

**BOARD and OKAP REVIEW COURSE**

**Immunology: Uveitis**

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## Immunology - UVEITIS

Inflammation – Delicate balance between useful and harmful ocular inflammation in a structure with a low threshold for irreversible damage and limited capacity for regeneration.

### Non-Immune Mechanism

Intact corneal epithelium and globe.  
Tears – Lysozyme, lactoperoxidase, lactoferrin, etc.

### Components of the Immune Response

Antigen, Antibody, B cells, T cells complement, neutrophils, monocytes/macrophages.

*Antigen (Ag)* – A substance capable of eliciting an immune response.

#### *S Antigen*

- Origins in photoreceptor region of retinal and pineal gland.
- Causes experimental autoimmune uveitis, T-cell response.
- Causes bilateral uveitis when injected at sites far from the globe.
- In humans, causes a condition similar to VKH and sympathetic ophthalmia.
- Inflammation primarily a type-4 hypersensitivity reaction

#### Antibody (Ab)

- Classes defined by their 2 heavy polypeptic chains.
- Antigen binds to the variable regions (Fab) defined by 2 light polypeptide chains.
- Monochronal antibodies:
  - o created by in vitro fusion of myeloma cells and antibody producing B cells producing a single, highly specific antibody.
  - o can be used as probes to explore nature of cell surface Ag+Ab.
  - o Elisa testing – enzyme linked immuno absorbent assay.
    - first links an enzyme to an Ab; creates a conjugate
    - expose conjugate to Ag creating an Ag-Ab Enzyme complex.
    - then expose substrate to complex to detect presence of Ag and measure reaction.

### Components

Antibody – produced by B cells

- IgG
  - o most abundant, can fix complement
  - o only Ab to cross the placenta, maternal Ab in newborn infant
  - o important role in almost all immune reactions including bacteria.
  - o major Ab produced during re-exposure to Ag, i.e., secondary or anamnestic response.
  - o performs opsonization (Igm does as well), i.e., Fab portion combines with Ag. The resulting Fab-Ab complex then triggers T cells and macrophages via their Fc portion.
- IgA
  - o 2<sup>nd</sup> most abundant

- monomeric shape
- important role against viruses
- found in tears and nasal, bronchial, and GI secretions
- IgM
  - largest Ab, pentameric shape
  - efficient agglutinator of particulate Ag
  - first Ab to appear in developing a Primary Immune Response.
  - fixes complement and performs opsinization like IgG.
- IgD
  - major B cell receptor on B cell surface
- IgE
  - important role in atopic reaction
  - has the ability to degranulate mast cells.

#### B cells

- originates from bursa of Fabricius in chickens
- bursal equivalent in man uncertain
- Important for humoral immunity
- polyclonal activation by pneumococcus cell walls, Pockweed

#### T cells

- "Thymus" derived cells
- responsible for cellular immunity
- Several types:
  - T – Helper cells = OKT4 = CD4+ = 60-80% total T cells
  - T – Suppressor cells = OKT8 = CD8+ = 20-30% total T cells
  - T – Natural killer cells = Tnk, spontaneously cytotoxic
  - Cyclosporin selectively interferes with T cell activation, particularly Th cells, inhibiting the synthesis of cytokines including interleukin 2
    - Inhibits chemotaxis of inflammatory cells especially eosinophils
  - In AIDS, see inversion of TH/TS ratio
  - T-cells secrete:
    - Interleukin 2
      - produced by Th cells
      - stimulates lymphocyte growth, i.e., Th, Ts, Tnc
      - deficient in AIDS patients
  - Interleukin 4
    - stimulates B cells and macrophages
  - Interferon
    - stimulates Class II Ag (Ii) expression on macrophages enhancing Ag presentation
  - Release interleukins and interferons.

#### ACAID = Anterior Chamber Acquired Immunodeviation

- Ag in the anterior chamber causes an increase in Ts cells, i.e., a suppression of T cell mediated immunity
- See an intact Ab, humoral immune response.
- Requires an intact ocular/splenic axis, i.e., need Ag processing in the spleen for this to occur.

#### Macrophages

- mobile phagocytic cells derived from bone marrow stem cells
- Secretes lysozyme, collagenases, elastase, etc.

