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ORIGINAL RESEARCH

A Systems Toxicology-based Approach Reveals Biological Pathways Dysregulated by Prenatal Arsenic Exposure

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Abstract

BACKGROUND Prenatal exposure to inorganic arsenic (iAs) is associated with dysregulated fetal gene and protein expression. Potential biological mechanisms that underlie these changes include, but are not limited to, changes to the epigenome.

OBJECTIVE The aim of the present study was to identify whether the expression of key genes, proteins, or both and their associated biological pathways are perturbed by compiling datasets from studies on prenatal arsenic exposure.

METHODS We compiled datasets from 12 studies that analyzed the relationship between prenatal iAs exposure and changes to the fetal epigenome (5-methyl cytosine), transcriptome (mRNA expression), and/or proteome (protein expression).

FINDINGS Across the 12 studies, a set of 845 unique genes was identified and found to enrich for their role in biological pathways, including the peroxisome proliferator-activated receptor, nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, and the glucocorticoid receptor. Tumor necrosis factor was identified as a putative cellular regulator underlying most (n = 277) of the identified iAs-associated gene or protein expression changes.

CONCLUSIONS The identification of the common set of genes across numerous human cohorts suggests a conserved biological response to prenatal arsenic exposure. The genes/proteins and their associated pathways may be useful in future mechanistic investigations of iAs associated diseases.

KEY WORDS CpG methylation, gene expression, inorganic arsenic, microRNA expression, protein expression

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INTRODUCTION

Inorganic arsenic (iAs) is ranked as the highest priority toxic agent by the Agency for Toxic Substances and Disease Registry.[1] Exposure to iAs primarily occurs via contaminated drinking water. In addition to the detrimental health consequences associated with chronic exposure in adults, prenatal exposure to iAs is associated with adverse birth outcomes and susceptibility to diseases later in life.[2] Specifically, prenatal iAs exposure has been associated with lower birth

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weight, preterm birth, reduced height and head circumference, increased susceptibility to infection, including inflammation and infectious disease, and later life cancers.[3]

A single molecular mechanism is unlikely to underlie these diverse health outcomes. For example, prenatal iAs exposure has been associated with changes to the fetal cord leukocyte epigenome, including changes to cytosine methylation (CpG), as well as altered transcription profiles, and changes in protein expression.[4-15] Thus, the pathophysiological consequences of prenatal iAs exposure are likely linked to complex dysregulation at the level of the epigenome, transcriptome, and proteome.

A growing body of literature supports the relationship between prenatal iAs exposure and changes to the fetal epigenome. With cord leukocytes as the primary biological sample of study, alterations in CpG methylation patterns in relation to prenatal iAs exposure have been observed in human population-based studies. Specifically, prenatal iAs exposure has been associated with both global CpG methylation changes as well as changes in specific tumor suppressors in peripheral blood leukocytes in a cohort in Bangladesh.[10] Gene-specific CpG methylation has been associated with iAs exposure in Bangladesh and Thailand[6,9] and genome-wide gene-specific changes observed in a pregnancy cohort in Mexico.[14] Interestingly, some alterations in CpG methylation profiles have been shown to be sex-specific.[6]

Studies focusing on changes at the level of the fetal cord leukocyte transcriptome analyzing altered gene expression have identified many target genes that are altered in relationship to prenatal iAs exposure. Altered patterns of gene expression related to inflammatory signaling pathways were observed in cord blood leukocyte samples collected from newborns exposed prenatally to varying levels of iAs in Thailand[8] and Mexico.[13,14] Similarly, gene expression has been shown to be altered in cord blood and placental tissues from a pregnancy cohort in New Hampshire.[7,11,12,15]

In terms of the investigation of protein expression, 2 studies have identified changes in protein abundance in relationship to prenatal iAs exposure. In a pregnancy cohort in Bangladesh, 18 proteins were analyzed in cord blood for their associations with maternal urinary iAs and 3 differentially expressed proteins were identified.[4] Using the largest proteome assessment to date related to prenatal iAs exposure, a panel of 507 proteins was assessed in newborns exposed to iAs prenatally in Gómez Palacio, Mexico. A set of 111 proteins was found to be associated with prenatal iAs exposure, which are known to be regulated by tumor necrosis factor (TNF) and are enriched in functionality related to immune/inflammatory response and cellular development/proliferation.[5]

Most of these aforementioned studies have examined the identified genes or proteins for biological pathways that are altered when exposed to prenatal iAs. However, the datasets have not been systematically evaluated to identify whether there are common genes or pathways that are dysregulated across multiple birth cohorts. Additionally, the genes altered at the level of the epigenome, transcriptome, and proteome have yet to be integrated across studies. Given that these genes and proteins are likely important contributors to environmental exposure-induced disease from prenatal iAs exposure, the identification of potential common biological pathways will aid in determining biomarkers of exposure or disease associated with iAs. We performed an analysis of datasets that assessed the molecular endpoints of epigenetic alterations (CpG methylation), gene expression, and protein expression in relationship to prenatal iAs exposure in human pregnancy cohort studies to identify key biological pathways that are perturbed as a result of prenatal exposure to iAs.

METHODS

Identifying Genes and Proteins Associated with iAs Exposure. To assess the relationship between prenatal iAs exposure from previous human cohort studies that evaluated CpG methylation, gene expression or protein expression changes, a literature review was performed in PubMed searching the terms, *prenatal arsenic exposure* plus one of the following terms, *gene expression, epigenetics, DNA methylation, CpG methylation*, and *protein expression*. From this search, 12 studies and their corresponding datasets were identified. Genes were included here if they were reported to be significantly associated with prenatal iAs exposure within the respective studies. Common gene identifiers were converted to an Entrez Gene number for each gene and 845 unique genes and proteins were identified across the 12 datasets.

Pathway Analyses. Genes or proteins were analyzed at a biological pathway level using 2 methods, namely Ingenuity Pathway Analysis (IPA; Ingenuity Systems®, Redwood City, CA, USA) and the Database for Annotation, Visualization, and Integrated Discovery (DAVID; david.ncifcrf.gov). Analyses were carried out for all genes (N = 845), as well

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