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Clinical effects of chemical exposures on mitochondrial function

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Abstract

Mitochondria are critical for the provision of ATP for cellular energy requirements. Tissue and organ functions are dependent on adequate ATP production, especially when energy demand is high. Mitochondria also play a role in a vast array of important biochemical pathways including apoptosis, generation and detoxification of reactive oxygen species, intracellular calcium regulation, steroid hormone and heme synthesis, and lipid metabolism. The complexity of mitochondrial structure and function facilitates its diverse roles but also enhances its vulnerability. Primary disorders of mitochondrial bioenergetics, or Primary Mitochondrial Diseases (PMD) are due to inherited genetic defects in the nuclear or mitochondrial genomes that result in defective oxidative phosphorylation capacity and cellular energy production. Secondary mitochondrial dysfunction is observed in a wide range of diseases such as Alzheimer's and Parkinson's disease. Several lines of evidence suggest that environmental exposures cause substantial mitochondrial dysfunction. Whereby literature from experimental and human studies on exposures associated with Alzheimer's and Parkinson's diseases exist, the significance of exposures as potential triggers in Primary Mitochondrial Disease (PMD) is an emerging clinical question that has not been systematically studied.

Keywords

Mitochondrial dysfunction; Electron transport chain; Oxidative phosphorylation; Neurodegenerative disorders; Mitochondrial toxin

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The authors have nothing to disclose.

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None declared.

1. Introduction

Mitochondria are intracellular double-membraned organelles that host a wide range of biochemical pathways including oxidative phosphorylation (OXPHOS), and key aspects of carbohydrate, amino acid, lipid and steroid metabolism. Mitochondria are critical for the provision of adenosine triphosphate (ATP) via OXPHOS for cellular energy requirements, calcium buffering, and are important transducers of intracellular signaling for initiation of apoptosis (Schapira, 2010). Mitochondrial dysfunction has been implicated in a wide range of diseases (Nunnari and Suomalainen, 2012). Mitochondrial disease pathogenesis and patient symptomatology has largely been attributed to an ATP production defect due to the historical tenet of mitochondria functioning as the cellular powerhouse. Independent of energy production capacity, however, is the role of mitochondria to produce metabolic signals that influence diverse cellular processes (Picard et al., 2016). Notably, mitochondrial signals alter the expression of several thousands of genes linked to central cellular functions (Elstner and Turnbull, 2012, Zhang et al., 2013, Tsukikawa et al., 2013). A growing body of research has uncovered many aspects of mitochondrial biology beyond energy (ATP) production, including transcriptional remodeling within the nucleus, mitochondrial dynamics and quality control, inter-mitochondrial communication, intercellular transfer of mitochondria, mitochondrial regulation of inflammatory processes and immune function, mitochondrial regulation of brain functions, and modulation of physiological processes across organ systems (Picard et al., 2016). Overall, mitochondria respond to genetic factors and metabolic and neuroendocrine signals by undergoing functional and morphological changes, generate signals that influence a large number of cellular functions, and contribute to the complexity of diverse disease pathogenesis (Picard et al., 2016).

2. Environmental toxins and deleterious effect on mitochondria

The environment plays a significant role in human health and disease. A systematic study conducted by The World Health Organization (WHO) estimated that 22% of global disease burden, including mental, behavioral and neurological disorder, are due to preventable environmental factors (Carneiro et al., 2006). Environmental factors were defined as “the physical, chemical and biologic environment to the human host and related behavior, but only those parts that could reasonably be modified”. Environmental toxins are pervasive in all aspects of patient’s lives, including those found in the air, water, soil, food, and consumer products. Effects from exposures may be lifelong. Children experience a disproportionate share of environmental disease burden (Pruss-Ustun and Corvalan, 2007). Pesticides, smoke, mycotoxins, polychlorinated biphenyls (PCBs), and arsenic are among the most common environmental toxins (Chen et al., 2017). Environmental pollutants includes heavy metals, which are naturally occurring elements having wide distribution in the environment due to numerous industrial, domestic, agricultural, medical, and technological applications (Tchounwou et al., 2012). In addition to ubiquitously present environmental toxins, specific occupational exposure to toxic chemicals such as organophosphate pesticides and phthalates incur increased health risks above that of the general population (No, 2013). Toxins may impact on human health at the molecular (DNA, RNA, or protein), organelle (mitochondria, lysosome, or membranes), cellular (growth inhibition or cell death), tissue, organ, and systemic levels (Chen et al., 2017). Adverse health effects of environmental toxicants are

determined by dose, route of exposure, toxicokinetic and toxicodynamic balance, and genetic susceptibility, in addition to acute or chronic exposures that may cumulatively result in bioaccumulation (Chen et al., 2017). Specific to metals, exposure is also determined by valence state, particle size, solubility, biotransformation, and chemical form (Tchounwou et al., 2012). Some chemicals are able to cross the blood brain barrier, and some can cross the placenta to accumulate in the fetus (No, 2013), resulting in adverse pregnancy outcomes (Krieg et al., 2016), congenital malformations (Sarmah et al., 2016), neurodevelopmental problems (Rzhetsky et al., 2014) or other potential long-term consequences (Hochoy, 2014, Huang et al., 2014). Other than environmental toxins, drug induced-inhibition of the mitochondrial electron transport chain (ETC) enzyme activities or uncoupling of mitochondrial OXPHOS capacity is also a well-recognized cause of mitochondrial toxicity (Wallace, 2007, Wallace, 2014, Dornfeld et al., 2015, Wallace, 2015).

2.1. Mitochondrial vulnerability to toxins

In recent years, the deleterious effect of environmental toxins on mitochondrial function has been studied extensively in humans (Eldakroory et al., 2016, Cremonese et al., 2017, Hongsibsong et al., 2017, Sittitoon et al., 2017) and model organisms such as rodents (O'Brien and Wallace, 2004, Suzuki et al., 2008, Butenhoff et al., 2009, Butenhoff et al., 2012), fish (Ge et al., 2017), zebrafish (Bestman et al., 2015, Liu et al., 2015, Jia et al., 2016, Chen et al., 2016, Raftery et al., 2017), *Caenorhabditis elegans* (*C. elegans*) (Zhou et al., 2013, Liu et al., 2015, Wyatt et al., 2017), and cellular models (Zieminska et al., 2016, D'Mello et al., 2017, Yang et al., 2017). A large number of environmental factors including 1-methyl-4-phenyl-1, 2, 3, 6-tetra-hydropyridine (MPTP), and pesticides such as rotenone and paraquat are now widely-recognized mitochondrial toxins (Backer and Weinstein, 1980, Harmon and Sanborn, 1982, Nicklas et al., 1987, Youngster et al., 1987) and specifically, neurotoxins. Several factors that contribute to the vulnerability of mitochondria to environmental toxins are discussed below. Reported mechanism(s) of action of select environmental toxins included in this review on mitochondrial function are summarized in Table 1.

2.1.1. Accumulation in mitochondria—The high lipid content of mitochondrial membranes facilitates accumulation of lipophilic compounds such as polycyclic aromatic hydrocarbons (PAHs) (Backer and Weinstein, 1982), alkylating agents (Wunderlich et al., 1972) and cationic metals such as lead, cadmium, mercury, and manganese (Meyer et al., 2013). The mitochondrial matrix has a negative charge and slightly alkaline pH, which facilitates accumulation of amphiphilic xenobiotics, ethidium bromide, paraquat, and 1-methyl-4-phenylpyridinium (MPP⁺) (Cohen, 2010, Meyer et al., 2013). The mitochondrial cytochrome P450 system may also activate relatively non-reactive chemicals, such as PAHs and mycotoxins (Genter et al., 2006, Omura, 2006, Dong et al., 2009).

2.1.2. Environmental toxins and mitochondrial dysfunction—Mitochondrial DNA (mtDNA) is a circular intron-free genome consisting of 16,569 nucleotides in humans, is maternally inherited through oocytes, is present in multiple copies within each mitochondrion and cell; and are anchored to the inner mitochondrial membrane (Meyer et al., 2013). mtDNA is potentially more prone to damage than nuclear DNA (nDNA) due to

the tendency of lipophilic and charged chemicals to accumulate in the mitochondria (Wunderlich et al., 1970, Wunderlich et al., 1972, Backer and Weinstein, 1982, Cohen, 2010), the proximity of mtDNA to ETC-mediated production of reactive oxygen species (ROS), and the absence of chromatin packing and many DNA repair pathways (Larsen et al., 2005, Meyer, 2010, Gonzalez-Hunt et al., 2014, Roubicek and de Souza-Pinto, 2017). Mitochondria and mitochondrial DNA as relevant targets for environmental contaminants was recently reviewed, and included in this Special Issue (Roubicek and de Souza Pinto, 2017).

With age, mtDNA mutations accumulate in post-mitotic tissues that can lead to mitochondrial dysfunction, decreased OXPHOS capacity, and decreased expression of antioxidant enzymes, collectively resulting in the net overproduction of ROS (Harmon et al., 1987, Nank et al., 1987; Finkel and Holbrook, 2000; Denzel et al., 2014; Storm et al., 2014). Excessive ROS attenuates the bioenergetic function of mitochondria by causing more mutations in both nuclear DNA and mtDNA, further impairing cellular OXPHOS capacity. In turn, oxidatively damaged proteins and mitochondria accumulate and overwhelm the protein and organelle quality control systems (Buchberger et al., 2010, Denzel et al., 2014, Storm et al., 2014).

Other than the effects of toxins on the ETC, other metabolic pathways within the mitochondria can also be disrupted, including the Tricarboxylic Acid (TCA) cycle that is disrupted by compounds such as fluoroacetate, and fatty acid oxidation (FAO) that can be disrupted by alkyl acids (Wallace, 2015) and antibiotics such as tetracyclines (Cohen, 2010). Chemical toxins are also able to induce mtDNA adducts that may inhibit mitochondrial transcription or interfere with the function of DNA polymerase gamma (Pol γ) (Cline, 2012, Meyer et al. 2013), which performs all of the replicative and repair-associated DNA synthesis in mitochondria. Disruption of mitochondrial gene expression or mutagenesis of mtDNA may therefore be a clinically important consequence of environmental exposures.

2.1.3. Environmental complex I inhibitors—The ETC is comprised of 5 distinct complexes. The discoveries of MPTP parkinsonism and complex I deficiency within the substantia nigra of human Parkinson disease (PD) brains (Schapira et al., 1990) raised the possibility that ETC complex I inhibitors present in the environment may contribute to the etiology of neurodegenerative disorders. Toxin-related complex I inhibition would reduce ATP production, increase ROS production, and initiate the self-amplifying cycle of events that potentiate mitochondrial dysfunction, as described above. Several chemicals that are established inhibitors of ETC include anti-mycin A (complex III inhibitor), cyanide (complex IV inhibitor), and carbon monoxide (complex IV inhibitor) (Wallace, 2008). Naturally occurring, lipophilic complex I inhibitors include annonacin and rotenone, both known to cause parkinsonism. Annonacin exposure is related to consumption of fruit and infusions of the leaves of *Annona muricata* that is endemic to the island of Guadeloupe, which is lipophilic and readily crosses biological membranes (Caparros-Lefebvre and Elbaz, 1999, Lannuzel et al., 2007). Rotenone is mainly derived from the roots and stems of *Lonchocarpus* and *Derris* species, and has been widely used as a pesticide and piscicide, but was withdrawn from the market in many countries due to its toxicity. MPTP and rotenone are widely used to model behavioral syndromes, particularly PD. Many more naturally

occurring lipophilic compounds of herbal, microbial, or synthetic origin have been studied further in rat brain neuronal cultures, and shown to range in potency from moderate (1-methyl-4-phenylpyridinium, MPP, IC₅₀ 2.6 mM) to high (roliniastatin 2, IC₅₀ 0.9 nM) (Sherer et al., 2007, Hollerhage et al., 2009). Recognition and awareness of potent ETC complex I inhibitors in the environment and its role in neurodegenerative diseases is therefore crucial.

