Structure & Function of immune system

Consists of

1. Lymphoid organs: Central (Bone marrow, Thymus) and Peripheral (Lymph node, spleen, MALT)
2. Lymphoid cells: T cell, B Cell, NK Cells
3. Other cells: Phagocytes, mast cells, platelets
4. Cytokines: Interleukins, interferons, Tumour necrosis factor, colony stimulating factor etc
Lymphoid organs:

a) Primary (central) lymphoid organs:
   Thymus & bone marrow
b) Secondary (peripheral) lymphoid organs:
   Lymph nodes, spleen & MALT.

**Pluripotent stem cell:**
All cell of blood first originates from yolk sac at 6-8 wks, later fetal liver, finally in bone marrow just before birth and for rest of life. After puberty haemopoiesis is confined to pelvis, vertebrae, sternum, skull and rib bones.

The stem cells mature into T & B cells in the primary (central) lymphoid organs (thymus & bone marrow), respectively. After maturation in central lymphoid organs they reach secondary lymphoid organs (spleen, lymph node, MALT), where they are exposed to antigen and appropriate immune response takes place.
Central (Primary) lymphoid organs:

Thymus:

- Develops from 3rd & 4th pharyngeal pouch at 6th wk of gestation. Developed at 3rd month.
- Progenitor T cells originate in bone marrow, reach thymus & differentiate into thymic lymphoid cells (thymocytes).
- Only 1% of the lymphocytes leave the thymus & are called thymus (T) dependent cells (or T-cells). Rest are destroyed locally.
- Lymphocyte proliferation in thymus is not dependant on ag. stimulation.
- Lymphocytes are ‘educated’ in thymus so that they become capable of mounting cell mediated immune response.
Bone marrow:

- Progenitor B cells develop in bone marrow & mature there into antibody producing lymphocytes called **B-cells**.
- Following appropriate antigenic stimulation B-cells transform into plasma cells & secrete abs.
Peripheral lymphoid organs:

**Lymph nodes:**
- Phagocytose foreign materials including microorganisms.
- Help in proliferation & circulation of T & B cells.
- Enlarge following local antigenic stimulation.
- The cortical follicles & medullary cords contain B lymphocytes & the paracortical area contains T lymphocytes.

**Spleen:**
- Largest lymphoid organ
- Immunological function is directed against blood borne agents.
- Acts as reserve for blood & as systemic filter for foreign particles.
Mucosa associated lymphoid tissue (MALT):

- The lymphoid tissue present in mucosa lining the alimentary (Payer’s patches), respiratory, genitourinary & other lumina & surfaces are collectively called as MALT.

- MALT contains both T & B cells.

- IgA is predominantly produced locally. (Local immunity) Other immunoglobulins IgG, IgM & IgE may also be produced locally.

- Antigen exposure at one site may lead to production of specific antibodies at other mucosal or secretory sites also.
Cells of the lymphoreticular system:

Lymphocytes, macrophages, dendritic cells, granulocytes (neutrophils, eosinophils, basophils, mast cells)

Lymphocytes:
- Constitute 20-45% of leucocyte population.
- T & B cells have naïve lymphocytes and lymphoblasts.
- Naïve or resting lymphocytes (small lymphocytes) are inactive till interacts with antigen.
- Lymphoblasts are formed when naïve cells interact with antigen in presence of IL-7. Lymphoblasts differentiate to effector and memory cells.

Effector cells: Large lymphocytes, short-life. Effector T cells induce helper and cytotoxic cells. Effector B cells are antibody producing plasma cells.

Memory cells: Dormant till antigen stimulation. Rapidly becomes effector cells, long life span.
**T-cells**

Make 70-80% of lymphocytes.

Have T cell receptors (TCR) on their surface. TCR responsible for antigen recognition processed by antigen presenting cells (APC) like macrophages.

Responsible for CMI (Cell mediated immunity)
Cluster of differentiation: (CD)
“International Workshops for Leucocytes Differentiation Antigens” designated names to diff. markers.

CD molecules are cell surface markers, designated with a particular function

Over 364 CD markers have been identified so far.

<table>
<thead>
<tr>
<th>CD No.</th>
<th>Cell type assocn.</th>
<th>Former designation</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4</td>
<td>Helper T cell</td>
<td>T4, Leu3</td>
</tr>
<tr>
<td>CD8</td>
<td>Suppress or/ Cytotoxic T cell</td>
<td>T8, Leu2</td>
</tr>
</tbody>
</table>
Effector T cells.

