Course: Immunology

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Lecture: Specific Immunity (HMI and CMI), Primary and Secondary Immune Response.

B and T cells Biology, Activation, Immunological role in HMI and CMI.

Cells involved in specific immune responses:

1) **Antigen Presenting Cell (APC):** These cells are the messengers between innate (non-specific) immunity and the adaptive (specific). Specialized APC are macrophage (MØ), B-cells and Dendric cells (DC).

Roles of Antigen Presenting Cell (APC):

1. Engulfment of foreign Ag, processing it and presenting it (or a polypeptide from it) on the surface near the Major Histocompatibility Complex MHC class I or II.
2. Communication during the immune response between immune cells especially T- cells to induce the proper immune response cellular or humolar.
3. Secretion of cytokines which are substances (glycoproteins) that regulate the immune response.

2) Lymphocytes:

The immune system depends on the Lymphocytes:

- **B-cells or B-lymphocytes.**
- **T-cells or T-lymphocytes.**
- **Natural killer cells (NK).**

B-cells are responsible for Antibody mediated immunity (Humoral immunity HMI). And T-cells are responsible for cell mediated immunity (cellular immunity CMI).

In addition to MHC classes, each T-lymphocyte has surface molecules to give the cell identity:

1- **Clusters of Differentiation (CD):** They are major surface markers (Ag) of T-cells, T-cells are classified according to the presence of these CD marker:

T helper cells: $CD3^+$ $CD4^+$ $CD8^-$
T cytotoxic cells: $CD3^+$ $CD4^-$ $CD8^+$

Note: NK cells have no CD markers on the surface so they are usually called null cells.

2- **T-cell Receptors (TCR):** they are proteins on the T-cells surface represent the places (or regions) of binding to the presented Ag on the APC surface. TCR is the accessory (help) of $CD4^+$ (T-helper) and $CD8^+$ (T-cytotoxic) cells during recognizing foreign Ag presented near MHC and increase the storage of binding. TCR and CD3 is usually called TCR- complex.

NOTE: **B-cells** are able to be APC by internalization of Ag inside the cell and do the processing and presenting, which will be discussed later.

Dendric cells: cells found only in mammalian immune system; their function is to engulf and process Ag then presents it on the surface to other immune cells. Found in tissues that in contact with external environment such as skin, lung stomach and intestine. Their name comes from their branches projects.

Differences between B and T cells

Properties	B-lymphocyte	T-lymphocyte
Site of maturation	Bone marrow (bursa in chickens)	Thymus
Surface markers	Immunoglobulins	CD markers(clusters of differentiation)
Product after Ag stimulation	Plasma cells which secrets Abs	Sensitized T-cells
General function	Abs production and APC	Regulating (Helping or suppressing) immune response and CMI
Types	No types	T-helper, T-cytotoxic and T-suppressor

Types of Lymphocytes and their functions

Lymphocytes	Surface Markers	Function
T helper cells (Th)	CD3, CD4	Help other cells T and B in their function
Cytotoxic T cells (Tc)	CD3, CD8	Kill and lyse target cells that express foreign Ag (cell contain intracellular pathogen or tumor cells).
T suppressor cells (Ts)	CD3, CD8	Inhibit the immune function of other lymphocytes
T memory cells	---------	Long live cells recognize Ag of first cellular immune response.
B lymphocytes	Ig	Differentiate to plasma cells, which produce Abs against Ag.
Plasma cells	Ig	Secrete Abs.
B memory cells	Ig	Long live cells recognize Ag of first humoral immune response.
Natural killer cells(NK)	---------	Kill and lyse target cells that express foreign

NOTE: When Ag succeeds to inter the body; the results of the invasion can be the followings:

- **Dose of Ag is not enough or the Ag is hapten:**

1. No response or Tolerance occurs, when the immune system do not response to the Ag.
2. Phagocytosis and complement activation leading to non-specific immune response against without memory.

- **Enough Ag dose (complete Ag):**

The Ag induces a specific immune response against it (either CMI or HMI) and memory to remember the same Ag next time. Induction of the

immune response depends on: Ag dose, Ag type, Immune system health, genetic factors and control.

