Immunity

(1) Non – specific (innate) immunity

Characters:
(1) Non – specific: does not need special recognition of the foreign cell.
(2) Innate: does not need previous exposure.
(3) Rapid: acts directly against foreign or abnormal cell.

Includes:
1- Mechanical & chemical barriers
(a) Epithelium
(b) Mucous secretion of the respiratory tract
(c) Acid secretion of the stomach.

2- Non-specific cellular defense mechanisms
(a) Microphages: neutrophils & eosinophils & produce cytokines
(b) Macrophages: monocytes & tissue macrophages
(c) Natural killer (NK) cells: non T, non B lymphocytes (1st line of defense against viral infections)

3- Non-specific humoral mechanisms
(1) Lysosymes ⇒ lysis of bacteria
(2) Interferons (IFN) (α, β, γ IFN):
   Functions: 1- α, β IFN have antiviral effects
             2- α IFN ↑↑ activity of NK cells ⇒ used in treatment of cancer
             3- γ IFN ⇒ a potent activator of macrophages.
(3) Acute phase proteins: (CRP) during acute inflammation
(4) Properdin system: proteins that activate complement system.
(5) Complement system: plasma proteins present in blood & activated by 2 pathways

(2) Specific (acquired immunity)

Characters:
☐ Specific: must 1st recognize the antigen to be activated & destroy it.
☐ Acquired: depends on previous exposure to antigens
☐ Remembers: a 2nd exposure to the same antigen ⇒ more rapid & strong response (2ry response)

Acquired immunity differs from innate immunity in specificity & memory from 1st exposure

Types of acquired immunity: (2)

<table>
<thead>
<tr>
<th>(1) Humoral immunity</th>
<th>(2) Cellular immunity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Due to activated B lymphocytes (secrete antibodies)</td>
<td>Due to activated T- lymphocytes</td>
</tr>
<tr>
<td>Major defense against bacterial infection</td>
<td>The major defense against viral, fungal, few bacterial infections &amp; is responsible for allergic reaction &amp; rejection of transplants</td>
</tr>
</tbody>
</table>

Antigen: foreign substance (big M.W > 10.000) stimulate immune system to produce immune response
Hapten: small molecule by itself cannot produce immune response
Hapten + body protein = recognized complex ⇒ immune response

Antigen recognition:

Antigen 1st time enters the body

B- lymphocytes (direct recognition)
Antigen binds directly with a specific receptor on B- cells

Or

T- lymphocytes (indirect recognition)
Antigen 1st ingested by "antigen presenting cell" ⇒ partially digested & presented to a specific receptor on T cells
Antigen presentation:
Antigens are phagocytosed, partially digested & presented to the specific T-lymphocyte

Antigen presenting cells (APCs) include: macrophages, dendritic cells in lymph nodes & spleen, Langerhans cell in the skin & B-lymphocytes.

Major histocompatibility complex (MHC):
- MHC (human leucocytic antigen "HLA"): is a glycoprotein present on cell membranes
- MHC is important in immune recognition & response to differentiate self from non-self
- MHC is 2 types (according to site & function)

<table>
<thead>
<tr>
<th>Class I (MHC-I)</th>
<th>Class II (MHC-II)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present on all nucleated cells.</td>
<td>Present on the surface of APCs</td>
</tr>
<tr>
<td>Coupled to the peptide fragments (from protein synthesis) within the cell</td>
<td>Coupled to peptide products (from antigen digestion)</td>
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</table>

(1) Cell–mediated immune response

1- Exposure to the antigen.
2- Presentation by the adjacent APC.
3- Activation of specific lymphocytes.
   Formation of memory T-lymphocytes \( \Rightarrow \) more rapid response on 2\(^{nd} \) exposure to the same antigen
4- Recognition of T- cell to the processed antigen (with MHC) via TCR on cell membrane of T-cells
5- Interaction between T-cell & APC through glycoproteins (cluster of differentiation "CD") on the surface of T-cells.
6- All T-cell have CD3 complex & either CD4 molecules (interact with MHC- II) or CD8 molecules (interact with MHC- I)

Types & functions of activated T-lymphocytes: according to cell surface receptors into:

CD4 T cells T-helper (Th) cells:
- (Th) cells are the most numerous types of T cells & recognize the antigen accompanied by MHC-II
- Function: stimulate other cells in immune system (the major regulator of all immune responses)
- Functionally divided into: Th-1 & Th-2

<table>
<thead>
<tr>
<th>Th-1</th>
<th>Th-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secrete interleukin-2 (IL-2) &amp; interferon (INF(\beta))</td>
<td>Secrete IL-4, 5, 6</td>
</tr>
<tr>
<td>Stimulate the growth &amp; proliferation of cytotoxic &amp; suppressor T-cells.</td>
<td>Stimulate B-cell growth, differentiation &amp; antibody production.</td>
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</table>

