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Integrating mitochondriomics in children's environmental health

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Abstract

The amount of scientific research linking environmental exposures and childhood health outcomes continues to grow; yet few studies have teased out the mechanisms involved in environmentally-induced diseases. Cells can respond to environmental stressors in many ways: inducing oxidative stress/inflammation, changes in energy production and epigenetic alterations. Mitochondria, tiny organelles that each retains their own DNA, are exquisitely sensitive to environmental insults and are thought to be central players in these pathways. While it is intuitive that mitochondria play an important role in disease processes, given that every cell of our body is dependent on energy metabolism, it is less clear how environmental exposures impact mitochondrial mechanisms that may lead to enhanced risk of disease. Many of the effects of the environment are initiated *in utero* and integrating mitochondriomics into children's environmental health studies is a critical priority. This review will highlight (i) the importance of exploring environmental mitochondriomics in children's environmental health, (ii) why environmental mitochondriomics is well suited to biomarker development in this context, and (iii) how molecular and epigenetic changes in mitochondria and mitochondrial DNA (mtDNA) may reflect exposures linked to childhood health outcomes.

Keywords

environmental health; children; mitochondria; copy number; neurodevelopment; asthma; biomarkers; environmental exposure

Environmental Mitochondriomics and Child Health

In this review, we examine the current literature and expert opinions on environmental mitochondriomics (EM), a new area of research dedicated to discovering in mitochondria novel sensors and mediators of environmental effects. While it is intuitive that mitochondria

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play an important role in disease processes, given that every cell of our body is dependent on energy metabolism, it is less clear how environmental exposures impact mitochondrial mechanisms that may lead to enhanced risk of disease. This review will highlight why environmental mitochondriomics is well suited to biomarker development and how molecular and epigenetic changes in mitochondrial (mtDNA) may reflect exposures linked to childhood health outcomes. While there are many child health outcomes that could be explored with respect to environmental mitochondriomics given their mitochondrial underpinnings (Fleischman *et al.*, 2009; Simoes *et al.*, 2012; Flaquer *et al.*, 2014; Knoll *et al.*, 2013; Legido *et al.*, 2013) (Fig. 1), we will focus on two of the most common health concerns in childhood which are supported by a solid foundation of research suggesting mitochondriomics is likely a promising biomarker platform to explore – asthma and neurodevelopment.

Asthma and Neurodevelopment: Model Outcomes for Mitochondriomics

Childhood Asthma and the Mitochondria

Asthma is the most common chronic inflammatory/respiratory disease among children worldwide, and its prevalence continues to rise (Anandan *et al.*, 2010). While the origins of asthma are likely multi-factorial, the underlying mechanisms leading to reduced lung function and exaggerated airway responsiveness involve chronic airway inflammation associated with a cycle of injury, repair and remodeling (Holgate, 1997; Holt *et al.*, 2005). Notably, airway inflammation and remodeling begin and progress even in the presymptomatic state in early childhood (Morgan *et al.*, 2005; Pohunek *et al.*, 2005). Furthermore, the fundamental cause of airway inflammation is aberrant and/or excessive immune responses to various environmental factors (Holt *et al.*, 2005) and the most common cause of chronic airway inflammation in early childhood is arguably asthma.

Mitochondria are important to the inflammatory process for many reasons. Inflammation is triggered by exposure of the airway epithelial cells to oxidative stress, a process mediated by reactive oxygen species (ROS) (Riedl and Nel, 2008). Endogenous ROS are primarily a product of the mitochondria. If mitochondria are not functioning properly, this can lead to excess ROS ultimately boosting inflammation. It is possible an excessive amount of ROS can damage the mitochondria until apoptosis of airway epithelial cells occurs (Trian *et al.*, 2007; Simoes *et al.*, 2012). Further, mitochondria are key players in human eosinophil apoptosis and survival (Ilmarinen *et al.*, 2014); eosinophils are cells of the innate immune system primarily involved in the allergic inflammatory response in chronic asthma (Felton *et al.*, 2014).

The preferential importance of maternal history of atopy or asthma as a risk factor for childhood asthma is one of the most consistent and reproducible observations in asthma epidemiology (Martinez *et al.*, 1995; Litonjua *et al.*, 1998; Celedon *et al.*, 2003; Tan *et al.*, 2007; Barrett, 2008; Lim *et al.*, 2010). The consistency of these relationships and their fairly early onset suggest a genetic influence that perhaps involves the mitochondrial genome, predominantly inherited from the mother (Giles *et al.*, 1980). While the evidence demonstrating the presence of mitochondrial dysfunction in asthma is not abundant, there does appear to be enough literature supporting an association between mitochondrial

dysfunction and atopy (Raby *et al.*, 2007; Chodaczek *et al.*, 2009), respiratory morbidity (Schmuczerova *et al.*, 2009; Meert *et al.*, 2012; Ostroukhova *et al.*, 2012) and asthma risk (Heinzmann *et al.*, 2003; Zifa *et al.*, 2012; Flaquer *et al.*, 2014).

Child Neurodevelopment and the Mitochondria

The developing fetus and infant are most vulnerable owing to the rapid differentiation of the central nervous system *in utero* and early life (Landrigan *et al.*, 1999; Rice and Barone, 2000). Neurocognitive and behavioral deficits in childhood, including problems with learning, attention, conduct, depression and anxiety affect up to 20% of U.S. children, placing a burden on education and healthcare systems (Froehlich *et al.*, 2007; Boulet *et al.*, 2009; Montes *et al.*, 2012). However, the potential loss of functioning early in life as a result of environmental factors may result in diminished academic and economic productivity that persists over the life span (Trasande *et al.*, 2005). Weiss (2000) estimated that a U.S. population average decrease of 1% in IQ, caused by an environmental toxicant, would result in an annual cost of \$50 billion in lost economic productivity and increased special educational needs amounting to a lifespan cost estimate in the trillions. Fewer than 25% of childhood neurodevelopmental disabilities have an identified cause, signifying the need to examine candidate neurotoxicants and programming mechanisms that may be amenable to intervention strategies.

