Toxic responses of the immune system

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Immune system

Immunity is a homeostatic process, a series of delicately balanced, complex, multicellular, and physiologic mechanisms that allow an individual to distinguish foreign material from "self" and neutralize and/or eliminate the foreign matter.
Immunotoxicology can be defined as the study of adverse effects on the immune system resulting from occupational, inadvertent, or therapeutic exposure to drugs, environmental chemicals and biological materials.
Continuum of immunotoxicity? (Adverse outcome of immunotoxicity?)

- Decreased immunocompetence (immunosuppression) may result in repeated, more severe, or prolonged infections as well as the development of cancer.
- Immunoenhancement may lead to immune-mediated diseases such as hypersensitivity responses or autoimmune disease.
Continuum of immunotoxicity:

Figure 12-1. The continuum of immunotoxicology. Immune toxicity results from xenobiotic-induced suppression or enhancement of immune function.
Organs of immune system
Immune system

Innate/Natural Immunity (non-specific responses)

1. Skin
2. Mucous membranes & secretions
3. Normal flora

Adaptive/Acquired Immunity (specific responses)

1. Innate immune cells
2. Inflammation
3. Complement
4. Antimicrobial substances

Specialized Lymphocytes
1. B cells (produce antibodies)
2. T cells
   A. Helper T cells
   B. Killer T cells
Innate immunity

Reflexes such as coughing, sneezing, and elevation in body temperature are also a part of innate immunity.
Antigen Processing:

Figure 12-7. Antigen processing by the MHCII pathway. Antigen is engulfed by an APC (DC, macrophage, or B cell), degraded, and loaded onto MHCII. The MHCII–peptide complex is then expressed on the surface of the APC for presentation to CD4+ Th cells.
Antigen

- An antigen is defined functionally as a substance that can elicit the production of a specific antibody and can be specifically bound by that antibody.
- Generally antigens are about 10KDa, Smaller antigens are termed haptens and must be conjugated with carrier molecules (larger antigens) to elicit a specific response.
Antibody; immunoglobulin

Fragment Antigen Binding

IgG

Fab (binds epitope)

hinge

light chain

heavy chain

Fc (binds to phagocytes, activates complement pathway)

Fragment Crystalizable

S-S bond
Immunomodulation by Xenobiotics

- The expansive and versatile nature of the immune system renders it susceptible to modulation by a wide variety of xenobiotics.
- Many xenobiotics exhibit immunosuppressive actions, whereas some are immunomodulatory, meaning they might produce immune suppression and immune enhancement. Regardless of the end effect (immune suppression, immune enhancement, hypersensitivity, or autoimmunity)
Several mechanisms exist by which these chemicals act:

First, the mechanisms are likely to be multifaceted involving several proteins, signaling cascades, or receptors.

Second, whether a xenobiotic produces a particular immune effect might depend on the concentration or dose of the xenobiotic, the mode and/or magnitude of cellular stimulation, and the kinetic relationship between exposure to the xenobiotic and exposure to the immune stimulant (i.e., antigen, mitogen, and pharmacological agent).
Third, xenobiotic exposures rarely occur in one chemical at a time; thus, the effects and/or mechanisms observed might be attributable to several chemicals or classes of chemicals. Finally, determination for immune system effects and/or mechanisms by xenobiotics in humans might be further confounded by the physiological or immunological state of the individual.
Immunomodulation by Xenobiotics (immune suppression, immune enhancement, hypersensitivity, and autoimmunity)

- **Halogenated aromatic hydrocarbons (HAH)**: Polychlorinated biphenyls, Polybrominated biphenyls binding of HAH to aromatic hydrocarbon receptor (AHR) ultimately results in upregulation of certain proteins with a net immunosuppressive effect.

- **Pesticide**: can be both immunosuppressive and immunoenhancing

- **Metals**: at high concentrations usually exert immunosuppressive effects; however, at lower concentrations, immune enhancement is often observed.
Immunomodulation by Xenobiotics (immune suppression, immune enhancement, hypersensitivity, and autoimmunity)

- **Solvents and Related Chemicals:** benzene, haloalkanes and haloalkenes, glycols and glycol ethers, and nitrosamines: can produce immune suppression.

- **Mycotoxins:** secondary metabolites of fungi, aflatoxin, ochratoxin, vomitoxin.

- **Natural and Synthetic Hormones:** profound changes in immune activity can result from very slight changes in concentrations of hormones.
Immunomodulation by Xenobiotics (immune suppression, immune enhancement, hypersensitivity, and autoimmunity)

- **Therapeutic Agents**: Immunosuppressive Agents, AIDS-Therapeutics, Anti-inflammatory Agents, Biologics such as recombinant DNA–derived proteins (vaccine)

- **Drugs of abuse**: such as cannabinoids, opioids, cocaine, methamphetamine, and ethanol exhibit immunosuppressive actions.