CD8 T cells T-cytotoxic (Tc) cells recognize antigens accompanied by MHC-I

Functions:
1- Tc \( \Rightarrow \) direct attack & lysis of cells by secreting perforins \( \Rightarrow \) perforations in target cell membrane
2- Tc are important defense against viral infection & cancer cells.
3- Tc are responsible for rejection of transplants of foreign tissues & delayed allergic reactions

(2) Humoral immune response

1- Recognition of B- lymphocytes to the antigen (via antibodies on the surface of B cell)
2- Binding of B- lymphocytes to the antigen.
3- Activation of B- lymphocytes \( \Rightarrow \) proliferation & differentiation into plasma cells (produce antibodies) & memory B cells (responsible for more effective 2ry response)
4- Full activation of B-lymphocytes needs Th2 cells \( \Rightarrow \) produce B-lymphocyte growth factors (IL4, 5, 6)

<table>
<thead>
<tr>
<th>Primary antibody response</th>
<th>Secondary antibody response</th>
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<tbody>
<tr>
<td>Following the 1(^{st} ) exposure to an antigen, antibodies appear in plasma after about 8 days (induction period) ( \Rightarrow ) ( \uparrow \uparrow ) to reach a high level (within weeks) ( \Rightarrow ) then ( \downarrow \downarrow ) rapidly.</td>
<td>On 2(^{nd} ) exposure to the same antigen, the conc. of the antibody produced is much higher than the 1(^{st} ) exposure. This enhanced 2ry response is the basis of immunological memory</td>
</tr>
<tr>
<td>The antibodies formed are the IgM.</td>
<td>The antibodies former are of IgG.</td>
</tr>
</tbody>
</table>
Antigen – antibody interaction:
Binding of the antigen to the antibody \( \Rightarrow \) destruction of the antigen by the following mechanisms:
1- Neutralization: or inactivation of the antigen
2- Opsonization: antibodies coat the antigens \( \Rightarrow \) stimulating their phagocytosis.
3- Agglutination: antibodies agglutinate antigens (agglutination of RBCs in incompatible blood transfusion)
4- Activation of NK cells
5- Activation of the complement system.

Communication between cells in the immune system (cytokines):
- **Cytokines**: are hormone-like chemical messengers
  - Secreted by lymphocytes, macrophages, endothelial cells, nervous & glial cells.
  - **Cytokines play a role in** haemopoiesis, macrophage activation, chronic inflammation, growth & differentiation of T & B lymphocytes
  - Cytokines include interleukins, colony stimulating factors & tumor necrosis factors.

Recognition of self:
The specific immunity has the ability to distinguish between self & non-self.

**Mechanisms:**
1- **Clonal deletion**: The lymphocytes that react with self antigens are eliminated in the thymus during early development.
2- **Clonal anergy**: when cells are exposed to a high conc. of antigen (self antigen) in absence of lymphokines \( \Rightarrow \) the activated cells become hyporesponsive to this antigen.
3- **Inhibition by suppressor T-cells**.

**The fetus is not rejected as a foreign graft by the mother because:**
1- The placental trophoblast doesn’t express classes I & II MCH genes but expresses HLA-G gene instead, so antibodies against fetal proteins do not develop.
2- ↓↓ in maternal antibody production during pregnancy.

Active & passive immunity:
**Active immunity**: antibodies are made by the individual cells after vaccination (using killed organisms or their toxins after attenuation) to produce a 1ry response followed by immunological memory.

**Passive immunity**: antibodies are transferred from one person to another or from animals to humans.

Tissue transplantation:
**Grafting organs from one person to another or from one place to another in the same person**
The main problem facing grafting is **rejection of the graft** by T lymphocytes.
Due to tissue antigens (HLA) or MHC complex that differ from one person to another.

**To overcome rejection:**
1- Administration of glucocorticoids which inhibit cytotoxic T-cell proliferation.
2- Using anti lymphocyte globulin or monoclonal antibodies against T lymphocytes.
3- Total lymphoid tissue irradiation.

Acquired immune deficiency syndrome (AIDS):
**Cause**: human immunodeficiency virus (HIV) infection mainly through infected blood, sexual contact

**Characters**: ↓↓ in the number of the circulating CD\(_4\) T-helper cells.
- The loss of the helper cell \( \Rightarrow \) failure of proliferation of CD\(_8\)- cytotoxic & B cells \( \Rightarrow \) loss of immune functions & death from infections with normally non pathogenic bacteria or cancer.

