Immune dysfunction in children with prenatal immunotoxicant exposures

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Developmental Immunology

• Immune system develops extensively in the fetal period and the first months after birth

• Normal maturation dependent upon specific processes
  • At different time points
  • In different body compartments

⇒ Early-life immune system a moving toxicological target for xenobiotic interactions
Immunotoxicity - outcomes

Antigen/chemical

Hyper-sensitivity
Allergic diseases
Asthma

Immunosuppression
Infections
Reduced vaccination responses

Auto-immunity
Perfluoroalkyl substances (PFAS, PFC)

• Widely used
  – E.g. food packaging, water and oil repellents for leather, paper and textiles, inks, varnishes, waxes, lubricants, hydraulic oils, fire fighting foams

• Consist of a fully fluorinated carbon chain and different functional groups
  – PFOS: perfluorooctane sulfonate
  – PFOA: perflurooctanoate

• Important sources
  – Diet (consumption of lean fish, fish liver, shrimps and meat)
    • Well absorbed after oral administration
  – Indoor air and house dust

• Cross human placenta

• Transferred to amniotic fluid and breast milk

• Long half-lifes (PFOS 4.8 years; PFOA 3.5 years; PFHxS 7.3 years)
Possible health effects of PFAS exposure

• Animal studies
  – Hepatotoxicity
  – Liver, testicular and pancreatic tumours
  – Reproductive and developmental toxicity
  – Neurotoxicity
  – Immunotoxicity

• Human studies
  ? Birth outcomes
  • gestational age, birth weight, birth length, head circumference, abdominal circumference
  ? Reproductive toxicity
  • Sperm quality, time to pregnancy
  ? Neurodevelopment
  Immunotoxicity
Immunotoxicity
Vaccination responses

- Inverse relationship between maternal PFAS (sum of PFOS, PFOA, PFHxS) and levels of anti-diphteria titres at age 5 years (Grandjean et al. 2012)
- In adults, elevated PFOA is associated with reduced antibody titre rise, particularly to A/H3N2 influenza virus (pre- vs post-vaccination) (Looker et al. 2013)
Immunotoxicity
Common infections

- Prenatal exposure to PFOA and PFOS is not associated with increased risk of hospitalisation for infectious diseases in early childhood (Fei et al. 2010)
  - Sum of any hospitalisation of the child due to infectious diseases

- No association between exposure to PFOA during pregnancy and infectious diseases in the children (C8 Project Panel Study, 2012)
  - Infections the last 12 months including flu and common colds

- No association between exposure to PFOA and PFOS and otitis media the first 18 months of life (Okada et al. 2012)
Immunotoxicity
Sensitisation and allergic diseases
Asthma and asthma like symptoms

• **Wang et al. 2011**
  – Maternal PFOA and PFOS correlated positively with cord blood IgE levels but not with serum levels at age 2 years (total IgE)
  – No associations between PFOA and PFOS and atopic dermatitis

• **Okada et al. 2012**
  – Maternal PFOA correlated negatively with cord blood IgE levels among female infants
  – No association between maternal PFOA and PFOS and food allergy, eczema or wheezing at 18 months of age

• **C8 Project Panel Study, 2012**
  – Pattern of decreasing asthma risk in children by quartiles of maternal PFOA
  – Not a probable link between exposure to PFOA and asthma

• **Okada et al. 2014**
  – An association between maternal PFTrDA (perfluorotridecanoate) and decreased risk of developing eczema in female girls at age 2 years
• 205 mother-child pairs
  – Subcohort of the Norwegian Mother and Child Cohort Study (MoBa)

• Health outcomes
  – Asthma and asthma-like symptoms
  – Eczema
  – Allergy (airways, food)
  – Common infections
    • Gastroenteritis, common cold, pneumonia and urinary tract infections

• Serology at age 3 years
  – Vaccination titres
    • Rubella, measles, tetanus and \textit{Haemophilus influenzae} type b (Hib)
  – Allergen-specific IgE (Phadiatop infant)

• Whole-genome gene expression in cord blood
  – N=120
PFAS measurements in maternal samples

- 19 PFAS
- PFOA, PFNA, PFOS, PFHxS
- 99 maternal samples at the time of delivery
- 66 of these have microarray data in cord blood