Immunomodulation by Xenobiotics (immune suppression, immune enhancement, hypersensitivity, and autoimmunity)

- Ultraviolet radiation (UVR): UV-induced immunomodulation can lead to several adverse health consequences, including a pivotal role during the process of skin carcinogenesis.
Xenobiotic induction of hypersensitivity or autoimmunity

- When an individual’s immune system responds in a manner producing tissue damage, it could result in hypersensitivity or autoimmunity, which could be exacerbated, or even induced, by another xenobiotic.
Mechanisms of Xenobiotic induction of hypersensitivity or autoimmunity

- Xenobiotic
  - Protein
    - Antigenic determinant
      - Hapten/protein conjugate
      - Altered protein
      - Native protein
        - Hypersensitivity
        - Disease state
        - Autoimmunity
          - Mechanism of action
            - IgE (type I)
            - Antibody-dependent cytolysis (type II)
            - Complement-dependent cytolysis (type II)
            - Immune complex-mediated (type III)
            - CD4+/CD8+ T cells (type IV)
            - B cells

Figure 12-23. Schematic diagram of xenobiotic induction of hypersensitivity or autoimmunity. The mechanisms by which xenobiotics induce hypersensitivity or autoimmunity can overlap, although IgE production is most often associated with hypersensitivity.
Coombs and Gell classification of hypersensitivity

All four types of hypersensitivity reactions require prior exposure leading to sensitization to elicit a reaction upon subsequent challenge.
Classification of hypersensitivity

- Type I (Immediate Hypersensitivity)
- Type II (Antibody-Dependent Cytotoxic Hypersensitivity)
- Type III (Immune Complex–Mediated Hypersensitivity)
- Type IV cell delayed-type hypersensitivity (DTH) response.
Type I hypersensitivity reaction:

Figure 12-14. Type I hypersensitivity reaction. Metabolized penicillin is a hapten that conjugates with a protein. The conjugated hapten cross-links IgE antibodies on mast cells. IgE cross-linking causes mast-cell degranulation and releasing histamine and other proinflammatory mediators.
Type II hypersensitivity reaction:

![Diagram showing complement-independent and complement-dependent cytolysis](image)

**Figure 12-15. Type II hypersensitivity reactions.** In complement-independent cytolysis, antigen becomes attached to a normal cell, which can be recognized by IgG. A cell capable of cytolysis (CTL, NK cell) binds to IgG via its Fc receptor and kills the antigen-coated cell. In complement-dependent cytolysis, antigen becomes attached to a normal cell, which can be recognized by IgG. Complement gets activated by the classical pathway (antigen–antibody complexes) and C3a and C5a bind complement receptors.
Type III hypersensitivity reaction:

**Figure 12-16.** Type III hypersensitivity reactions. IgG is produced against an antigen and antigen–antibody complexes form, which can become deposited in tissue. Complement gets activated by the classical pathway (antigen–antibody complexes), and platelets also interact with complexes. Following complement-mediated cytolysis, released chemotactic factors attract neutrophils and macrophages, causing additional inflammation and tissue damage.
Type III hypersensitivity reaction (Immune Complex–Mediated Hypersensitivity):

Type II and III immunopathies include anemia, leukopenia, thrombocytopenia, pneumonitis, vasculitis, lupus-like reactions, or glomerulonephritis, and are often indistinguishable from autoimmune reactions.
Type IV hypersensitivity reaction:

Figure 12-17. Type IV hypersensitivity sensitization. A hapten permeates the epidermis and forms a complex with a carrier protein. The conjugated hapten gets engulfed by Langerhan’s cells, which migrate to the lymph node and present antigen to CD4+ T cells in the context of MHCII. CD4+ T cells activate, proliferate, and differentiate into Th or Tc cells and memory T cells.
Type IV hypersensitivity reaction:

![Diagram showing Type IV hypersensitivity reaction with Inflammation, Hapten, Cytokines, Carrier protein, Epidermis, Langerhan’s cell, Dermis, Lymphatic vessel, and Lymph node.]
Xenobiotic induced-hypersensitivity

- Metals: Metals and metallic substances, including metallic salts, are responsible or producing contact and pulmonary hypersensitivity reactions. Platinum, cobalt, chromium, nickel, and beryllium are commonly implicated.
Drugs: Hypersensitivity responses to drugs are among the major types of unpredictable drug reactions. Immunologic mechanisms of hypersensitivity reactions to drugs include types I to IV. Penicillin is the most common agent involved in drug allergy.
Latex: Natural rubber latex is used in the manufacture of over 40,000 products from balloons to surgical gloves. Allergic reactions to natural rubber latex products have become an important occupational health concern with increased use of universal precautions, particularly latex gloves, to combat the spread of blood borne pathogens. Hypersensitivity to latex usually occurs via a type I or type IV reaction. Dermatologic reactions to latex include irritant dermatitis and contact dermatitis.
Latex Allergy:

When the allergen contacts the IgE proteins on the mast cells, these cells explode, releasing the histamine, which causes the allergy symptoms.
Xenobiotic induced-hypersensitivity

