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Sources, mechanisms, and consequences of chemical-induced mitochondrial toxicity:

Submitted for consideration for the Special Issue of Toxicology on "Chemical Mitochondrial Toxicity"

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Abstract

Mitochondrial function is critical for health, as demonstrated by the effects of mitochondrial toxicity, mutations in genes encoding mitochondrial proteins, and the role of mitochondrial dysfunction in many chronic diseases. However, much basic mitochondrial biology is still being discovered. Furthermore, the details of how different environmental exposures affect mitochondria, how mitochondria respond to stressors, and how genetic variation affecting mitochondrial function alters response to exposures are areas of rapid research growth. This Special Issue was created to highlight and review cutting-edge areas of research into chemical effects on mitochondrial function. We anticipate that it will stimulate additional research into the mechanisms by which chemical exposures impact mitochondria, the biological processes that protect mitochondria from such impacts, and the health consequences that result when defense and homeostatic mechanisms are overcome.

Keywords

Mitochondrial toxicity; mitochondrial disease; mitochondrial DNA; human health; mitochondrial homeostasis

Mitochondrial function is critical for health. This is demonstrated both by the large number of diseases caused by mutations in nuclear and mitochondrial genes that code for mitochondrial proteins (Chinnery et al. 2004; DiMauro and Davidzon 2005; Howell et al. 2005; Wallace 2005), and by the critical role that mitochondrial dysfunction plays in a large number of chronic diseases (Coskun et al. 2012; D'Aquila et al. 2015; de Moura et al. 2010; Szklarczyk et al. 2014; Tulah and Birch-Machin 2013; Van Houten et al. 2016; Wallace

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Conflict of interest

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2005). Genetic contributions to most chronic disease are modest, and environmental contributors are poorly understood (Bookman et al. 2011; Rappaport 2012; Rappaport et al. 2014). Therefore, as chronic disease becomes more and more important in the US and globally, the potential health significance of environmental exposures that perturb mitochondrial function will grow.

Research into mitochondrial pathways of chemical toxicity is accelerating. While sporadic reports of mitochondrial toxicity of various chemicals appear throughout decades of literature, including classic mitochondrial poisons such as rotenone and carbon monoxide, an understanding of how common this may be emerged when Drs. Dyken and Will showed that 35% of pharmaceutically relevant molecules tested were mitotoxic (Dykens et al. 2008; Dykens et al. 2007; Dykens and Will 2007). This is further supported by recent high-throughput ***in vitro*** toxicity screening efforts, including those of the National Toxicology Program (Attene-Ramos et al. 2015; Attene-Ramos et al. 2013; Houck et al. 2009; Shah et al. 2015; Wills et al. 2015). Several recent publications (Bestman et al. 2015; Kovacic et al. 2005; Meyer et al. 2013; Moreira et al. 2011; Sabri 1998; Shaughnessy et al. 2010) discuss the growing evidence that many pollutants affect mitochondria, although in many cases mitochondria are not the only subcellular target. Importantly, in some cases, effects may persist long after exposure ceases, as has been documented for adriamycin's effect on cardiomyocytes (Berthiaume and Wallace 2007b), or the long-term effects of nucleoside reverse transcriptase inhibitors on mitochondrial function in after ***in utero*** exposure (Chan et al. 2007; Liu et al. 2016). Examples of such persistent effects are also presented by Dr. Ballinger and colleagues and Dr. Meyer and colleagues in this issue (references).

Some individuals are at particular risk of mitotoxic exposures. Developmental exposure to mitochondrial toxicants can be particularly deleterious, causing both short- and long-term toxicity, as documented for many mitotoxicants including nucleoside reverse transcriptase inhibitors, arsenic, and dichloroacetate (Berthiaume and Wallace 2007a, b; Ditzel et al. 2015; Divi et al. 2010; Wood et al. 2015). It is also quite likely that mitochondrial toxicity is significantly exacerbated in the approximately 1 in 4,000 persons who suffer from a mitochondrial disease (Chinnery et al. 2004; DiMauro and Davidzon 2005; Howell et al. 2005; Wallace 2005). These diseases, while individually rare, are caused by deficiencies in a wide range of mitochondrial processes (Chinnery et al. 2004; DiMauro and Davidzon 2005; Howell et al. 2005; Wallace 2005). It is therefore critical that we expand our in-depth understanding of specific mechanisms of mitochondrial toxicity, our knowledge of the role of mitochondrial biology in homeostatic and defense processes, and our ability to conduct relatively high-throughput testing of gene-environment interactions. This special issue is designed to bring the reader up to speed on a variety of cutting-edge areas of research into mitochondrial (dys)function, and how chemicals can impact mitochondrial biology.

Unfortunately, compared to the relatively extensive toxicity testing carried out for pharmaceuticals, the tens of thousands of pollutant and industrial chemicals to which individuals may be exposed are much less well-tested for toxicity of any sort, including mitochondrial effects. New methods for screening and studying mitochondrial toxicity are addressed by many papers in this issue, and in particular by Dr. Wills (this issue reference), who outlines mechanisms, systems, and acute versus chronic effects.