The mitochondria play an important role in neurodevelopment. They regulate innate immune responses that can have broad consequences for brain development and susceptibility to damage (Hagberg *et al.*, 2014). During fetal and postnatal brain development, new mitochondria are being formed and present mitochondria are growing rapidly (e.g. mitochondrial biogenesis) as the brain has a high demand for energy and thus neurons contain a large number of mitochondria. Mitochondrial biogenesis is highly regulated; proteins encoded by nuclear and mitochondrial DNA are needed (Scarpulla, 2011). Many mitochondrial functions and pathophysiological responses in the immature and adult brain vary. As reviewed by Hagberg *et al.* (2014), mitochondrial respiratory activity, and protein and respiratory enzyme content are lower in the immature brain compared to the adult brain. A role of mitochondria in neurogenesis and synaptic plasticity has been established (Vayssiere *et al.*, 1992; Mattson *et al.*, 2008; Streck *et al.*, 2014) signifying their importance in normal neurodevelopment.

Mitochondrial dysfunction (MD) has been extensively researched with regard to autism spectrum disorders (ASDs) with several reviews highlighting the potential role of MD in ASDs (Palmieri and Persico, 2010; Rossignol and Frye, 2012; Legido *et al.*, 2013). Several lines of evidence suggest that suboptimal mitochondrial energy metabolism (e.g. high lactate, increased lactate to pyruvate ratio, increased alanine and low carnitine) and electron transport chain (ETC) abnormalities are linked to ASDs (Oliveira *et al.*, 2005; Correia *et al.*, 2006; Weissman *et al.*, 2008; Rossignol and Frye, 2012). Evidence of the first mtDNA mutations associated with ASDs was published in 1999 and 2000 (Sue *et al.*, 1999; Graf *et al.*, 2000), mtDNA mutations A3243G [often associated with mitochondrial encephalopathy with lactic acidosis (MELAS) and seizures] (Sue *et al.*, 1999; Pons *et al.*, 2004) and G8363A in mtDNA tRNA^{lys} (Graf *et al.*, 2000). Other mtDNA mutations and abnormalities

(e.g. mtDNA copy number) have been identified in patients with ASD (Weissman *et al.*, 2008; Giulivi *et al.*, 2010; Legido *et al.*, 2013; Napoli *et al.*, 2013). Subsequently, progressive increases in mtDNA A3243G heteroplasmy (defined below in *Molecular archive of past environments and cumulative risk*), can lead to abrupt transcriptional reprogramming (Picard *et al.*, 2014). Few studies have investigated the influence of mitochondrial dysfunction on other neurodevelopmental disorders; however, findings suggest mitochondrial respiratory chain defects are present in attention deficit hyperactivity disorder (Papa *et al.*, 2000; Fagundes *et al.*, 2007; Bradstreet *et al.* 2010) as well as other psychiatric disorders (Rezin *et al.*, 2009; Scaglia, 2010). While research supports a role of mitochondrial dysfunction in child neurodevelopment, it is unclear whether MD is primary etiology or secondary to other causes such as environmental exposures.

Novel Biomarkers for Environmental Health Risk

Mitochondria: The Power House

Mitochondrial cell biology—Mitochondria play a central role in many cellular processes, notably cellular energy delivery through ATP. They consume oxygen (O₂) and produce ATP by electron transport and oxidative phosphorylation taking place across the respiratory chain complexes located in the inner mitochondrial membrane (O'Connor and Adams, 2010). The mitochondrial genome also differs in many ways from the nuclear genome. First, mitochondria are the only organelles in human cells to possess their own genomes and are predominantly maternal transmission (Giles *et al.*, 1980). Each human cell contains several hundred to >1000 mitochondria, each carrying 2–10 copies of mtDNA. The mitochondrial genome is double-stranded and circular containing approximately 16500 nucleotides; it encodes 13 peptides for oxidative phosphorylation, and 22 transfer ribonucleic acids (tRNAs) and 2 ribosomal RNAs (rRNAs) essential for protein synthesis within the mitochondria (Li *et al.*, 2012). The mitochondrial genome contains fewer, yet evenly dispersed, CpG dinucleotides compared with nDNA and lacks retrotransposons (Byun and Baccarelli, 2014).

The importance of mitochondria in fetoplacental development—The placenta is a key regulator of fetal development as it facilitates nutrient supply to and waste removal from the fetus; alterations in placental function can mediate fetal programming (Wu *et al.*, 2012). Placental metabolic activity throughout gestation is sustained by increasing mitochondrial activity (i.e. mitochondrial oxidative phosphorylation) and biogenesis (Bax and Bloxam, 1997; Leduc *et al.*, 2010). Animal and human studies have shown that altered mitochondrial function affects subsequent fetal and placental development (Wakefield *et al.*, 2011; Mandò *et al.*, 2014). Conversely, maternal factors such as obesity (Mele *et al.*, 2014) and malnutrition (Mayeur *et al.*, 2013) have been shown to induce impaired placental mitochondrial function leading to fetoplacental growth deficits.

Susceptibility to environmental toxicants—Mitochondria are vulnerable to damage by ROS and during normal energy production they are the main source of endogenous ROS in most mammalian cells (Shaughnessy *et al.*, 2014). When the production of ROS is greater than the inherent antioxidant defenses, a condition known as oxidative stress occurs (Burton

and Jauniaux, 2011). Mitochondrial proteins and mtDNA are also vulnerable to exogenous insults leading to the alteration of mtDNA integrity, electron transport chain activity, modifying membrane potential, ion transport and apoptotic signaling (Meyer *et al.*, 2013). Damaged mitochondria can produce 10 times more hydrogen peroxide than undamaged mitochondria (Grivennikova *et al.*, 2010). All of these factors are involved in mitochondrial dysfunction.

