2 and 14.5 years of life in men and women, respectively [7]. Individuals who quit smoking before the age of 44 gain almost a decade of life, compared to those who continue to smoke [8]. Even those individuals who quit between the ages of 45–54 gain an average of 6 years of life relative to those who continue to smoke, highlighting the need for counseling patients of any age on smoking cessation and providing resources for the treatment of nicotine addiction [8]. Despite declines in tobacco cigarette smoking in high-income societies like the United States (**U.S.**), a re-emergence of nicotine addiction and related disease is possible due to the manufacture and sale of alternative tobacco products such as electronic cigarettes (**e-cigarettes**). Further, even in countries that have declines in tobacco cigarette smoking prevalence, certain vulnerable populations (low socioeconomic status, lower education, etc.) continue to have a high smoking prevalence suggesting the need for targeted interventions [9–11].

The most recent World Health Organization (**WHO**) modelled data shows that 92% of the world's population live in areas where the air quality levels are not in compliance with air quality standards [4]. Climate change is also altering the levels and composition of outdoor (ambient) air pollution and without policies aimed at reducing carbon emissions these changes are likely to continue, further increasing the global burden of environmental disease [12, 13]. In 2010, ambient and indoor (household) air pollution were estimated to be

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responsible for 3 million and 3.9 million deaths that year, respectively [3, 4, 14], making them the 4th and 9th leading risk factors for global disease burden [2].

Mitochondria are highly sensitive to environmental toxicants and the individual components of tobacco smoke and air pollution. Environmental toxicant exposure induces changes in mitochondrial respiration and metabolism [15–25], oxidant generation [26–31], mitochondrial DNA (**mtDNA**) damage and copy number [25, 29, 30, 32–36], network formation and structure [19, 37–39], clearance of dysfunctional mitochondria through mitophagy [40], apoptosis [24], and reduction-oxidation (**redox**) signaling [24, 27]. Mitochondria contain many iron-rich enzymes making the proteins within the organelle particularly sensitive to oxidant inactivation [41–43]. Inactivation of manganese superoxide dismutase (the mitochondrial form of superoxide dismutase) leads to further oxidant generation, and many of the respiratory complexes within the mitochondrion contain heme groups that are subject to inactivation or inhibition by oxidants or carbon monoxide, which directly affects mitochondrial ATP production [43, 44]. Several studies have shown that the mtDNA is prone to oxidant/toxicant-induced damage through the formation of strand breaks, thymidine dimer formation, bulky adducts and mtDNA copy number depletion or deletions ([reviewed in 45]). Thus, environmental toxicant-linked mitochondrial abnormalities likely play a causal or contributory role in disease development and pathogenesis and may serve as biomarkers of toxicant-induced injury.

Mitochondria form a dynamic network within cells undergoing cycles of fission into smaller, rounder mitochondria and fusion re-forming into string-like networks [46–50]. The state of the mitochondrial network has been directly linked to the functional status of individual mitochondria [49, 50]. Mitochondria with lower membrane potentials are often smaller, more rounded and are thought to be targeted for removal through mitophagy, a specialized form of autophagy [46–50]. An inability to remove dysfunctional mitochondria can lead to cellular dysfunction and if sustained, apoptosis [51]. Interestingly, cessation of exposure to toxicants often results in restoration of mitochondrial networks, decreased oxidant production, and improved oxidative phosphorylation [17, 52]. Hence, the improvements associated with cessation of exposure may be the result of improved clearance of dysfunctional/damaged mitochondria and replacement with a healthy mitochondrial network, through mitochondrial biogenesis.

Our review outlines the contribution of mitochondrial abnormalities to the pathologies resulting from tobacco smoke and air pollution exposure. The chemical composition of tobacco smoke and air pollution are discussed with an emphasis on their similar chemical components that likely explain the similar disease risk profiles attributed to tobacco smoke or air pollution exposure. We also provide an overview on mitochondrial function and genetics. After a brief background on the diseases associated or caused by exposure to tobacco smoke and air pollution, we discuss the potential contribution of mitochondrial abnormalities to the pathogenesis. We provide potential future directions regarding the utility of mitochondrial markers of function and/or damage as biomarkers for monitoring the possible health effects of environmental toxicants and how mitochondrial genetic variation may impact individual susceptibility to disease.

2. CHEMICAL COMPOSITION

Both tobacco smoke and air pollution consist of complex mixtures of gaseous and particulate components that vary in chemical composition and are the result of the combustion of organic compounds. While the complex nature of this mixture makes it difficult to tease out the chemicals responsible for the toxicity of tobacco smoke and air pollution, the toxicity of some of the largest classes of chemicals have been clearly demonstrated, especially particulate matter [53]. Particulate matter (PM) may consist of many different chemicals but the size of the particle plays a major role in determining its toxicity, with the smaller particles (≤10 μm in diameter, PM_{10}) capable of reaching the deep lung [54]. Fine particulate matter (≤2.5 μm in diameter, $PM_{2.5}$) is of particular concern due to its potent toxicity especially within the pulmonary and cardiovascular systems [55–57]. Additionally, the combination of chemicals present in tobacco smoke and air pollution likely contributes to the overall toxicity of these environmental pollutants [58]. The similarities in chemical composition of air pollutants and tobacco smoke likely explain their similar toxicities and overlapping health effects.

2.1 TOBACCO SMOKE

Tobacco smoke is estimated to contain thousands of chemicals, present in particulate matter and gas phases, and is known to be a significant source of oxidants [59, 60]. Tobacco smoke is divided into main stream smoke (smoke directly inhaled by the smoker) and side stream smoke, which encompasses the smoke coming off the sides of the burning tobacco product plus smoke exhaled by the smoker (collectively known as second-hand smoke). Both mainstream and side stream smoke consist of carbon monoxide, polycyclic aromatic hydrocarbons, tobacco-specific nitrosamines, nitrogen oxides, aldehydes, volatile organic compounds, nicotine, fine particulate matter, and oxidants [59, 61]. The composition of main stream and side stream smoke is similar, but the concentrations of these toxicants and carcinogens differ, largely due to differences in combustion temperatures [59, 60]. For a comprehensive review on the chemical composition of tobacco smoke, the review by Stedman, R.L. is an excellent resource [59].