- Secretes Interleukin 1 = leukocyte activating factor, which activates T cells.
- Role in Ag presentation
- Stimulated by interleukin 4

### Immunogenetics

- Major histocompatibility complex (MHC) = Human Leukocyte Antigen (HLA) in man = Transplantation Antigens
- Located on chromosome #6
- Three major classes:
  - o Class I = proteins found on all nucleated cells surfaces and controlled by loci A, B and C.
    - principal antigenic target in allograft rejection
    - strength of immune reaction determined by these antigens sitting on the cell surface.
    - recognized by Tc when attacking virally infected cells
  - o Class II = cell surface proteins (Ia proteins) expressed by loci D/Dr also known as the Ir gene.
    - immune cooperation between cellular subtypes only occurs if all subtypes share the Ir (D/Dr) antigenic surface proteins.

#### *Some Ocular Diseases and their HLA Associates*

<b>Disease</b>	<b>Antigen</b>	<b>Relative Risk</b>
Acute anterior uveitis	HLA-B27 (C) HLA-B8 (BA)	10 5
Ankylosing spondylitis	HLA-B27 (C) HLA-B7 (BA)	100
Behcet's disease	HLA-B51 (O) (?C)	4-6
Birdshot retinochoroidopathy	HLA-A29 (C)	49
Ocular Pemphigoid	HLA-B12 (C)	3-4
Presumed ocular histoplasmosis	HLA-B7, DR2 (C)	11.8
Reiter's Syndrome	HLA-B27 (C)	40
Rheumatoid arthritis	HLA-DR4 (C)	11.0
Sympathetic ophthalmia	HLA-A11 (M)	3.9
Vogt-Koyanagi-Harada disease	MT-3 (O)	74.5

\*C-Caucasian, BA-Black American, O-Oriental, M-Mixed Ethnic study

Attributions – Uveitis – fundamental and clinical practice  
Robert B. Nussenblatt and Alan G. Palestine

- HLA B-27 positive uveitis patients tend to be younger with inflammation characterized by exuberant fibrinous reaction and unilateral non granulomatous disease.
  - Long term prognosis same as HLA-B27 negative patients
  - 1-6% of general population but present in 50-60% of patients with acute iritis
  - triad of acute iritis, spondylitis and HLA-B27 associated with:
    - Ankylosing spondylitis
    - Reiter's Syndrome
    - Psoriatic arthritis
    - Inflammatory bowel disease

Class III =

- o Complement

- A series of 11 serum proteins that interact in an enzymatic cascade.
- leads to cell death by structural and functional alterations of cell membranes
- triggered by a classic and alternate pathway
  - classic = triggered by the binding of Fc portions of IgM and IgG which are bound to Ag
  - alternate = activated by bacterial endotoxins and lipopolysaccharides derived from bacteria cell walls.
- Complement fragments C3a, C4a, C5a are anaphylactic, i.e., increase vascular permeability, hence augmenting recruitment of inflammatory mediators.
- C5a – chemotactic, i.e., receptor for it found in macrophages and neutrophils.

### *Types of Immune Mechanisms and Relation to Disease*

- Type I = Hypersensitivity
  - Inciting Ag combines with IgE bound to mast cells and basophils releasing vasoactive substances producing specific effects on target organs: skin = rash, lungs = asthma, blood vessels = shock.
  - Example: hay fever, atopic conjunctivitis
- Type II = Antibody Dependent Cell Mediated Cytotoxicity (ADCC)
  - Ab (IgM or IgG) hooks up with Tc cell triggering a cytotoxic reaction.
  - Examples: ocular pemphagoid, blood transfusion reaction.
- Type III = Immune Complex Disease
  - Ag/Ab complexes trigger the complement cascade which in turn attacks cells capable of causing tissue damage.
  - Examples: Arthus reaction, Behcet disease, Phacoanaphylaxis, systemic lupus erythematosus, rheumatoid arthritis, serum sickness
- Type IV = Delayed Type Hypersensitivity = Cellular Immune Response
  - Mediated solely by T cells
  - Examples: PPD, Sarcoid, Sympathetic Ophthalmia
  - Response to viruses mostly mediated