Mitochondria also vary from tissue to tissue with different cell types being differentially sensitized to environmental toxicants. The placenta, for example, has a high reliance on mitochondrial function; this may mean that dysfunction could more easily result in cell death as a result of increased ROS production (Meyer *et al.*, 2013). In addition, research suggests that mtDNA repair capacity and antioxidant defense mechanisms also vary by cell type, with brain tissue expressly having a low repair capacity (Szczesny *et al.*, 2010) and neurons having low antioxidant defenses and/or high inherent oxidative stress (Crouch *et al.*, 2007).

A large number of environmental toxicants may exert their effect through the production of ROS, oxidative stress and inflammation. Mitochondrial function can be altered by oxidative stress and inflammation (Lee and Wei, 2000). In turn, dysfunctional mitochondria produce additional oxidation that may sustain systemic oxidative stress (Lee and Wei, 2000) which may alter developmental programming of key regulatory systems affecting respiratory and neurodevelopment in children.

Molecular Archive of Past Environments and Cumulative Risk

Studies have identified a set of mtDNA-based molecular markers associated with mitochondrial dysfunction and oxidative stress; these include mtDNA oxidation (Lin *et al.*, 2008), heteroplasmy (Sondheimer *et al.*, 2011) and copy number (mtDNAcn) (Hou *et al.*, 2010). In blood, mtDNA accumulates oxidative damage over time – as reflected in 8-hydroxy-2'-deoxyguanosine (8-OHdG) levels in mtDNA (Mecocci *et al.*, 1998). To compensate for oxidation and damage, more copies of mtDNA are replicated, thus leading to increased mtDNAcn (Liu *et al.*, 2006). Perhaps owing to its continuing exposure to mitochondrial ROS, mitochondrial DNA has a fairly high mutation rate. When a new mutation arises in the mtDNA of a cell, a mixed population of mtDNAs is generated; this is known as mitochondrial heteroplasmy (MH). MH is a common phenomenon. Baseline levels of MH are commonly detectable owing to the limited mtDNA protection from oxidative stress (Chinnery *et al.*, 2012; Li *et al.*, 2012). Baseline MH is hypothetically tolerated by the cell that carries multiple mitochondria each with multiple mtDNA copies. MH becomes symptomatic when it reaches a threshold affecting the cellular functioning presumably due to oxidative insults and replication errors (Golden and Melov, 2001; Graziewicz *et al.*, 2002; Szibor and Holtz, 2003; Sondheimer *et al.*, 2011). Therefore, the degree of mtDNAcn and/or heteroplasmy may be considered as a 'biological clock' that measures past exposure to oxidative stress.

Compared with mitochondrial DNA oxidative damage, copy number and mutations, which have been more widely studied in relation to environmental exposures and disease risk,

mitochondrial epigenetics is still in its infancy but is fast growing. Mitochondrial epigenetics has been a point of contention in the literature. One of the first reports on mtDNA methylation was published in 1971 (Vanyushin *et al.*, 1971). Many studies supported this finding in the years following (Kudriashova *et al.*, 1976; Shock *et al.*, 2011; Bellizzi *et al.*, 2013) while others found no evidence of CpG methylation in human mtDNA (Hong *et al.*, 2013). Given that oxidative stress in the nucleus has been shown to alter nuclear DNA methylation, numerous environmental toxicants may be potential candidates with important links to mitochondrial epigenetics. To date, no studies have investigated the association between mitochondrial epigenetics and asthma and/or neurodevelopment despite the plethora of research implicating mitochondrial mechanisms in the development of a large number of childhood conditions, such as asthma, obesity, insulin resistance, autism and attention problems (Fleischman *et al.*, 2009; Bradstreet *et al.*, 2010; Giulivi *et al.*, 2010; Stephens *et al.*, 2011; Meert *et al.*, 2012; Anitha *et al.*, 2013; Hernandez-Aguilera *et al.*, 2013; Killeen *et al.*, 2013; Oguzkan-Balci *et al.*, 2013). Further, chronic diseases with mitochondrial underpinnings, such as asthma and various neurodevelopmental conditions, do not follow Mendelian inheritance. Therefore, despite the debate, there is increasing interest in studying the role of mitochondrial epigenetics in environmentally-induced diseases.

Mitochondrial markers such as RNA modification (i.e. RNA methylation) and miRNAs should also be explored (Barrey *et al.*, 2011; Motorin and Helm, 2011; Byun and Baccarelli, 2014). Mitochondrial RNA accounts for 5% of total cellular RNA in most tissues, but can be as high as 30% in tissues with a high metabolic demand such as the heart (Mercer *et al.*, 2011); however, additional work is needed in describing mitochondrial RNA/miRNAs and their role in regulating mitochondrial gene expression. Further, cellular reprogramming may begin with mitochondrial response (e.g. changes in mitochondrial copy number) and followed by changes in nDNA genes coding for mitochondrial proteins making the cross-talk between the mitochondrial and nuclear genome an important area of research (Shaughnessy *et al.*, 2014). Regardless of the mitochondrial marker (s) one chooses to utilize, careful consideration should be given when designing epidemiological studies (Byun and Baccarelli, 2014). It has been suggested that integrating multiple mitochondrial endpoints would be the most efficient way to probe the extent of systemic oxidative stress for many clinical outcomes (Chan *et al.*, 2013).

Mitochondrial Markers of Environmental Exposures

According to the World Health Organization's Global Plan of Action for Children's Health and the Environment, each year over 3 million children under the age of five die as a result of environmentally-related illnesses (WHO, 2009). Environmental mitochondriomics is in its infancy with respect to environmental health research with nearly all studies occurring after 2010; even more scarce are studies examining prenatal and early-life exposures (Table 1). The research detailed below ranges from *in vitro/in vivo* animal studies to large epidemiological cohort analyses; however, it is critical to recognize that many of the effects of the environment are initiated *in utero* and thus the need to integrate mitochondriomics into children's environmental health.

