Epigenetic effects of arsenic and other toxic metals

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• What is known about toxic metals and their impact on the epigenome?

• Can we integrate epigenetic data into the risk assessment framework?

• What research gaps exist related to our understanding of toxic metal-epigenome relationships?
Arsenic: continues to poison the water of millions around the globe

EPA limit 10 ppb

More than 100 million people
Arsenic and other toxic metals are contaminating the water of residents in North Carolina

>2 million people

UNC SRP, Fry, Serre, Gray and DHHS
>63,000 wells over 10 yrs
1436 wells >10 ppb
Hundreds > 50 ppb
Max=800 ppb

Sanders et al. Environ Int 2012
Arsenic and other toxic metals are contaminating the water of residents in North Carolina.

Increased risk of birth defects in relationship to toxic metals.

Sanders et al. BMC Public Health 2014
Arsenic: continues to poison the water of millions around the globe

Lower birthweight in relationship to prenatal arsenic exposure
Early life exposures associated with both short and long term health effects

CD1 mice

hepatocellular carcinomas

Permanent changes in gene expression

Prenatal exposure

adulthood

Prenatal and early life exposure to inorganic arsenic is associated with adult onset disease.
Does prenatal arsenic exposure alter the fetal epigenome?

DNA methylation, miRNA and protein expression are altered, links to immune response and lower birthweight.

Ray et al. Frontiers in Genetics 2014
Rojas et al. Tox Sci 2015
Laine et al. EHP 2015
Rager et al. Tox Sci 2014
Bailey et al. Tox Sci 2014
Risk assessment process:
Defining associations between health outcomes and exposure.
To determine levels of exposure at which negative health outcomes associated with the exposure are minimized.
Epigenetics-Risk Assessment

* Inform understanding of biological mechanisms and mode of action of contaminant-disease relationships

* Include epigenetic modification in dose-response estimates between contaminant and disease

* Potential to be used as both biomarkers of exposure and effect

* Predict inter-individual differences in outcomes responders and non-responders to exposure
Arsenic

*In vitro:* lung, liver, colon, prostate, skin, urothelial cells

*Human samples:* bladder tumors, blood

Key genes with altered functionality associated with epigenetic modifications:

Tumor suppressors: **P53, P16, RASSF1A**
Are there genes with altered CpG methylation that play a role in contaminant metabolism?
AS3MT methylation: Associated with gene expression

Important for exposure assessment as methylation of AS3MT will influence an individual’s ability to metabolize arsenic.


http://127.0.0.1:8081/plosone/article?id=info:doi/10.1371/journal.pone.0053732
Cadmium

*In vitro:* prostate, leukemia, lung, prostate

**Human samples:** blood

Key genes with altered functionality associated with epigenetic modifications:

Tumor suppressors and DNA repair: **P16, RASSF1A, MSH2**
Can we identify biological mechanisms that explain how contaminants target specific genes for altered CpG methylation?
Cadmium exposure and the epigenome
Exposure-associated patterns of DNA methylation in leukocytes from mother-baby pairs

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Cd-associated genes with altered CpG methylation are enriched for MTF binding sites

Important for understanding a mechanism by which contaminants may impact specific genes

Metal responsive transcription factor
Transcription factor occupancy theory

A. Activation of transcription factor leaves the promoter region *inaccessible* to DNMT

B. Inhibition of transcription factor leaves the promoter region *accessible* to DNMT
Research Gaps

- Need increased **samples sizes** for human cohort-based studies
- Need to compare results across different **tissues**, and assess **temporal stability** of changes
- Need to examine relationship between epigenetic modification and **functional changes in gene or protein expression**
- Need to examine relationship between epigenetic modifications and **disease**
Conclusions

- Strong evidence that toxic metals impact the epigenome.
- In many cases these modifications are targeting critical cellular processes (DNA repair machinery, cell cycle control genes, tumor suppressors).
- The relationship between these changes and functional consequences (changes in gene or protein expression, or cellular response, or health endpoints) is not well established.
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