Major Histocompatibility MHC

They are genes **encoding** for proteins found on the surface of all human and animals cells. They have an important role in giving the identity of the cell and in the communication with the immune system cells and regulation of immune response:

MHC class I: found on the surface of all nucleated cells, have role in tissues and organs transplantation.

MHC class II: found on the surface of all immune cells especially APC.

MHC class III: found on the surface of certain cells for some complement components receptors.

Cytokines: proteins produced by many cells act as mediators between cells and regulate other cells function. They include:

1. Monokines, cytokines produced by mononuclear phagocytic cells.
2. Lymphokines, cytokines produced by activated lymphocytes, especially Th cells.
3. Interleukins (IL-), cytokines that act as mediators between leukocytes.
4. Interferons (IFN-), cytokines that play a major role in the innate immunity.

NOTE: Interferones have many types α, β and γ.

IFN-γ: Is the immune interferone, it is antiviral protein, produced from T-cells and MØ and activates monocytes and MØ.

Antibody mediated Immune Response

(Humeral Mediated Immunity, HMI)

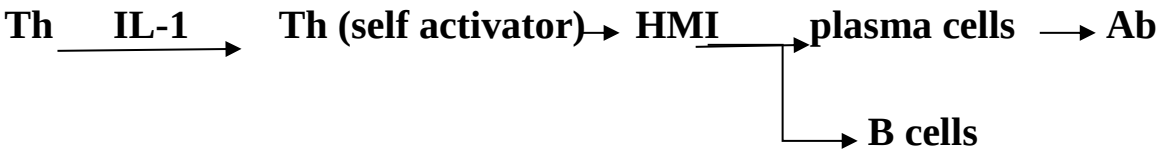
1. The name Humoral came from the old Greek word (humor) mean fluids.
2. The products of this specific immune response is specific Abs (able to react with the same Ag started the immune response) and memory B-cells.
3. HMI starts with **B-cell activation**:

   B-cells have normal Ag receptors on the surface they are natural Igs, these Igs are able to form Ag-Ab complex on the surface of B-cell. This complex will be internalized inside B-cell, then the foreign Ag will be processed within B-cell and presented (or polypeptides from it) on the surface of B-cell near MHC class II and now B-cell is APC.

   T-helper (Th) cells come near the APC B-cell and by the help of TCR and CD4; Th will interact and communicate with APC B-cell and Th cell will be activated and release cytokines or lymphokines (IL-2, IL-4, IL-5 and IFN-γ), these products will induce other B-cells for dividing, proliferation and differentiation. IgM will be the first Ig produced then B- cell will switch to make IgG. This response is called **T-dependent Ag immune response.** The other type of response is **T-independent Ag immune response,** this type of Ag stimulates B-cells without need for T-helper lymphocytes interfere.

4. After B-cells activation, series of events happen (proliferation, clonal expansion, division and maturation), ending with Ab and memory B-cells production. These series of events called B-cell Maturation.

5. During the second exposure to the same Ag that started the first immune response (perhaps after year from first exposure), the B-memory cells will remember the Ag and will be activated and divide into a clone of plasma cells to start the **Secondary immune response** (Memory response).



Differences between T-dependent Ag and T-independent Ag

No.	T-dependent Ag	T-independent Ag
1	Strong response	less
2	need T-cell interaction	Stimulate and activate B-cells directly
3	protein mainly	Lipids (LPS) or polysaccharides (capsules)
4	produce IgM then switch to IgG	produce IgM only
5	Produce B-memory cells	Do not produce B-memory because there is no cytokines in this response

Interleukins involved in specific immune response:

IL-1 ------Source: (Monocytes, Macrophage, DC, NK, B-cells)

Action:

1. T-cells activation by induce IL-2 production.
2. Induce B-cells differentiation and maturation.
3. Induce NK cytotoxicity.
4. Inflammation and fever.
5. MØ activation.

IL-2 ------ Source: (T- helper cells)

Action:

a. Induce proliferation of activated T and B- cells.
b. Induce Tc and NK cytotoxicity to kill tumor cell and bacteria.
c. Activation of monocytes and macrophage.

Cell mediated Immune Response
(Cellular Mediated Immunity, CMI)

This response occurs against cells, which are called **Target cells.** During both HMI and CMI, T-helper cells recognize foreign Ag processed on the surface of APC. If this Ag was processed and presented near MHC class II, then Th cells will activate HMI by B- cells activation, but if the presented Ag on APC was near MHC class I, then Th cells will activate CMI by activation of Tc, NK and MØ. Th cells able to activate and regulate CMI and HMI by many cytokines production.