Ambient air pollution—Overlapping research suggests a role for mitochondria in the toxicity of ambient air pollution, in part due to the central role that oxidative stress plays in air pollution toxicity (Peretz *et al.*, 2007; Wright and Baccarelli, 2007; Allen *et al.*, 2009; Lodovici and Bigagli, 2011; Wright and Brunst, 2013). Over a decade ago, Li *et al.* (2003) demonstrated in two murine cell lines that ultrafine particles localize in the mitochondria and induce major structural damage; however, it was not until recently that epidemiological studies started examining the relationship between ambient air pollution and mitochondrial dysfunction. Research now suggests that exposure to air pollution, including particulate matter, benzene, diesel exhaust particles and polycyclic aromatic hydrocarbons (PAHs), is associated with changes in mtDNA copy number in the placenta (Janssen *et al.*, 2012) and blood (Hou *et al.*, 2010, 2013; Carugno *et al.*, 2012; Byun *et al.*, 2013; Pavanello *et al.*, 2013; Pieters *et al.*, 2013). Diesel exhaust particles and black carbon are also capable of inducing mitochondrial dysfunction in alveolar macrophages (Zhao *et al.*, 2009). More recent work has demonstrated an effect of air pollutants on mtDNA methylation (Byun *et al.*, 2013). Further, air pollutant exposure-related inflammation (Wittkopp *et al.*, 2013) and cognition (Colicino *et al.*, 2014) has been shown to be modified by an individual's mitochondrial genetic background. These findings suggest mtDNA markers of oxidative damage, copy number, methylation and genetics may serve as novel biomarkers and/or causal mediators in air pollution research.

Tobacco smoke—It has been demonstrated that tobacco smoke is involved in mitochondrial fragmentation, defined as mitochondria shorter than 1 μm without fusion to other mitochondria, in human bronchial epithelial and airway smooth muscle cells and cell senescence (Hara *et al.*, 2013; Aravamudan *et al.*, 2014). Accelerated cellular senescence resulting from tobacco smoke exposure has been implicated in the pathogenesis of asthma (Albrecht *et al.*, 2014). Earlier studies have shown that tobacco smoke can affect mitochondrial structure and function in alveolar macrophages of the lung (Ballinger *et al.*, 1996) and mtDNA changes such as copy number and heteroplasmy in buccal cells (Tan *et al.*, 2008). The effects of early-life tobacco smoke exposure on mitochondrial dysfunction have also been characterized by decreases in mitochondrial antioxidant capacity, mtDNA copy number and mitochondrial potential/mass (Westbrook *et al.*, 2010; Micale *et al.*, 2013). Given these findings, mitochondriomic changes may serve not only a mechanistic function in the pathway from tobacco smoke exposure to disease (e.g. respiratory outcomes), but also as a 'biomarker of exposure'.

Metals—In 2009, Wang *et al.* (2009) investigated the toxicity of lead exposure on the placenta and found that the placenta of rats that consumed 0.025% lead acetate during gestation were characterized by mitochondria that were swollen, showed distended endoplasmic reticula and a decreased ribosomal number on membranes. Cadmium, another toxic metal, has also been shown to cause mitochondrial dysfunction through reducing ATP production (Kurochkin *et al.*, 2011) and altering mitochondria morphology (Vergilio Cdos and de Melo, 2013). The toxicity of exogenous zinc exposure has been shown to induce mitochondrial dysfunction, elevate the production of ROS and increase expression of adaptive and inflammatory genes (Wu *et al.*, 2013; Zhao *et al.*, 2013). Mercury, methylmercury and manganese have also been shown to induce mitochondrial dysfunction

(Mori *et al.*, 2007; Hernandez *et al.*, 2011; Carocci *et al.*, 2014). It is clear that metal exposures have previously been linked to mitochondrial markers of mitochondrial dysfunction; what is less clear is whether metal exposures specifically impact mitochondrial DNA markers such as copy number, heteroplasmy or epigenetics (Hou *et al.*, 2010; Byun *et al.*, 2013). While the amount of literature supporting the use of mtDNA markers for metal exposure is limited, studies have shown exposure to metal-rich particulate to be associated with mtDNA methylation (Byun *et al.*, 2013) and aluminum exposure resulting in decreases in mtDNA copy number and oxidation (Sharma *et al.*, 2013).

Endocrine disruptors (BPA, phthalates)—While environmental endocrine disruption in child health is a rapidly growing area of research, compared with the previously discussed environmental exposures, the literature on endocrine disruptors is less comprehensive with respect to mitochondrial dysfunction. Bisphenol A (BPA) and phthalates are commonly used products in plastics, both with endocrine-disrupting characteristics. BPA has been implicated in mitochondrial dysfunction, particularly by depleting ATP, decreasing mitochondrial mass and dysregulation of membrane potential (Lin *et al.*, 2013) as well as increases in mtDNA copy number in lymphoblasts from children with autism and their unaffected siblings (Kaur *et al.*, 2014). Phthalates have been shown to alter mitochondrial mass in cardiac cells (Posnack *et al.*, 2012) and the mitochondrial membrane potential in immune cells (Rosado-Berrios *et al.*, 2011). Other endocrine disruptors can decrease mtDNA copy number and ATP content, and increase mtDNA deletions in human trophoblast cells; trophoblasts are specialized cells of the placenta and play an important role in the maternal–fetal interface (Chen *et al.*, 2010; Du *et al.*, 2014).

