immunopathology

Dr. Ameer Dhahir
Objectives.

• Explaining the causes of immune deficiency with clinical examples.
• Explaining important examples of inappropriate or excessive immune response.
• Discussing the pathogenesis of autoimmune diseases.
• Defining amyloidosis and its relation to immune disorders.
Disorders of immune system are

- Inadequate immune response:
  - Primary: genetic disorders
  - Secondary: drugs or disease

- Excessive or inappropriate immune response.
Primary immune deficiency

- **X-linked agammaglobulinemia (Bruton disease):**
  failure of pre-B cell to form B-cell:
  » Bacterial infection
  » Autoimmune diseases

- **Isolated IgA-deficiency:** reduced IgA level:
  » Asymptomatic
  » Diarrhea and respiratory infection
  » Autoimmune diseases

- **Hyper-IgM syndrome:** fail to produce IgA, IgG, and IgE.

- **Thymic hypoplasia (DiGeorge syndrome):** fail to form T cells associated with hypoparathyroidism and facial abnormalities.

- **Severe combined immune deficiency syndrome:** defects in both B and T cell differentiation
Acquired immune deficiency syndrome (AIDS) pathogenesis:

- The virus gains entry to T-cells by attaching to surface CD$_4$ molecules.
- It takes over cellular metabolism to synthesize new virus.
- Infect other CD$_4$+cells, particularly macrophages & dendritic cells.
- HIV envelope gp$_{120}$ must also bind to other cell surface molecules (co-receptors) to facilitate cell entry.
• the HIV genome enters the cytoplasm of the cell and undergoes reverse transcription…?
• cDNA enters the nucleus & integrates into the host genome.
• proviral DNA may be transcribed to form complete viral particles that bud from the cell membrane, leading to cell death.
AIDS: Opportunistic infections

The appearance of Pneumocystis jiroveci grossly in lung is shown here. Note that this is an extensive pneumonia.

At low magnification, note the appearance of Pneumocystis jiroveci in lung with exudate in nearly every alveolus.
Mycobacterium tuberculosis infection of lung, with upper lung field granulomatous and cavitary disease.

Mycobacterium tuberculosis infection of lung is shown here with numerous red rods seen with acid fast staining.
Kaposi's sarcoma typically produces one or more reddish purple nodules on the skin.

Kaposi's sarcoma microscopically produces slit-like vascular spaces in the dermis of the skin.
Progressive multifocal leukoencephalopathy (PML) appears grossly as irregular areas of granularity in white matter which bear some resemblance to the plaques of demyelination with multiple sclerosis.
Inappropriate or excessive immune response:
Transplant rejection:

- is a complex immunologic phenomenon involving both cell- & humoral-mediated hypersensitivity responses of the host.
- directed against histocompatibility antigens, human leukocytes antigens (HLA) on the donor allograft.
- blood vessels are important targets of the host's immune response.
Transplant rejection can be:

• Hyperacute: minutes to a few hours:
  » result of pre-formed humoral host antibodies
  » Previous rejection of a transplant
  » Multiparous women
  » Previous blood transfusion.

• Acute : within days or weeks :
  » mediated by both humoral & cell-mediated mechanisms
  » may appear after cessation of immunosuppressive therapy

• Chronic rejection : months to years:
  » slow breakdown of the host's tolerance to the graft
  » inadequate immune suppression.
  » does not respond to standard immunosuppressant
Autoimmune diseases
Autoimmune diseases

• immune reactions against self-antigens i.e., break down of tolerance to self antigen.
• Some autoimmune diseases have a genetic component; e.g. certain diseases are associated with particular HLA histocompatibility types.
• autoimmune disease can be triggered by a microbial infection.
Immunological tolerance

• are regulatory mechanisms that present normally to prevent the occurrence of autoimmune diseases.
• Failure of such mechanisms is responsible for the pathogenesis of autoimmune diseases.
• T- and B-cells bearing molecules (receptors) that react with self antigen must be either eliminated or down-regulated.
Immunological tolerance (cont.)

- the process of T-cell tolerance is much more important than B-cell tolerance in the avoidance of autoimmunity.
- self-reacting-B-cells will not be able to produce auto-antibodies unless they receive appropriate T-cell help.
- tolerance arise inside the thymus (thymic tolerance) or outside the thymus (peripheral tolerance).
Thymic tolerance

• achieved through eliminating all T-cells capable of recognizing self-proteins. This is not, however, induced to many tissue-specific proteins.
Peripheral tolerance: involve many mechanisms:

1) Immunological ignorance: invisible or low level antigen: eg., vitreous humour..apoptosis?

2) Anergy: loss of second signal from antigen presenting cells

3) Suppression: suppressor T-cells; CD8+.

4) B-cell tolerance: lack of T-cell help for cell antigens.
Breakdown of tolerance autoimmune diseases

- Overcoming peripheral tolerance.
  - Molecular mimicry.
  - Epitope spreading
Overcoming peripheral tolerance:

- excessive access of self-antigens to antigen presenting cells
- excessive nonspecific signaling.
- alterations in which self-antigens are presented to the immune system (virus, ROS, drugs).