Autoimmune diseases:
Antibodies are formed against patient's own tissues
- e.g. insulin dependent diabetes (antibodies against pancreatic B-cells)
- & myasthenia gravis (antibodies against nicotinic cholinergic receptors in muscles)
Autoimmune diseases usually occur after destruction of some body tissues \( \Rightarrow \) release considerable quantities of antigens \( \Rightarrow \) circulate in the body \( \Rightarrow \) acquired immunity against own tissues
Blood groups

Blood groups are classified according to the presence or absence of certain antigens (mucopolysaccharide) on the RBCs membrane (A & B antigens)

A-B-O SYSTEM

<table>
<thead>
<tr>
<th>Group</th>
<th>A</th>
<th>B</th>
<th>AB</th>
<th>O</th>
</tr>
</thead>
<tbody>
<tr>
<td>%</td>
<td>40%</td>
<td>10%</td>
<td>5%</td>
<td>45%</td>
</tr>
<tr>
<td>RBCs antigens</td>
<td>A</td>
<td>B</td>
<td>A &amp; B</td>
<td>–</td>
</tr>
<tr>
<td>Plasma antibodies</td>
<td>Anti B</td>
<td>Anti A</td>
<td>–</td>
<td>Anti-A &amp; Anti-B</td>
</tr>
</tbody>
</table>

Importance of ABO system:
(1) **Blood transfusion**: cross matching test should be done before blood transfusion
   - If the transfused blood is incompatible,
     - The antigens of donor RBCs are agglutinated by the corresponding antibodies in recipient plasma ⇒ hemolysis
     - The donor’s plasma antibodies are diluted in the recipient blood.
     - Antigen = agglutinogen
     - Antibody = agglutinin
   - Group O is a universal donor (no antigens on RBCs)
   - Group AB is a universal recipient (no antibodies in plasma)

(2) **Medicolegal use**: excludes paternity (It is a good –ve test)
   - A, B, & O agglutinogens are inherited. O is recessive while A & B are co-dominant antigens.

Rh factor (D factor)

- It is an antigen present on the surface of RBCs. It was first discovered in Rhesus monkey.
- 85% of people are Rh +ve (have D antigen)
- 15% of people are Rh -ve (have no D antigen)
- Normally there are no anti Rh (anti-D) antibodies in Rh +ve & Rh –ve people but it can be formed

Importance of Rh factor:
(1) **Erythroblastosis fetalis**: Rhesus hemolytic disease of the newly born
   - This disease occurs if:
     - Rh (–ve) female is married from an Rh (+ve) male, so the fetus will be Rh (+ve).
     - At delivery of the first baby, fetal RBCs enter the maternal circulation.
     - The mother becomes sensitized & produce anti – D agglutinins (IgG)
     - During next pregnancy, maternal antibodies (IgG) cross the placenta causing agglutination & hemolysis of fetal RBCs, SO:
       - (1) the baby will have severe anaemia & jaundice: due to excessive formation of bilirubin ⇒ crosses the undeveloped blood brain barrier ⇒ brain damage (kernicterus)
       - (2) The fetus is born dead in severe cases.

   - The first baby usually born normal but may be affected
     (if the mother was previously sensitized by Rh (+ve) blood transfusion).
   - Rh antibodies (IgG) can cross the placenta
   - ABO antibodies (IgM) can’t cross the placenta, so no fetal complication.
Prevention:
1. Rh (–ve) female should never receive Rh +ve blood.
2. When Rh –ve female delivers Rh + ve fetus, anti-D antibodies are given to her immediately after delivery to neutralize the D antigen of the Rh +ve fetal cells to prevent sensitization of the mother.

Treatment: replacement of the blood of the baby with Rh –ve O blood by repeated exchange transfusion

(2) Repeated blood transfusion:
- If Rh –ve person is transfused with Rh +ve blood, he will produce agglutinins against Rh factor.
- If this person is transfused (later on) with Rh +ve blood, agglutination will occur.

Blood transfusion

Indications:
1. To restore whole blood as in hemorrhage (loss of > 20% of blood)
2. To restore one element of blood (RBCs, WBCs, platelets, plasma proteins or clotting factors)
3. Erythroblastosis fetalis

Precautions:
1. Blood must be compatible by cross matching test before transfusion.
2. Rh –ve person should receive Rh –ve blood.
3. Free from blood-borne diseases & free from contamination.
4. Fresh blood i.e. stored at 4°C for no more than 21 days.
5. High Hb content.

Complications:
1. Hemolytic complication (incompatible blood transfusion):
   - agglutination of the donor’s RBCs with recipient antibodies
   - a. Blockage of blood capillaries: backache & joint pain
   - & anginal pain: (if blockage of coronary Vs)
   - b. Hemolysis follows which leads to release of:
     2. K+: from RBCs & hyperkalemia (↑↑K’) & cardiac arrhythmia
     3. Hb: from RBCs & ↑↑ bilirubin & hemolytic jaundice
     (yellow coloration of skin & mucous membranes)
     - acid hematin & blockage of renal tubules & renal failure
     - ↑↑ blood viscosity & heart failure

   Hemolytic reactions are more with ABO incompatibility than Rh incompatibility

2. Mechanical complications: air or fat embolism.
3. Infective complications: e.g. infective hepatitis, AIDS or malaria.
4. Physical complications: excessive transfusion & overloading of the circulation & heart failure