2.1.4. Metal toxins and mitochondrial dysfunction—Heavy metals are potential environmental toxicants and pollutants. In biological systems, heavy metals have been reported to affect cellular organelles and components such as cell membrane, mitochondria, lysosome, endoplasmic reticulum, nuclei, and enzymes involved in metabolism, detoxification, and damage repair (Wang and Shi, 2001). Metal ions are pro-inflammatory, and interact with DNA and nuclear proteins, causing DNA damage and conformational changes that may lead to cell cycle modulation, carcinogenesis, or apoptosis (Beyersmann and Hartwig, 2008). For a review of mitochondrial dysfunction as a trigger of innate immune responses and inflammation, please refer to West (2017). Biological transition metals, such as iron, copper, zinc, magnesium and manganese, are essential co-factors for at least one-third to one-half of all proteins (Andreini et al., 2008, Waldron et al., 2009). Copper and iron are metabolically utilized due to their ability to redox cycle, with iron being the most abundant (Chege and McColl, 2014). In the event of metal ion misregulation, this redox ability has the potential to produce toxic radicals via the Haber-Weiss and Fenton reactions, leading to mitochondrial oxidative stress and eventually neuronal death (Nunez et al., 2012). ROS production and oxidative stress therefore play a key role in the toxicity and carcinogenicity of metals such as arsenic (Yedjou and Tchounwou, 2006, Yedjou and Tchounwou, 2007), cadmium (Tchounwou et al., 2001), chromium (Patlolla et al., 2009a,b), lead (Tchounwou et al., 2004, Yedjou et al., 2008), and mercury (Sutton and Tchounwou, 2007).

3. Environmental toxins and neurodegenerative disorders with mitochondrial dysfunction

Defects in mitochondrial function cause diverse and complex human diseases. The contribution of mitochondrial dysfunction has been reported in major environment-related multifactorial diseases, such as respiratory disease (Bialas et al., 2016), viral infections (Wnek et al., 2016), neurological disorders (Giannoccaro et al., 2017, Swerdlow et al., 2017), cardiovascular diseases (Sabbah, 2016), and cancer (Srinivasan et al., 2017). Although harmful exposure to environmental pollutants is ubiquitous among all populations, disease manifestation occurs in only a subset of the population. Interaction between environmental factors and genetic predisposition e.g., ecogenetic variants (Saneto et al., 2013) is therefore likely to be a necessary prerequisite to disease manifestation. While the specific causative agents and underlying mechanisms that lead to diseases are not fully understood, a growing body of epidemiologic and animal model studies support a link between environmental exposure and neurologic, metabolic, respiratory, cancer, developmental and reproductive toxicity in humans. Here, we summarize experimental evidence for select environmental toxins that have been implicated in the disease

pathogenesis of two neurodegenerative disorders which share a common feature of mitochondrial dysfunction, Alzheimer's disease (AD) and Parkinson's disease (PD). We also discuss the available evidence for toxin exposure in primary (genetic) mitochondrial diseases (PMD).

3.1. Alzheimer's disease

AD is the most common cause of dementia, with more than 30 million people projected to be affected in the next 20 years (Onyango et al., 2017). AD is now the third leading cause of death in the United States, after cardiovascular disease and cancer (James et al., 2014). Familial, autosomal dominant AD accounts for 5–10% of all AD cases, while late onset, sporadic cases account for 90–95% of all AD cases (Onyango et al., 2017). No genetic etiology other than conferred risk associated to susceptibility alleles has been identified for sporadic AD (Masoud et al., 2016). This suggests that environmental and/or epigenetic factors play an important role in initiating and influencing the cascade of events that contributes to the emergence of AD (Lunnon and Mill, 2013). A link to environmental exposure has been described for ingested, absorbed and inhaled toxins (Bredesen, 2016). Key neuropathologic features are p-amyloid plaques and neurofibrillary tangles.

The possible relationship between oxidative stress and AD originally derived from the free radical hypothesis of aging, suggesting that age-related accumulation of ROS could be responsible of damage to major cell components (Beal, 2005). The role of mitochondrial dysfunction and increased oxidative damage has been reported in the pathogenesis of AD (Anandatheerthavarada et al., 2003, Bonda et al., 2010, Ferreira et al., 2012, Guo et al., 2013). Environmental exposure also likely contribute to AD disease pathogenesis by inducing mitochondrial oxidative stress.

3.1.1. Pesticides—Most organophosphates evaluated have been shown to induce oxidative stress (Pearson and Patel, 2016). **Chlorpyrifos (CPF)** is an organophosphate (OP) that is widely used as an agricultural insecticide. CPF produces oxidative stress when examined in PC 12 cells (Slotkin and Seidler, 2010), and mitofusin 1-mediated mitochondrial fragmentation in human induced pluripotent stem cells (iPSC) (Yamada et al., 2017), and is associated with cognitive impairment. **Dichlorodiphenyltrichloroethane (DDT)** is an organochlorine insecticide that has been banned from agricultural use. Its active metabolite, dichlorodiphenyldichloroethylene (DDE), activates the mitochondrial apoptosis pathway (Song et al., 2008). **Paraquat (PQ)**, is a commonly used herbicide that preferentially affects the nigrostriatum and accumulates in cerebral cortex and hippocampus (Prasad et al., 2009), and is reported to act as a redox cycling agent capable of generating ROS (McCormack et al., 2005, Czerniczyniec et al., 2015) and reduces mitochondrial ETC activity, as a complex I inhibitor (Castello et al., 2007).

3.1.1.1. Animal and experimental studies of pesticide exposure and AD: Degeneration of hippocampal cholinergic neurons, as happens in AD, results in memory deficits attributable to loss of cholinergic modulation of hippocampal synaptic circuits. In SN56 cells, a cholinergic murine neuroblastoma cell line, CPF was shown to induce acute (30–50 mM) and long-term (from 1 to 20 mM), concentration-dependent, cell death (del Pino et al.,

2015). In rats, exposure to a single subcutaneous (s.c.) dose of 250 mg/kg CPF and subsequent intracerebroventricular β -amyloid ($A\beta$) infusion for 15 days resulted in altered memory spatial task and reduced microtubule associated proteins in the prefrontal cortex (Ruiz-Munoz et al., 2011). In a AD transgenic mouse model carrying the Swedish amyloid- β protein precursor ($A\beta$ PP) mutation for AD, a single s.c. dose of 50 mg/kg CPF was associated with increased $A\beta$ levels eight months after exposure (Salazar et al., 2011). In another study of eight doses of 25 mg/kg of CPF distributed over four weeks in the same transgenic mouse model, no significant increase in β - amyloid levels were found but impaired memory was observed (Peris-Sampedro et al., 2014). In a recent study, neither elevated $A\beta$ levels nor changes in memory acquisition were identified in amyloid precursor protein (APP) transgenic mice (Tg2576) treated with CPF (25 mg/Kg/twice weekly/4 weeks, intragastric), including on analysis 6 months later (Peris-Sampedro et al., 2014).

In a study of DDT and AD, human neuroglioma H4- $A\beta$ PPSwe cells treated with DDT revealed significantly increased levels of $A\beta$ protein precursor ($A\beta$ PP) and β -site $A\beta$ PP-cleaving enzyme (BACE), as well as impaired clearance and extracellular degradation of $A\beta$ peptides (Li et al., 2015). In cultured SY5Y differentiated neuronal cells, exposure to 1- μ M DDE or DDT for 48 h significantly increased APP levels by almost 50% (Richardson et al., 2014). These studies demonstrate the association between exposures and AD, but did not report any specific evaluation of mitochondrial dysfunction.

Treatment of wild type and Tg2576 mice with PQ (10 mg/kg/twice a week/3 weeks) produced a significant increase in $A\beta$ levels that was associated with increased 4-HNE and nitrotyrosine levels consistent with mitochondrial oxidative damage in cerebral cortex, leading to the impairment of learning and memory. Interestingly, the overexpression of peroxiredoxin 3, a mitochondrial antioxidant defense enzyme produced an improvement in cognitive functions and a significant reduction in $A\beta$ levels (Chen et al., 2012).

3.1.2. Metals—Lead (Pb) is a heavy metal well known for its neurological toxic effects. Exposure to Pb occurs via inhalation of lead-contaminated dust particles or aerosols, and ingestion of Pb-contaminated food, water, and paints (Tchounwou et al., 2012). Pb affects cognitive abilities, intelligence, memory, speed processing and motor functions in children (Chin-Chan et al., 2015). Pb ions have been shown to alter mitochondrial respiration and ADP-phosphorylation (Dumas et al., 1985). **Aluminum (Al)** is the third most common metal element. Increasing environmental exposure to Al has been recognized in recent years (Bondy, 2014). Al is naturally abundant, causes remarkable cellular toxicity at low nanomolar concentrations (Alexandrov et al., 2015), and has a high affinity for the large pyramidal neurons of the human brain hippocampus (Bhattacharjee et al., 2013), and has been shown to promote amyloid aggregation and accumulation, a key feature of AD neuropathology (Exley, 2005, Rodella et al., 2008, Walton and Wang, 2009). Al has been reported to increase protein and DNA oxidation; increased lipid peroxidation and decreased polyunsaturated fatty acids in AD brain (Kandimalla et al., 2016); and the ability of Al to generate free radicals, reduce ETC activity and decreased ATP synthesis in rat brains (Kumar et al., 2011). **Mercury (Hg)** is a heavy metal that exists as elemental mercury vapor (Hg_0), inorganic and the organic mercury compounds [211], of which methylmercury ($MeHg$) is the most common. Hg is ubiquitous in the environment. Major sources of

chronic, low level mercury exposure are dental amalgams and fish consumption. MeHg crosses the blood brain barrier due to its ability to bind to cysteine, and is known to disrupt neurodevelopment (Johansson et al., 2007, Kumar et al., 2011), and associated with memory loss and altered cognition in adults (Wojcik et al., 2006, Chang et al., 2008). In terms of mitochondrial dysfunction, MeHg is reported to increase ROS levels and decrease glutathione levels (Yee and Choi, 1994, Manfroi et al., 2004).