2 types: CD4 Helper T-cells and CD8 cytotoxic T-cells

**CD4 cells:** Recognize antigen processed by APC and present with MHC-II. They secrete cytokines which modulate cellular and humoral immunity (CMI & AMI)

**CD8 cells:** Recognize intracellular antigens (Viral / tumour), processed by any nucleated cell and presented along with MHC-1. Destroys virus infected cells and tumour cells.

- CD4, CD8 balance activity leads to optimal response.
- Overactivity of helper & decreased activity of suppressor cells leads to autoimmunity.
- Diminished helper function & increased suppressor function leads to immunodeficiency.
- Helper cells constitute 65% & suppressor cells constitute 35% of T cells. Normal Ratio 2:1.
T-cell maturation:

**Stem cell**

- CD7
- Pro-T cells: Yolk sac, Fetal liver, Bone marrow

**Pre-T cell**

- CD7
- CD2
- CD3

**Cytoplasm**

- CD7,2,3

**IMMATURE T-CELLS**

- Thymus cortex
- Thymus medulla & later peripheral blood

**CD7,2,3 TCRδγ**

**MATURE T-CELLS**

- HELPER / INDUCER CELL
- CYTOTOXIC / SUPPRESSOR CELL

- CD7,2,3,4, TCRαβ
- CD7,2,3,8, TCRαβ
**B-cells**

- Makes 10-15% of lymphocytes.
- Proliferation in bone marrow first, later peripheral lymphoid organs.
- Initial stages of development independent of antigenic stimulation.
- Responsible for AMI (Antibody mediated immunity or humoral immunity).
B-cell maturation:

- **Stem cell** → **Pro-B cell** → **Pre-B Cell**

- **IgM**
  - **IgM** → **IgG1,2,3 or 4**
  - **IgM** → **IgA1 or 2**
  - **IgM** → **IgE**

- **IgD**
  - **IgD** → **IgG1,2,3 or 4**
  - **IgD** → **IgA1 or 2**
  - **IgD** → **IgE**

- **IgA**
  - **IgA** → **IgG1,2,3 or 4**
  - **IgA** → **IgA1 or 2**
  - **IgA** → **IgE**

- **IgE**
  - **IgE** → **IgG1,2,3 or 4**
  - **IgE** → **IgA1 or 2**
  - **IgE** → **IgE**

- **IgM producing Plasma + Memory cells**

- **Antigen independent**
- **Bone marrow**

- **Antigen dependent**
- **Peripheral organs**

- **MARS Learning Centre**
Null cells:
Lymphocytes (5%) lacking distinguishing phenotypic markers characteristic of T or B cells are known as null cells. Neither T or B cells. Intermediate between T & B.

Types:
1) Killer (K cells).
2) Natural killer cells (NK Cells).

1) Killer (K cells):
- Possess receptors for Fc part of IgG.
- Can lyse or kill cells sensitized by IgG.
- Responsible for ab. Mediated cytotoxicity.

2) Natural killer cells (NK Cells): (10-15%) 
- Similar to CD8, have cytotoxicity towards malignant & viral infected cells.
- Not ab. Dependent or MHC restricted & do not require sensitization by prior antigenic contact.
Other cells of immune system

Macrophages, dendritic cells, granulocytic cells (Neutrophils, eosinophils, basophils), mast cells.

Macrophages:

Monocytes: Largest blood cell, migrate to tissue to transform into tissue macrophages

Tissue macrophages: Kupffer cell (liver), Microglial cell (Brain), mesangial cell (kidney), alveolar macrophages (Lungs), histiocytes (Connective tissue) etc
**Function of macrophages:**

1. Phagocytosis
2. Antigen presentation
3. Secretory products of macrophages with various biologic activity - Enzymes (Lysozymes, lipase etc), Free radicals ($\text{H}_2\text{O}_2, \text{O}_2$), Cytokines (Interferon, interleukin, TNF-$\alpha$), growth factors, coagulation factors, complement factors (C5, C8, Factor B, D, I)

**Dendritic cells:**

They are APCs non-phagocytic in nature. Capture, process and present antigens to Helper T cells.
Granulocytic cells:
1. Neutrophils: Principal phagocytes
2. Eosinophils: Limited phagocytic activity, elevated in allergy and helminth infections
3. Basophils: Granules rich in histamine. Plays major role in anaphylaxis (Type-1 hypersensitivity).