All these occur when there is inflammation or tissue destruction.

Examples: uveitis & orchitis
Molecular mimicry

• structural similarity between self-antigens and microbial antigens
• this will cause expansion of the responsive T-cell population recognizing the self-peptide if local conditions allow.
• example, rheumatic heart disease...? (Streptococcal M).
epitope spreading:

• the resulting immunological mediated inflammation and tissue damage may allow presentation of further peptides.
• The immune response broadens and local tissue damage accelerates.
Autoimmunity results from multiple factors:

- **Susceptibility genes** that may interfere with self-tolerance.
- **Environmental triggers** (tissue injury, inflammation) that promote lymphocyte entry into tissues, activation of self-reactive lymphocytes, and tissue damage.

Pathogenesis of Autoimmunity
Pathogenesis of Autoimmunity

Postulated role of infections in autoimmunity. Infections may promote activation of self-reactive lymphocytes by inducing the expression of costimulators (A), or microbial antigens may mimic self-antigens and activate self-reactive lymphocytes as a cross-reaction (B).
Etiology of autoimmune diseases:

• The interaction between Genetic and Environmental factors is important in the pathogenesis of autoimmune diseases.
Genetic factors in autoimmune diseases

• supported by:
  » Different autoimmune diseases may cluster within the same family
  » Subclinical autoimmunity is common among family members.

• The strongest association is with MHC molecule because of their role in:
  » T-cell function
  » Control of immunity and inflammation (Ag- presentation)
Environmental factors in autoimmune diseases

1) **Hormones:**
   - More in female
   - In reproductive age, estrogen
   - Experimental ovary removal reduces the incidence

2) **Infections:** molecular mimicry

3) **Drugs:**
   - may involve mechanisms comparable to molecular mimicry
   - Genetic variation in drug metabolism is also important.
   - Slow metabolism increases the risk...why?

4) **UV radiation:**
   - modifying self-antigens to become immunogenic
   - enhancing death of the cells  → expression of hidden antigen
## Examples of autoimmune diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>Main organ involved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic lupus erythematosus</td>
<td>Skin, kidney, joints, heart, lung</td>
</tr>
<tr>
<td>progressive systemic sclerosis</td>
<td>Skin, gut, lung</td>
</tr>
<tr>
<td>Polymyositis-dermatomyositis</td>
<td>Skeletal muscle, skin</td>
</tr>
<tr>
<td>Rheumatoid disease</td>
<td>Joints, lungs, systemic vessels</td>
</tr>
</tbody>
</table>
Amyloidosis
Amyloidosis

- Abnormal deposition of proteinaceous materials in tissue interstitium causing clinical disorders.
- Many cases result from deposition of plasma cell derived proteins (AL-amyloid).
- Progressive accumulation causes pressure atrophy at adjacent cells.
- May be systemic (primary or secondary) or localized.
Here is a chronic renal disease that may actually increase the size of the kidney. This is amyloidosis. Pale deposits of amyloid are present in the cortex, most prominently at the upper center.
The amorphous pink deposits of amyloid may be found in and around arteries, in interstitium, or in glomeruli.
Here are Congo red stained deposits of amyloid in the adrenal cortex. Amyloid may collect in adrenal as well as other organs.
Chemical nature of amyloid:

- **AL**: plasma cell derived Ig light chain
- **AA**: synthesized by the liver important in inflammation.
- **Aβ**: cerebral lesions of Alzheimer disease.
- **Transthyretin (TTR)**, A mutant TTR is deposited in familial amyloid polyneuropathies.
- **β₂–microglobulin**, component of the MHC class I molecules
Primary amyloidosis:

- **AL type**
  - usually systemic
  - Example include Multiple myeloma associated amyloidosis (M spike on PEP and Bence Jones protein in urine.

- **AA types**: associated with infections (e.g., TB) and autoimmune diseases.

- **Heredofamilial amyloidosis (AA)**: familial Mediterranean fever.

- **Localized amyloidosis (AL)**: localized mass.

- **Endocrine amyloid (TTR)**

- **Amyloid of aging (TTR)**
Pathogenesis:

- elevated SAA levels through the influence of cytokines ($IL_1$, $IL_6$) on liver cells in response to tissue injury and inflammation.
- enzyme defect that results in the incomplete breakdown of SAA.
- S &S depend on site, amount & duration of the deposition.
Summary

• Immune disorders are either due deficient or excess or inappropriate responses.
• Primary immune deficiency are genetic disorders that affect mainly T cell/B cell function.
• Acquired immune deficiency syndrome (AIDS) is a viral disease that attacks the immune system with manifestations related to that.
Summary (cont.)

• The mechanisms of autoimmune diseases involve defects in the immune tolerance that maintain the immune system non reactive to self antigens.

• Genetic and environmental factors underlie the pathogenesis of autoimmune diseases.

• Amyloidosis is an abnormal protein deposition that may associate immune related cell disorders.