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Immunotoxicology

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Section A

Overview of Immunotoxicology
Definition

- **Immunotoxicology** is an adverse or inappropriate change in the structure or function of the immune system after exposure to a foreign substance (xenobiotic)
Potential Effects of Chemical Exposure on Immunological Function

May lead to enhanced susceptibility to disease

Immuno-enhancement

May lead to immune-mediated disease (hypersensitivity, autoimmunity)

Immuno-suppression

Homeostasis

No effect

May lead to enhanced susceptibility to disease
Cardinal Characteristics of the Immune System

- Specificity
- Memory
- Ability to distinguish self from non-self
Differentiation of hematopoietic stem cells
Cytokines

- Molecular mediators of immune and inflammatory reactions
  - Interleukins
  - Interferons
  - Haemopoietic growth factors
  - Tumor necrosis factors
  - Transforming growth factors
Section B

The Basics of an Immune Response
Lymphocyte Cloning

- Lymphocytes are clonally distributed with respect to antigen specificity
- Each clone of lymphocytes has unique membrane receptor for antigen
Interaction of Lymphocytes

With Antigen Results in Clonal Expansion
Daughter Cells Resulting from Clonal Expansion

- They either remain as long-lived memory cells or differentiate into effector cells.
Memory Cells and Effector Cells

- **Memory cells**
  - Provide for an accelerated and more vigorous response following a second encounter with the same antigen

- **Effector cells**
  - Either directly or indirectly cause the elimination of antigen
Two Main Types of Lymphocytes

- T Lymphocytes
- B Lymphocytes

- Memory
- Specificity
- Distinguish Self From Non-Self
Diversity of T Lymphocytes

- T
- Division and Differentiation
- Immunological Memory
- Effector Cells
- Regulatory Cells
T Effector Cells

Cytotoxic T Lymphocytes
- Destruction of virus-infected host cells

Cytokine producing cells
- Augmentation of macrophage function and other aspects of protective immunity
Th → IL-2, TNF, IFN\(\gamma\) → Delayed Hypersensitivity

Th → IL-4, IL-5, IL-6, IL-10, IL-13 → IgE Production

\(\text{(inhibitory)}\)
Cytokines Produced by the Two Main Classes of TH Cells Exert Reciprocal Antagonistic Effects on IgE Antibody Production

IFN-γ

Inhibits

IgE

Promotes

IL-4

TH1

TH2
The End-Cell of B Lymphocyte Differentiation Is the Plasma Cell
Antibody Structure

Biological Effector Function

Antigen Binding
Functions of Antibodies

- Lysis with complement
- Opsonization for phagocytosis
- Neutralization of toxins
- Protection of mucosal surfaces
- Transplacental transfer
General Schematic of Antigen Processing and Presentation
T Lymphocytes Recognize Processed Antigen Presented with “Self” (Major Histocompatibility Complex) Molecules
TH Cells and the Regulation of IgE Antibody Production

TH cells help antibody respond to antigen.
Section C

Immunologically Mediated Tissue Injury
Immunologically Mediated Tissue Injury

- While immune responses constitute a protective mechanism to foreign organisms, they can lead to tissue damage.
- An immune response that results in tissue injury is broadly referred to as a hypersensitivity reaction.
- Such responses are classified into four categories based on the immune mechanisms involved.
Classification of Immunologic Diseases

- **Type I**: immediate hypersensitivity
  - IgE antibody; mast cells
- **Type II**: antibody-mediated
  - IgM, IgG antibodies against tissue or cell surface antigens
Classification of Immunologic Diseases

- **Type III**: immune complexes of IgG or IgM antibodies
- **Type IV**: delayed-type hypersensitivity
  - Sensitized CD4 lymphocytes, macrophages
Antigen → T Cell

CD4 → TCR → Class II + peptide → Antigen-Presenting Cell (APC)

TH2 → IgE → Coombs and Gell Classification

TH2 → IgM, IgG → II

TH2 → IgM, IgG → III

TH1 → DTH Cells → IV
Hapten

- A **hapten** is a substance that is too small to induce an immune response (i.e., low-molecular-weight chemicals)
- Haptens can induce an immune response when they bind to a larger carrier molecule (i.e., protein) to form a hapten-carrier conjugate (adduct)
Schematic Diagram of Chemical Interaction Leading to Hypersensitivity Reactions or Autoimmunity

