Immunology in Rheumatic Diseases

Knowledge of immunology forms the basis of understanding many of the Rheumatologic diseases and has become the focus of many exciting new treatment strategies .......

AIMS OF THIS LECTURE
- Introduce the important components of the immune system
- Show how they interact & protect the body (IMMUNITY)
- Without attacking itself (TOLERANCE)
- Demonstrate what happens when things go wrong & the body turns against itself (AUTOIMMUNITY)
- Provide examples of immunology in clinical Rheumatology

Topics covered
1. Immune mechanisms
2. Tolerance
3. Autoimmunity
4. Rheumatologic diseases
   - Rheumatoid arthritis
   - Systemic Lupus Erythematosus
   - Spondarthropathies
   - Inflammatory myopathies
   - Systemic sclerosis
   - Osteoarthritis

Immune Mechanisms
- Overview
- Specific components
  - Physical barrier
  - Complement
  - Cells
  - MHC
  - Cytokines
- Activation of adaptive immune system by the innate system

1. IMMUNE MECHANISMS
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Immunity Can Be Divided Into 2 Main Components:

1. Innate immunity
   - Rapid acting, nonspecific

2. Specific or adaptive immunity
   - Slower onset of action
   - Targets pathogens that escape the innate immune system
   - Activated by the innate immune system

Barriers against infection

- Microorganisms are kept out of the body by:
  - Skin
  - Bactericidal fluids eg tears
  - Secretion of mucous
  - Gastric acid
  - Microbial antagonism

Complement

- A group of serum proteins which act in an enzymatic cascade
- Produce molecules involved in
  - Cell lysis
  - Phagocytosis
  - Inflammation

Cells in the Innate System (1)

- NK (Natural killer) cells
  - Large granular lymphocyte
  - Lyses viral infected cells & tumor cells
  - Note the smaller NK cell destroying its target cell by pore forming perforins

Cells in the Innate System (2)

- Phagocytic cells
  1. Neutrophils
     - 70% of circulating WCC
     - Major circulating phagocytic cell
  2. Macrophages
     - Large phagocytic cell derived from blood monocyte
     - Also acts as an antigen presenting cell (APC)
**Cells in the Innate System (3)**
- Eosinophils
  - Granulocytes important in the killing of parasites
- Mast cells
  - Contain abundant granules
  - Complement components
  - Trigger degranulation
  - Results in release of inflammatory mediators including histamine & leukotrienes

**Cells in the adaptive system (1)**
- B & T lymphocytes
  - Are the major cells of the adaptive system
- CD4 T cells
  - Help to stimulate B cell antibody production
  - Activate macrophages
- CD8 T cells (cytotoxic cells)
  - Kill target cells expressing foreign antigen

**Cells in the adaptive system (2)**
- B cells
  - May mature to become plasma cells producing antibodies. The function of antibodies are to:
    - Directly stimulate or neutralise its target
    - Activate complement
    - Form a bridge between the target & cytotoxic cell (eg macrophages & NK cells) → Antibody dependant cellular cytotoxicity (ADCC)
  - Act as antigen presenting cells
    - (More about these cells later......)

**Antigen Presenting Cells**
- Unlike the other cells, T_H cells only recognise antigen that is properly presented with MHC by other cells
- These specialised cells are called antigen presenting cells
- They include macrophages, B cells, fibroblasts & dendritic cells

**Major Histocompatibility Complex (MHC)**
- Antigen is ingested by the antigen presenting cell then presented on its surface in molecules called major Histocompatibility complex
- MHC are also the molecules responsible for rejection in transplant organs

**Major Histocompatibility Complex**
- MHC proteins = HLA (Human Leucocyte Antigen) in humans
- Molecules on cell surfaces which can display antigen
- Products of a region of highly polymorphogenic genes on chromosome 6
- 2 types:
  - Class I
  - Class II
Comparison of MHC Class I & II Molecules