3.1.2.1. Animal and experimental studies of metal exposure and AD.: A recent study investigated exposure to Pb, Arsenic (As) and Cadmium (Cd) and their combination in the AD-amyloid pathway in male rats exposed from gestational day 5 to postnatal day 80 through drinking water at their concentrations detected in groundwater. They reported that metal exposure activated the synthesis of Ab in the frontal cortex and/or hippocampus, mediated by an increase in APP, and in APP-processing enzymes such as BACE1 at postnatal days 24 (post-weaning) and 90 (adulthood). All metals were found to increase the APP production, although Pb was the most potent (Ashok et al., 2015). Increased levels of malondialdehyde (MDA), reduced activity of antioxidant enzymes superoxide dismutase, catalase and glutathione-S-transferase, and the induction of IL-1 α and IL-1 β in the frontal cortex was also identified (Ashok et al., 2015). Chronic oral Al administration in rats (20 g/day) in the food/twice weekly from 6 months of age increased A β production by raising the levels of APP in hippocampal and cortical tissues (Walton and Wang, 2009). Cultured rat cortical neurons exposed to Al (50 μ M for 48 days) showed an accumulation of A β , and induced conformational changes in A β and enhanced its aggregation forming fibrillar deposits on the surface of cultured neurons. Further, A β aggregates were dissolved by the addition of desferroxamine, a chelator of Al (Exley et al., 1993, Kawahara et al., 2001). Inorganic Hg levels of 36 ng Hg/g (0.18 μ Mol Hg) has been related to increased oxidative stress and cell damage (Olivieri et al., 2000, Olivieri et al., 2002). Increased secretion of A β -40 and A β -42 in SHSY5Y neuroblastoma cells exposed to 50 μ g/dL of inorganic Hg was associated with ROS overproduction (Olivieri et al., 2000). In a study of aggregating brain-cell cultures of fetal rat telencephalon, exposure to MeHg (10^{-7} - 10^{-9} M/10–50 days) produced increased APP and ROS levels (Monnet-Tschudi et al., 2006). Rat pheochromocytoma (PC12) cells exposed to both inorganic and organic (MeHg) Hg (10–1000 nM) showed a dose-dependent overproduction of A β -40 as well as reduction in A β degradation by Neprilysin (NEP) (Song and Choi, 2013). Oral administration of 20–2000 μ g/kg/day/4 weeks of MeHg produced a dose-dependent increase in A β -42 in the hippocampus of male rats, but not significant changes in APP or NEP protein levels (Kim et al., 2014).

3.2. Parkinson's disease

Parkinson's disease (PD) is a chronic progressive neurodegenerative disease, affecting at least 1% of the population over the age of 55. It is the second most common neurodegenerative disorder after AD. PD is characterized by motor symptoms such as resting tremor, rigidity and bradykinesia, and non-motor symptoms such as dementia and mood disturbance (Marsden, 1994). PD symptoms are attributed to profound depletion of striatal dopamine (DA) due to progressive loss of dopaminergic neurons in the substantia nigra pars compacta. Key neuropathology is the presence of Lewy bodies (LB) in the

surviving neurons, which are eosinophilic cytoplasmic inclusions containing aggregates of protein such as α -synuclein (α -syn) accumulation. There is ample evidence of mitochondrial dysfunction in PD that includes complex I inhibition, oxidative stress, PINK1 and DJI dysfunction, and an interaction between parkin and PINK1 that influences mitochondrial dynamics (Schapira, 2010). Familial, autosomal dominant cases occur in 5–10% of cases. Considerable evidence suggests a multifactorial etiology for PD, involving genetic and environmental factors. Aging is the main risk factor for PD (Tanner and Goldman, 1996). However, epidemiological evidence suggests that exposure to environmental toxins such as pesticides, metals, solvents and flame-retardants could increase the risk of developing PD, in comparison to tobacco consumption which has been reported to confer protection against PD (Hatcher et al., 2008, Gao and Hong, 2011). The role of environmental factors and mitochondrial dysfunction in the pathophysiology of PD was first suggested by the discovery of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) Parkinsonism (Hartley et al., 1994). MPTP is able to penetrate the brain, where conversion to the active metabolite is dependent on the presence of monoamine oxidase B in glia. The active metabolite of MPTP is 1-methyl-4-phenylpyridinium (MPP), which is selective for dopaminergic neurons and acts by inhibiting complex I of the ETC (Nicklas et al., 1985), causes selective degeneration of nigrostriatal neurons and increased ROS production (Cleeter et al., 1992). MPP has since been widely used to model PD (Schapira, 2010).

For a review of mitochondrial dysfunction in glial cells and its implications for neuronal homeostasis and survival in PD, please see Rose et al. (2017).

3.2.1. Pesticides—The main mechanisms proposed for the relationship between pesticide exposure and PD are inhibition of mitochondrial complex I and oxidative stress (Sanchez-Santed et al., 2016). **PQ** is taken up into dopaminergic terminals and causes cellular toxicity by oxidative stress (Chin-Chan et al., 2015). Repeated administrations of PQ to adult mice and rats (5–10 mg/Kg/week/at least 3 weeks, i.p.) increase ROS levels in the striatal homogenate, induce a dose-dependent decrease in dopaminergic neurons from the substantia nigra, a decline in striatal dopamine nerve terminal density, and a neurobehavioral syndrome characterized by reduced ambulatory activity (Brooks et al., 1999, McCormack et al., 2002, Kuter et al., 2010). Combined exposure to the fungicide Maneb (MB) and PQ in rural workers was reported to increase the risk of developing PD by 75% in agricultural areas of California (Costello et al., 2009). Animal studies investigating the effects of concurrent exposure to PQ and MB in adult mice reported significant dopamine (DA) fiber loss, altered DA turnover and decreased locomotor activity (Thiruchelvam et al., 2000, Wills et al., 2012). **Rotenone** can freely cross the blood-brain barrier. Rotenone treatment in animal models (1.5–3 mg/kg/day/up to 3 weeks) produces bradykinesia, postural instability and rigidity, reduces the tyrosine hydroxylase-positive neurons in the substance nigra, induces a loss of striatal dopamine, and the accumulation of α -synuclein and poly-ubiquitin positive aggregates in remaining dopaminergic neurons (Betarbet et al., 2000, Sherer et al., 2003, Cannon et al., 2009). **Dieldrin** is a lipophilic organochlorine that has bioaccumulated in soil and environmental residues despite being banned in the 1970s in most developed countries. Dieldrin has been shown to be relatively selective dopaminergic neurotoxin in mesencephalic cultures (Sanchez-Ramos et al., 1998),

depletes intracellular DA levels (Hatcher et al., 2007), induces a conformational change in α -syn (Uversky et al., 2001), depolarize mitochondrial membrane potential and generates ROS (Chun et al., 2001), and apoptosis (Kitazawa et al., 2001). Perinatal exposure of mice to low levels of dieldrin (0.3, 1, or 3 mg/kg every 3 days) resulted in a long-term enhancement of protein and mRNA levels of the DAT and vesicular monoamine transporter 2 (VMAT2) (Richardson et al., 2006). When dieldrin-exposed mice were challenged with MPTP (2×10 mg/kg s.c.) at 12 weeks of age, DA neurons appeared to be more susceptible to degeneration (Miller et al., 1999).

3.2.2. Metals—Prolonged occupational exposure to metals including manganese (Mn), iron, mercury, zinc, aluminum, copper, and lead, may be a risk factor for PD-like disorder (Gorell et al., 1999, Wang et al., 2006). The underlying mechanism is unclear, however evidence of oxidative stress is well documented in PD brains (Chege and McColl, 2014), hence the hypothesis that heavy metal accumulation in brain causes neurodegenerative disorders by contributing to oxidative stress.

3.2.2.1. Animal models and experimental studies of metal exposure in PD: **Animal models and experimental studies Iron** may play a significant role in PD neurodegeneration. The infusion of iron into rat brains results in parkinsonism and behavioral changes (Ben-Shachar and Youdim, 1991, Sengstock et al., 1993). In mice, the 8-hydroxyquinoline metal ion chelator, clioquinol prevented neurodegeneration in PD models (Kaur et al., 2003). Ferritin is a key metal ion storage protein. Ferritin transgenic mice have been shown to be resistant to PQ-induced neuronal loss and lipid peroxidation, possibly by avoiding the generation of ROS (McCormack et al., 2005). **Manganese** exposure has been reported to cause overexpression of synuclein in neuroblastoma cells (SH-SY5Y) and implicated to be involved in neuronal apoptosis (Li et al., 2010, Covy and Giasson, 2011). Mn induces caspase-dependent apoptosis (Smith et al., 2017). PCI 2 cells treated with 2 mM MnCl₂ for 36 h demonstrated increased apoptosis related to increased ROS and mitochondrial dysfunction (Zeng et al., 2006). Further, treatments with antioxidants prevented Mn-induced apoptosis (Deng et al., 2015). Human neuroblastoma cells treated with Mn (0–100 mM, 5 h) increased mitochondrial H2O₂ production in a dose dependent manner; with a concomitant increase in SOD2 activity (Fernandes et al., 2017).

3.3. Primary mitochondrial disease

Primary mitochondrial disease (PMD) is the collective term for a heterogeneous group of genetic disorders characterized by defective OXPHOS capacity. The minimal combined prevalence of PMD is 1 in 4300 (Gorman et al., 2015). These disorders are clinically diverse and can manifest at any age. Clinical manifestations are often multi-systemic and progressive, commonly involving high-energy organ systems that are highly dependent on mitochondrial OXPHOS capacity such as brain, skeletal muscles, and heart. Disease onset can occur at any age. The diverse nature of mitochondrial diseases highlights the many roles mitochondria play in cells and tissues. The current minimal estimate of the total number of mitochondrial proteins is 1158 (Calvo et al., 2016). The majority of these proteins are encoded by nuclear DNA (nDNA), with only 13 mitochondrial proteins encoded by mitochondrial DNA (mtDNA). Thus, mitochondria OXPHOS is under the dual control of

both the mitochondrial and nuclear genomes (Craven et al., 2017). Reflecting the diverse functions occurring within mitochondria, only 150 mitochondrial proteins are directly involved in OXPHOS function and ATP production (Gorman et al., 2016). The remaining mitoproteome components include proteins involved in the assembly of the ETC complexes, maintenance and expression of mtDNA, mitochondrial protein synthesis, and mitochondrial dynamics (Lightowlers et al., 2015).

A summary of the association between environmental exposure and AD and PD was included in this review to highlight the contrasting absence of similar studies in PMD. The emerging association between environmental toxin exposure and neurodegenerative disease is of considerable public health importance, given the increasing prevalence of neurodegenerative disease and environmental pollution in some geographic areas worldwide. Although the conclusion from epidemiological studies is variable, this may result from inherent scientific constraints of studying diseases that lack specific biomarkers, a lack of optimal quantitative methods to measure chronic exposures, a lack of inclusion of relevant confounding variables such as co-exposure to toxic compounds, genetic variants, and lifestyle, among others (Chin-Chan et al., 2015). Nevertheless, these epidemiological studies along with experimental data have served to highlight the potential risk of developing AD and PD from exposure to environmental pollutants such as pesticides and metals.

Whereby epigenetic mechanisms have long been hypothesized as the likely explanation for sporadic cases of AD and PD, PMD is defined by a primary inherited genetic defect in the nuclear or mitochondrial genomes. However, it is noteworthy that the underlying mechanism of variable disease expression and age of onset in PMD is not well understood. Given the knowledge that most, if not all, environmental toxins converge upon a shared mechanism of mitochondrial dysfunction and oxidative stress, it is plausible that environmental factors play a role in the penetrance and/or onset of overt disease manifestation(s) in individuals known to carry a PMD genetic defect. Please refer to Chan (2017) for a review of inherited mitochondrial genomic instability and chemical exposures.

