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Prenatal particulate matter exposure and mitochondrial dysfunction at the maternal-fetal interface: Effect modification by maternal lifetime trauma and child sex

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ABSTRACT

Background: Prenatal ambient fine particulate matter ($PM_{2.5}$) and maternal chronic psychosocial stress have independently been linked to changes in mithochondrial DNA copy number (mtDNAcn), a marker of mitochondrial response and dysfunction. Further, overlapping research shows sex-specific effects of $PM_{2.5}$ and stress on developmental outcomes. Interactions among $PM_{2.5}$, maternal stress, and child sex have not been examined in this context.

Methods: We examined associations among exposure to prenatal $PM_{2.5}$, maternal lifetime traumatic stressors, and mtDNAcn at birth in a sociodemographically diverse pregnancy cohort ($N = 167$). Mothers' daily exposure to $PM_{2.5}$ over gestation was estimated using a satellite-based spatio-temporally resolved prediction model. Lifetime exposure to traumatic stressors was ascertained using the Life Stressor Checklist-Revised; exposure was categorized as high vs. low based on a median split. Quantitative real-time polymerase chain reaction (qPCR) was used to determine mtDNAcn in placenta and cord blood leukocytes. Bayesian Distributed Lag Interaction regression models (BDLIMs) were used to statistically model and visualize the $PM_{2.5}$ timing-dependent pattern of associations with mtDNAcn and explore effect modification by maternal lifetime trauma and child sex.

Results: Increased $PM_{2.5}$ exposure across pregnancy was associated with decreased mtDNAcn in cord blood (cumulative effect estimate = −0.78; 95%CI −1.41, −0.16). Higher maternal lifetime trauma was associated with reduced mtDNAcn in placenta ($\beta = -0.33$; 95%CI −0.63, −0.02). Among women reporting low trauma, increased $PM_{2.5}$ exposure late in pregnancy (30–38 weeks gestation) was significantly associated with decreased mtDNAcn in placenta; no significant association was found in the high trauma group. BDLIMs identified a significant 3-way interaction between $PM_{2.5}$, maternal trauma, and child sex. Specifically, $PM_{2.5}$ exposure between 25 and 40 weeks gestation was significantly associated with increased placental mtDNAcn among boys of mothers reporting high trauma. In contrast, $PM_{2.5}$ exposure in this same window was significantly associated with decreased placental mtDNAcn among girls of mothers reporting low trauma. Similar 3-way interactive effects

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were observed in cord blood.
Conclusions: These results indicate that joint exposure to $PM_{2.5}$ in late pregnancy and maternal lifetime trauma influence mtDNAcn at the maternal-fetal interface in a sex-specific manner. Additional studies will assist in understanding if the sex-specific patterns reflect distinct pathophysiological processes in addition to mitochondrial dysfunction.

1. Introduction

Gestational exposure to ambient fine particulate matter ($PM_{2.5}$) has been linked to correlates of chronic disease risk (e.g., low birth weight, preterm delivery) (Malmqvist et al., 2011; Lamichhane et al., 2015) and adverse child health outcomes (e.g., poorer cognition, asthma) (Brunst et al., 2015; Basagana et al., 2016). Similarly, maternal psychosocial stress has been associated with preterm birth, low birth weight, and adverse child respiratory and neurodevelopmental outcomes (Henrichs et al., 2010; van de Loo et al., 2016; Grote et al., 2010; Seng et al., 2011; Hohwu et al., 2014; Scheinost et al., 2016). Maternal trauma, in particular, has been shown to have a lasting impact on fetal development even if occurring remote from pregnancy (Sternthal et al., 2009). While mechanisms involved in the toxicity of PM and maternal psychosocial stress/trauma are complex, evolving epidemiological and biological evidence suggests both exposures trigger a cellular stress response and may result in oxidative damage (Romieu et al., 2008; Traboulsi et al., 2017; Yang et al., 2017; Colaianna et al., 2013; Jorgensen, 2013; Aschbacher et al., 2013; Irie et al., 2000; Gidron et al., 2006).

Mitochondria facilitate cellular energy delivery through the production of adenosine-5′-triposphate (ATP) via oxidative phosphorylation. Mitochondrial function is critical to maintaining appropriate energy supply (i.e., ATP), cell functions/signaling, and fetal vitality. Cells contain numerous mitochondria, each containing multiple copies of mitochondrial DNA (mtDNA). The number of mtDNA copies in a cell can be used as a biomarker of mitochondrial response and dysfunction in the presence of oxidative damage. Changes in energy demands can trigger or reduce mitochondrial biogenesis, hallmarked by increases or decreases in mtDNA level, respectively (Shaughnessy et al., 2014; Carelli et al., 2015; Meyer et al., 2017). Thus, the process of regulating mtDNAcn is very dynamic and little is known about other potential upstream regulators of mtDNAcn (Shaughnessy et al., 2014; Carelli et al., 2015).

