Environmental Exposures and Immune Function

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Images: leadminorityreport.net; cytokines_nordicbiosite.dk; brighamandwomens.org; bpabottles.cbc.ca; cleanandhealthyme.org; sciencedaily.org; genderandhealth.ca
Immunoregulatory balance is key to maintaining health and preventing disease

Survival from infection or cancer

Reaction & elimination

Naïve cells & Immunological homeostasis

Down-regulation & tolerance

Ignore ‘self’ and harmless environmental antigens
Immunoregulatory balance is key to maintaining health and preventing disease.

- **Survival from infection or cancer**
- **Pathology/Death from infection or cancer**

**Reaction & elimination**

- **Hypersensitivities/Allergies**
- **Autoimmune diseases**

**Down-regulation & tolerance**

- **Naïve cells & Immunological homeostasis**
- **Ignore ‘self’ and harmless environmental antigens**
Many factors are known to influence the function of the immune system

- Age
- Sex (including endocrine status)
- Genetics (and epigenetics)
- Physical fitness
- Nutritional and psychological status
- Existing biota (infection, normal microflora)
- Physical environment (seasonal changes, geographical location)
- Exposures to exogenous chemicals (good or bad)
Immunotoxicology/Immunopharmacology encompass three important areas

**Academic research**
What is the mechanism?
Can we develop or refine new therapies by understanding toxicity?
Can we improve public health by defining causality?

**Government research**
Is something immunotoxic?
What are the health risks?
Is there a safe level of exposure?

**Industry research**
How can we modulate or use the immune system to treat disease?
Will a new drug have unexpected and detrimental effects on the immune system?
Chemicals for which we know something about how they modulate the immune system

e.g. Dioxins, Benzene, Tobacco smoke

- known
- partly known
- unknown

e.g. Cyclosporin A, Therapeutic monoclonal antibodies
Examples of exogenous chemicals that modulate the immune system

**Inducers of Immunosuppression**
- Pharmaceuticals (e.g., cyclosporin A, glucocorticoids, chemoRx)
- Benzene
- Dioxins (TCDD) and some dioxin-like compounds
- Polyaromatic hydrocarbons (e.g., benzo(a)pyrene)
- Tobacco Smoke
- Illegal drugs (e.g., cocaine, cannabianoids)

**Inducers of Hypersensitivity**
- Many pharmaceuticals (e.g., penicillin)
- Nickel
- Thimerosal
- Latex rubber
- Food Proteins
- Formaldehyde
- Particulate pollutants (e.g., diesel exhaust particles)

**Inducers of Autoimmunity**
- Some pharmaceuticals (e.g., halothane)
- Trichloroethylene
- Mercury
Potential mechanisms of Immune Suppression

1. Loss of function or death of precursor cells
2. Blockage or skewing of cell signaling cascades
3. Preventing or deregulating cell differentiation
4. Inhibition of cell proliferation
5. Inhibition of immune cell function
6. Growth of the “wrong” cell type, or inappropriate secretion of cytokines or other regulatory factors
7. Incorrect or insufficient antigen presentation
Potential Mechanisms for Immune Enhancement

1. Failure or delay of down-regulatory mechanisms
2. Impaired cell death mechanisms
3. Uncontrolled cell proliferation, or proliferation of the “wrong” type of cell
4. Skewing of cell differentiation
5. Inappropriate secretion of cytokines or other regulatory factors
6. Recognition and response to self or harmless antigens
7. Trafficking of immune cells to restricted sites
There are a lot of ways to alter the function of the immune system!

- Changing the proliferation and differentiation of immune cells
  - Progenitor cell types
  - Mature peripheral leukocytes
- Changing cellular trafficking
- Changing signal transduction cascades
- Dysregulation of tolerance mechanisms
- Changing antigen processing and presentation
- Increasing or decreasing cell death mechanisms
- Changing the cytokines, chemokines, adhesion molecules and/or their receptors, enzymes, free radicals…… expressed on or secreted by immune cells

*and they are not mutually exclusive*
How do environmental chemicals influence immune responses to infectious agents?

Genetics & Epigenetics

Infectious Disease

Environmental Exposures

Age

Many endocrine disrupting chemicals (EDCs) bind nuclear receptors

**Steroid hormone receptor family**
- Estrogen receptors (ERs)
- Androgen receptor (AR)
- Glucocorticoid receptor (GR)

**PAS family**
- AHR
- HIF1α
- CLOCK
- BMAL
- Per
- Sim

**Heterodimeric nuclear receptors**
- Peroxisome-proliferator-activated receptors (PPARs)
- Thyroid hormone receptor (TR)
- Liver X receptors (LXR)

**Monomeric nuclear receptors**
- Retinoid-related orphan receptors (RORs)
- Steroidogenic factor like (SF1)
- COUP-TFII
Why do we care about the AHR?

✓ The aryl hydrocarbon receptor (AHR) is a ligand-activated transcription factor that binds hundreds of chemicals.

✓ Cells of the immune system express the AHR.

✓ Chemicals (ligands) that bind to the AHR are “good” and “bad,” and both types of ligands influence many aspects of immune function in adult animal models.

✓ We don’t yet understand role of the AHR in normal immune system development and function.

✓ Environmentally-derived AHR ligands cross the placenta and accumulate in breast milk.

✓ Recent epidemiology studies suggest AHR binding pollutants affect the human immune system.
Exploring the effects of AHR binding pollutants on the immune response to respiratory viral infection

Increasing viral dose enhances severity of infection

AHR activation enhances the severity of infection

Lawrence & Vorderstrasse (2013)
Studying the effects of AHR activation on the immune response to respiratory viral infection

Determining how different AHR ligands modulate the immune response to respiratory infections

- Adult exposure
  - Cellular targets
    - Mechanisms

- Developmental Exposure
  - Cellular targets
    - Mechanisms
Some key findings: Both direct and developmental AHR activation disrupts the immune response to influenza A virus

- **Epithelial cells** release influenza virus into the lung.
- **Dendritic cells** (DC) activate **CD4** T helper cells.
- The activated **CD4** cells migrate to the lymph nodes and activate **CD8** cytotoxic T lymphocytes (CTLs). The process takes 1-3 days.
- The **CD8** CTLs then migrate to the lung, where they release **IFNγ**.
- The **IFNγ** activates **B cells** to **activation, expansion, and isotype switching**, taking 4-6 days.
- After 7-9 days, the activated **B cells** release antibodies.

Adapted from Head and Lawrence (2009)
Implications and Significance

Environmental chemicals may alter vulnerability to clinically severe outcomes of infection.