Psychosocial stress—Increasing evidence suggests chronic social stress promotes oxidative stress and thus oxidative damage (Irie *et al.*, 2000; Gidron *et al.*, 2006; Aschbacher *et al.*, 2013; Colaianna *et al.*, 2013; Jorgensen, 2013). For example, women caring for a chronically ill child who endorsed greater perceived stress had higher systemic oxidative stress (Epel *et al.*, 2004). Evidence that social stress and other physical environmental toxins (e.g. ambient air pollutants) may influence common physiological pathways (e.g. oxidative stress) suggests that while not a physical toxin, social stress may also impact mitochondrial functioning, a mechanism that is key to our body's stress response (Manoli *et al.*, 2007; Gimsa *et al.*, 2009; Song *et al.*, 2009; Filipovic *et al.*, 2011; Gong *et al.*, 2011; Chakravarty *et al.*, 2013; Howerton and Bale, 2014). There are numerous animal studies to support this hypothesis, most pertaining to neurodevelopment. For instance, chronic stress in rats (immobilization for 6 h during 21 days) induces mitochondrial dysfunction in the brain, at least in part due to the overproduction of nitric oxide (NO) via inducible NO synthase (iNOS) (Madrigal *et al.*, 2001). With respect to mtDNA biomarkers, mtDNA variations have been shown to influence anxiety-like behavior and hormone response to stress in mice and zebrafish (Gimsa *et al.*, 2009; Chakravarty *et al.*, 2013). Interestingly, prenatal stress has been linked to mtDNA oxidation and cognitive dysfunction among female rats (Song *et al.*, 2009), which may shed light on gender differences. More recent animal studies also demonstrated associations between early life stress and mitochondrial changes linked to neurodevelopmental deficits (Moller *et al.*, 2013). To date, child health studies of prenatal social stress, mitochondrial dysfunction, and

asthma and/or neurodevelopment have not been conducted. The evidence for social stress affecting mitochondrial function in the human lung or placenta is also non-existent, and thus is an area in need of further investigation given the relationship between maternal stress, stress-mechanisms and childhood respiratory symptoms (Wright *et al.*, 2013; Wright and Brunst, 2014).

Nutritional factors—Maternal and postnatal macronutrient consumption of fat, protein, sugar and carbohydrates as well as fatty acids such as docosahexaenoic acid (DHA) have been shown to alter mitochondrial function/content/methylation in multiple organs and tissues (Mitchell *et al.*, 2009; Feng *et al.*, 2012; Burgueno *et al.*, 2013; Jia *et al.*, 2013; Ahn *et al.*, 2014; Jousse *et al.*, 2014; Mortensen *et al.*, 2014). Many studies also support a role for micronutrients such as vitamins B, C, E and polyphenols in regulating mitochondrial function (Depeint *et al.*, 2006; Tannetta *et al.*, 2008; Wang *et al.*, 2014). In 2014, resveratrol, a natural polyphenol in various foods and beverages such as grapes, red wine, peanuts, chocolate and certain berries, was shown to exert antioxidative, anti-inflammatory activities (Birrell *et al.*, 2005; Rahman *et al.*, 2006), significantly decreasing apoptosis by increasing mitochondrial biogenesis, and reducing oxidative stress of regulatory T cells (Tregs) in mice fed a high-fat diet. This is particularly interesting due to the role of Tregs in allergy/asthma development (Nguyen *et al.*, 2008; Robinson, 2009; Brunst *et al.*, 2013). Vitamin B plays a key role in the cellular pathways for methyl transfers (e.g. methyl-donors) which are believed to be required for mitochondrial protein and nucleic acid synthesis (Depeint *et al.*, 2006). Ketogenic diets (high-fat, adequate-protein, low-carbohydrate diets) are able to restore mitochondrial function in the prenatal valproic acid (VPA) rodent model of ASD that exhibits mitochondrial dysfunction (Ahn *et al.*, 2014). Further, maternal DHA intake can prevent prenatal stress-induced impairment in learning and memory and the modulation of mitochondrial metabolism likely plays a key role in DHA protection (Feng *et al.*, 2012). While the evidence suggests a critical role of the mitochondria linking maternal/postnatal diet to chronic disease and child health, to date, there have been no human studies to confirm the usefulness of mitochondrial markers in studies of early-life nutrition (e.g. prenatal or postnatal) and its effects on asthma and/or neurodevelopment.

Co-exposures and cumulative risk—In addition, understanding the potential synergistic effects of physical and social toxins will more completely inform children's environmental health risk given the shared physiological mechanisms that are at play (Wright, 2009). For instance, children exposed to social stress (community violence) and ambient air pollution (NO₂) are at a greater risk of developing asthma (Clougherty *et al.*, 2007). Conversely, socially enriched environments may protect children from the toxic effects of other environmental hazards (Schneider *et al.*, 2001; Laviola *et al.*, 2008). This integrated framework, incorporating mitochondriomics, may have particular implications for prevention and intervention of neurodevelopmental and respiratory outcomes in high-risk children.

New Research and Future Directions

There are numerous opportunities for new research advancements in mitochondriomics from a basic science standpoint including metabolomics, improvement of high-throughput

screening, 3D imaging and better sequencing for mtDNA (Shaughnessy *et al.*, 2014). Focused investigations on the crosstalk between exposures and mitochondriomics in environmental health are also needed given mitochondria may represent an environmental target (Meyer *et al.*, 2013). Specifically regarding children's environmental health, a better understanding of how critical windows of susceptibility impact mitochondrial biomarkers are needed. For instance, increases in mtDNA copy number tend to compensate for mtDNA damage, but this differs by cell type and developmental stage creating potential windows of vulnerability (Carling *et al.*, 2011). Of the studies outlined in this review, only two human studies, focused on children's environmental health, incorporated mitochondriomics (Wang *et al.*, 2009; Janssen *et al.*, 2012); in total there were only 10 human studies conducted across all exposures examined with the majority being conducted with respect to air pollution. Clearly there is a need to examine the utility and usefulness of incorporating mitochondriomics in more environmental health studies. Not only are toxicological animal studies, which investigate other tissues/cell types including immune and airway epithelial cells to neurons and the placenta needed, but also studies conducted in large-scale pregnancy and birth cohorts.