Several well characterized PMD gene-drug treatment interactions support this notion. Several genetic mutations, in both genomes, confer disease risk on exposure to specific drug treatment. Individuals who carry the m.1555A > G mutation on the mitochondrial 12 s rRNA are at risk of irreversible ototoxicity following administration of aminoglycoside antibiotics (Fischel-Ghodsian et al., 1993). Individuals who carry *POLG* mutations affecting the polymerase responsible for mtDNA replication develop fulminant liver failure on exposure to valproate, a drug commonly used to treat seizures and migraine; it is noteworthy that the onset of liver dysfunction ensues over weeks of exposure, suggesting a possible environmental trigger (Cohen, 2010, Saneto et al., 2010). In individuals harboring the ETC complex I subunit *ND4* m. 11778A > G mutation that causes Leber Hereditary Optic Neuropathy (LHON), antibiotics erythromycin and ethambutol have been reported to precipitate optic atrophy (Yu-Wai-Man et al., 2011).

Most pathogenic mtDNA mutations are heteroplasmic, with individual cells having different proportions of mutant and wild-type mtDNA. Increasing levels of heteroplasmy are often associated with increasing severity of mitochondrial disease. Individuals who carry the

familial mtDNA tRNA-leucine m.3243A > G mutation that typically causes mitochondrial encephalopathy, lactic acidosis and strokes (“MELAS”) at high mutation heteroplasmy levels may only manifest sensorineural deafness or diabetes at low heteroplasmy levels below 30%. Although tissue heteroplasmy may contribute to this clinical heterogeneity, such phenotypic variability also raises the possibility of external environmental factors. There is likely to be more than a single environmental factor that alters risk of disease penetrance, however, as families share environmental exposures that would not alone explain the marked intrafamilial clinical heterogeneity.

The most well defined PMD gene-environmental interaction is described between LHON and lifestyle-related environmental toxins. LHON is caused by a maternally inherited mitochondrial DNA (mtDNA) mutation in one of several complex I subunit (Wallace and Lott, 2017). Affected LHON patients develop a late-teen to early 20 s acute-onset, sequentially bilateral, central-vision loss resulting in central scotoma due to the death of retinal ganglion cells. Generally, all maternal relatives carry the causal mtDNA mutation, yet have widely variable disease penetrance with only some maternal relatives developing blindness. Interestingly, a gender difference is seen with males being about four times more likely to develop blindness than females (Wallace and Lott, 2017). Smoking and excessive alcohol consumption, which create oxidative stress, increase symptomatic penetrance of the common LHON mutations (Amaral-Fernandes et al., 2011, Sadun et al., 2011, Giordano et al., 2015, Carelli et al., 2016). A review of mitochondrial toxicity of tobacco smoke and air pollution is included in this Special Issue (Ballinger, 2017).

Important cellular events are typically detected in some manner by the mitochondria, thereby altering energy production, calcium flux, and the apoptotic process. It is not surprising therefore that this highly complex organelle may be prone to environmental-induced dysfunction (Wallace, 2008). The clinical suspicion shared by mitochondrial physicians is that for a subset of PMD patients, environmental insults may trigger new disease manifestations or exacerbate symptoms (Cohen, 2010). Therefore, the complex etiology of PMD may well extend beyond defined genetic causes (Wallace, 2008).

4. Drug induced mitochondrial dysfunction

The diverse effects of pharmacological agents on mitochondrial function are expanding and have been reviewed elsewhere (Wallace, 2008, Cohen, 2010, Wallace, 2014). The scope and diversity of chemical compounds that have been demonstrated to inhibit the ETC is large and remains a challenging field (Wallace, 2015). It is important to note that experimental evidence for mitochondrial toxicity should not be used to inform clinical practice. Indeed, the evidence for a drug having mitochondrial toxicity in most cases is based on the inhibition of the individual ETC complex enzymes in *vitro*, bringing the practical clinical relevance for management of any one patient into question. Many medications that are listed as mitochondrial toxins have been used for years without obvious increased risk or incident in those with PMD (Cohen, 2010). Only a select number of drug treatments have documented clinical toxicity, which includes depakote (valproic acid) that causes hepatopathy; antiretrovirals that cause peripheral neuropathy, hepatopathy and myopathy;

and aminoglycoside antibiotics that cause ototoxicity, cardiac dysfunction, and renal toxicity (Avula et al., 2014).

5. Conclusion

Mitochondria act as environmental sensors, where direct impact of environmental toxins on diverse aspects of mitochondrial metabolism, oxidative stress, mtDNA genetics, and signaling response are to be expected. Available experimental evidence increasingly supports a link between exposure to environmental toxins and common neurodegenerative diseases that share a common feature of mitochondrial dysfunction. A need for future studies that specifically focus on the impact of environmental toxins in PMD is also clear. An association of smoking and excessive alcohol consumption causing LHON disease expression demonstrates the clear interaction of environmental exposures and mitochondrial disease patient counseling and care. Overall, further study of the role of environmental toxins in PMD penetrance and severity may potentially uncover other exposure-disease associations that have clinical consequences.

We recognize the significant challenges inherent in conducting studies of environmental toxins. First, the complexities of documenting exposure are substantial. Quantitative methods of measuring exposure are currently lacking. Retrospective exposure is often documented with the use of questionnaires which imposes limitations, but remains an important challenge to address due to the potential of early/perinatal exposure to environmental hazards playing a causal role in the later development of disease manifestations. Second, the relatively low prevalence of PMD at 1:4300 across all ages and the relatively small patient cohort bring challenges regarding data analysis due to variability in biological and temporal data, and highlights the need for multicenter studies. Lastly, effects of environmental exposure are unlikely to be due to a single agent. Therefore, unless there were important geographic implications, it would be important to apply this study on a personalized medicine basis and include exposures to non-targeted toxins in the analysis, which would increase the complexity of analysis. Nevertheless, growing evidence suggests that environmental toxins play a role in both primary and secondary mitochondrial disorders and warrant further study.

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Abbreviations:

α-syn	α -synuclein
AD	Alzheimer's Disease
Al	aluminum
C. elegans	Caenorhabditis elegans
CPF	chlorpyrifos

DA	dopamine
DDE	dichlorodiphenyldichloroethylene
DDT	dichlorodiphenyltrichloroethane
ETC	electron transport chain
FAO	fatty acid oxidation
Hg	mercury
Mn	manganese
mtDNA	mitochondrial DNA
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MPP	1-methyl-4-phenylpyridinium
nDNA	nuclear DNA
OP	organophosphate
OXPHOS	oxidative phosphorylation
PD	Parkinson's disease
PQ	paraquat
Pb	lead
PAH	polycyclic aromatic hydrocarbons
PCB	polychlorinated biphenyls
Poly	polymerase gamma
PMD	primary mitochondrial disease

References

- Alexandrov PN , Kruck TP , Lukiw WJ , 2015 Nanomolar aluminum induces expression of the inflammatory systemic biomarker C-reactive protein (CRP) in human brain microvessel endothelial cells (hBMECs). *J. Inorg. Biochem* 152, 210–213.26265215
- Amaral-Fernandes MS , Marcondes AM , do Amor Divino Miranda PM , Maciel-Guerra AT , Sartorato EL , 2011 Mutations for Leber hereditary optic neuropathy in patients with alcohol and tobacco optic neuropathy. *Mol. Vis* 17, 3175–3179.22194643
- Anandatheerthavarada HK , Biswas G , Robin MA , Avadhani NG , 2003 Mitochondrial targeting and a novel transmembrane arrest of Alzheimer's amyloid precursor protein impairs mitochondrial function in neuronal cells. *J. Cell Biol* 161 (1), 41–54.12695498
- Andreini C , Bertini I , Cavallaro G , Holliday GL , Thornton JM , 2008 Metal ions in biological catalysis: from enzyme databases to general principles. *J. Biol. Inorg. Chem* 13 (8), 1205–1218.18604568

- Ashok A , Rai NK , Tripathi S , Bandyopadhyay S , 2015 Exposure to As-, Cd-, and Pb-mixture induces Abeta, amyloidogenic APP processing and cognitive impairments via oxidative stress-dependent neuroinflammation in young rats. *Toxicol. Sci* 143 (1), 64–80.25288670
- Avula S , Parikh S , Demarest S , Kurz J , Gropman A , 2014 Treatment of mitochondrial disorders. *Curr. Treat. Options Neurol* 16 (6), 292.24700433
- Backer JM , Weinstein IB , 1980 Mitochondrial DNA is a major cellular target for a dihydrodiol-epoxide derivative of benzo [a] pyrene. *Science* 209 (4453), 297–299.6770466
- Backer JM , Weinstein IB , 1982 Interaction of benzo(a)pyrene and its dihydrodiol-epoxide derivative with nuclear and mitochondrial DNA in C3H10T 1/2 cell cultures. *Cancer Res* 42 (7), 2764–2769.6282450
- Beal MF , 2005 Mitochondria take center stage in aging and neurodegeneration. *Ann. Neurol* 58 (4), 495–505.16178023
- Ben-Shachar D , Youdim MB , 1991 Intraneural iron injection induces behavioral and biochemical parkinsonism in rats. *J. Neurochem* 57 (6), 2133–2135.1940919
- Bestman JE , Stackley KD , Rahn JJ , Williamson TJ , Chan SS , 2015 The cellular and molecular progression of mitochondrial dysfunction induced by 2,4-dinitrophenol in developing zebrafish embryos. *Differentiation* 89 (3–4), 51–69.25771346
- Betarbet R , Sherer TB , MacKenzie G , Garcia-Osuna M , Panov AV , Greenamyre JT , 2000 Chronic systemic pesticide exposure reproduces features of Parkinson's disease. *Nat. Neurosci* 3 (12), 1301–1306.11100151
- Beyersmann D , Hartwig A , 2008 Carcinogenic metal compounds: recent insight into molecular and cellular mechanisms. *Arch. Toxicol* 82 (8), 493–512.18496671
- Bhattacharjee S , Zhao Y , Hill JM , Culicchia F , Kruck TP , Percy ME , Pogue AI , Walton JR , Lukiw WJ , 2013 Selective accumulation of aluminum in cerebral arteries in Alzheimer's disease (AD). *J. Inorg. Biochem* 126, 35–37.23764827
- Bialas AJ , Sitarek P , Milkowska-Dymanowska J , Piotrowski WJ , Gorski P , 2016 The role of mitochondria and oxidative/antioxidative imbalance in pathobiology of chronic obstructive pulmonary disease. *Oxid. Med. Cell Longev* 2016, 7808576.28105251
- Bonda DJ , Wang X , Perry G , Nunomura A , Tabaton M , Zhu X , Smith MA , 2010 Oxidative stress in Alzheimer disease: a possibility for prevention. *Neuropharmacology* 59 (4–5), 290–294.20394761
- Bondy SC , 2014 Prolonged exposure to low levels of aluminum leads to changes associated with brain aging and neurodegeneration. *Toxicology* 315, 1–7.24189189
- Bredesen DE , 2016 Inhalational Alzheimer's disease: an unrecognized – and treatable – epidemic. *Aging (Albany NY)* 8 (2), 304–313.26870879
- Brooks AI , Chadwick CA , Gelbard HA , Cory-Slechta DA , Federoff HJ , 1999 Paraquat elicited neurobehavioral syndrome caused by dopaminergic neuron loss. *Brain Res* 823 (1–2), 1–10.10095006
- Buchberger A , Bukau B , Sommer T , 2010 Protein quality control in the cytosol and the endoplasmic reticulum: brothers in arms. *Mol. Cell* 40 (2), 238–252.20965419
- Butenhoff JL , Ehresman DJ , Chang SC , Parker GA , Stump DG , 2009 Gestational and lactational exposure to potassium perfluorooctanesulfonate (K + PFOS) in rats: developmental neurotoxicity. *Reprod. Toxicol* 27 (3–4), 319–330.19162172
- Butenhoff JL , Bjork JA , Chang SC , Ehresman DJ , Parker GA , Das K , Lau C , Lieder PH , van Otterdijk FM , Wallace KB , 2012 Toxicological evaluation of ammonium perfluorobutyrate in rats: twenty-eight-day and ninety-day oral gavage studies. *Reprod. Toxicol* 33 (4), 513–530.21878386
- Calvo SE , Clauser KR , Mootha VK , 2016 MitoCarta2. 0: an updated inventory of mammalian mitochondrial proteins. *Nucleic Acids Res* 44 (D1), D1251–D1257.26450961
- Cannon JR , Tapias V , Na HM , Honick AS , Drolet RE , Greenamyre JT , 2009 A highly reproducible rotenone model of Parkinson's disease. *Neurobiol. Dis* 34 (2), 279–290.19385059
- Caparros-Lefebvre D , Elbaz A , 1999 Possible relation of atypical parkinsonism in the French West Indies with consumption of tropical plants: a case-control study. *Caribbean Parkinsonism Study Group. Lancet* 354 (9175), 281–286.10440304