2.2 AIR POLLUTION

Household air pollution is generated from incomplete combustion of solid or unrefined fuels during the burning of wood, coal, and other biomass for cooking, light and warmth [2, 3, 14, 62–65]. Household air pollution is a major health risk among impoverished communities in low-and middle-income countries, with women and children having higher health risks due to increased exposure durations relative to men [2, 3, 64, 65]. The level and composition of pollutants in household air varies depending upon the ventilation, stove efficiency, source of fuel, duration of exposure, and temperature of combustion [2, 3, 64, 65].

Ambient air pollution is primarily generated by industry and motor vehicle exhaust, although globally, household air pollution contributed an estimated 16% of ambient particulate matter pollution in 2010, with estimates reaching as high as 30% in India in 2012 [2, 65]. Some studies include both passive and active smoking, burning of biomass both indoors and outdoors, and wind-blown dust as sources of ambient pollution [2]. Like

household air pollution, ambient air pollution also varies based on the source of fuel exposure duration and combustion temperatures with added variables of industrial activity intensity, level of motor vehicle exhaust, time of day, time of year, weather conditions, local geography and geographical region [66–68].

The primary toxicants or toxicant mixtures associated with air pollution are similar for household and ambient air pollution and include particulate matter, ozone, carbon monoxide, nitrogen dioxide and sulfur dioxide [12, 67, 69]. Some fuel sources, such as coal, are highly variable, having very different heating values and containing different levels of impurities such as sulfur, arsenic, silica, lead and mercury which are additional pollutants that can be released into the air during combustion [64].

3. MITOCHONDRIA

Mitochondrial toxicity resulting from pharmaceutical use has been appreciated for many years. Many drugs, including antibiotics, nucleoside reverse transcriptase inhibitors and chemotherapeutics have been identified to have unintended effects on multiple mitochondrial functions or responses (e.g. oxidant generation) [reviewed in 45]. It is perhaps not surprising that many environmental toxins also “target” the mitochondrion, either through the specific inhibitory action of a mitochondrial enzyme, and/or through the accumulation of a compound due the intrinsic characteristics of the organelle. Lipophilic compounds accumulate in mitochondrial membranes and cationic metals, xenobiotics (including MPP and paraquat) are known to accumulate within the organelle as well [45], likely due the net negative charge and alkaline pH of the organelle’s matrix. These characteristics in addition to the association of the mtDNA with the inner membrane (lipophilic environment), lack of histones, relatively low level of associated proteins for protection (nucleoids), and the presence of cytochrome P450 in mitochondria which can metabolize compounds into active toxins make the organelle a likely target for environmental toxins [45].

Mitochondria originated as separate bacterial organisms that were endocytosed by a primitive prokaryotic “host” cell approximately a billion years ago [7071, 72]. This symbiotic relationship within the proto-eukaryotic cell provided advantages for survival. In addition to the stereotypical characterization of the mitochondrion as the “powerplants of the cell,” mitochondria have evolved to play important roles in the inter-related processes of immune responses, cell signaling, metabolism (bioenergetics and biosynthesis), and nuclear gene expression [reviewed in 73]. Another consequence of this endosymbiosis is that our genome (as eukaryotes) is a genetic hybrid that consists of the nuclear and mitochondrial genomes (the majority of “mitochondrial” genes encoded by the ancestral mtDNA have been relocated to the nucleus, a process known as endosymbiotic gene transfer). As a result, the two genomes must be coordinately regulated, and the mitochondrion and its “host” are inseparably linked for eukaryotic cell survival and propagation, both genetically and functionally.

3.1. FUNCTIONS

The mitochondrion serves as a source of cellular metabolites (through the citric acid cycle), ATP and oxidants (through electron transport and oxidative phosphorylation), as well as thermal energy (Figure 1). As ATP levels rise and energetic demand decreases, electron

carriers remain in a reduced state for longer periods of time, allowing free electrons to readily react with molecular oxygen to form superoxide [74]. Superoxide is subsequently converted to hydrogen peroxide, a freely diffusible signaling molecule, by manganese superoxide dismutase. In the presence of nitric oxide, superoxide forms peroxynitrite, a reactive nitrogen species (**RNS**) that acts as an oxidant, or alternatively, can further react with carbon dioxide to form nitrosoperoxycarbonate, that is capable forming nitrotyrosine adducts [26, 75–79]. Contrary to widespread perception, mitochondrial oxidants are not merely "byproducts" of metabolism, but instead, serve as cell signaling mediators for the regulation of metabolism. Mitochondrial oxidants play a role in signaling that alters gene expression of proteins involved in inflammation[80], cell death[81], and appetite control [82], as well as the MAP kinase and Akt pathways [83] (please see Bonini review herein, "*Oxidative signaling in mitochondrial homeostasis*" Chapter 4). Consequently, under conditions of positive energy balance (excess reducing equivalents and ATP) or the presence of mitochondrial inhibitors (e.g. components of tobacco smoke such as carbon monoxide and cyanide) mitochondrial oxidant production is altered which may cause damage to mtDNA and impact multiple cell functions by altering the aforementioned cell signaling pathways [84].

3.2. GENETICS AND MUTATION

Each cell contains hundreds to thousands of mitochondria, and each mitochondrion has 2–10 copies of mtDNA, resulting in thousands of mtDNA copies per cell [85, 86]. The mtDNA in mammals encodes 37 genes (13 polypeptides, 22 tRNAs and 2 rRNAs) [87]. The mtDNA is especially vulnerable to damage by reactive oxidant species (**ROS**) as it is tethered to the highly hydrophobic inner mitochondrial membrane within close proximity to sites of ROS generation, and is 93% coding (compared to the nuclear genome which is 2% coding), which means damage to the mtDNA is likely to affect a coding region. Since the 13 polypeptide subunits encoded by the mtDNA are the key catalytic proteins in electron transport complexes (I, III, IV and ATP synthase), mtDNA missense mutations can potentially alter mitochondrial functions. In this respect, mtDNA polymorphisms considered to represent "normal" genetic variation, have been linked with different bioenergetic capacities that may provide an adaptive advantage or altered disease susceptibility [88–90].