<table>
<thead>
<tr>
<th></th>
<th>Class I</th>
<th>Class II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genes</td>
<td>HLA A/B/C</td>
<td>HLA D</td>
</tr>
<tr>
<td>Expressed on</td>
<td>All nucleated cells</td>
<td>APCs - B cells, macrophages &amp; dendritic cells</td>
</tr>
<tr>
<td>Size</td>
<td>9 to 10 amino acids (smaller)</td>
<td>12 to 28 amino acids (larger)</td>
</tr>
<tr>
<td>Source of antigen displayed</td>
<td>Intracellular eg viral infections</td>
<td>Extracellular eg bacterial infections</td>
</tr>
<tr>
<td>Antigen presented to</td>
<td>CD8+ T cells</td>
<td>CD4+ cells</td>
</tr>
</tbody>
</table>

( APC = Antigen presenting cell)

Activation of the Adaptive Immune System

Antigens that escape the innate immune system encounter the adaptive system

Adaptive immune system - powerful ∴ must be activated

Activation of the Adaptive Immune System

In this diagram, the macrophage represents the innate system & the T_h cell, the adaptive system

1. APC eg Macrophage ingests Ag
2. Ag presented on cell surface with MHC
3. T cell recognises its cognate Ag
4. 2nd signal required = protein on APC + a T_h cell receptor
5. ACTIVATION & 6. Cytokine production

Do these steps look familiar?

1. Ag (virus) ingested
2. Ag presented on cell surface with MHC
3. T cell recognises its cognate Ag
4. 2nd signal required = protein on APC + a T cell receptor
5. ACTIVATION & 6. Cytokine production

Cytokines

Cells of the immune system communicate with each other using cytokines

This diagram shows the immune system in action. Take a closer look...
Cytokines
- Protein hormones
- Mediate the effect of the innate & specific immunity
- Autocrine/paracrine/endocrine
- Effects include cell activation, division, apoptosis, movement

Cytokine types
- Interleukins - produced by leukocytes & have effects mainly on WBC
- Chemokines - chemoattractants
- Colony stimulating factors - differentiation & proliferation of stem cells
- Interferons - interfere with viral replication
- Eg. IL-2 a growth factor that stimulates CTLs & NK cells to proliferate
  TNF activates primed macrophages & NK cells

Cells & cytokine production
Cells produce different subgroups of cytokines which will instruct the innate & adaptive systems to produce cells & antibodies against specific antigens.

Here is an example:

<table>
<thead>
<tr>
<th>Cells</th>
<th>Cytokines</th>
<th>Antigen</th>
</tr>
</thead>
<tbody>
<tr>
<td>T_{H1} (CD4)</td>
<td>IL-2, IFN-γ, TNF</td>
<td>Viruses, Bacteria</td>
</tr>
<tr>
<td>T_{H0}</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T_{L2} (CD8)</td>
<td>IL-4, IL-5, IL-10</td>
<td>Parasites</td>
</tr>
</tbody>
</table>

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Tolerance Is

the immunologic unresponsiveness to self antigens
- It allows the immune system to protect the body without turning against itself
- The focus is on the adaptive immune system
- T & B cells must be able to discriminate self from non-self
- This occurs centrally & peripherally

Central T Cell Tolerance
- T cells are produced in the bone marrow & migrate to the thymus
- Here they go through a rigorous selections process
- Only T cells that react to antigen but not self exit
- The rest die by apoptosis

NEJM 2001;344(9): 655 - 664.
Peripheral T Cell Tolerance

If autoreactive T cells enter the circulation, there are several mechanisms that can prevent an autoimmune reaction.

B Cell Tolerance

- CENTRAL
  - Clonal deletion of autoreactive B cells in the bone marrow, spleen & lymph nodes.

- PERIPHERAL
  - Lack of help from T cells is the predominant factor.