Mast cells:
1. Present on skin, connective tissue of organs and mucosa of alimentary and respiratory tract.
2. Like basophils, play role in anaphylaxis
Cytokines

They are chemical substances serving as messengers, mediating interaction and communication between various cells of immune system.

Cytokines include those which were earlier known as

**Lymphokines**: Produced by lymphocytes

**Monokines**: Produced by monocytes

**Interleukins**: Produced by WBCs (Acts on same or different WBC)

**Chemokines**: Involved in chemotaxis and leukocyte behaviour.
<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Interleukins</strong></td>
<td></td>
</tr>
<tr>
<td>IL-1 to IL-13 and IL-17</td>
<td>Various WBCs</td>
</tr>
<tr>
<td><strong>Interferons (IFN)</strong></td>
<td></td>
</tr>
<tr>
<td>IFN - α</td>
<td>Leukocytes</td>
</tr>
<tr>
<td>IFN - β</td>
<td>Fibroblasts</td>
</tr>
<tr>
<td>IFN - γ</td>
<td>T-H, T-C, NK cells</td>
</tr>
<tr>
<td><strong>Tumour necrosis factor (TNF)</strong></td>
<td></td>
</tr>
<tr>
<td>TNF- α</td>
<td>Macrophage</td>
</tr>
<tr>
<td>TNF - β</td>
<td>T-H, T-C</td>
</tr>
<tr>
<td><strong>Colony stimulating factor (CSF)</strong></td>
<td></td>
</tr>
<tr>
<td>GM-CSF</td>
<td>Fibroblasts, endothelium, T-cells, macrophages</td>
</tr>
<tr>
<td>G-CSF</td>
<td>Bone marrow stromal cells, macrophages</td>
</tr>
<tr>
<td>M-CSF</td>
<td>Fibroblasts, endothelium</td>
</tr>
<tr>
<td><strong>Others</strong></td>
<td></td>
</tr>
<tr>
<td>TGF - β</td>
<td>Macrophages, mast cells, T &amp; B cells, platelets</td>
</tr>
</tbody>
</table>
**Interleukins (IL):**

Secreted by leucocytes (WBCs). Many types- IL1, IL2, IL3 etc.

**IL1:** Produced by APC (Macrophages, fibroblasts etc.).

It is an endogenous pyrogen acting on thalamus to produce fever, promotes inflammation and production of acute phase proteins. Stimulates IL2 production.

**IL2:** Produced by activated CD4 T cells. Promotes growth of T & B cells.

**IL4:** Stimulate B cells to produce antibodies.
**Interferons:**

3 types: αβγ.

γ Interferon: Activates macrophages by increasing antigen intake, elevating intracellular enzymes, enhancing antigen presentation to CD4 cells by the MHC Class II.

αβ Interferons: Inhibit replication of virus in host cells.

**CSF:** Stimulates growth & differentiation of bone marrow progenitor cells.

**TNF:** 2 types: αβ. Kills virus infected & tumour cells.

TNF β: Released by CD8 T cells kills cells foreign to our body, like microbes, cancer & transplanted cells.

TNF α: Produced by macrophages. Lyses tumour cells & eliminates bacteria & parasites. Called “Cachectin” because it breaks down muscle protein.
Cytokines and diseases:

Pathogenesis of many diseases is characterized by increased expression of cytokines.

Eg:

1. Septic shock by Gram negative bacteria (E.coli, Neisseria). Endotoxins released by them stimulate macrophages to release IL-1, TNF-α.
2. Toxic shock syndrome: S.aureus toxin stimulate macrophages to release IL-1, TNF-α.
3. Cancers: IL-6 elevated in cervical and balder cancers
4. Chaga’s disease: Caused by parasite Trypanosoma cruzi blocks IL-2 activity leading to T-H cell inhibition which leads to immunosuppression
Cytokines uses:

- INF-α is used in treatment of Hepatitis B, C, hairy cell leukaemia, multiple myeloma and chronic myeloid leukaemia.
- INF-β used to treat multiple sclerosis
- INF-γ used to treat chronic granulomatous disease
Major histocompatibility complex (MHC):

MHC is a group of genes coding for host cell surface molecules that bind to the peptide fragment derived from pathogens and display them on host cell surface for recognition by appropriate T-Cells.