4. TOBACCO SMOKE TOXICITY

Active and passive cigarette smoke decrease mitochondrial respiration and membrane potential leading to decreased ATP content and increased oxidant production in a variety of tissues in a dose- and time-dependent manner [15–21, 23, 25, 27–30, 32, 33, 37, 52, 91, 92]. Mitochondria are rich in enzymes with active sites easily modified and inactivated by ROS/RNS from the inhalation of tobacco smoke, or from oxidant generation within the mitochondrion (please see Bonini review herein, "*Oxidative signaling in mitochondrial homeostasis*" Chapter 4). For example, it has been shown that decreased activity of the mitochondrial isoform of superoxide dismutase, manganese SOD or SOD2, increases susceptibility to tobacco smoke exposure [27] and can be inactivated in mice through nitration, a consequence of nitrosoperoxycarbonate formation associated with side-stream tobacco cigarette exposure [32]. Further, inactivation of oxidative phosphorylation complexes by ROS/RNS directly impairs proton pumping efficiency leading to decreased mitochondrial

membrane potential and ATP production [93]. Importantly, studies have shown that cessation of both active and passive smoking improves various measures of mitochondrial function [17, 52].

Other effects of tobacco cigarette smoke include changes in mitochondrial morphology [19, 37, 38] promoting mitophagy in both cell culture and animal models [37], the formation of mtDNA adducts [94], increased mtDNA damage [34] and alterations in mtDNA copy number [35]. Acrolein, one of the primary reactive aldehydes within tobacco cigarette smoke, forms bulky DNA adducts which are likely to persist in the mtDNA due to the inefficiency of the mitochondrial DNA polymerase ɣ resulting in transversions [94]. However, whether acrolein is one of the primary drivers of mtDNA damage following tobacco smoke exposure has yet to be determined. Components found within tobacco cigarette smoke such as benzene induce alterations in mtDNA copy number [36], however it is important to note that mtDNA copy number is influenced by several factors including age and health status. Differences in mtDNA copy number may be obscured by comorbidities [95] and may be difficult to attribute directly to toxicant exposure. Overall, mtDNA damage may serve as a more reliable indicator of tobacco smoke-induced injury than copy number, based on the conflicting observations concerning copy number [30, 33, 96]. However, differences in mtDNA copy number or damage may be difficult to detect following acute exposures or if sufficient time passes between exposure and sample collection, due to DNA repair and/or mitophagy (removal of mitochondria with damaged mtDNA and restoring mitochondrial function) [46–49]. Some of the challenges of interpreting alterations in mtDNA copy number and damage to toxicant exposure can be overcome through study design and by determining whether similar alterations are observed across multiple models.

4.1 PULMONARY DISEASES

COPD, emphysema, chronic bronchitis, asthma, obstruction of the small airways, pulmonary hypertension, and acute respiratory illnesses such as pneumonia are all pulmonary diseases causally linked to active smoking in adults [97]. In children and adolescents, active smoking causes both impaired lung growth and function as well as asthma- related symptoms and poor asthma control [97]. The lung has defense mechanisms against foreign materials that are inhaled which primarily consist of mucociliary clearance, the alveolar-epithelial barrier and the inflammatory immune response [97, 98]. However, tobacco smoke and its constituents (especially acrolein, formaldehyde, and oxidants) overwhelm the pulmonary defense systems leading to damage to the cilia and overproduction of mucus thus impairing clearance and disrupting the tight junctions of the epithelial barrier [97, 99]. Both the tar and gas phases of tobacco smoke contain high levels of free radicals (as many as 10^{17} and 10^{15} spins/gram, respectively) [100]. These free radicals react to form ROS and RNS [97, 100, 101] such as the semiquinone radical (tar phase) and the peroxyl radical (gas phase) both of which can contribute to superoxide and hydroxyl radical formation, and the formation of non-radical oxidants, such as hydrogen peroxide [100]. Collectively, the radicals and oxidants generated can cause damage to proteins, lipids, and DNA, inactivate antiproteases, deplete antioxidants, and promote a proinflammatory environment by enhancing the phagocytotic respiratory burst and expression of proinflammatory mediator genes in the lung [97, 101].

MtDNA damage, copy number, mitochondrial membrane potential, mitochondrial respiration, ATP content and structural damage have all been observed in tobacco cigarette smoke induced pulmonary disease. MtDNA damage and deletions were shown to be higher in brochoalveolar lavage tissues of smokers compared to cells from non-smokers [34]. Nuclear DNA damage was also observed, but the mtDNA damage was significantly higher, while analysis of nuclear DNA to mtDNA ratios showed no significant differences [34]. In another study, mtDNA copy number in circulating blood mononuclear cells displayed a dose-dependent increase with the number of cigarettes smoked per day [35]. Treatment of primary human bronchial and alveolar epithelial cells with tobacco cigarette smoke-extract (the water-soluble portion of tobacco cigarette smoke) resulted in a dose-dependent decrease in membrane potential, ATP-linked oxygen consumption (and thus ATP content) suggesting impaired oxidative phosphorylation [15, 28]. Acrolein exposure induced similar dose-dependent decreases in mitochondrial respiration and resulted in substrate switching to preserve glucose for ATP production in pulmonary alveolar cells, which likely has implications for surfactant production [16]. The similar effects of acrolein and cigarette smoke extract on mitochondrial function in pulmonary alveolar cells suggest that acrolein may be one of the key mediators of cigarette smoke-induced pulmonary toxicity.

In addition to the effects on mitochondrial function, treatment of cultured human bronchial epithelial cells with tobacco cigarette smoke extract resulted in mitochondrial structural abnormalities as well including mitochondrial network fragmentation, mitochondrial swelling, and a loss of cristae[19, 37, 38]. The structural abonormalties in the mitochondria could be attenuated by silencing the mitochondrial fission mediator Fis1 suggestive of up-regulation of mitochondrial fission[19, 37, 38]. Antioxidant treatment also improved mitochondrial morphology and networks suggesting that oxidative stress likely plays a role in the structural abnormalities induced by tobacco smoke exposure [19, 37, 38]. Similar structural abnormalities were also observed in primary human bronchial epithelial cells collected from COPD patients including a loss of mitochondrial cristae and elongated mitochondria that was associated with a down-regulation of genes involved in mitochondrial biogenesis (PGC1α, TFAM) and mitophagy (PINK1) [19]. Tobacco cigarette smoke extract treatment in human bronchial epithelial cells increased mitochondrial oxidant generation and activated mitophagy through Parkin and Pink1 which lead to alterations in cellular phenotype consistent with cellular senescence [40]. The increase in oxidant production was not observed in cells lacking mitochondria, suggesting that mitochondria were the primary source of oxidants under conditions of tobacco cigarette smoke exposure [28]. In mice, eight weeks of tobacco cigarette smoke exposure lead to an up-regulation of proteins involved in oxidative phosphorylation, mitochondrial fusion, and mitochondrial oxidants within the lung tissue suggesting a potential compensation for mitochondrial impairments and dysfunction [17]. Hence, acute cigarette smoke exposure appears to induce mitochondrial fission and removal of damaged mitochondria through mitophagy but continued exposure may impair the ability of lung epithelial cells to remove and replace damaged and dysfunctional mitochondria ultimately resulting in diseases such as COPD.