Autoimmunity

- Breakdown in mechanisms preserving tolerance to self
- Severe enough to cause a pathological condition

Autoimmune diseases

- Organ specific e.g.
  - Insulin dependant diabetes
  - Myasthenia gravis

- Multisystem e.g.
  - Rheumatoid arthritis
  - SLE

Molecular mimicry:
The antigen looks similar to a self-peptide. As a result, the body produces an immune response to the trigger factor as well as to self.
Autoantibodies in Connective Tissue Diseases

- Produced by B cells
- May pathogenic eg.
  - Form immune complexes in lupus nephritis
- Markers of certain diseases
- Not diagnostic
  - Apart from rheumatic disorders, they may be found in normal population & with other conditions
  - Therefore only test when clinically indicated.

Autoantibodies associated with disease

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>AUTOANTIBODY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid Arthritis</td>
<td>Rheumatoid factor</td>
</tr>
<tr>
<td>SLE</td>
<td>ANA, dsDNA, Smith</td>
</tr>
<tr>
<td>Scleroderma</td>
<td>ANA, centromere, topoisomerase</td>
</tr>
<tr>
<td>Antiphospholipid Syndrome</td>
<td>Anticardiolipin (ACLA)</td>
</tr>
<tr>
<td>Sjogren's syndrome</td>
<td>Ro, La</td>
</tr>
<tr>
<td>Polymyositis</td>
<td>Jo-1</td>
</tr>
<tr>
<td>Dermatomyositis</td>
<td>Mi-2</td>
</tr>
<tr>
<td>Wegener's granulomatosis</td>
<td>C-ANCA</td>
</tr>
</tbody>
</table>

Cellular Targets for autoantibodies

- Ab to intercellular proteins
  - Proteinase 3
  - cANCA
- Ab to cell membrane proteins
  - ACLA
- Ab to IgG
  - Rheumatoid factor
- Antinuclear antibodies (ANA)
  - dsDNA
  - ENA – Smith, Ro, La, RNP
  - Centromere, topoisomerase
- Ribosomal & lysosomal components
  - tRNA synthetase
  - AntiJo 1

This diagram depicts the autoantibodies & their respective target antigens

Rheumatoid Arthritis

A symmetrical peripheral polyarthritis of unknown aetiology that leads to joint deformity & destruction due to erosion of cartilage & bone

The immune mechanisms in RA

- Note:
  1. The interaction between the cells of the innate & adaptive immune systems
  2. The cytokines produced are targets for newer therapy in RA

NEJM 2001; 344 (12): 907 - 916
The inflammatory process results in damage to cartilage & bone

Systemic Lupus Erythematosus
A generalised connective tissue disorder affecting many organs and characterised by the production of many autoantibodies

Lupus Nephritis
- The kidney biopsy on the right is from a patient with diffuse proliferative lupus nephritis shows massive deposits of IgG on immunofluorescence

Rheumatoid Factor
- Rheumatoid Factor is an autoantibody produced in RA
- It is however produced in several other conditions; the clinical features are important in making the diagnosis

ARA Criteria for the diagnosis of SLE
- Note:
  1. Many organs can be affected
  2. Several auto-antibodies are associated with SLE

Ankylosing Spondylitis
AS is a chronic inflammatory disease of the axial skeleton manifested by back pain & progressive stiffness of the spine
Ankylosing Spondylitis

- The prevalence of the MHC, HLA B27 is high in Caucasians but rare in Black populations with Ankylosing Spondylitis

Dermatomyositis

An idiopathic inflammatory myopathy associated with certain characteristic cutaneous manifestations

Note: the inflammatory infiltrate in the muscle biopsy of this patient with Dermatomyositis

Scleroderma

The term encompasses a heterogeneous group of conditions linked by the presence of thickened sclerotic skin lesions

The inflammatory process in Scleroderma results in marked fibrotic process responsible for many of the clinical features

Scleroderma Lung Disease

2 important lung diseases which occur due to the inflammatory process in Scleroderma
Osteoarthritis

Immune mechanisms have even been shown to play a role in OA.......

References

4. UpToDate 12.3

References (cont)


The End............