Biomarkers of mitochondrial dysfunction at the maternal-fetal interface that correlate with in utero environmental exposures can provide insight into the underlying involvement of mitochondrial bioenergetics in chronic disease programming. Changes in mtDNAcn as a result of prenatal PM have been observed in both umbilical cord blood (a marker more accurately reflecting the state of the fetus) and placenta (a key regulator of the external environmental and maternal fetal signaling (Nugent and Bale, 2015)) with some studies observing sex-specific effects (Clemente et al., 2016; Janssen et al., 2012; Rosa et al., 2017a). Further, emerging data suggest that timing of PM exposure during pregnancy may be a key factor in triggering a mitochondrial response. Recent studies demonstrate that increased exposure to $PM_{2.5}$ during the third trimester (35–40 weeks gestation) of pregnancy was associated with decreased mtDNAcn in cord blood (Janssen et al., 2012; Rosa et al., 2017a). Studies examining associations between stress and stress correlates (e.g., psychological functioning) and mtDNAcn in maternal-fetal biomarkers remain sparse and have shown conflicting results (Wang et al., 2017; Brunst et al., 2017). Moreover, while ambient $PM_{2.5}$ and maternal psychosocial stress can have synergistic effects on developmental outcomes (Islam et al., 2011; Shankardass et al., 2009; Rosa et al., 2017b), this is the first study to examine the combined effects of in utero $PM_{2.5}$ and maternal psychosocial stress exposure on mtDNAcn assessed at birth.

We leveraged daily prenatal $PM_{2.5}$ exposure estimates over pregnancy in the PRogramming of Intergernational Stress Mechanisms (PRISM) study and implemented Bayesian Distributed Lag Interaction models (BDLIMs) (Wilson et al., 2017a) to statistically examine and visualize the $PM_{2.5}$ time-dependent pattern of associations with mtDNAcn in placenta and cord blood. These models also allowed for the assessment of interactive effects with maternal lifetime trauma and child sex.

2. Methods

2.1. Sample

Between March 2011 and August 2012, $N = 167$ women were recruited (26.9 ± 8.1 weeks gestation) from prenatal clinics at the Beth Israel Deaconess Medical Center (BIDMC). Eligibility criteria included: (a) English- or Spanish-speaking; (b) age ≥ 18 years at enrollment; and (c) singleton pregnancies. Mothers who endorsed drinking ≥ 7 alcoholic drinks/week prior to pregnancy or any alcohol following pregnancy recognition were excluded given prior association with child health problems of interest to the study (Testa et al., 2003; Patra et al., 2011). Procedures were approved by the relevant institutions' human studies committees; written consent was obtained in the participant's primary language.

2.2. Placenta and cord blood collection

Among the 167 women, 147 cord blood samples were collected prior to clotting and 162 provided acceptable placenta samples collected within 30–60 min after birth[72% ($n = 121$) of participants had both placenta and cord blood samples collected]. Placenta samples (~1–2 cm^3) were taken on the fetal side approximately 4 cm from the cord insertion site in four quadrants, taking care to avoid large vessels as per a published protocol (De Carli et al., 2017). The deciduas and fetal membranes were removed, the sample was rinsed in a cold PBS bath, cut into smaller pieces (~0.1 cm^3), and placed into 1 ml of RNA*later*™ RNA Stabilization Reagent (Qiagen). Samples in RNA*later* were placed at −4 °C for ≤ 24 h; excess RNA*later* was then removed and samples were placed at −80 °C until DNA extraction. Cord blood samples were collected at delivery in EDTA-tubes, centrifuged to obtain buffy coat fraction, and stored at −20 °C until DNA extraction.

2.3. Mitochondrial DNA copy number

Placenta and cord blood DNA extraction was conducted using the Maxwell 16 automated DNA extraction system (Promega – Madison, WI, USA). Relative mtDNAcn was measured using quantitative real-time-PCR (Andreu et al., 2009) which simultaneously measured the abundance of two gene targets- a mitochondrial gene (mt 12S) and a nuclear gene (RNAse P). Relative mtDNAcn was calculated as the ratio of abundance of these two genes (Zhong et al., 2016). Samples were run in triplicate and averaged; the CV was 6% and the interplate variation was 3%.

2.4. Maternal lifetime trauma exposure

Our group has previously shown that increased maternal lifetime stress/trauma exposure, as compared with a measure of current life events in pregnancy, was a better predictor of decreased mtDNAcn in placenta (Brunst et al., 2017). Given this finding, we chose to look at