4.2 CARDIOVASCULAR DISEASE

Smoking is a leading risk factor for cardiovascular disease and stroke [9, 102] and together they account for the majority of smoking-related deaths in the U.S. [9, 103, 104]. Approximately one-third of coronary heart disease deaths are attributed to tobacco smoke exposure and active smokers have 2–4 times increased risk for stroke [9, 102]. Non-smokers exposed routinely to secondhand smoke in the work place or home, have a 25–30% increase in the risk for coronary heart disease – even brief exposures to secondhand smoke have been reported to increase platelet aggregation and damage to the endothelium which is central to vascular homeostasis [97, 102].

Tobacco cigarette smoke exposure alters mtDNA copy number and induces damage to the mitochondrial genome in cardiac and vascular tissues which is associated with cardiovascular disease [32, 33, 105]. In a murine model of atherosclerosis, *in utero* or *neonatal* exposure to second-hand tobacco cigarette smoke induced mtDNA damage and deletions, and increased mtDNA copy number within the vasculature compared to filter air exposed controls [29, 33]. Many of these same associations were also observed in non-human primates following perinatal exposure to side-stream tobacco smoke [30]. However, within the non-human primate vasculature, mtDNA copy number was decreased with exposure in contrast to the observations within the vasculature of mice [30, 33]. Notably, the effects of second-hand tobacco cigarette smoke exposure during early development persisted into adulthood and was associated with increased atherogenesis [33].

Within the vasculature, damaged mitochondria produce increased oxidants that impact nitric oxide signaling and pro-atherogenic pathways [106–108]. Similarly, increased mtDNA damage, oxidant production, and inactivation of mitochondrial proteins (e.g. antioxidants and electron transport complexes) have been observed in the vasculature of mice exposed to cigarette smoke, and associate with increased atherogenesis [27, 33, 91]. Concomitantly, aconitase inactivation (a marker for superoxide levels) was elevated in heart and vascular tissues of mice exposed to tobacco smoke [27, 33, 105]. Perinatal tobacco cigarette smoke exposure in non-human primates also increased measures of mitochondrial oxidative stress including increased 3-nitrotyrosine and decreased cytochrome c oxidase activity within the abdominal aorta [30]. Further, perinatal exposure was associated with increased cellularity in the subintimal space of the aorta, suggestive of increased inflammation consequent of altered mitochondrial redox signaling [30]. Importantly, the effects of developmental exposure to tobacco smoke have been shown to have implications for adult vascular disease development in animal models [29, 30, 33].

Tobacco smoke exposure induces cardiac mitochondrial damage and dysfunction. Components of tobacco smoke directly inhibit or inactivate several mitochondrial proteins within the heart [23, 24, 42, 52, 109]. Rabbits exposed to tobacco cigarette smoke for a single 30-minute session or 30 minutes twice a day for 2 and 8 weeks (3 cigarettes each session) had decreased myocardial mitochondrial respiration compared to non-exposed rabbits [20, 21]. A similar study found that tobacco cigarette smoke exposure of rabbits decreased levels of coenzyme Q and cytochrome c oxidase activity within cardiac mitochondria compared to those of non-exposed rabbits [18]. Collectively, these studies are consistent with tobacco smoke exposure mediated dysfunction of electron transport chain components (in this case,

cytochrome c oxidase, which would result in decreased respiration) that impact ATP production. More specifically, carbon monoxide exposure in rabbits resulted in small, swollen mitochondria having condensed cristae compared to those observed from unexposed animals [39]. Because it is well known that carbon monoxide competes with oxygen for heme binding within cytochrome c oxidase, it is likely that this component of cigarette smoke contributes to inhibiting oxygen consumption and thus inhibits oxidative phosphorylation and decreases ATP generation [24, 42, 109] Consequently, it is not surprising that cytochrome c oxidase activity was found to be lower in peripheral blood lymphocytes from heavy smokers relative to non-smokers [23, 52].

4.3 CANCER

Tobacco smoke contains at least 72 known carcinogens ([reviewed in 110, 111]) and is a known cause of all histological types of lung cancer (small-cell, large-cell, squamous and adenocarcinoma) with 90% of all lung cancer cases caused by tobacco smoke [97, 111–119]. Smoking is also causally linked to cancers of the upper aerodigestive tract (oral, oropharynx, hypopharynx, larynx and oesophagus) as well as pancreas, stomach, bladder, kidney, cervix and acute myeloid leukemia [97, 111, 112, 120–128]. It is likely that there are even more, yet undiscovered carcinogens in tobacco smoke and the presence of carcinogens in alternative tobacco products is currently under investigation. Furthermore, some chemical components that are not considered carcinogens, such as nicotine, have been shown to enhance carcinogenicity by promoting tumor growth through stimulation of angiogenesis and inhibition of apoptosis both *in vitro* and in mouse models of lung cancer [119, 129, 130].

Whereas there is ample evidence that tobacco cigarette smoke exposure can play a role in oncogenesis, the literature examining direct links between tobacco smoke exposure, mitochondria, and cancer is limited. However, it has been observed that changes in mitochondrial function [131–134], oxidant production/signaling [135–137], mtDNA copy number [35, 132], and mtDNA mutagenesis [132, 136, 138, 139] impact tumorgenicity [133, 136], malignancy [134], metastatic capacity [135, 140, 141] and resistance to anti-cancer therapy [142]. Recently, differential mitochondrial bioenergetics linked to mitochondrial haplotype background has been shown to effect tumor latency and metastatic progression in a spontaneous mammary tumor model in mice [89]. Many of the alterations in mitochondrial biology associated with oncogenesis have also been altered by tobacco smoke exposure suggesting a possible link but further investigation is needed.