Chemical

Protein

Antigenic determinant

Naïve protein

Altered protein

Hapten/protein conjugate

Disease state

Autoimmunity

Hypersensitivity

Mechanism of action

Effect

Adjuvancy

CD8+

Ab-Dependent cytotoxicity

Complement-mediated cytotoxicity

Immune-complex Mediated

IgE

CD4+

Exacerbate

Preexisting disease

Induce disease

Exacerbate

Preexisting disease

Induce disease
Allergic (Hypersensitivity) Reactions Take Place in Two Stages

First encounter with antigen \quad \Rightarrow \quad \text{Sensitization phase}

Second or subsequent encounter with antigen \quad \Rightarrow \quad \text{Elicitation phase}
Immunologic Mechanism of Contact Sensitization (Skin)

**INDUCTION**
- Allergen
- Class II MHC
- Langerhans Cell
- Via Afferent Lymphatics
- Peripheral Lymph Node
- IL-1
- IL-2
- IL-2 Receptor
- Proliferation

**ELICITATION**
- Allergen
- Sensitized T-Lymphoblast
- Memory T-Cell
- Sensitized T-Cell
- Mediator Release
- Swelling Erythema Vesiculation
Development of Allergic Contact Dermatitis, a Delayed Hypersensitivity Reaction

Primary contact
- T-cells → T memory cells
- No dermatitis

Secondary contact
- T memory cells → Many active cells
- Dermatitis

Poison ivy catechol molecules → Catechols combined with skin proteins

Skin protein

7-10 days

1-2 days
Contact Dermatitis

Contact dermatitis around a healing rug burn.
Question

- The skin and lungs are often target organs of toxicity by immune-mediated mechanisms — Why?
Section D

Case Studies: TMA and Beryllium
Respiratory Allergy Sensitization Phase

- Encounter with Antigen
- Dermal Inhalation
- IgE ANTIBODY
- Binds to Tissue Mast Cells
Respiratory Allergy
Elicitation Phase

Second or subsequent encounter with Antigen

Antigen Cross-Links
Mast Cell-Bound
IgE Antibody

Respiratory Tract

Degranulation

Vasoactive Amine
Leukotrienes

Vasodilation Bronchoconstriction
Trimellitic Anhydride

*Elicits Immediate Hypersensitivity in Lung*

- TMA covalently reacts with protein to form immunogenic hapten-protein conjugates which can elicit the formation of IgE antibody as detected by RAST

- (Radioallergosorbent Test) measures IgE antibody in serum with a radioactive indicator system
Immunogenic Hapten–Protein Conjugates

Example of how a chemical covalently reacts with protein to form immunogenic hapten–protein conjugates
### Average Airborne TMA Dust Concentrations

*As Measured for Several Different Jobs*

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<td>2.1</td>
<td>0.0006</td>
<td>0.01</td>
<td>0.01</td>
<td>0.03</td>
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<td>0.0002</td>
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<td>0.0007</td>
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*Average TMA dust concentration of 5 years*
## Annual Determinations of Total Antibody and Specific IgE Bound to $^{123}$ I-TM-HAS from 1979–1983

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<td>Worker</td>
<td>TMA Exposure</td>
<td>TMA-Induced Symptoms</td>
<td>Total Antibody (ng/ml $^{123}\text{i}$-TM-HSA Bound)</td>
<td>Specific IgE (ng/ml $^{123}\text{i}$-TM-HSA Bound)</td>
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<tr>
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<td>0</td>
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<td>Operator</td>
<td>LRSS</td>
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<td>Irritant or none</td>
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*Initial clinical evaluations and total antibody and specific IgE binding to $^{125}\text{i}$-TM-HAS of 20 workers—group 1*
Beryllium Induces Delayed Type Hypersensitivity in Lung

- Following inhalation exposure, beryllium can have a half-life from several weeks to 6 months in the lungs.
- In the lungs, beryllium can act as a direct irritant leading to non-specific inflammation.
- In susceptible individuals (3–6%), beryllium exposure results in a DTH response.
Lymphocyte Stimulation Test

- Whole blood and saline
- Centrifugation
- Ficoll Isopaque
- Separated blood
- Cultivation
- Glass fibre filter
- Incorporation of thymidine
- Antigen suspension
- Culture medium
- Measure radioactivity
In vitro proliferation of purified T-cells (A) and T-cell subpopulations (B) from the lungs and blood of patients with chronic beryllium disease and controls in response to beryllium