- Present on almost all human cells
- Human MHC antigens are synonymous to human leucocyte antigens (HLA) (First discovered on Leucocytes)
- Genetic sequence of MHC genes different for every individual
- Allograft rejection/acceptance because of MHC. Greater the difference in MHC, greater chance of rejection. Hence called histocompatibility antigens
- HLA (MHC) complex of genes is located on the short arm of chromosome 6.
Major histocompatibility complex (MHC):

- HLA consists of 3 separate classes of molecules: Class I, Class II & Class III.

**MHC/HLA Class I:**
- Has 3 genes- HLA-A, HLA-B, HLA-C. Forms α-chain of MHC-I
- Present on all nucleated cells (except sperm cells) and platelets. Absent on RBCs
- They present peptide antigen to CD-8

**MHC/HLA Class II:**
- Has HLA-DP, HLA-DQ, HLA-DR genes. Forms α & β-chain of MHC-II.
- Located on surface of APCs
- They present peptide antigen to CD-4
Major histocompatibility complex (MHC):

MHC/HLA Class III:

- Not involved in antigen presentation.
- Carries genes coding for Complement factors (C2, C4, C3 convertase, factor B, properdin), heat shock proteins, TNF-α & β, treoid-hydroxylases
HLA class I: (MHC-I)

Present on all nucleated cells (except sperm cells) and platelets. Absent on RBCs

They are principle ags. involved in graft rejection (allografts) & cell mediated cytolysis.

Structure:

Class I molecules consists of a heavy peptide chain (alpha chain) linked to smaller beta-2 microglobulin (beta chain). Alpha chain has 3 globoid domains (alpha1,2,3) which protrude from the cell membrane & a small length of transmembrane C terminus reaching into cytoplasm.

The distal domains (alpha1 &2) are folded to form a cavity or groove b/n them. Protein antigens processed by macrophages or dendritic cells form small peptides & are bound to this groove for presentation to CD8 T cells.

Antigen presentation pathway is cytosolic

A T-cell will recognize the ag. only when presented as a complex with the MHC class I molecule & not otherwise (MHC restriction). When presented so the CD8 cytotoxic killer cell destroys the target cell (like virus infected or tumour cell).
**HLA Class II: (MHC-II)**

Found only on surface of APCs.

**Structure:**

It consists of an alpha & beta chain. Each chain has 2 domains. The proximal domain (α2,β2) is constant. Distal domain (α1,β1) is variable & has ag-binding site for recognition by CD4 lymphocytes.

They are primarily responsible for **graft-versus-host response** and mixed leucocyte response.

Antigen presentation pathway is endocytic.
Functions of MHC:

- Helps maximise protection against microbial infection.
- Prevents microbes with related antigenic make up sneaking past host immune defences.
- Implicated in a no. of non immunological phenomenon such as individual odour. (Body weight in mice & egg laying in chickens)

MHC restriction:

Processing & presentation of ag. to T cells require both the cells self determinants coded by the same MHC genes. T cells can accept the processed ag. only if its presented by macrophages carrying on its surface the self-MHC determinant known as immune associated (IA) ag. When macrophage bears diff. IA ag. it cannot cooperate with T cell. This is known as MHC restriction.
**HLA typing:**

HLA typing is primarily used for testing compatibility b/n recipients & potential donors before tissue transplantation. Also has applications in disputed paternity & anthropological studies.

Typing is done serologically by microcytotoxicity, mixed leucocyte reaction (MLR) & primed lymphocyte typing (PLT). Molecular methods are used widely now.

**Diseases associated with HLA alleles:**

<table>
<thead>
<tr>
<th>HLA allele</th>
<th>Associated disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLA-B27</td>
<td>Ankylosing spondylosis, reactive arthritis (Yersinia, Salmonella, Gonocci), Reiter’s syndrome</td>
</tr>
<tr>
<td>DR-2</td>
<td>Multiple sclerosis, Goodpasture’s syndrome</td>
</tr>
<tr>
<td>DR-3</td>
<td>Myasthenia gravis, SLE</td>
</tr>
<tr>
<td>DR-3/DR-4</td>
<td>Insulin-dependent Diabetes mellitus</td>
</tr>
<tr>
<td>DR-4</td>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td>A3/B14</td>
<td>Hereditary haemochromatosis</td>
</tr>
</tbody>
</table>