4.4 DIABETES

Tobacco smoking is correlated with both the development and exacerbation of type 2 diabetes, the most prevalent form of diabetes accounting for 90–95% of all cases [9, 97, 143–155]. Smoking decreases glucose tolerance, insulin sensitivity, and adiponectin levels while promoting hyperinsulinemia, insulin resistance, elevated glycosylated hemoglobin levels, increased fasting blood glucose levels, dyslipidemia and post-prandial lipid intolerance, all of which are associated with the diabetic phenotype [9, 97, 155–160]. A meta-analysis of 46 studies published between 1995–2010 revealed that on average, smokers have a 30–40% increased relative risk for developing type 2 diabetes compared to nonsmokers [9]. This risk for diabetes increases in a dose-dependent manner with light

smokers (less than 20 cigarettes per day) having a 25% increased relative risk while heavy smokers (more than 20 cigarettes per day) have a 50–60% increased risk [9]. Smokers also experience poorer control of their diabetes than nonsmokers [9, 97, 154]. Cessation of smoking improves insulin sensitivity, despite weight gain, [97, 161, 162] and lowers the relative risk for diabetes to a level similar to that of nonsmokers in both women and men, ≥5 and ≥10 years after quitting, respectively [143, 163]. One study, however, reported an 11% improvement in insulin sensitivity after only 8 weeks after smoking cessation suggesting improvements in insulin sensitivity following cessation may occur at even earlier time points [161].

Similar to cancer, the literature linking tobacco smoke, mitochondria and diabetes is not extensive. However, like cancer, there are strong associations between mitochondrial function and diabetes. Maternally Inherited Diabetes and Deafness (MIDD or Ballinger – Wallace Syndrome, OMIM #520000) is characterized by adult onset of sensorineural hearing loss and diabetes (non-insulin dependent). MIDD has been linked with several different mtDNA mutations [164–166] that manifest in altered mitochondrial function. Additionally, numerous reports have associated varied levels of mitochondrial oxidant production with insulin secretion [167–169] or β cell dysfunction [170, 171] (low or high, respectively), with some research showing that they act as necessary signals for glucose induced insulin secretion in rat and mouse islets [167, 168] as well as hypothalamic glucose sensing in rat hypothalamus both *in vivo* and *ex vivo* [172]. Insulin secretion relies on the closure of ATP-sensitive potassium channels [173], which cause an influx of Ca^{2+} resulting in exocytosis of insulin vesicles [173–177].

Hence, insulin secretion is highly dependent and sensitive to changes in mitochondrial linked ATP production [175–177]. Finally, it has been suggested that diabetes [178–180] and diabetic complications [181] are significantly influenced by mitochondrial genetic background suggesting that mtDNA mutations induced by cigarette smoke exposure may alter diabetes risk. Because tobacco cigarette smoke exposure is also linked with mtDNA damage, altered mitochondrial function, increased oxidant production, it is highly likely that associations between tobacco smoke exposure and diabetic risk are modulated via processes that involve the mitochondrion. Further studies in this area are required.

4.5 REPRODUCTIVE AND DEVELOPMENTAL EFFECTS

Smoking strongly associates with reduced fertility in women and maternal smoking during pregnancy is considered a causal factor of complications including increased incidence of preeclampsia, preterm delivery, and placental abnormalities [182–189]. Maternal smoking or exposure to second hand smoke is also a major cause of infant morbidity, mortality, fetal growth restriction, and low birth weight resulting from placental abnormalities [188, 190–193]. Even after adjustment for birth weight, infants of mothers who smoke have higher mortality rates than infants of non-smokers with maternal smoking increasing the risk of stillbirth by 40–60% [192].

Tobacco smoke exposure-induced alterations in mitochondrial function may contribute to growth restriction *in utero*, subsequent low birth weight, and other developmental outcomes [25, 92, 194, 195]. Placental abnormalities resulting from tobacco smoke exposure have been attributed to hypoxia and nicotine-mediated vasoconstriction [188, 190–193]. Carbon

monoxide is a major contributor to the hypoxic *in utero* environment resulting from maternal tobacco smoking due to its greater affinity for fetal hemoglobin preventing oxygen loading and unloading[196–198]. Carbon monoxide also binds to complex IV of the electron transport chain inhibiting its activity which likely further contributes to impairments in meeting the high energetic needs of the developing fetus[24, 42, 109]. The fetal brain is especially sensitive to carbon monoxide toxicity due to its high oxygen consumption and glucose demands which may play a role in the association of cognitive deficits and neurobehavioral effects with maternal smoking [199, 200].

Mitochondrial abnormalities and impairments have been described in placental tissue from mothers who smoked during pregnancy [25]. Mitochondria isolated from the placenta of mothers who smoked during pregnancy had a lower respiratory control index and decreased cytochrome c oxidoreductase (complex III) activity compared to placental mitochondria from non-smoking mothers, consistent with impaired mitochondrial respiration [25]. Further, complex III activity was inversely related to the number of cigarettes smoked per day and trended towards an association with low birth weights suggesting that mitochondrial dysfunction may contribute to growth restriction *in utero* [25]. According to the Barker hypothesis, developmental exposures to environmental toxicants may result in genetic reprogramming impacting cardiometabolic disease risk later in life and mitochondria may be a key mediator of this reprogramming [201, 202].

Smoking is the leading cause of erectile dysfunction in males between the ages of 20–40, which is not entirely surprising considering the well described effects of smoking on vascular function [203–208]. Smokers have impaired endothelial-dependent vasodilation that is the result of oxidant scavenging of a key vasodilator, nitric oxide, which also plays a central role in dilation of the penile vasculature during stimulation of an erection [207, 208]. Increased mitochondrial oxidant production contributes to endothelial damage by scavenging nitric oxide and consequently, smoking-induced increases in mitochondrial oxidant production may play a role in the impaired vasodilation and subsequent erectile dysfunction in smokers[106].

Tobacco cigarette smoke exposure is also linked to decreased fertility in men [203–206] with several studies reporting decreased sperm motility with mitochondrial dysfunction and/or damage [209, 210]. Mitochondria located within the tail of sperm are required to generate the energy to drive the cellular motors in the flagellum and if damaged, may not be able to provide sufficient energy resulting in reduced motility [209, 210]. Again, whether the effects of tobacco smoke act through mitochondrial dysfunction is not yet clear. Nevertheless, tobacco smoke exposure decreases mitochondrial function, and therefore it is possible that this could provide a link between the observed association of cigarette smoke and decreased male fertility.

5.0 TOXICITY OF AIR POLLUTION

The six main ambient air pollutants are particulate matter, ground-level ozone, lead, carbon monoxide, nitrogen oxides and sulfur dioxide, termed criteria air pollutants by the United States Environmental Protection Agency. In this review, we have focused on particulate

matter and ozone as these are the most well studied pollutants with regards to mitochondrial toxicity.

