Lecture 29: Treatment of Allergies & Hypersensitivity Reactions II-IV

Chapter 15 - Roitt

Treatment Strategies for Allergies
- Environmental - limit exposure to allergen
- Drugs - Antihistamines, mast cell stabilizers, corticosteroids (reduce inflammation), leukotriene inhibitors.
- Hyposensitization - slow, prolonged immunization with allergen appears to reduce sensitivity. This probably involves a change in antibody production from IgE to IgG, i.e. class switching is from IgM \( \rightarrow \) IgG instead of IgM \( \rightarrow \) IgE. IgG inhibits IgE activation of mast cells.
- Immunotherapy - administration of humanized anti-IgE monoclonal antibodies (Omalizumab - clinically approved). Binds to CH₂ domain of IgE.

Hypersensitivity II (IgM + IgG/Macrophage/NK)
- Antibody-mediated destruction of cells.
- Binding of specific antibody to antigen on the surface of a cell facilitates its destruction.
- Basis of several autoimmune diseases.

2A. Sensitization:
- Modified proteins on surface of cells generate a B-cell response via C3b enhanced phagocytosis by macrophages & T₄, response.
- Drug-induced Reactions: Drugs adsorb to cell membrane proteins and act as hapten-carrier conjugates; blood cells most commonly affected. Most Ab are directed to the modified protein, and thus the reaction subsides as antigen is eliminated.
  - Cross-reactivity is a possibility, leading to chronic conditions.
  - Presence of B-memory cells can lead to rapid response for subsequent uses of the drug.

2 B/C. Activation & Effector Functions.

i. Complement-mediated Reactions
- Specific antibody binds to antigen on target cell membrane
- C₁q of the classical pathway binds to the Fc region of specific antibody, triggering the complement cascade that leads to lysis of target cell
- Phagocytes can bind Ab-Ag complex directly via C3b receptors.
- Mediators released by phagocytes cause inflammation and tissue damage

ii. Macrophage
- Munching of opsonized target cell (and C3b opsonized antibodies), via C3b and Fc receptors.
iii. Antibody-Dependent Cell-mediated Cytotoxicity (ADCC)
   - Specific antibody binds to antigen on target cell.
   - NK cells bearing Fc receptors bind to the specific antibody \( \text{phagocytosis does not occur} \).
   - NK cells kill by:
     a) \( \text{Fas} \), \( \text{Fas L} \).
     b) \( \text{Perforin} / \text{granzyme} \).

Type III Hypersensitivity (Neutrophil)

3A Sensitization:
- Binding of antibody \( \text{IgG, IgM} \) to antigen (formation of immune complex) in solution causes IC deposition in tissues, kidney, skin, joints, heart, brain, small blood vessels.

3B/C Activation and Effector:
- Complement activation.
- Release of the anaphylatoxins C5a and C3a result in increased vascular permeability and recruitment and activation of neutrophils that release proteases and inflammatory mediators while attempting endocytosis of complex.
- Severity and nature depends on the quantity, size, and distribution of immune complexes.

Localized reaction: Arthus reaction
- Immune complexes accumulate near site of antigen introduction (e.g., insect bite, injection, inhalation of bacterial or fungal spores).
- Inflammation, localized tissue damage, and necrosis occur over 4-8 hours.
- This disorder comprises many occupational diseases:
  - Farmer's lung: allergy to spores of bacterium on rotting hay, pulmonary inflammation
  - Pigeon breeder's, cheese washer's, maple bark stripper's, paprika worker's, thached roof worker's diseases

Systemic reaction: e.g., serum sickness
- Response to foreign protein such as Ig (Ig therapy for treatment of various disorders).
- Immune complexes are formed after repeated prolonged administration and deposited in tissues.
- Symptoms: fever, joint pain, rash.

(Figures from "Immunology – A short course")
Type IV Hypersensitivity – DTH delayed type hypersensitivity (T\textsubscript{H1} + Macrophages):

4A. Sensitization phase
First exposure: antigen is captured by APCs (likely dendritic cells); presented by MHC II to CD4\textsuperscript{+} T\textsubscript{H} cells, which differentiate into a T\textsubscript{DTH} subset (T\textsubscript{DTH}; antigen-specific memory T cells)
- Time frame: 1-2 weeks after primary contact with antigen
- Triggered by:
  - hapten-like molecules (chemicals)
  - Metal ions (nickel chromium)
  - foreign tissue grafts

4B. Activation phase
Re-exposure to antigen, which is recognized by sensitized, antigen-specific T\textsubscript{DTH} cells in skin. Activated by D.C. and macrophages in skin.
- T\textsubscript{DTH} cells secrete cytokines,
  i. MCP-1: monocyte chemotactic protein
  ii. MIF: macrophage migratory inhibitory factor
  iii. IFN-γ: recruits and activates macrophages
- Time frame: 1-3 days after secondary contact with antigen

4C. Effector phase
Principal effector cells – monocytes recruited, they then become macrophages
- Phagocytosis
- Lytic enzymes,
- reactive oxygen species like NO
- TNF-α

If antigen persists, then activity of the macrophage is prolonged. Phagocytosis continues. Degradative enzymes and reactive oxygen species from macrophages can leak into surrounding tissue, causing extensive damage. Symptoms can last for weeks and become chronic.