Adverse Effects of Arsenic on the Immune Response of the Lungs to Pseudomonas Infection

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Outline

• Sources of arsenic exposure

• Arsenic and human health

• Innate immune function of the lung in response to *Pseudomonas* infection

• Arsenic suppresses the innate immune function of lung epithelial cells and professional immune cells (macrophages)
ATSDR list of substances that pose the most threat to public health

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<th>SUBSTANCE NAME</th>
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[https://www.atsdr.cdc.gov/spl/](https://www.atsdr.cdc.gov/spl/)
Sources of arsenic exposure

- Arsenic in water
- Apple juice
- Wine glasses
- Brown rice
- Kellogg's Rice Krispies

Google images and EHP
Arsenic exposure in the US

- Total arsenic consumption in the US from water, rice and rice-based products is 10-25 ppb/day per person.

- This is equal to drinking 1 to 2.5 liters of water/day containing 10 ppb of arsenic (EPA limit).
Arsenic in well water.
~3 million drink well water > 10 ppb
Arsenic and human disease
Arsenic enhances viral and bacterial infections in zebrafish

Prenatal exposure to iAs is associated with dysregulated fetal immune gene and protein expression

ORIGINAL RESEARCH

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

Jessica E. Laine, MS, Rebecca C. Fry, PhD

Chapel Hill, NC

Arsenic enhances lung infections in infants

In utero arsenic exposure increases the risk of infections and respiratory symptoms in infants

How does low-dose arsenic increase *Pseudomonas aeruginosa* lung infections?

What is the mechanism?
Pseudomonas aeruginosa (Pa)

- *Pa* is a ubiquitous, opportunistic pathogen that is found in burn wounds, UTIs, and lungs in patients with COPD and CF
- *Pa* develops drug resistant biofilms
Innate immunity in the lung

Pathogens (bacteria, viruses)

Mucus

Antimicrobial peptides

Epithelial cells

IL-8, CXCL1, CXCL2

IL-1β

Antigen presentation

Neutrophils

Macrophages

Images-fineartamerica.com
Arsenic reduces chloride secretion by lung epithelial cells

*Goodale, Barnaby and Stanton, 2016*
Arsenic increases the ubiquitination and proteasomal degradation of CFTR

Bomberger and Stanton, J. Biol. Chem. 2012
iArsenic reduces *Pa* stimulated IL-8 and CXCL1 secretion by lung epithelial cells

**A**

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iArsenic reduces *Pa* stimulated IL-1β secretion by human macrophages

Notch and Stanton, unpublished, 2016
MMA reduces *Pa* stimulated IL-1β secretion by macrophages

Notch and Stanton, unpublished, 2016
DMA has no effect on Pa stimulated IL-1β secretion by macrophages

Notch and Stanton, unpublished, 2016
Arsenic reduces MCC and cytokine secretion and thereby enhances bacterial infection.

Pathogens (bacteria, viruses)

Antimicrobial peptides

Mucus

Epithelial cells

Antigen presentation

MCC

IL-8, CXCL1, IL-1β

Macrophages

Neutrophils

Images-fineartamerica.com
RNAseq to identify novel genes and pathways affected by arsenic

1) Human lung cells in cell culture (6 donors)

2) Exposed cells to 0, 5, 10 or 50 ppb As (25% iAs, 25% MMA, 50% DMA) for 6 days

3) RNA seq analysis of gene expression

4) Media collected for cytokine analysis
Arsenic decreases antimicrobial peptide gene expression

**Lysozyme**

- 33% decrease

**Cysteine-rich secretory protein 3**

- 46% decrease

Goodale and Stanton, unpublished, 2016
Arsenic decreases antigen presentation pathway gene expression

Goodale and Stanton, unpublished, 2016
Dartmouth Superfund Program
Educational/Outreach Activities to Reduce Exposure to Arsenic in the US
EPA environmental educational program

Building school and community collaborations to eliminate arsenic from drinking water in Maine and New Hampshire: A model for the US
EPA environmental education grant

- All About Arsenic website (http://www.allaboutarsenic.org/)
- Creation of classroom arsenic curriculum with a focus on watershed and home well testing
- Partnership with community partners to expand work on private wells
Encouraging/facilitating well water testing for arsenic

http://www.dartmouth.edu/~toxmetal/
Yes, EPA rules may be too lenient. Some filters reduce lead, pesticides, chlorine, arsenic, antibiotics and hormones found in regulated public water supplies.
Zero Water filters remove arsenic from drinking water

I have no financial stake or anything financial or otherwise to gain from promoting the use of ZERO WATER filters.
Research supported by P42ES007373 from the National Institute of Environmental Health Sciences.