Particulate Matter—The United States Environmental Protection Agency monitors the levels of particulate matter especially PM_{10} and $PM_{2.5}$. Even with $PM_{2.5}$, sub-fractions have been shown to have distinct effects on pathophysiology with ultrafine particles (≤0.1μM in diameter, $PM_{0.1}$) being cleared more slowly, retained longer in the lung and able to have significant effects even 6 days after inhalation compared to only 1 day with the larger $PM_{2.5}$ fraction [211]. Particulate matter is a major component of both household and ambient air pollution and has been implicated in mitochondrial toxicity [212–217]. Organic PM is formed by gas-to-particle conversion or incomplete combustion of fuels [212]. In contrast, engineered PM is generated for use in the production of paint, cosmetics, plastics, paper, and other materials released into the environment during manufacture, distribution and consumer use [213]. Ammonium, elemental carbon, organic carbon matter, nitrate, silicon, sodium and sulfate make up about 80% of PM in ambient air; although these components vary regionally and seasonally [218].

PM has been shown to accumulate within the mitochondrion [212] and can disrupt mitochondrial membrane potential [214], damage mitochondrial structure [212], alter the mtDNA (strand breaks and methylation) [214,215–217], and activate the mitochondrial programmed apoptosis in pulmonary tissues. Exposure of murine macrophage and human bronchial epithelial cell lines to diesel exhaust particles suspended in the culture media resulted in a preferential accumulation of $PM_{0.1}$ within the mitochondrion [212]. Further, the accumulation of $PM_{0.1}$ in mitochondria was further shown to cause structural damage to cristae and induced the formation of myelin figures, indicative of mitochondrial membrane damage [212]. In contrast, PM_{10} or $PM_{2.5}$ were sequestered in vacuoles rather than mitochondria causing minimal mitochondrial damage [212]. Iron-derived free radicals in ambient air particulate matter can also cause DNA damage and decrease mitochondrial membrane potential, ultimately leading to cell death of alveolar epithelial cells via the intrinsic pathway in a dose and time dependent manner [214]. Pre-treatment of cells with iron chelators and free radical scavengers protected the alveolar epithelial cells from particulate matter induced-DNA damage, mitochondrial dysfunction, and apoptosis [214]. Most larger particles (>0.1μM) are cleared upon entering the respiratory tract; however, $PM_{0.1}$ have been shown to cross the blood-brain barrier and disseminate through the blood to non-pulmonary organ systems [219, 220]. Exposure of rat and human glial cell lines or primary hepatocytes to one of the most widely used engineered $PM_{0.1}$, titanium dioxide $PM_{0.1}$, induces oxidative stress [213], causes mitochondrial depolarization [212]. Similarly, exposure of primary rat hepatocytes to titanium dioxide $PM_{0.1}$ suspended in the culture medium for 2.5h induces oxidative stress and causes a loss of mitochondrial membrane potential [221].

Ozone—Ozone has many adverse health effects and is generated through the interaction of volatile organic compounds and nitrogen oxides in the presence of light [69]. Ozone is a component of ambient air pollution [68], although the precursors for ozone formation are present in household air pollution [64]. As mentioned previously, in many low- and middle-income countries, household air pollution is a significant contributor to ambient air

pollution [2, 65]. It is well described that exposure to ozone induces oxidative stress [222–224]. Proposed mechanisms include the reaction of oxidants with unsaturated fatty acids to form lipid ozonation products and the reaction of secondary products formed in the epithelial lining fluid such as aldehydes, hydrogen peroxide and organic radicals [222–224]. Ozone also enhances oxidative stress by depleting antioxidants and surfactants in the epithelial lining fluid [225]. Mitochondrial toxicity has been implicated in the pathology of ozone-induced pulmonary and cardiovascular disease including perturbed mitochondrial bioenergetics, decreased mitochondrial membrane potential, increased mitochondrial oxidant production and mtDNA damage in mice, non-human primates and humans [96, 226]. In addition, pulmonary ozone exposure decreased endothelial nitric oxide synthase protein levels and indices of nitric oxide production, resulting in vascular dysfunction and accelerated atherogenesis in mice [96]. Treatment with the mitochondrial-targeted antioxidant MitoQ, lowered both mitochondrial and cellular oxidant levels, restored membrane potential and attenuated the ozone-induced airway hyper-responsiveness (see **Section 5.1**) suggesting that ozone mediates its effects, in part, by increasing mitochondrial oxidant production [226]. Exposure of rats to ozone levels observed in high pollution cities (0.25ppm) caused chronic oxidative stress in the hippocampus, neurodegeneration, and mitochondrial dysfunction [227]. Ozone exposure has also been linked to beta amyloid accumulation in the mitochondria of rat hippocampal cells and may be linked to the development of Alzheimer's disease due to air pollution [227].

5.1 PULMONARY DISEASES

Particulate matter and ozone along with the rest of the criteria air pollutants cause, trigger, and exacerbate pulmonary diseases in both children and adults while also impairing lung development in children [228–233]. The extended duration and heavy breathing associated with manual labor of certain occupations (e.g. transportation, landscaping, construction) as well as the increased exposure to household air pollution among women, children and the elderly in low- and middle-income countries (who spend more time indoors than male adults) results in a greater burden of exposure and subsequent greater pulmonary disease in these sub-populations [14, 63–65, 229, 234]. The increasing prevalence of acute respiratory diseases has also been linked to climate change and alterations in ground level ozone pollution distribution [228, 229]. Mice exposed to ozone (3 parts per million, 3 hours/day, twice a week for 1 or 6 weeks) exhibit phenotypes similar to human patients with COPD including lung inflammation and airway hyper-responsiveness [226, 235]. Mitochondria isolated from the lungs of ozone-exposed mice have increased levels of mitochondrial ROS at both the 1-week and 6-week time points, decreased ATP content, decreased mitochondrial electron transport chain complex I enzyme activity and decreased protein levels of complexes I, III and V compared to control air-exposed mice [226]. Treatment of these ozone-exposed mice with MitoQ (5mg/kg intraperitoneally), an antioxidant that targets the mitochondrion, significantly increased mitochondrial membrane potential and decreased the following: ozone-induced airway hyper-responsiveness, bronchoalveolar lavage total cell counts, keratinocyte-derived cytokine levels, mitochondrial ROS levels and cellular ROS levels [226]. In contrast, a similar study with a slightly lower ozone exposure of 2.5 parts per million showed that N-acetylcysteine treatment did not attenuate ozone-induced lung injury in the same mouse model of COPD [235.235]. The improvement observed in pulmonary function with

MitoQ but not N-acetylcysteine suggests that mitochondrially targeted therapies to be more efficacious and that mitochondrial oxidants play a pivotal role in ozone-induced lung injury [235].