- Carelli V , d'Adamo P , Valentino ML , La Morgia C , Ross-Cisneros FN , Caporali L , Maresca A , Loguercio Polosa P , Barboni P , De Negri A , Sadun F , Karanjia R , Salomao SR , Berezovsky A , Chicani F , Moraes M , MoraesFilho M , Belfort R , Sadun AA , 2016 Parsing the differences in affected with LHON: genetic versus environmental triggers of disease conversion. *Brain* 139 (Pt 3), e17.
- Carneiro FF , Oliveira ML , Netto GF , Galvao LA , Cancio JA , Bonini EM , Corvalan CF , 2006 Meeting report: development of environmental health indicators in Brazil and other countries in the americas. *Environ. Health Perspect* 114 (9), 1407–1408.16966096
- Castello PR , Drechsel DA , Patel M , 2007 Mitochondria are a major source of paraquat-induced reactive oxygen species production in the brain. *J. Biol. Chem* 282 (19), 14186–14193.17389593
- Chan SSL , 2017 Inherited mitochondrial genomic instability and chemical exposures. *Toxicology* 391 75–83.28756246
- Chang JW , Pai MC , Chen HL , Guo HR , Su HJ , Lee CC , 2008 Cognitive function and blood methylmercury in adults living near a deserted chloralkali factory. *Environ. Res* 108 (3), 334–339.18675410
- Chege PM , McColl G , 2014 *Caenorhabditis elegans*: a model to investigate oxidative stress and metal dyshomeostasis in Parkinson's disease. *Front. Aging Neurosci* 6, 89.24904406
- Chen L , Yoo SE , Na R , Liu Y , Ran Q , 2012 Cognitive impairment and increased Abeta levels induced by paraquat exposure are attenuated by enhanced removal of mitochondrial H₂O₂. *Neurobiol. Aging* 33 (2), e415–e426 (432).
- Chen L , Mo H , Zhao L , Gao W , Wang S , Cromie MM , Lu C , Wang JS , Shen CL , 2017 Therapeutic properties of green tea against environmental insults. *J. Nutr. Biochem* 40, 1–13.27723473
- Chin-Chan M , Navarro-Yepes J , Quintanilla-Vega B , 2015 Environmental pollutants as risk factors for neurodegenerative disorders: Alzheimer and Parkinson diseases. *Front. Cell. Neurosci* 9, 124.25914621
- Chun HS , Gibson GE , DeGiorgio LA , Zhang H , Kidd VJ , Son JH , 2001 Dopaminergic cell death induced by MPP(-t-), oxidant and specific neurotoxins shares the common molecular mechanism. *J. Neurochem* 76 (4), 1010–1021.11181820
- Cleeter MW , Cooper JM , Schapira AH , 1992 Irreversible inhibition of mitochondrial complex I by 1-methyl-4-phenylpyridinium: evidence for free radical involvement. *J. Neurochem* 58 (2), 786–789.1729421
- Cline SD , 2012 Mitochondrial DNA damage and its consequences for mitochondrial gene expression. *Biochim. Biophys. Acta* 1819 (9–10), 979–991.22728831
- Cohen BH , 2010 Pharmacologic effects on mitochondrial function. *Dev. Disabil. Res. Rev* 16 (2), 189–199.20818734
- Costello S , Cockburn M , Bronstein J , Zhang X , Ritz B , 2009 Parkinson's disease and residential exposure to maneb and paraquat from agricultural applications in the central valley of California. *Am. J. Epidemiol* 169 (8), 919–926.19270050
- Covy JP , Giasson BI , 2011 alpha-Synuclein, leucine-rich repeat kinase-2, and manganese in the pathogenesis of Parkinson disease. *Neurotoxicology* 32 (5), 622–629.21238487
- Craven L , Alston CL , Taylor RW , Turnbull DM , 2017 Recent advances in mitochondrial disease. *Annu. Rev. Genomics Hum. Genet*
- Cremonese C , Piccoli C , Pasqualotto F , Clapauch R , Koifman RJ , Koifman S , Freire C , 2017 Occupational exposure to pesticides, reproductive hormone levels and sperm quality in young Brazilian men. *Reprod. Toxicol* 67, 174–185.28077271
- Czerniczyniec A , Lanza EM , Karadayian AG , Bustamante J , Lores-Arnaiz S , 2015 Impairment of striatal mitochondrial function by acute paraquat poisoning. *J. Bioenerg. Biomembr* 47 (5), 395–408.26350412
- D'Mello F , Braidly N , Marcal H , Guillemin G , Rossi F , Chinian M , Laurent D , Teo C , Neilan BA , 2017 Cytotoxic effects of environmental toxins on human glial cells. *Neurotox. Res* 31 (2), 245–258.27796937

- Deng Y., Jiao C, Mi C, Xu B, Li Y, Wang F, Liu W, Xu Z, 2015 Melatonin inhibits manganese-induced motor dysfunction and neuronal loss in mice: involvement of oxidative stress and dopaminergic neurodegeneration. *Mol. Neurobiol* 51 (1), 68–88.24969583
- Denzel MS, Storm NJ, Gutschmidt A, Baddi R, Hinze Y, Jarosch E, Sommer T, Hoppe T, Antebi A, 2014 Hexosamine pathway metabolites enhance protein quality control and prolong life. *Cell* 156 (6), 1167–1178.24630720
- Dong H, Dalton TP, Miller ML, Chen Y, Uno S, Shi Z, Shertzer HG, Bansal S, Avadhani NG, Nebert DW, 2009 Knock-in mouse lines expressing either mitochondrial or microsomal CYP1A1: differing responses to dietary benzo [a] pyrene as proof of principle. *Mol. Pharmacol* 75 (3), 555–567.19047483
- Dornfeld K, Madden M, Skildum A, Wallace KB, 2015 Aspartate facilitates mitochondrial function, growth arrest and survival during doxorubicin exposure. *ABBV Cell Cycle* 14 (20), 3282–3291.
- Dumas P, Gueldry D, Loireau A, Chomard P, Buthieau AM, Autissier N, 1985 [Effects of lead poisoning on properties of brain mitochondria in young rats]. *C. R. Seances Soc. Biol. Fil* 179 (2), 175–183.2990636
- Eldakroory SA, Morsi DE, Abdel-Rahman RH, Roshdy S, Gouida MS, Khashaba EO, 2016 Correlation between toxic organochlorine pesticides and breast cancer. *Hum. Exp. Toxicol*, 10.1177/0960327116685887. [Epub ahead of print].
- Elstner M, Turnbull DM, 2012 Transcriptome analysis in mitochondrial disorders. *Brain Res. Bull* 88 (4), 285–293.21856382
- Exley C, Price NC, Kelly SM, Birchall JD, 1993 An interaction of beta-amyloid with aluminium in vitro. *FEBS Lett* 324 (3), 293–295.8405368
- Exley C, 2005 The aluminium-amyloid cascade hypothesis and Alzheimer's disease. *Subcell. Biochem* 38, 225–234.15709481
- Fernandes J, Hao L, Bijli KM, Chandler JD, Orr M, Hu X, Jones DP, Go YM, 2017 From the cover: manganese stimulates mitochondrial H₂O₂ production in SH-SY5Y human neuroblastoma cells over physiologic as well as toxicologic range. *Toxicol. Sci* 155 (1), 213–223.27701121
- Ferreiro E, Baldeiras I, Ferreira IL, Costa RO, Rego AC, Pereira CF, Oliveira CR, 2012 Mitochondrial- and endoplasmic reticulum-associated oxidative stress in Alzheimer's disease: from pathogenesis to biomarkers. *Int. J. Cell Biol* 2012, 735206.22701485
- Fetterman JL, Sammy MJ, Ballinger SW, 2017 Mitochondrial toxicity of tobacco smoke and air pollution. *Toxicology* 391, 18–33.28838641
- Finkel T, Holbrook NJ, 2000 Oxidants, oxidative stress and the biology of ageing. *Nature* 408 (6809), 239–247.11089981
- Fischel-Ghodsian N, Prezant TR, Bu X, Oztas S, 1993 Mitochondrial ribosomal RNA gene mutation in a patient with sporadic aminoglycoside ototoxicity. *Am. J. Otolaryngol* 14 (6), 399–403.8285309
- Gao HM, Hong JS, 2011 Gene-environment interactions: key to unraveling the mystery of Parkinson's disease. *Prog. Neurobiol* 94 (1), 1–19.21439347
- Ge T, Han J, Qi Y, Gu X, Ma L, Zhang C, Naeem S, Huang D, 2017 The toxic effects of chlorophenols and associated mechanisms in fish. *Aquat. Toxicol* 184, 78–93.28119128
- Genter MB, Clay CD, Dalton TP, Dong H, Nebert DW, Shertzer HG, 2006 Comparison of mouse hepatic mitochondrial versus microsomal cytochromes P450 following TCDD treatment. *Biochem. Biophys. Res. Commun* 342 (4), 1375–1381.16516144
- Giannoccaro MP, La Morgia C, Rizzo G, Carelli V, 2017 Mitochondrial DNA and primary mitochondrial dysfunction in Parkinson's disease. *Mov. Disord*
- Giordano L, Deceglie S, d'Adamo P, Valentino ML, La Morgia C, Fracasso F, Roberti M, Cappellari M, Petrosillo G, Ciaravolo S, Parente D, Giordano C, Maresca A, Iommarini L, Del Dotto V, Ghelli AM, Salomao SR, Berezovsky A, Belfort R, Sadun AA, Carelli V, Loguercio Polosa P, Cantatore P, 2015 Cigarette toxicity triggers Leber's hereditary optic neuropathy by affecting mtDNA copy number, oxidative phosphorylation and ROS detoxification pathways. *Cell. Death. Dis* 6, e2021.26673666
- Gonzalez-Hunt CP, Leung MC, Bodhicharla RK, McKeever MG, Arrant AE, Margillo KM, Ryde IT, Cyr DD, Kosmaczewski SG, Hammarlund M, Meyer JN, 2014 Exposure to mitochondrial

genotoxins and dopaminergic neurodegeneration in *Caenorhabditis elegans*. *PLoS One* 9 (12), e14459.

