Transcriptomic gender differences in newborns upon prenatal exposure to Polycyclic Aromatic Hydrocarbons in relation to birth weight

Kevin Hochstenbach

BioDetectors, 2016
Lausanne, Switzerland
Contents

Background

- Polycyclic Aromatic Hydrocarbons (PAHs)
- Why newborns?
- Health implications: birth weight
- Why gender differences?
- Toxicogenomics

Results
Polycyclic Aromatic Hydrocarbons

Group of organic compounds that occur naturally in mixtures

Incomplete combustion:
- Tobacco smoke, wood smoke
- Air pollution
- Grilled, smoked foods
- Occupational exposure

Health implications are a public concern
- Carcinogens
- Immunotoxicants
- Developmental toxins

9th BioDetectors conference
Lausanne, Switzerland
In utero: a critical window of exposure

- Fetal vulnerability
  - Cell proliferation
  - Detoxification system
  - DNA repair
  - Immune system

13th century
Renaissance
1940s
Health implications fetal exposure PAHs

- Cross the placental barrier and affect:
  - Respiratory symptoms, asthma and wheezing
  - Neurological and cognitive health outcomes
  - Birth outcomes

- Birth weight influences
  - Survival and perinatal morbidity
  - Subsequent health and development.
  - Associated with leukemia and other chronic diseases.

- Birth weight more strongly affected in males

- Gender differences in gene expression responses

Toxicogenomics
Toxicogenomics

"normal situation"

DNA 
Gene 1 
Gene 2 
Gene 3 

RNA

Protein

"Normal" cell function

Compare

"After exposure"

DNA
Gene 1 
Gene 2 
Gene 3 

RNA

Protein

Altered cell function

Compare
Toxicogenomics

Normal situation

Label with green

Gene 1

After exposure

Gene 2

Gene 3

Label with red

Up-regulation

Down-regulation

No regulation
Transcriptomic gender differences

Research Article

Global Gene Expression Analysis in Cord Blood Reveals Gender-Specific Differences in Response to Carcinogenic Exposure In Utero

Kevin Hochstenbach¹, Danitsja M. van Leeuwen¹, Hans Gmuender⁴, Ralf W. Gottschalk¹, Martinus Løvik⁵, Berit Granum⁵, Unni Nygaard⁵, Ellen Namork⁵, Micheline Kirsch-Volders⁶, Ilse Decordier⁶, Kim Vande Loock⁶, Harrie Besselink², Margareta Törnqvist⁷, Hans von Stedingk⁷, Per Rydberg⁷, Jos C.S. Kleinjans¹, Henk van Loveren¹,³, and Joost H.M. van Delft¹

# Transcriptomic gender differences

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Process</th>
<th># Significant Processes Males/Females</th>
<th>T-Value Males</th>
<th>P-Value Males</th>
<th>T-Value Females</th>
<th>P-Value Females</th>
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<td>T-cell receptor signaling pathway</td>
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<td>8.5</td>
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*Cancer Epidemiol Biomarkers Prev. 2012;21(10):1756-67*

9th BioDetectors conference
Lausanne, Switzerland
Are there transcriptomic gender differences in newborns upon prenatal exposure to PAHs in relation to birth weight??

ERC project
Coordinator: Prof. Tim Nawrot
Funding FWO grant
PAHs/BaP

Ligand binding

AHR

HSP90

HSP90

XAP2

ARNT

Nuclear translocation

Nucleus

Cytoplasm

PAHs/BaP

CYP1A1

BaP

BPDE

ROS

Mt DNA damage

Mitochondrion

Caspases

Cytochrome C

Nucl. DNA damage

Biotransformation: ROS/DNA reactive intermediates

Toxicity

Luciferase

Biotransformation enzymes

Endoplasmatic Reticulum

XRE

BAK/BAX

Biotransformation enzymes

PAHs/BaP
Meet-in-the-middle approach

PAH-CALUX → Association → Birth weight

PAH
Associated genes and processes

Overlap
Associated processes

Gene expression at birth

PAH
Associated genes and processes
### PAH-induced gene expression - Common

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<td>Immune response</td>
<td>6</td>
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<tr>
<td>GPCR</td>
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</tr>
<tr>
<td>Proteosome</td>
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<tr>
<td>DNA repair</td>
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<td>Embryogenesis</td>
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Consensus Enrichment analyses
Q value 0.05
## PAH-induced gene expression - Females

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## PAH-induced gene expression - Males

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Meet-in-the-middle: Overlap common

- PAH: 54 Associated processes
- BW: 129 Associated processes
- Overlapping processes: 40
Meet-in-the-middle: Overlap common

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<td>DNA repair</td>
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Meet-in-the-middle: Overlap males

- **PAH**
  - Associated processes: 331
  - Overlapping processes: 109

- **BW**
  - Associated processes: 615
Meet-in-the-middle: Overlap males

- EGF – Ras - ERK - PI3K-Akt
- TCR signaling-NFkB cascade
- IL-1 p38
- Cyclin E during G1/S transition

Cell cycle regulation

TCR signaling-NFkB cascade

Cancer

Wnt signaling

ATM

Senescence/Apoptosis

BARD1

Biotransformation

Complexation between folic acid and PAHs

Protective against PAH-DNA adduct formation

Vitamin E

Glycobiology

Cyclin E during G1/S transition

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Take home message!

- Gender-specific PAH-Birth weight association through modulation of the fetal transcriptome:
  - Higher transcriptomic response in male newborns upon prenatal PAH exposure

- Possible gender-specific PAH mechanisms-of-action
  - Epigenetics
  - DNA damage:
    - Cell cycle regulation
    - P38/JNK
    - Apoptosis
  - Folate
  - Vitamine E
Ongoing and future research

Develop a toxicogenomics-based biomarker indicative of in utero exposure to PAHs

Apply additional PAH-CALUX on subset to validate developed biomarker

Measure PAH adducts and its newly developed transcriptome signature in cord blood of 850+ newborns within the ENVIRONAGE birth cohort by means of qRT-PCR

Identify transcriptomic profiles in cord blood associated with the effects of in utero PAH exposure on:
- Telomere length
- Neurodevelopment
- Follow up data on immune functionality.
<table>
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<tbody>
<tr>
<td>Tim Nawrot</td>
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<td>Ellen Winckelmans</td>
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