5.2 CARDIOVASCULAR DISEASE

Both short and long term exposure to air pollution (especially $PM_{2.5}$, PM_{10}, ground level ozone) increase the risk of cardiovascular events (hypertensive episodes, myocardial infarction, cardiac arrhythmia, stroke and heart failure) and cardiovascular attributed mortality, especially in individuals with pre-existent cardiovascular disease, the elderly, those that live in urban areas, impoverished communities where unrefined fuels are used indoors and certain occupations [234, 236–244]. In adults of more advanced age, increased exposure to ambient air pollution is positively associated with increased mtDNA to nuclear DNA ratio and blood pressure [245]. $PM_{2.5}$ exposure caused structural damage to mitochondria in rat myocardial tissues including mitochondrial swelling, crista disorder and vacuole formation in a dose dependent manner [246]. Mice exposed to PM for 3h exhibited impaired cardiac contractility with decreased mitochondrial respiration and ATP production [247]. Exposure of healthy rats to diesel exhaust for one month caused decreased mitochondrial aconitase activity in the cardiac tissues [248]. Mice exposed to ozone (0.5 ppm, 8h/day for 5 days) had increased heart rate, increased blood pressure and impaired aortic endothelial dependent vasoconstriction while also increasing markers of oxidative/nitrosative stress (increased lipid peroxidation by products, decreased aconitase activity, increased protein nitration) compared to filtered air controls [96]. Aortas from mice and infant non-human primates exposed to ozone had increased levels of mtDNA damage compared to filtered air controls [96]. Furthermore, atherosclerosis prone apolipoprotein E-deficient ($apoE^{-/-}$) mice exposed to ozone also exhibited increased atherosclerosis compared to filtered air controls [96]. These data taken together suggest that air pollution induced cardiovascular disease at least in part through mitochondrial toxicity.

5.3 CANCER

Ambient air pollution has been causally linked to cancers of the brain, nervous and endocrine systems, skin, cervix, oropharynx, ovary, kidney, liver, bladder, rectum, prostate, breast and blood [249–262] with risk increasing dose- dependently in many cases. Both household and ambient air pollution have been causally linked to lung cancer [64, 249–251, 263–265]. Studies of ambient air pollution and cancer have focused on highly exposed cohorts (e.g. occupational exposure, residence proximity) [249, 251, 252, 254–256, 258, 259, 266] and urban areas [250, 253, 257, 260–263, 265]. Studies of indoor air pollution and cancer have focused on emissions from incomplete combustion of solid or unrefined fuels (high temperature heating of wood, coal, and other biomass for cooking, light and warmth) in low-and middle-income countries or rural areas where alternative fuel sources are either unavailable or cost prohibitive [64, 65, 264]. In Asia (southern, southeastern and eastern), Oceania, and sub-Saharan Africa (eastern, central and western), household air pollution from solid fuels is ranked in the top four risk factors for disease burden, outranking ambient air pollution [2]. The World Health Organization estimates that three billion people are exposed to these emissions on a daily basis causing 4.3 million premature deaths a year, 17% of which are from lung cancer [65].

Similar to tobacco smoke, the literature on air pollution effects on mitochondrial toxicity in cancer is limited. It is well established that both ozone and PM mediate carcinogenesis through ROS generation [267–271]. Diesel exhaust particles have been shown to induce ROS production, decrease mitochondrial membrane potential, increase mitochondrial structural damage and uncoupling of oxidative phosphorylation [270]. Furthermore, studies in human lung carcinoma cell lines as well as primary human and rat lung cell cultures suggest that PM induces apoptosis by increasing mitochondrial ROS production leading to increased p53 expression as well as mitochondria-regulated apoptosis which is thought to cause remodeling and malignant transformation of airway epithelial cells [269].

5.4 DIABETES

Cohort studies suggest that long term exposure to air pollution, specifically $PM_{2.5}$ and nitrogen dioxide, is associated with increased risk of developing type 2 diabetes and increased diabetes-related mortality [272–279]. As with tobacco smoke, research on air pollution induced mitochondrial toxicity in diabetes pathogenesis is limited, however the few performed studies yielded results suggesting that this area of study should be pursued [280, 281]. C57BL/6 mice fed a high fat diet (42% fat, for 34 weeks) had increased adipose inflammation and increased insulin resistance when exposed to $PM_{2.5}$ (6h/day, 5 days/week, for 24 weeks) compared to filtered air exposed controls [280]. Exposing this same strain of mouse to $PM_{2.5}$ for a longer period (40 weeks) but on a standard chow diet still caused insulin resistance and glucose intolerance [282]. This prolonged exposure to $PM_{2.5}$ also decreased mitochondrial number in visceral adipose and decreased mitochondrial size in interscapular brown adipose [282] consistent with a role for mitochondria in air pollution induced type 2 diabetes.

5.5 REPRODUCTIVE AND DEVELOPMENTAL EFFECTS

Ambient air pollution exposure is associated with adverse reproductive health and outcomes in both women and men [283–303]. Air pollution has been associated with increased sperm abnormalities including aneuploidy, head morphology and motility decreasing fertility in men [283, 300, 304]. The effects of developmental exposure are of great concern especially for pregnant women who live in urban areas with high levels of ambient air pollution or in low- and middle-income countries where women may have extended duration of exposure to household air pollution [14, 62–65]. Air pollution has been associated with negative pregnancy outcomes [284, 285, 287–290, 293, 298, 299], including low birth weight [292–295, 302], respiratory illnesses [301] and mortality [301, 303] in the fetus, newborn and infant. Increased *in utero* exposure to $PM_{2.5}$, especially in the first trimester of pregnancy, is positively associated with placental mtDNA methylation (in both the displacement loop and the sequence which encodes the mitochondrial ribosomal 12S rRNA) [215]. Conversely, increased *in utero* exposure to $PM_{2.5}$ or PM_{10} is negatively associated with mtDNA content with the most significant association in the third trimester [215, 216]. MtDNA methylation is controversial because the mtDNA does not have many CpG nucleotides [305–307] and thus, most of the methylations are on non-CpG cytosines [305]. Consequently, the techniques used to identify CpG methylation in nuclear DNA may not be appropriate for detecting mtDNA methylation [305]. Furthermore, there was little evidence that any of the three catalytically active DNA methyltransferases could access the mitochondrion [215, 305–307] until recently

when it was discovered that DNA methyltransferase 1 could target mitochondria [308]. Nevertheless, methylation in certain key regions of the mtDNA can have detrimental effects on replication and transcription of mtDNA (displacement loop methylation) [215, 305], or translation of mtDNA encoded RNA (12S rRNA methylation) [215].