<table>
<thead>
<tr>
<th>Compound</th>
<th>Mean (ng/ml)</th>
<th>Median</th>
<th>Min-Max</th>
<th>IQR</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFOA Perfluorooctanoate</td>
<td>1.1</td>
<td>1.1</td>
<td>0.2 - 2.7</td>
<td>0.8 - 1.4</td>
</tr>
<tr>
<td>PFNA Perfluorononanoate</td>
<td>0.3</td>
<td>0.3</td>
<td>&lt; 0.05 - 0.9</td>
<td>0.2 - 0.4</td>
</tr>
<tr>
<td>PFHxS Perfluorohexane sulfonate</td>
<td>0.3</td>
<td>0.3</td>
<td>&lt; 0.05 - 2.8</td>
<td>0.2 - 0.3</td>
</tr>
<tr>
<td>PFOS Perfluorooctane sulfonate</td>
<td>5.6</td>
<td>5.5</td>
<td>1.4 - 11.0</td>
<td>3.8 - 7.1</td>
</tr>
</tbody>
</table>
• Statistical analyses – Health outcomes
  – Maternal PFAS vs common cold, gastroenteritis
    • Poisson regression analyses
  – Maternal PFAS vs rubella titres
    • Linear regression analyses

• Statistical analyses – gene expression
  – Maternal PFAS vs gene expression
  – Gene expression vs rubella vaccine response and/or common cold
  – Pearson’s correlation analyses
Maternal PFAS vs vaccination responses (at age 3 years)

- Inverse relationship between maternal PFAS and rubella titres in children at age 3 years

<table>
<thead>
<tr>
<th>PFAS</th>
<th>β</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFOA</td>
<td>-0.40</td>
<td>-0.64, -0.17</td>
<td>0.001</td>
</tr>
<tr>
<td>PFNA</td>
<td>-1.38</td>
<td>-2.35, -0.40</td>
<td>0.007</td>
</tr>
<tr>
<td>PFHxS</td>
<td>-0.38</td>
<td>-0.66, -0.11</td>
<td>0.008</td>
</tr>
<tr>
<td>PFOS</td>
<td>-0.08</td>
<td>-0.14, -0.02</td>
<td>0.007</td>
</tr>
</tbody>
</table>

Granum et al., 2013
Maternal PFAS vs clinical health outcomes (until age 3 years)

• Positive association between maternal PFOA and PFNA and the no. of episodes of common cold
  – PFOA: $\beta=0.42 \ (0.21, \ 0.62), \ p<0.001$
  – PFNA: $\beta=0.74 \ (0.05, \ 1.43), \ p=0.036$

• Positive association between maternal PFOA and PFHxS and the no. of episodes of gastroenteritis
  – PFOA: $\beta=0.31 \ (0.00, \ 0.61), \ p=0.048$
  – PFHxS: $\beta=0.35 \ (0.10, \ 0.61), \ p=0.007$

• No associations between maternal PFAS and eczema, wheeze, asthma or allergen-specific IgE antibodies

Granum et al., 2013
Cord blood gene expression

- We identified genes correlated with
  - PFAS measurements (2 or more compounds) in maternal blood
    - 578 genes
  - Episodes of common cold in child (until age 3 years)
    - 580 genes
  - Rubella titres in child (at age 3 years)
    - 1231 genes
Preliminary pathway analyses

• NF-κB activation
  – A key role in inflammation, immunity, cell proliferation, apoptosis, cytokine production in T cells and monocytes/macrophages
  – Different PFAS inhibited, at different levels, the signaling pathways regulating NF-κB activation in THP-1 cells (Corsini et al., 2012)
  – Induction of several cytokines and immunological adhesion molecules, both at the single gene level and at pathway level

Pennings et al., manuscript in preparation
Summary – PFAS and immunotoxicity

• Evidence of immunosuppressive actions
  – Increased risk of infections
  – Reduced vaccination titres
• Effects on allergic diseases and asthma are not well-known
• Mechanisms are not well-known
  – PPAR
  – NF-κB activation
• More studies on other PFAS than PFOS and PFOA are warranted
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