For some exposures, such as ambient air pollution, it may be more difficult to eliminate exposure. A therapy that could remove mtDNA damage would be advantageous in some instances. For instance, a fertilized nucleus from an oocyte burdened with mtDNA mutations is injected into the cytoplasm of an enucleated donor oocyte carrying mutation free mtDNA; this is known as mitochondrial replacement (MR) and has been successful in producing healthy offspring (Sato *et al.*, 2005; Amato *et al.*, 2014). Could MR gene therapy help women with mitochondrial disease or excessive mitochondrial DNA damage or dysfunction as a result of environmental exposures have healthy children (Reinhardt *et al.*, 2013)? The clinical application of MR is still in its infancy and has many challenges and raises some ethical issues (Amato *et al.*, 2014; Koch, 2014); however, MR could be beneficial when prevention is not an option and thus holds many promises.

Conclusions

Mitochondrial markers have properties that make them exceptionally well suited for biomarker development, as they: (i) have been shown to be persistently altered in blood/tissues by environmental exposures (data derived from mostly animal studies); and (ii) can mark the presence of damaged blood mitochondria, a primary source of systemic oxidative stress to which the brain and lungs are particularly vulnerable. Further work is needed to determine the utility of mitochondrial markers with respect to children's environmental health. However, it is possible that mitochondrial markers can serve as exposure biomarkers; biomarkers of child health outcomes (i.e. asthma/neurodevelopment); and/or biomarkers of child health outcomes specific to environmental exposure effects.

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Figure 1.
Conceptual model linking environmental mitochondriomics to child health outcomes.

Studies investigating the association between environmental exposures and mitochondrial markers

Table 1

Exposure Category	Author	Study description	Study sample	Exposure (s)	Biomarker(s)	Significant Findings	Comment(s)
Air pollution	Li <i>et al.</i> 2003	<i>In vitro</i>	RAW 264.7 and BEAS-2B murine cell lines	PM ₁₀ , PM _{2.5} , UFPs	Mitochondria morphology	UFPs localized in mitochondria and induced structural damage	Cell lines mimic oxidative stress response in pulmonary alveolar macrophages and bronchial epithelial cells
	Hou <i>et al.</i> 2010	Brescia, Italy-Steel Plant	63 healthy male workers	PM ₁₀ , PM ₁	mtDNAcn in blood	PM positively associated with mtDNAcn	Metal exposures examined (see below)
	Janssen <i>et al.</i> 2012	Genk, Belgium	178 Newborns	PM ₁₀ , NO ₂ , distance to major road	mtDNAcn in placental tissue and cord blood	PM ₁₀ associated with 16.1% decrease in placental mtDNAcn; increase in distance to major road resulted in increased placental mtDNAcn	No association found for cord blood mtDNAcn
	Hou <i>et al.</i> 2013	Beijing, China	120 men and women (60 truck drivers; 60 office workers)	PM _{2.5} , Elemental Carbon (EC)	mtDNAcn in blood	Increased EC and PM ₁₀ exposure associated with decreased mtDNAcn in all participants	No association found with PM _{2.5}
	Byun <i>et al.</i> 2013	Brescia, Italy; Milan, Italy; Beijing, China	40 male participants from each location (20 high/20 low exposed)	PM ₁ (Brescia), air benzene (Milan), and EC (Beijing)	mtDNA methylation in 3 regions (MT-TF, MT-RNR1, D-loop) and mtDNAcn in blood	High PM ₁ associated with higher MT-TF and MT-RNR1 methylation; MT-RNR1 methylation positively correlated with mtDNAcn; D-loop was not associated with PM ₁ exposure; No effects on mtDNA methylation from benzene or EC	Participants were steel workers (Brescia), gas-station attendants (Milan), and truck drivers (Beijing); PM ₁ was rich in metals
	Camugno <i>et al.</i> 2012	Genoa, Milan, and Cagliari Italy	519 men and women (341 exposed, 178 referents)	Low-level air benzene	mtDNAcn in blood	In each city, benzene-exposed had higher mtDNAcn than referents; IQR increase in exposure associated with 10% increase in	Sub analysis (Milan participants only) showed mtDNAcn to be associated with LINE-1 hypomethylation

Exposure Category	Author	Study description	Study sample	Exposure (s)	Biomarker(s)	Significant Findings	Comment(s)
Tobacco Smoke	Pavanello <i>et al.</i> 2013	Poland	46 coke-oven workers; 44 matched controls (all men)	Polycyclic aromatic hydrocarbons (PAHs)	mtDNA in blood	mtDNA across cities and p15 hypermethylation	Matched on gender and ethnicity
	Witkopp <i>et al.</i> 2013	Los Angeles, CA	60 elderly men and women over 65 years	Traffic-related air pollution (TRAP)- PAH, BC, NOx, and CO	mtDNA haplogroups H & U	Increases in inflammation biomarkers (IL-6 and TNF- α) associated with higher TRAP exposure; associations were the strongest for haplogroups H	All participants had confirmed coronary artery disease and were non-smokers
	Colicino <i>et al.</i> 2014	United States, VA Normative Aging Study	582 elderly men	Black Carbon (BC)	Nine mtDNA haplogroups categorized into 4 clusters	Largest effect of BC on cognitive impairment observed for haplogroups I, W, and X; moderate effect for J and T; no effect for H, V, K, or U haplogroups	mtDNA haplotypes may modify individual susceptibility to BC cognitive effects
	Hara <i>et al.</i> 2013	<i>In vitro</i>	Human bronchial epithelial cells	Cigarette smoke extract (CSE)	Mitochondrial morphology and ROS production	CSE induced mitochondrial fragmentation and ROS production; this resulted in cellular senescence	Cellular senescence has been implicated in asthma development [Albrecht <i>et al.</i> 2014]
	Ballinger <i>et al.</i> 1996	<i>In vivo</i>	Human bronchoalveolar lavage tissues	Tissues from smokers and non-smokers	mtDNA damage and deletions	Smokers 5.6 times more mtDNA damage including a 4.9 kb mtDNA deletion	mtDNA damage assessed by Q-XLPCR
	Westbrook <i>et al.</i> 2010	<i>In vivo</i>	M. mulatta non-human primates	Low levels ETS (1 mg/m ³) from gestation to 1 year	Mitochondrial function and mtDNA damage (mtDNAcn) in aortic tissues and blood	Perinatal ETS exposure associated with mitochondrial dysfunction and mtDNAcn in aortic tissues; mtDNA damage also observed in blood	Mitochondrial function assessed by cytochrome oxidase activity
	Micale <i>et al.</i> 2013	<i>In vivo</i>	Swiss H mice	CS exposure for 4 weeks starting at birth or 4 months of age	Mitochondrial potential/mass	Exposure to CS affected mitochondrial potential/mass in young mice	Control mice were sham-exposed