6. FUTURE DIRECTIONS

6.1 TOXICITY RELATED TO NEW AND EMERGING TOBACCO PRODUCTS

New and emerging tobacco products such as e-cigarettes have become increasingly popular and are often used in combination with tobacco cigarettes [309, 310]. Many of these alternative tobacco products are viewed as a potential means for reducing tobacco-induced disease burden in smokers and as a potential mechanism for aiding smokers in cessation. However, the few studies performed assessing cessation with e-cigarette use have been scarce, small in scale, and had ambiguous results that are often difficult to interpret [311], Moreover, the acute and chronic health effects of e-cigarettes and other alternative products are largely unknown and consequently, studies designed to evaluate risk for cellular injury associated with e-cigarette use are required. Measures of mitochondrial damage and function may provide a means to assess potential injury.

E-cigarettes likely contain fewer toxicants than tobacco cigarettes but they are not toxicant-free. Mass-spectrometry analysis has already demonstrated the presence of aldehydes, free radicals, and metals which are known mitochondrial toxicants and may act through similar disease mechanisms as those triggered by cigarette smoke exposure [312–317]. Other tobacco products including hookahs, little cigars, and cigarillos combust tobacco leaves in a fashion very similar to traditional cigarettes and therefore, likely contain the same toxicants and carcinogens found in tobacco cigarette smoke. Consequently, hookah, little cigar, and cigarillo smoke exposure likely induce similar changes to mitochondrial physiology as tobacco cigarette smoke exposure and ultimately, are expected to induce similar morbidities and mortalities but require future investigation. The uncertainty of the chronic effects of e-cigarette and other alternative tobacco product use will likely continue for some time until large scale, longitudinal studies can be performed. However, as we gain a clearer picture regarding the chemical composition of the emitted vapors and smoke given off by these products, we will be able to draw conclusions regarding whether those chemicals at the levels observed have already shown effects on mitochondrial function and disease pathways.

6.2 TOXICITY RELATED TO MITOCHONDRIAL – NUCLEAR GENETIC BACKGROUND

The genetic basis for common disease susceptibility and environmental exposure sensitivity is not well understood. Studies have investigated this question often finding associations of variants with phenotypes in smaller sample cohorts, but these associations are usually lost in more broad-based or larger cohort studies. Our current viewpoint of genetic susceptibility, which typically interrogates only the nuclear genome may, in part, explain differences in disease susceptibility and environmental exposure sensitivity. Mitochondrial genetic variation may be a missing component that modifies penetrance or alters the symptoms associated with a disease. Several reports have shown that certain rare forms of blindness are linked to pathogenic mtDNA mutations and become less penetrant in individuals of African

ancestry. Similarly, certain mtDNA polymorphisms alter individual susceptibility to non-syndromic sensorineural deafness, especially in individuals exposed to aminoglycosides [318–320]. The evidence showing that mitochondrial genetic background influences disease susceptibility, including cancer, heart disease, and longevity is growing [89, 90, 321, 322]. Collectively, these studies have focused on the impact of the mtDNA on disease susceptibility, and while important, a relatively unexplored area of study is the interaction of the two genomes (mitochondrial and nuclear) upon individual response to environmental stimuli (including toxicants). We hypothesize that certain nuclear mutations which convey increased susceptibility to environmental toxicants may have altered penetrance due to the combined influence of mitochondrial genetic background, age, and pre-existent health status. Consequently, a future direction of precision medicine should include an evaluation of both mitochondrial and nuclear genetic backgrounds when considering of the genetic aspects of individual risk.

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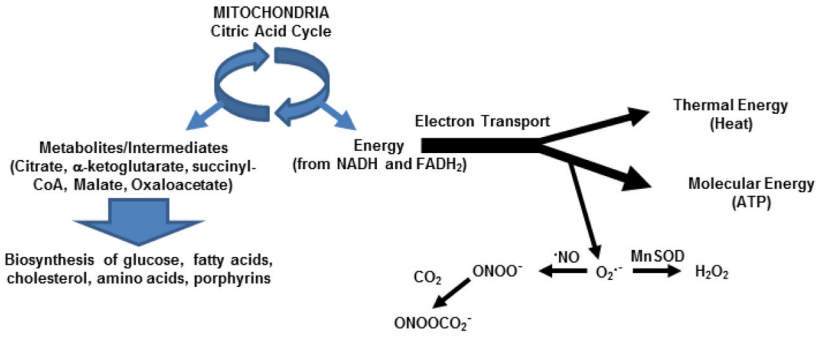

Figure 1. Mitochondrial functions

The citric acid cycle serves as a source of metabolic intermediates (citrate, a-ketoglutarate, etc) for several biosynthetic pathways (glucose, fatty acid, cholesterol synthesis, etc), and electron transport. Energy derived from electrons as they move through the electron transport complexes is utilized to pump protons across the inner mitochondrial membrane to form an electrochemical gradient; this conserved energy is used to generate molecular energy (ATP) at ATP synthase. Energy not conserved for proton pumping is lost in the form of thermal energy (heat). Under conditions of increased ATP/ADP ratios, electron acceptors remain in the reduced state for longer periods of time, and therefore electrons can also react with molecular oxygen to form the oxidant superoxide ($O_2^{\cdot -}$), that can be converted to hydrogen peroxide (H_2O_2), a cell-signaling molecule by manganese superoxide dismutase (MnSOD) in the mitochondrion, or alternatively, react with nitric oxide ($^{\cdot}NO$) to form peroxynitrite ($ONOO^-$), an oxidant, which in the presence of carbon dioxide (CO_2), can form nitrosoperoxycarbonate ($ONOOCO_2^-$), a nitrating agent.