- Gorell JM , Johnson CC , Rybicki BA , Peterson EL , Kortsha GX , Brown GG , Richardson RJ , 1999 Occupational exposure to manganese, copper, lead, iron, mercury and zinc and the risk of Parkinson's disease. *Neurotoxicology* 20 (2–3), 239–247.10385887
- Gorman GS , Schaefer AM , Ng Y , Gomez N , Blakely EL , Alston CL , Feeney C , Horvath R , Yu-Wai-Man P , Chinnery PF , Taylor RW , Turnbull DM , McFarland R , 2015 Prevalence of nuclear and mitochondrial DNA mutations related to adult mitochondrial disease. *Ann. Neurol* 77 (5), 753–759.25652200
- Gorman GS , Chinnery PF , DiMauro S , Hirano M , Koga Y , McFarland R , Suomalainen A , Thorburn DR , Zeviani M , Turnbull DM , 2016 Mitochondrial diseases. *Nat. Rev. Dis. Primers* 2, 16080.27775730
- Guo C , Sun L , Chen X , Zhang D , 2013 Oxidative stress, mitochondrial damage and neurodegenerative diseases. *Neural Regen. Res* 8 (21), 2003–2014.25206509
- Harmon HJ , Sanborn MR , 1982 Effect of naphthalene on respiration in heart mitochondria and intact cultured cells. *Environ. Res* 29 (1), 160–173.6216100
- Harmon HJ , Nank S , Floyd RA , 1987 Age-dependent changes in rat brain mitochondria of synaptic and non-synaptic origins. *Mech. Ageing Dev* 38 (2), 167–177.3037204
- Hartley A , Stone JM , Heron C , Cooper JM , Schapira AH , 1994 Complex I inhibitors induce dose-dependent apoptosis in PC12 cells: relevance to Parkinson's disease. *J. Neurochem* 63 (5), 1987–1990.7931358
- Hatcher JM , Richardson JR , Guillot TS , McCormack AL , Di Monte DA , Jones DP , Pennell KD , Miller GW , 2007 Dieldrin exposure induces oxidative damage in the mouse nigrostriatal dopamine system. *Exp. Neurol* 204 (2), 619–630.17291500
- Hatcher JM , Pennell KD , Miller GW , 2008 Parkinson's disease and pesticides: a toxicological perspective. *Trends Pharmacol. Sci* 29 (6), 322–329.18453001
- Hoche B , 2014 More than genes: the advanced fetal programming hypothesis. *J. Reprod. Immunol* 104–105, 8–11.
- Hollerhage M , Matusch A , Champy P , Lombes A , Ruberg M , Oertel WH , Hoglinger GU , 2009 Natural lipophilic inhibitors of mitochondrial complex I are candidate toxins for sporadic neurodegenerative tau pathologies. *Exp. Neurol* 220 (1), 133–142.19682988
- Hongsibsong S , Sittitoon N , Sapbamrer R , 2017 Association of health symptoms with low-level exposure to organophosphates, DNA, damage, AChE activity, and occupational knowledge and practice among rice, corn, and double-crop farmers. *J. Occup. Health* 59 (2), 165–176. 10.1539/joh.16-0107-OA. Epub 2017 Jan 11.28077823
- Huang B , Jiang C , Luo J , Cui Y , Qin L , Liu J , 2014 Maternal exposure to bisphenol A may increase the risks of Parkinson's disease through down-regulation of fetal IGF-1 expression. *Med. Hypotheses* 82 (3), 245–249.24468574
- James BD , Leurgans SE , Hebert LE , Scherr PA , Yaffe K , Bennett DA , 2014 Contribution of Alzheimer disease to mortality in the United States. *Neurology* 82 (12), 1045–1050.24598707
- Jia J , Chen Q , Lauridsen TL , 2016 A systematic investigation into the environmental fate of microcystins and the potential risk: study in Lake Taihu. *Toxins (Basel)* 8 (6).
- Johansson C , Castoldi AF , Onishchenko N , Manzo L , Vahter M , Ceccatelli S , 2007 Neurobehavioural and molecular changes induced by methylmercury exposure during development. *Neurotox. Res* 11 (3–4), 241–260.17449462
- Kandimalla R , Vallamkonda J , Corgiat EB , Gill KD , 2016 Understanding aspects of aluminum exposure in Alzheimer's disease development. *Brain Pathol* 26 (2), 139–154.26494454
- Kaur D , Yantiri F , Rajagopalan S , Kumar J , Mo JQ , Boonplueang R , Viswanath V , Jacobs R , Yang L , Beal MF , DiMonte D , Volitaskis I , Ellerby L , Cherny RA , Bush AI , Andersen JK , 2003 Genetic or pharmacological iron chelation prevents MPTP-induced neurotoxicity in vivo: a novel therapy for Parkinson's disease. *Neuron* 37 (6), 899–909.12670420
- Kawahara M , Kato M , Kuroda Y , 2001 Effects of aluminum on the neurotoxicity of primary cultured neurons and on the aggregation of beta-amyloid protein. *Brain Res. Bull* 55 (2), 211–217.11470317

- Kim DK , Park JD , Choi BS , 2014 Mercury-induced amyloid-beta (Abeta) accumulation in the brain is mediated by disruption of Abeta transport. *J. Toxicol. Sci* 39 (4), 625–635.25056787
- Kitazawa M , Anantharam V , Kanthasamy AG , 2001 Dieldrin-induced oxidative stress and neurochemical changes contribute to apoptotic cell death in dopaminergic cells. *Free Radic. Biol. Med* 31 (11), 1473–1485.11728820
- Krieg SA , Shahine LK , Lathi RB , 2016 Environmental exposure to endocrine-disrupting chemicals and miscarriage. *Fertil. Steril* 106 (4), 941–947.27473347
- Kumar A , Prakash A , Dogra S , 2011 Neuroprotective effect of carvedilol against aluminium induced toxicity: possible behavioral and biochemical alterations in rats. *Pharmacol. Rep* 63 (4), 915–923.22001979
- Kuter K , Nowak P , Golembiowska K , Ossowska K , 2010 Increased reactive oxygen species production in the brain after repeated low-dose pesticide paraquat exposure in rats. A comparison with peripheral tissues. *Neurochem. Res* 35 (8), 1121–1130.20369291
- Lannuzel A , Hoglinger GU , Verhaeghe S , Gire L , Belson S , Escobar-Khondiker M , Poullain P , Oertel WH , Hirsch EC , Dubois B , Ruberg M , 2007 Atypical par-kinsonism in Guadeloupe: a common risk factor for two closely related phenotypes? *Brain* 130 (Pt 3), 816–827.17303592
- Larsen NB , Rasmussen M , Rasmussen LJ , 2005 Nuclear and mitochondrial DNA repair: similar pathways? *Mitochondrion* 5 (2), 89–108.16050976
- Li Y , Sun L , Cai T , Zhang Y , Lv S , Wang Y , Ye L , 2010 alpha-Synuclein overexpression during manganese-induced apoptosis in SH-SY5Y neuroblastoma cells. *Brain Res. Bull* 81 (4–5), 428–433.19932157
- Li G , Kim C , Kim J , Yoon H , Zhou H , Kim J , 2015 Common pesticide, di-chlorodiphenyltrichloroethane (DDT), increases amyloid-beta levels by impairing the function of ABCA1 and IDE: implication for Alzheimer's disease. *J. Alzheimers Dis* 46 (1), 109–122.25720399
- Lightowlers RN , Taylor RW , Turnbull DM , 2015 Mutations causing mitochondrial disease: what is new and what challenges remain? *Science* 349 (6255), 1494–1499.26404827
- Liu Z , Tang R , Li D , Hu Q , Wang Y , 2015 Subacute microcystin-LR exposure alters the metabolism of thyroid hormones in juvenile zebrafish (*Danio Rerio*). *Toxins (Basel)* 7 (2), 337–352.25647779
- Lunnon K , Mill J , 2013 Epigenetic studies in Alzheimer's disease: current findings, caveats, and considerations for future studies. *Am. J. Med. Genet. B Neuropsychiatr. Genet* 162B (8), 789–799.24038819
- Manfroi CB , Schwalm FD , Cereser V , Abreu F , Oliveira A , Bizarro L , Rocha JB , Frizzo ME , Souza DO , Farina M , 2004 Maternal milk as methylmercury source for suckling mice: neurotoxic effects involved with the cerebellar glutamatergic system. *Toxicol. Sci* 81 (1), 172–178.15201443
- Marsden CD , 1994 Parkinson's disease. *J. Neurol. Neurosurg. Psychiatry* 57 (6), 672–681.7755681
- Masoud AM , Bihagi SW , Machan JT , Zawia NH , Renahan WE , 2016 Early-life exposure to lead (Pb) alters the expression of microRNA that target proteins associated with Alzheimer's disease. *J. Alzheimers Dis* 51 (4), 1257–1264.26923026
- McCormack AL , Thiruchelvam M , Manning-Bog AB , Thiffault C , Langston JW , Cory-Slechta DA , Di Monte DA , 2002 Environmental risk factors and Parkinson's disease: selective degeneration of nigral dopaminergic neurons caused by the herbicide paraquat. *Neurobiol. Dis* 10 (2), 119–127.12127150
- McCormack AL , Atienza JG , Johnston LC , Andersen JK , Vu S , Di Monte DA , 2005 Role of oxidative stress in paraquat-induced dopaminergic cell degeneration. *J. Neurochem* 93 (4), 1030–1037.15857406
- Meyer JN , Leung MC , Rooney JP , Sandoel A , Hengartner MO , Kisby GE , Bess AS , 2013 Mitochondria as a target of environmental toxicants. *Toxicol. Sci* 134 (1), 1–17.23629515
- Meyer JN , 2010 QPCR: a tool for analysis of mitochondrial and nuclear DNA damage in ecotoxicology. *Ecotoxicology* 19 (4), 804–811.20049526
- Miller GW , Gainetdinov RR , Levey AI , Caron MG , 1999 Dopamine transporters and neuronal injury. *Trends Pharmacol. Sci* 20 (10), 424–429.10498956