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Metals	Aravamudan <i>et al.</i> 2014	<i>In vitro</i>	Non-asthmatic human airway smooth muscle cells	CS exposure	Mitochondrial fragmentation and morphology	CSE induced fragmentation and damaged mitochondria via increased expression of mitochondrial fission protein dynamin-related protein (Drp1) and decreased fusion protein mitofusin (Mfn)	Mitochondrial fission/fusion proteins can influence ROS production, cell proliferation, and apoptosis
	Hou <i>et al.</i> 2010	Brescia, Italy-Steel Plant	63 healthy male workers	Airborne Metals: chromium, lead, arsenic, nickel, manganese	mtDNAcn in blood	Metal concentrations were not associated with MtDNAcn	Ambient air pollution exposures examined (see above)
	Wang <i>et al.</i> 2009	<i>In vivo</i> and human study (Shandong, China)	Wistar rats; Han Chinese pregnant women (n = 67)	Lead acetate exposure during gestation (rats) and blood lead levels	Mitochondrial structure/number	In the rat placenta mitochondria were swollen, decreased in number, endoplasmic reticula were distended and ribosomal number on membranes decreased; no abnormal structure was observed in human placenta	Damaged cytoplasmic organelles may interfere with oxygen exchange and nutrition at the maternal-fetal interface
	Vergilio Cdos & de Melo 2013	<i>In vitro</i>	Human hepatic carcinoma cells	Cadmium	Mitochondrial function	Cd treated cells displayed a progressive loss of mitochondrial function leading to apoptotic events	Disorganized endoplasmic reticula also observed
	Kurochkin <i>et al.</i> 2011	<i>In vivo</i>	Crassostrea virginica (eastern oyster)	Cadmium	Mitochondrial function	Cadmium exposure inhibited substrate oxidation and stimulated proton conductance across inner mitochondrial membrane	Cadmium effects were largely ROS independent
	Hernandez <i>et al.</i> 2011	<i>In vitro</i>	Neocortical and cerebellar granular neurons	Manganese	Mitochondrial function	Manganese exposure lead to mitochondrial homeostasis dysfunction	Ascorbate protected against Mn-induced neurotoxicity
	Sharma <i>et al.</i> 2013	<i>In vivo</i>	Male albino Wistar Rats	Aluminum lactate	Mitochondrial DNA oxidation, mtDNAcn, ROS levels, citrate	After 12 weeks of exposure, Hippocampus and	Decreases in mRNA levels of mitochondrial

Exposure Category	Author	Study description	Study sample	Exposure (s)	Biomarker(s)	Significant Findings	Comment(s)
Endocrine Disruptors	Lin <i>et al.</i> 2013	<i>In vitro</i>	INS-1 β cells	Bisphenol A (BPA)	Mitochondrial function and gene expression	After BPA exposure, ATP depletion, cytochrome c release, loss in mitochondrial mass and membrane potential, and altered expression of genes involved in mitochondrial function was observed After BPA exposure, ATP depletion, cytochrome c release, loss in mitochondrial mass and membrane potential, and altered expression of genes involved in mitochondrial function was observed	encoded subunits were observed as well as reduced expression of nuclear encoded subunits of the electron transport chain Cells also became progressively apoptotic after BPA exposure
	Kaur <i>et al.</i> 2014	<i>In vitro</i>	Lymphoblastoid cells from autistic and control children	BPA	Mitochondrial function	BPA was associated with decreased mitochondrial membrane potential in both groups. Increases in mtDNA were observed in the unaffected siblings group	Control children were age-matched unaffected siblings
	Posnack <i>et al.</i> 2012	<i>In vitro</i>	Rat cardiomyocytes	Di (2-ethylhexyl) phthalate (DEHP)	Mitochondrial mass, gene expression	DEHP exposure resulted in the up-regulation of genes associated with mitochondrial import and an increase in mitochondrial mass	DEHP concentration comparable to clinical exposure (50–100 $\mu\text{g/mL}$, 72 hr)
	Rosado-Berrios <i>et al.</i> 2011	<i>In vitro</i>	Human TK6 lymphoblast cells	DEHP and monoethylhexyl phthalate (MEHP)	Mitochondrial membrane permeability, ROS generation	DEHP and MEHP were associated with increased ROS production and affected the mitochondrial membrane potential; MEHP is more toxic and promotes higher	The IC50 at 24 hr was approximately 250 μM for both compounds. The longer the exposure time the lower the IC50's