- Formaldehyde: Formaldehyde is used as a preservative, sterilant, and fumigant. Additional exposures come from the textile industry, where it is used to improve wrinkle resistance, and in the furniture, auto upholstery, and resins industries. Occupational exposure to formaldehyde has been associated both with the occurrence of asthma and increased respiratory allergic responses to other stimuli.
Sources of Formaldehyde inside the home:

- Building materials
  - Pressed wood products
    - Particleboard
    - Hardwood plywood paneling
    - Medium density fiberboard
- Smoking
- Household products
- Un-vented, fuel-burning appliances

- Manufactured products
  - Permanent press qualities to clothing and drapery
  - Component of glues and adhesives
  - Preservative in paints
When heat is applied in the Brazilian blowout process causes the methylene glycol to dehydrate, yielding formaldehyde gas and water vapors.
Sources of Formaldehyde:

\[
\begin{align*}
\text{Formaldehyde} & \quad + \quad \text{H}_2\text{O} \quad \rightarrow \quad \text{Methylene glycol} \\
\text{H} & \quad \backslash \quad \text{H} & \quad \text{H} & \quad \text{HO} \quad \text{OH} \\
& \quad \text{Water} & \quad \text{H} & \quad \text{H}
\end{align*}
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**KERATIN TREATMENT DANGERS**

FORMALDEHYDE

The trouble with formaldehyde in beauty products is that it’s a known carcinogen, meaning ingesting, inhaling or exposing skin to it could potentially cause cancer.
Food and Genetically Modified Organisms: Awareness of hypersensitivity reactions to foods and genetically modified organisms (or crops; GMOs) has increased in the last several years. The most common food allergens are milk, egg, peanuts and other tree nuts, fish, shellfish, soy, and wheat. Hypersensitivity to peanuts occurs primarily via a type I reaction, and the IgE responses may include shortness of breath, asthma, and anaphylaxis.
Autoimmunity:

NORMAL IMMUNE RESPONSE

- Antigens invade
- Antibodies form
- Antibodies remove invading antigens
- Antibodies remain and protect

AUTOIMMUNE DISEASE

- Immune system forms antibodies to self-antigens
- Antibodies attack self-antigens
- Inflammation and tissue damage
Induction of Autoimmune Disease: Genes versus Environment

The development of autoimmune disease depends on a combination of genetic and environmental factors.

Environmental factors:
- Infections
- Diet
- Hormones
- Drugs

Genetic predisposition

30% 70%

Autoimmune disease
Autoimmunity:

- There are numerous reports of xenobiotics that have been associated with autoimmunity; xenobiotic-induced autoimmunity,
Xenobiotic-induced autoimmunity:

- **Methyldopa**: Platelets and erythrocytes are targeted by the immune system in individuals treated with this drug, resulting in thrombocytopenia and hemolytic anemia.

- **Hydralazine, Isoniazid and Procainamide**: All three drugs produce autoimmunity, which is manifested as a systemic lupus erythematosus-like syndrome.
# Autoimmune Reactions to Xenobiotics

## Table 12-6 Chemical Agents Known to Be Associated with Autoimmunity

<table>
<thead>
<tr>
<th>Proposed Antigenic Chemical</th>
<th>Clinical Manifestations</th>
<th>Department</th>
</tr>
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<tbody>
<tr>
<td>Drugs</td>
<td></td>
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<tr>
<td>Methyldopa</td>
<td>Hemolytic anemia</td>
<td>Rhesus antigens</td>
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<td>Hydralazine</td>
<td>SLE-like syndrome</td>
<td>Myeloperoxidase</td>
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<tr>
<td>Isoniazid</td>
<td>SLE-like syndrome</td>
<td>Myeloperoxidase</td>
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<td>Procainamide</td>
<td>SLE-like syndrome</td>
<td>DNA</td>
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<td>Halothane</td>
<td>Autoimmune hepatitis</td>
<td>Liver microsomal proteins</td>
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<td>Nondrug chemicals</td>
<td></td>
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<tr>
<td>Vinyl chloride</td>
<td>Scleroderma-like syndrome</td>
<td>Abnormal protein synthesized in liver</td>
</tr>
<tr>
<td>Mercury</td>
<td>Glomerular neuropathy</td>
<td>Glomerular basement membrane protein</td>
</tr>
<tr>
<td>Silica</td>
<td>Scleroderma</td>
<td>Most likely acts as an adjuvant</td>
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</tbody>
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Chemicals implicated in Autoimmunity:

<table>
<thead>
<tr>
<th>Manifestation</th>
<th>Implicated Chemical</th>
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<tbody>
<tr>
<td>Scleroderma</td>
<td>Solvents (toluene, xylene)</td>
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<tr>
<td></td>
<td>Tryptophan</td>
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<td></td>
<td>Silicones</td>
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<td>Systemic lupus erythematosus</td>
<td>Phenothiazines</td>
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<td></td>
<td>Penicillamine</td>
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<td>Propylthiouracil</td>
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<td>L-Dopa</td>
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<td>Lithium carbonate</td>
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<td></td>
<td>Trichloroethylene</td>
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<td></td>
<td>Silicones</td>
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