- Monnet-Tschudi F , Zurich MG , Boschat C , Corbaz A , Honegger P , 2006 Involvement of environmental mercury and lead in the etiology of neurodegenerative diseases. *Rev. Environ. Health* 21 (2), 105–117.16898674
- Nicklas WJ , Vyas I , Heikkila RE , 1985 Inhibition of NADH-linked oxidation in brain mitochondria by 1-methyl-4-phenyl-pyridine, a metabolite of the neurotoxin, 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine. *Life Sci* 36 (26), 2503–2508.2861548
- Nicklas WJ , Youngster SK , Kindt MV , Heikkila RE , 1987 MPTP, MPP + and mitochondrial function. *Life Sci* 40 (8), 721–729.3100899
- No ACO , 2013 Exposure to toxic environmental agents. *Obstet. Gynecol* 122 (4), 931–935.24084567
- Nunez MT , Urrutia P , Mena N , Aguirre P , Tapia V , Salazar J , 2012 Iron toxicity in neurodegeneration. *Biometals* 25 (4), 761–776.22318507
- Nunnari J , Suomalainen A , 2012 Mitochondria: in sickness and in health. *Cell* 148 (6), 1145–1159.22424226
- O'Brien TM , Wallace KB , 2004 Mitochondrial permeability transition as the critical target of N-acetyl perfluorooctane sulfonamide toxicity in vitro. *Toxicol. Sci* 82 (1), 333–340.15310855
- Olivieri G , Brack C , Muller-Spahn F , Stahelin HB , Herrmann M , Renard P , Brockhaus M , Hock C , 2000 Mercury induces cell cytotoxicity and oxidative stress and increases beta-amyloid secretion and tau phosphorylation in SHSY5Y neuroblastoma cells. *J. Neurochem* 74 (1), 231–236.10617124
- Olivieri G , Novakovic M , Savaskan E , Meier F , Baysang G , Brockhaus M , Muller-Spahn F , 2002 The effects of beta-estradiol on SHSY5Y neuroblastoma cells during heavy metal induced oxidative stress, neurotoxicity and beta-amyloid secretion. *Neuroscience* 113 (4), 849–855.12182891
- Omura T , 2006 Mitochondrial P450s. *Chem. Biol. Interact* 163 (1–2), 86–93.16884708
- Onyango IG , Khan SM , Bennett JP , 2017 Mitochondria in the pathophysiology of Alzheimer's and Parkinson's diseases. *Front. Biosci. (Landmark Ed)* 22, 854–872.27814651
- Patlolla AK , Barnes C , Hackett D , Tchounwou PB , 2009a Potassium dichromate induced cytotoxicity, genotoxicity and oxidative stress in human liver carcinoma (HepG2) cells. *Int. J. Environ. Res. Public Health* 6 (2), 643–653.19440407
- Patlolla AK , Barnes C , Yedjou C , Velma VR , Tchounwou PB , 2009b Oxidative stress, DNA damage, and antioxidant enzyme activity induced by hexavalent chromium in Sprague-Dawley rats. *Environ. Toxicol* 24 (1), 66–73.18508361
- Pearson JN , Patel M , 2016 The role of oxidative stress in organophosphate and nerve agent toxicity. *Ann. N. Y. Acad. Sci* 1378 (1), 17–24.27371936
- Peris-Sampedro F , Salazar JG , Cabre M , Reverie I , Domingo JL , Sanchez-Santed F , Colomina MT , 2014 Impaired retention in AbetaPP Swedish mice six months after oral exposure to chlorpyrifos. *Food Chem. Toxicol* 72, 289–294.25106752
- Picard M , Wallace DC , Burelle Y , 2016 The rise of mitochondria in medicine. *Mitochondrion* 30, 105–116.27423788
- Prasad K , Tarasewicz E , Mathew J , Strickland PA , Buckley B , Richardson JR , Richfield EK , 2009 Toxicokinetics and toxicodynamics of paraquat accumulation in mouse brain. *Exp. Neurol* 215 (2), 358–367.19084006
- Pruss-Ustun A , Corvalan C , 2007 How much disease burden can be prevented by environmental interventions? *Epidemiology* 18 (1), 167–178.16971860
- Raftery TD , Jayasundara N , Di Giulio RT , 2017 A bioenergetics assay for studying the effects of environmental stressors on mitochondrial function in vivo in zebrafish larvae. *Comp. Biochem. Physiol. C Toxicol. Pharmacol* 192, 23–32.27939721
- Richardson JR , Caudle WM , Wang M , Dean ED , Pennell KD , Miller GW , 2006 Developmental exposure to the pesticide dieldrin alters the dopamine system and increases neurotoxicity in an animal model of Parkinson's disease. *FASEB J* 20 (10), 1695–1697.16809432
- Richardson JR , Roy A , Shalat SL , von Stein RT , Hossain MM , Buckley B , Gearing M , Levey AI , German DC , 2014 Elevated serum pesticide levels and risk for Alzheimer disease. *JAMA Neurol* 71 (3), 284–290.24473795

- Rodella LF, Ricci F, Borsani E, Stacchiotti A, Foglio E, Favero G, Rezzani R, Mariani C, Bianchi R, 2008 Aluminium exposure induces Alzheimer's disease-like histopathological alterations in mouse brain. *Histol. Histopathol* 23 (4), 433–439.18228200
- Rose J, Brian C, Woods J, Pappa A, Panayiotidis M, Powers R, Franco R, 2017 Mitochondrial dysfunction in glial cells: implications for neuronal homeostasis and survival. *Toxicology* 391, 109–115.28655545
- Roubicek DA, de Souza Pinto NC, 2017 Mitochondria and mitochondrial DNA as relevant targets for environmental contaminants. *Toxicology* 391, 100–108.28655544
- Ruiz-Munoz AM, Nieto-Escamez FA, Aznar S, Colomina MT, Sanchez-Santed F, 2011 Cognitive and histological disturbances after chlorpyrifos exposure and chronic Abeta(1-42) infusions in Wistar rats. *Neurotoxicology* 32 (6), 836–844.21669222
- Rzhetsky A, Bagley SC, Wang K, Lyttle CS, Cook EH, Altman RB, Gibbons RD, 2014 Environmental and state-level regulatory factors affect the incidence of autism and intellectual disability. *PLoS Comput. Biol* 10 (3), e003518.
- Sabbah HN, 2016 Targeting mitochondrial dysfunction in the treatment of heart failure. *Expert Rev. Cardiovasc. Ther* 14 (12), 1305–1313.27758146
- Sadun AA, La Morgia C, Carelli V, 2011 Leber's hereditary optic neuropathy. *Curr. Treat. Options Neurol* 13 (1), 109–117.21063922
- Salazar JG, Ribes D, Cabre M, Domingo JL, Sanchez-Santed F, Colomina MT, 2011 Amyloid beta peptide levels increase in brain of AbetaPP Swedish mice after exposure to chlorpyrifos. *Curr. Alzheimer Res* 8 (7), 732–740.21592053
- Sanchez-Ramos J, Facca A, Basit A, Song S, 1998 Toxicity of dieldrin for dopaminergic neurons in mesencephalic cultures. *Exp. Neurol* 150 (2), 263–271.9527896
- Sanchez-Santed F, Colomina MT, Herrero Hernandez E, 2016 Organophosphate pesticide exposure and neurodegeneration. *Cortex* 74, 417–426.26687930
- Saneto RP, Lee IC, Koenig MK, Bao X, Weng SW, Naviaux RK, Wong LJ, 2010 POLG DNA testing as an emerging standard of care before instituting valproic acid therapy for pediatric seizure disorders. *Seizure* 19 (3), 140–146.20138553
- Saneto RP, Cohen BH, Copeland WC, Naviaux RK, 2013 Alpers-Huttenlocher syndrome. *Pediatr. Neurol* 48 (3), 167–178.23419467
- Sarmah S, Muralidharan P, Marrs JA, 2016 Common congenital anomalies: environmental causes and prevention with folic acid containing multivitamins. *Birth Defects Res. C Embryo Today* 108 (3), 274–286.27718306
- Schapira AH, Cooper JM, Dexter D, Clark JB, Jenner P, Marsden CD, 1990 Mitochondrial complex I deficiency in Parkinson's disease. *J. Neurochem* 54 (3), 823–827.2154550
- Schapira AH, 2010 Complex I: inhibitors, inhibition and neurodegeneration. *Exp. Neurol* 224 (2), 331–335.20362572
- Sengstock GJ, Olanow CW, Menzies RA, Dunn AJ, Arendash GW, 1993 Infusion of iron into the rat substantia nigra: nigral pathology and dose-dependent loss of striatal dopaminergic markers. *J. Neurosci. Res* 35 (1), 67–82.7685399
- Sherer TB, Betarbet R, Testa CM, Seo BB, Richardson JR, Kim JH, Miller GW, Yagi T, Matsuno-Yagi A, Greenamyre JT, 2003 Mechanism of toxicity in rotenone models of Parkinson's disease. *J. Neurosci* 23 (34), 10756–10764.14645467
- Sherer TB, Richardson JR, Testa CM, Seo BB, Panov AV, Yagi T, Matsuno-Yagi A, Miller GW, Greenamyre JT, 2007 Mechanism of toxicity of pesticides acting at complex I: relevance to environmental etiologies of Parkinson's disease. *J. Neurochem* 100 (6), 1469–1479.17241123
- Slotkin TA, Seidler FJ, 2010 Oxidative stress from diverse developmental neurotoxicants: antioxidants protect against lipid peroxidation without preventing cell loss. *Neurotoxicol. Teratol* 32 (2), 124–131.20004241
- Smith MR, Fernandes J, Go YM, Jones DP, 2017 Redox dynamics of manganese as a mitochondrial life-death switch. *Biochem. Biophys. Res. Commun* 482 (3), 388–398.28212723
- Song JW, Choi BS, 2013 Mercury induced the accumulation of amyloid beta (Abeta) in PC12Cells: the role of production and degradation of abeta. *Toxicol. Res* 29 (4), 235–240.24578793