Exposure Category	Author	Study description	Study sample	Exposure (s)	Biomarker(s)	Significant Findings	Comment(s)
Psychosocial Stress	Chen <i>et al.</i> 2010	<i>In vitro</i>	JAR cells	2, 3, 7, 8-tetra-chlorodibenzo-p-dioxin (TCDD)	mtDNAcn, mtDNA mutations, ROS production	levels of ROS production TCDD resulted in increased oxidative damage and mitochondrial dysfunction; decreases in mtDNAcn, ATP content, and increases in mtDNA deletions were also observed	Brunst <i>et al.</i> JAR cells are trophoblast-like cells; placental trophoblast cells are important for maternal-fetal crosstalk [Du <i>et al.</i> 2014]
	Gimsa <i>et al.</i> 2009	<i>In vivo</i>	C57BL/6 J mice	Elevated plus-maze test and social defeat	Two strains of mice with different mtDNA variations (AKR/J or FVB/N)	mt(FVB/N) mice showed increased anxiety after the stressor, reduced corticosterone response, and activation of serotonergic and dopaminergic neurotransmitter systems after repeated challenge	This study established a mouse model for studying the role of single nucleotide exchanges in mtDNA in the response to psychological stress
	Chakravarty <i>et al.</i> 2013	<i>In vivo</i>	Danio rerio (Zebrafish)	Chronic unpredictable stress (CUS); CUS paradigm used daily, involving at least 2 stressors, for 15 days	Mitochondrial proteomics analyses using mass spectrometry	18 proteins deregulated; 4 out of 18 were mitochondrial proteins (PHB2, SLC25A5, VDAC3, IDH2)	Stressors included restraint stress, social isolation, overcrowding, tank change, cold stress, heat stress, predator stress, dorsal body exposure, and alarm pheromone stress
	Filipovic <i>et al.</i> 2011	<i>In vivo</i>	Male Wistar rats	Acute, chronic, or combined stressors	Protein levels of p53 and cytochrome c in mitochondrial and cytosolic fractions; enzyme activity of MnSOD (oxidative stress) in brain tissue	Increased p53 and cytochrome c release into the cytoplasm was observed in the prefrontal cortex, but not the hippocampus, following combined stressors. Decreased mitochondrial MnSOD activity following combined stressors was	Results suggest tissue specific response to stress in the brain

Exposure Category	Author	Study description	Study sample	Exposure (s)	Biomarker(s)	Significant Findings	Comment(s)
Nutritional Factors	Gong <i>et al.</i> 2011	<i>In vivo</i>	C57 male mice	Chronic mild stress (CMS)	Mitochondrial function and ultrastructure in the mouse brain	observed in both brain structures. CMS inhibited mitochondrial respiration rates and dissipated mitochondrial membrane potential in the cortex, hypothalamus, and hippocampus; damaged mitochondrial structure also observed	Exposure to CMS was a paradigm developed to represent depression in an animal model
	Song <i>et al.</i> 2009	<i>In vivo</i>	Sprague-Dawley rats	Prenatal stress	Mitochondria 8-OH-dG levels	8-OH-dG levels were elevated in female and male prenatal stressed offspring; effects were stronger in female-stressed group	Prenatal stress group exposed to restraint stress during pregnancy 3x daily for 45 min
	Howerton and Bale 2014	<i>In vivo</i>	C57BL/6 J male mice; 129S1/SvImJ female mice	Early prenatal stress	Mitochondrial cytochrome c oxidase activity and gene expression analyses from the hypothalamus	Reduced mitochondrial function in EPS exposed males was verified by cytochrome c oxidase activity assays	Stressed received during days 1–7 of gestation
	Moller <i>et al.</i> 2013	<i>In vivo</i>	Male Sprague-Dawley rats	Social isolation rearing (SIR)	Mitochondrial function via ATP release	SIR resulted in increased striatal and decreased frontal cortical accumulation of ATP	SIR in rats is a valid animal model of schizophrenia
	Mortensen <i>et al.</i> 2014	<i>In vivo</i>	Fischer F344 rats	High fructose diet	Mitochondrial function in brain	High fructose exposed off spring exhibited increased mitochondrial respiration and decreased phosphorylation efficiency	Diet fed during gestation and lactation
	Ahn <i>et al.</i> 2014	<i>In vivo</i>	Sprague-Dawley rats-dams treated with valproic acid	Ketogenic diet (KD)	Mitochondrial bioenergetics	Prenatal exposure to VPA altered mitochondrial	VPA treatment results in a rodent model of

Exposure Category	Author	Study description	Study sample	Exposure (s)	Biomarker(s)	Significant Findings	Comment(s)
						respiration; this was restored after 14 days of diet respiration; this was restored after 14 days of diet respiration; this was restored after 14 days of diet	respiration; this was restored after 14 days of diet respiration; this was restored after 14 days of diet respiration; this was restored after 14 days of diet
	Jousse <i>et al.</i> 2014	<i>In vivo</i>	Balb/c mice	Low protein diet (LPD)	Mitochondrial-related gene expression, and mtDNA in white and brown adipose tissue and skeletal muscle	Gene expression changes were observed in white adipose tissue in LPD mice as was increases in mtDNA content; increased mitochondrial function was also observed in skeletal muscle	LPD contains 10% of protein; control group contains 22% starting at postnatal day 21
	Mitchell <i>et al.</i> 2009	<i>In vivo</i>	Swiss mice	High, medium, or low protein diets	Mitochondrial function in the embryos	Embryos from HPD females had elevated levels of ROS and ADP concentrations (metabolic stress); embryos from LPD exhibited reduced mitochondrial clustering	ROS, mitochondrial membrane potential and mitochondrial calcium levels assayed
	Feng <i>et al.</i> 2012	<i>In vivo</i>	Prenatally stressed rats	Docosahexaenoic acid (DHA)	Mitochondrial metabolism in the hippocampus	Prenatal stress resulted in changes in mitochondrial complexes I-V and enhanced expression of proteins involved in mitochondrial fusion/fission	Rats exposed to restraint stress on days 14-20 of pregnancy
	Burgueno <i>et al.</i> 2013	<i>In vivo</i>	Rats	High fat diet (HFD)	mtDNA in the liver	HFD during pregnancy associated with decreased liver mtDNA	Dams fed HFD for an 18-week period