The best known mitochondrial function is oxidative phosphorylation; however, mitochondria also generate reactive oxygen species (ROS); participate in apoptosis; carry out a variety of anabolic biochemical processes including synthesis of heme, iron-sulfur clusters, and steroids; contribute to energy production by other pathways including fatty acid oxidation and the Krebs cycle; generate molecules important in epigenetic and other processes, such as acetyl-coenzyme A; participate in regulation of intracellular calcium; and play key roles in innate immune function. Important homeostatic processes include replication of the mitochondrial genome, mitochondrial biogenesis, mitochondrial degradation pathways including mitophagy, as well as mitochondrial fusion and fission processes. Articles in this Special Issue describe many of these functions and their relation to chemical exposure in greater detail.

ROS may be as important a product of oxidative phosphorylation as ATP, due to the role ROS plays in signaling for cellular and mitochondrial homeostasis; ROS signaling is covered in detail by Dr. Bonini (this issue reference). The mitochondrial genome can be highly susceptible to DNA damaging agents compared to the nuclear genome, due in part to differences in DNA repair mechanisms (Copeland and Longley 2014; Scheibye-Knudsen et al. 2015), as described by Drs. de Souza Pinto and Roubicek (this issue reference). Dr. Chan discusses the susceptibility of organisms with inherited mitochondrial genomic instability to mitochondrial toxicants (this issue reference). Dr. Meyer and colleagues review the literature on the role of mitochondrial fusion and fission in response to toxicants (this issue reference), and Dr. West discusses the role of mitochondria in inflammation and the immune response (this issue reference). Dr. Weinhouse summarizes the current knowledge of how mitochondrial function influences epigenetic patterning, and vice versa (this issue reference).

Moving to higher-level biological effects of perturbed mitochondrial function, Dr. Franco focuses on the relationship between mitochondrial toxicity and neurodegeneration (this issue reference). Dr. Ballinger and colleagues review the consequences of air pollutant exposures on mitochondria (this issue reference), and Drs. Cunningham and Falk present a clinical perspective on some of the consequences of mitochondrial toxicity in the context of mitochondrial disease (this issue reference). Finally, the effects of mitotoxicants are not limited to humans. Indeed, animals have been informative of toxicity not just in the context of laboratory test organisms and sentinel species such as canaries used to detect carbon monoxide in coalmines, but also in wildlife epidemiology studies that have associated chemical exposures with cancer (McAloose and Newton 2009). Dr. Jayasundara describes what can be learned from the impacts of mitotoxicants on wildlife (this issue reference).

We note that there are additional emerging or controversial areas of research that we were unable to cover in this special issue. For example, Naviaux and colleagues have described a key mitochondrial role in mediating signals released as part of the cell danger response (Naviaux 2014), which may lead to an adaptive or hormetic response if the stressor is removed, or to chronic pathology if the exposure and response are long-term. The potential for “mitohormesis” (hormesis via mitochondrial pathways) resulting from a large number of mitochondrial “stressors” including diet, exercise, genetic deficiencies, as well as chemical exposure has gained significant attention outside of the field of toxicology (Yun and Finkel

2014), and should be considered by toxicologists, who have also begun to investigate hormetic responses (Calabrese et al. 2016). Another area of intense interest is the source of mitochondrial DNA (mtDNA) mutagenesis. MtDNA mutations are responsible for causing mitochondrial disease in approximately 1 in 5,000 people (Gorman et al. 2015). Although mtDNA is more prone to mutation than nuclear DNA over evolutionary time (Brown et al. 1979; Rebolledo-Jaramillo et al. 2014; Wallace 2010), the source of mtDNA mutations is unclear (Kennedy et al. 2013). Two hypotheses for the cause of mtDNA mutations have been the focus of most research: oxidative damage to mtDNA (Cooke et al. 2003; Loeb et al. 2005), and random errors of DNA replication by the mtDNA polymerase γ (Kennedy et al. 2013; Szczepanowska and Trifunovic 2015). The ROS hypothesis was attractive because the electron transport chain (ETC) is the major source of ROS production in most cells, mtDNA is anchored to the inner mitochondrial membrane adjacent to the ETC, and mitochondrial perturbations such as ETC inhibition can significantly increase mitochondrial ROS production (Fridovich 2004; Van Houten et al. 2006). Furthermore, empirical evidence demonstrates that mtDNA is very sensitive to ROS (Ballinger et al. 2000; Santos et al. 2006; Yakes and Van Houten 1997). Thus, if ROS were a major driver of mtDNA mutagenesis, protection from exposures that cause direct mitochondrial oxidative stress or mitochondrial dysfunction that leads to oxidative stress, could prevent mtDNA mutagenesis and mitochondrial disease. However, growing and compelling evidence indicates that oxidative stress is not a major driver of mtDNA mutagenesis (Ameur et al. 2011; Itsara et al. 2014; Szczepanowska and Trifunovic 2015), likely due to the fact that the mitochondrial genome has very robust base excision DNA repair machinery that corrects most oxidative DNA damage (Alexeyev et al. 2013; Scheibye-Knudsen et al. 2015). Despite the fact that mtDNA is highly sensitive to genotoxins that cause nonoxidative damage (Meyer et al. 2013), few studies have directly tested the hypothesis that environmental genotoxins causing nonoxidative damage drive mtDNA mutagenesis. However, a recent publication reported lack of evidence to support this hypothesis (Valente et al. 2016). Thus, this remains an area of intense interest.

We hope that this Special Issue will stimulate additional research into the effects of chemical exposures on mitochondria, the biological processes that protect mitochondria from such impacts, and the health consequences that result when defense and homeostatic mechanisms are overcome.

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