- Song Y , Liang X , Hu Y , Wang Y , Yu H , Yang K , 2008 p,p'-DDE induces mitochondria-mediated apoptosis of cultured rat Sertoli cells. *Toxicology* 253 (1–3), 53–61.18817839
- Srinivasan S , Guha M , Kashina A , Avadhani NG , 2017 Mitochondrial dysfunction and mitochondrial dynamics-the cancer connection. *Biochim. Biophys. Acta* 58 (8), 602–614. 10.1016/j.bbabo.2017.01.004. Epub 2017 Jan 16.
- Sutton DJ , Tchounwou PB , 2007 Mercury induces the externalization of phosphatidyl-serine in human renal proximal tubule (HK-2) cells. *Int. J. Environ. Res. Public Health* 4 (2), 138–144.17617677
- Suzuki S , Arnold LL , Muirhead D , Lu X , Le XC , Bjork JA , Wallace KB , Ohnishi T , Kakiuchi-Kiyota S , Pennington KL , Cohen SM , 2008 Inorganic arsenic-induced intramitochondrial granules in mouse urothelium. *Toxicol. Pathol* 36 (7), 999–1005.19126794
- Swerdlow RH , Koppel S , Weidling I , Hayley C , Ji Y , Wilkins HM , 2017 Mitochondria, cybrids, aging, and Alzheimer's disease. *Prog. Mol. Biol. Transl. Sci* 146, 259–302.28253988
- Tanner CM , Goldman SM , 1996 Epidemiology of Parkinson's disease. *Neurol. Clin* 14 (2), 317–335.8827174
- Tchounwou PB , Ishaque AB , Schneider J , 2001 Cytotoxicity and transcriptional activation of stress genes in human liver carcinoma cells (HepG2) exposed to cadmium chloride. *Mol. Cell. Biochem* 222 (1–2), 21–28.11678604
- Tchounwou PB , Yedjou CG , Foxx DN , Ishaque AB , Shen E , 2004 Lead-induced cytotoxicity and transcriptional activation of stress genes in human liver carcinoma (HepG2) cells. *Mol. Cell. Biochem* 255 (1–2), 161–170.14971657
- Tchounwou PB , Yedjou CG , Patlolla AK , Sutton DJ , 2012 Heavy metal toxicity and the environment. *EXS* 101, 133–164.22945569
- Thiruchelvam M , Brockel BJ , Richfield EK , Baggs RB , Cory-Slechta DA , 2000 Potentiated and preferential effects of combined paraquat and maneb on nigrostriatal dopamine systems: environmental risk factors for Parkinson's disease? *Brain Res* 873 (2), 225–234.10930548
- Uversky VN , Li J , Fink AL , 2001 Pesticides directly accelerate the rate of alpha-synuclein fibril formation: a possible factor in Parkinson's disease. *FEBS Lett* 500 (3), 105–108.
- Waldron KJ , Rutherford JC , Ford D , Robinson NJ , 2009 Metalloproteins and metal sensing. *Nature* 460 (7257), 823–830.19675642
- Wallace DC , Lott MT , 2017 Leber hereditary optic neuropathy: exemplar of an mtDNA disease. *Handb. Exp. Pharmacol*
- Wallace KB , 2007 Adriamycin-induced interference with cardiac mitochondrial calcium homeostasis. *Cardiovasc. Toxicol* 7 (2), 101–107.17652813
- Wallace KB , 2008 Mitochondrial off targets of drug therapy. *Trends Pharmacol. Sci* 29 (7), 361–366.18501972
- Wallace KB , 2014 Drug-induced mitochondrial neuropathy in children: a conceptual framework for critical windows of development. *J. Child Neurol* 29 (9), 1241–1248.25008905
- Wallace KB , 2015 Multiple targets for drug-induced mitochondrial toxicity. *Curr. Med. Chem* 22 (20), 2488–2492.25973981
- Walton JR , Wang MX , 2009 APP expression, distribution and accumulation are altered by aluminum in a rodent model for Alzheimer's disease. *J. Inorg. Biochem* 103 (11), 1548–1554.19818510
- Wang S , Shi X , 2001 Molecular mechanisms of metal toxicity and carcinogenesis. *Mol. Cell. Biochem* 222 (1–2), 3–9.11678608
- Wang X , Yang Y , Wang X , Xu S , 2006 The effect of occupational exposure to metals on the nervous system function in welders. *J. Occup. Health* 48 (2), 100–106.16612038
- West AP , 2017 Mitochondrial dysfunction as a trigger of innate immune responses and inflammation. *Toxicology* 391, 54–63.28765055
- Wills J , Credle J , Oaks AW , Duka V , Lee JH , Jones J , Sidhu A , 2012 Paraquat, but not maneb, induces synucleinopathy and tauopathy in striata of mice through inhibition of proteasomal and autophagic pathways. *PLoS One* 7 (1), e30745.22292029
- Wnek M , Ressel L , Ricci E , Rodriguez-Martinez C , Guerrero JC , Ismail Z , Smith C , Kipar A , Sodeik B , Chinnery PF , Solomon T , Griffiths MJ , 2016 Herpes simplex encephalitis is linked

with selective mitochondrial damage; a post-mortem and in vitro study. *Acta Neuropathol* 132 (3), 433–451.27457581

- Wojcik DP , Godfrey ME , Christie D , Haley BE , 2006 Mercury toxicity presenting as chronic fatigue, memory impairment and depression: diagnosis, treatment, susceptibility, and outcomes in a New Zealand general practice setting (1994–2006). *Neuro Endocrinol. Lett* 27 (4), 415–423.16891999
- Wunderlich V , Schutt M , Bottger M , Graffi A , 1970 Preferential alkylation of mitochondrial deoxyribonucleic acid by N-methyl-N-nitrosourea. *Biochem. J* 118 (1), 99–109.5472159
- Wunderlich V , Tetzlaff I , Graffi A , 1972 Studies on nitrosodimethylamine: preferential methylation of mitochondrial DNA in rats and hamsters. *Chem. Biol. Interact* 4 (2), 81–89.5058327
- Wyatt LH , Luz AL , Cao X , Maurer LL , Blawas AM , Aballay A , Pan WK , Meyer JN , 2017 Effects of methyl and inorganic mercury exposure on genome homeostasis and mitochondrial function in *Caenorhabditis elegans*. *DNA Repair (Amst)*
- Yamada S , Kubo Y , Yamazaki D , Sekino Y , Kanda Y , 2017 Chlorpyrifos inhibits neural induction via Mfn1-mediated mitochondrial dysfunction in human induced pluripotent stem cells. *Sci. Rep* 7, 40925.28112198
- Yang Y , Zong M , Xu W , Zhang Y , Wang B , Yang M , Tao L , 2017 Natural pyrethrins induces apoptosis in human hepatocyte cells via Bax- and Bcl-2-mediated mitochondrial pathway. *Chem. Biol. Interact* 262, 38–45.27939866
- Yedjou CG , Tchounwou PB , 2006 Oxidative stress in human leukemia (HL-60), human liver carcinoma (HepG2), and human (JURKAT-T) cells exposed to arsenic trioxide. *Met. Ions Biol. Med* 9, 298–303.26435679
- Yedjou CG , Tchounwou PB , 2007 In-vitro cytotoxic and genotoxic effects of arsenic trioxide on human leukemia (HL-60) cells using the MTT and alkaline single cell gel electrophoresis (Comet) assays. *Mol. Cell. Biochem* 301 (1–2), 123–130.17216127
- Yedjou CG , Waters D , Tchounwou PB , 2008 N-Acetyl-cysteine protection against lead-induced oxidative stress and genotoxicity in human liver carcinoma (HepG2) cells. *Met. Ions Biol. Med* 10, 419–424.26549975
- Yee S , Choi BH , 1994 Methylmercury poisoning induces oxidative stress in the mouse brain. *Exp. Mol. Pathol* 60 (3), 188–196.7957778
- Yu-Wai-Man P , Griffiths PG , Chinnery PF , 2011 Mitochondrial optic neuropathies – disease mechanisms and therapeutic strategies. *Prog. Retin. Eye Res* 30 (2), 81–114.21112411
- Zeng JP , Wang LX , Xia W , Hu XY , Kong F , Wu WF , Cui X , 2006 Mechanism of reactive oxygen species in manganese chloride-induced apoptosis in PC12 cells. *Zhonghua Lao Dong Wei Sheng Zhi Ye Bing Za Zhi* 24 (3), 157–160.16600136
- Zhang Z , Tsukikawa M , Peng M , Polyak E , Nakamaru-Ogiso E , Ostrovsky J , McCormack S , Place E , Clarke C , Reiner G , McCormick E , Rappaport E , Haas R , Baur JA , Falk MJ , 2013 Primary respiratory chain disease causes tissue-specific dysregulation of the global transcriptome and nutrient-sensing signaling network. *PLoS One* 8 (7), e69282.23894440
- Zhou S , Wang Z , Klaunig JE , 2013 *Caenorhabditis elegans* neuron degeneration and mitochondrial suppression caused by selected environmental chemicals. *Int. J. Biochem. Mol. Biol* 4 (4), 191–200.24380023
- Ziemińska E , Lenart J , Lazarewicz JW , 2016 Select putative neurodevelopmental toxins modify SNAP-25 expression in primary cultures of rat cerebellar granule cells. *Toxicology* 370, 86–93.27693314
- del Pino J , Moyano P , Anadon MJ , Garcia JM , Diaz MJ , Garcia J , Frejo MT , 2015 Acute and long-term exposure to chlorpyrifos induces cell death of basal forebrain cholinergic neurons through AChE variants alteration. *Toxicology* 336, 1–9.26210949

Table 1

Detailed mechanism of select toxin effects on mitochondria.

Compound	Animal or cellular study	Concentration and route of administration	Documented mechanism of action in mitochondria
Pesticides			
Chlorpyrifos (CPF)	PC12 cell line	30–50 μ M	<ul style="list-style-type: none"> Increased malondialdehyde concentrations [93].
	Human induced pluripotent stem cells (iPSCs)	30 μ M	<ul style="list-style-type: none"> Induces mitofusin 1-mediated mitochondrial fragmentation [94].
Dichlorodiphenyldichloroethylene (DDE)	Sertoli cells	30 μ M	<ul style="list-style-type: none"> Activates mitochondrial apoptosis pathway [95].
Paraquat (PQ)	C57BL/6 mice	10 mg/kg/week intraperitoneal (i.p.) for 4 weeks	<ul style="list-style-type: none"> Targets mitochondrial ETC complex I, formation of superoxide radicals [143].
	C57BL/6 mice	10 mg/kg/week intraperitoneal (i.p.) for 3 weeks	<ul style="list-style-type: none"> Increased brain lipid peroxidation levels [98].
	Sprague Dawley rat brain cultures	250 μ M for 5 min	<ul style="list-style-type: none"> Impairs mitochondrial function at the level of complex III to generate ROS [99].
Maneb (MB)	C57BL/6 mice	30 mg/kg i.p. twice a week/6 weeks	<ul style="list-style-type: none"> Inhibits mitochondrial ETC complex III [179].
Rotenone	Wistar rat brain isolated mitochondria	0.1–0.5 nmol/mg protein	<ul style="list-style-type: none"> Increases ROS production, cytochrome <i>C</i> release and apoptotic cell death [180].
	SK-N-MC Neuroblastoma cells	10–100 nmol	<ul style="list-style-type: none"> Decreased mitochondrial respiration and increased protein carbonyl levels [60].
Metal			
Lead (Pb)	Wistar rats	1%,2%,4% in oral chow	<ul style="list-style-type: none"> Alters mitochondrial respiration and ADP-phosphorylation [108].
Manganese [181]	Sprague Dawley rat astrocytes and microglia cell culture	0.1–10 μ M	<ul style="list-style-type: none"> Interacts with GSH to increase the GSSG:GSH ratio and reduce antioxidant capacity [182]
	Swiss Albino mice	15 mg/l in drinking water	<ul style="list-style-type: none"> Increased Hydrogen peroxide (H_2O_2) levels [120].
Aluminium (Al)	Wistar rats	10 mg/kg/day intragastric for 12 weeks	<ul style="list-style-type: none"> Impaired ETC complex III activity, decreased cytochrome levels, decreased ATP production and increased ROS production [183].
	Wistar rats	100 mg/kg in drinking water daily for six weeks	<ul style="list-style-type: none"> Increased lipid peroxidation and nitrite concentration and depleted reduced glutathione, superoxide dismutase, catalase levels [116].
Methylmercury (MeHg)	CBL57/6 mice	2.5 mg/kg i.p. up to 14 days	<ul style="list-style-type: none"> Increased superoxide anion and hydrogen peroxide levels in mouse

Compound	Animal or cellular study	Concentration and route of administration	Documented mechanism of action in mitochondria
	Swiss albino mice	15 mg/l in drinking water	brain, and decreased activity of activity of superoxide dismutase [76] [121]. • Increased brain hydrogen peroxide levels [120].