Long-term effects of early-life exposures on immunity and (infectious) disease risk

Fenna Sillé, Ph.D.
Department of Environmental Health Sciences, UC Berkeley School of Public Health
Department of Environmental Health & Engineering, Johns Hopkins Bloomberg School of Public Health

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Immunomodulation

Environmental exposures:
e.g. pharmaceuticals, pollutants, toxic chemicals, metals, mineral fibers, nanoparticles, dietary and microbiome metabolites

May lead to:
Autoimmune diseases; hypersensitivity & allergy; inflammatory diseases & tissue damage

Immuno-suppression

May lead to:
Enhanced susceptibility to cancer, (infectious) diseases

Homeostasis

No Effect

May lead to:
Enhanced susceptibility to cancer, (infectious) diseases

Immuno-enhancement

Arsenic, immunity & (infectious) disease risk
Arsenic prevalence

- Modeled global probability of geogenic arsenic in groundwater under reducing and high-pH/oxidizing aquifer conditions
- US EPA & WHO drinking water standard = 10 µg/L.
Arsenic exposure

Industrial & agricultural

Contaminated crops

Coal burning

Contaminated drinking water

Google Images, Wikimedia Commons, WHO
Arsenic-related adverse health effects

Skin lesions
Cancer (skin, lung, bladder & kidney)
Cardiovascular diseases
Reproductive effects
Diabetes
Respiratory diseases

PREVENTING DISEASE THROUGH HEALTHY ENVIRONMENTS

EXPOSURE TO ARSENIC:
A MAJOR PUBLIC HEALTH CONCERN

World Health Organization

LungCXR" by James Heilman, MD - Own work. CC BY-SA 3.0 Wikimedia Commons
Early-life exposure to arsenic in Chile

Early-life exposure to arsenic in Chile

Chile

Mejillones

Antofagasta

Santiago

New water source
Arsenic removal plant installed

Year

1950–1957
1958–1970
1971–1980
1981–1990
1991–2000

Arsenic concentration (µg/L)

> 40 years later

Standard Mortality Rate

Bronchiectasis
Other COPD
Lung cancer
All other deaths

Early-life exposure to arsenic in Chile

Rare evidence supporting the “Developmental Origins of Health and Disease” hypothesis.

Chile

> 40 years later

Early-life exposure to arsenic in Chile

Tuberculosis mortality

Arsenic prevalence


Probability
Arsenic > 10 µg/l
- 0 – 25 %
- 25 – 50 %
- 50 – 75 %
- 75 – 100 %
Tuberculosis incidence

Estimated TB incidence rates, 2014

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.


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Early-life exposure to arsenic

- **Gestational period**
  - 0 wks 10 20 30

- **Child development**
  - 42 0 years

- **Adulthood**
  - 18 45

**Increased disease incidence & mortality**

**Basic immune system complete**

**Early-life exposure to arsenic**

- **Adaptive Immune System**
  - T cells
  - Treg cells
  - B cells
  - Macrophages
  - NK cells
  - TH1 vs TH2 cells
  - Dendritic cells
  - Memory cells
General hypothesis: Exposure-induced immune developmental changes contribute to the persistent global burden of infectious and chronic diseases.

Study models: Arsenic & TB
Specific hypothesis:
Early-life exposure to arsenic alters macrophage development & function causing increased disease later in life.

Arsenic & macrophages

Cytokines/chemokines
Nitric Oxide
Signaling lipids

M1: Pro-inflammatory, Bactericidal activity, Tumor suppression
M2: Scavenging, Tissue repair, Angiogenesis, Tumor promotion
How does arsenic alter macrophages?

Homeostasis

Mouse bone marrow

Macrophages

Arsenic-treated macrophages

Metabolite analysis

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Arsenic alters signaling lipids expression

Homeostasis

Mouse bone marrow

Macrophages

Arsenic-treated macrophages

Metabolite analysis

Sillé et al, unpublished
Arsenic alters signaling lipids expression

Homeostasis

Pro-inflammatory and pro-tumorigenic signaling lipids

Sillé et al, unpublished
How does arsenic alter macrophages?

Homeostasis

Mouse bone marrow → Macrophages → Arsenic-treated macrophages → Signaling protein analysis

Google Images, Wikimedia Commons
Arsenic alters cytokine/chemokine expression

Homeostasis

Mouse bone marrow

Macrophages

Arsenic-treated macrophages

Signaling protein analysis

Relative units

- Unexposed
- MMA3 exposed (1uM)

Sillé et al, unpublished
Arsenic alters cytokine/chemokine expression

Homeostasis

Unexposed
MMA3 exposed (1uM)

Relative units

Sillé et al, unpublished
Does arsenic alter macrophage activation?

Macrophages

Arsenic-treated macrophages

TLR2 activation: PamCys3
Arsenic alters cytokine/chemokine expression in activated macrophages

Sillé et al, unpublished
Arsenic alters nitric oxide production in activated macrophages

Sillé et al, unpublished
Arsenic & macrophages

LPS or Bacteria
IFN-γ
GM-CSF

TNF-α
IL-6
IL-23
IL-1
IL-12p40
IFN-I
RNI
ROI
CXCL9
CXCL10
CXCL11
iNOS

TLRs

GLucocorticoids
IL-4
IL-13
IL-10
M-CSF


M1:
- Pro-inflammatory
- Bactericidal activity
- Tumor suppression

Arsenic

M2:
- Scavenging
- Tissue repair
- Angiogenesis
- Tumor promotion

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Arsenic-targeted pathways that favor tumor progression

Arsenic-targeted pathways relevant to TB

- NOD-like receptor signaling pathway
- TOLL-like receptor signaling pathway
- PPAR signaling pathway
Does arsenic alter tuberculosis outcome?

Mouse bone marrow

Macrophages

Arsenic-treated macrophages

Mycobacterium tuberculosis
Arsenic during differentiation alters *M. tuberculosis* infections

6hrs MMA3 + 24hrs *M. tuberculosis*

Sillé *et al.*, unpublished
Arsenic alters innate immunity & disease risk

**Arsenic**

**Macrophages**

**M1:**
- Pro-inflammatory
- Bactericidal activity
  
  *Tumor suppression*

**M2:**
- Scavenging
- Tissue repair
- Angiogenesis
  
  *Tumor promotion*

**TB susceptibility**
Next steps:

**Aim 1**

*In vitro*

Differentiation

**Aim 2**

*In vivo*

Early-life arsenic-exposed *mouse* studies

**Aim 3**

*Ex vivo*

Early-life arsenic-exposed *human* population study

Arsenic-treated macrophages
Next steps:

Screen for signaling molecules & metabolites

Test immune function during disease

Understand the long-term effects of early-life exposure

Identify biomarkers and maybe even therapeutic targets!
Thank you!

COLLEAGUES:
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  ➢ Daniel Medina-Cleghorn (UC Berkeley)
  ➢ Breanna Ford (UC Berkeley)

COLLABORATORS:
• Craig Steinmaus, MD, MPH (UC Berkeley)
• Catterina Ferreccio, MD, MPH (Pontificia Universidad Católica de Chile)
• Allan Smith, PhD (UC Berkeley)
• Lee Riley, MD, PhD (UC Berkeley)
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For further information please contact Fenna Sillé, PhD : FSILLE1@JHU.EDU