In addition, in both CMI and HMI, when Th cells recognize the foreign Ag, Th cells will start **T-cells activation** by series of events (expanding, clonal proliferation and differentiation), then become mature to give specific activated T-helper cells in HMI and give specific activated T-helper cells and memory T-cells in CMI.

Types of CMI response:

1. Defense against Tumor cells or cancer cells. Target cell is the cancer cells.
2. Grafts Rejection: Immune response against foreign cells or tissues that transplanted from other body even of the same species. Target cell is the foreign cells.
3. Defense against Mutation affected cells: defense against modified body cells or mutated cells with different surface Antigens due to radiation or chemical agents exposure. Target cell is the mutation cell with new Ags.
4. Defense against Intracellular parasite infected cells: Cellular immune response against infected cells with intracellular parasite (virus, bacteria, fungi and protozoa), with foreign Ag presented near MHC class I. Target cell is the infected cell with parasite.
5. Types 4 hypersensitivity (Delayed type of hypersensitivity by the action of T_{DTH} a type of cytotoxic T-cells). Target cell is the same body cells with immunocomplex precipitated on the surface.

Cells involved in this response:

1. **Antigen Presenting Cell (APC):** The most common APC in CMI are dendric cells DC, which act as APC. These cells process small parts of intracellular parasite body if the DC Dendric cell was infected with it or if it dies spontaneously and during clearing process in the site of infection.

2. **T-cell types:**

A. T-helper cells (Th):

1) Have central role in activation of this system by recognizing foreign or abnormal cells (have abnormal, modified, or intracellular parasite Ag).
2) Responsible for the production of cytokines to induce other cells and regulates the immune response.

B. Cytotoxic T- cells (Tc): These cells are responsible for killing and lysing target cells, hence sometimes they are called killer cells.

C. Natural Killer (NK) cells: These cells are responsible for killing and lysing target cells. These cells are called natural killer because they have non-specific receptors for Ags.

3. Macrophages: Have role in killing target cells, killing intracellular parasite inside MØ and production of cytokines (monokines) for other cells activation and regulation of functions.

Activation of CMI cells:

When T-helper cells recognize foreign Ag on the surface of target cell in association with (or near) MHC class I. The TCR and $CD4^+$ play role in recognition. Then Th cell will be activated and produce cytokines (especially IL-2 and IFN- **γ)**. These cytokines will activate Tc $CD8^+$ cells**,** MØ and NK cells. This activation will increase these cells ability for killing and became more effecter.

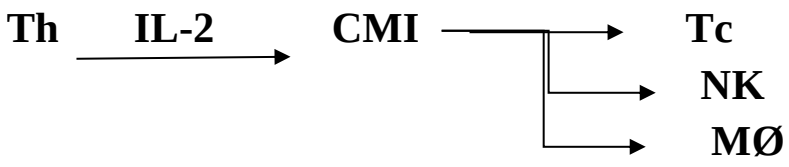
Mode of action for killing target cells:

After T-cytotoxic cells and NK cells activation by Th cells, T-cytotoxic cells come into close contact with target cell; they will bind to the Ag by their specific Ag receptors. While NK cells will attach to Ag (on Target cell surface) by their non-specific receptors for Ag.

T-cytotoxic cells and Nk cells will kill target cells by the following mechanisms:

a. Direct contact killing: Production of **perforin**, which is a protein able to form pores in target cell membrane at the point of contact between Tc cell and target cell, lead to osmotic lysis of target cell.
b. Indirect killing: By secretion of a toxin protein in the space between the two cells, which causes fragmentation of target cell nuclear DNA, then the death of target cell by **Apoptosis**: the programmed cell death.
c. Antibody-dependent cellular cytotoxicity **(ADCC)** killing: it is specific mode of killing occurs when the parasites Ags have ability to induce both HMI and CMI , target cells will be coated with specific Abs formed after HMI against some parts of intracellular parasite like virus. These Abs will bring Tc and NK cells very close to the target cell by acting like a bridge because Tc and NK have receptors to the constant region of Ab. Then Tc and NK cells will be activated and kill the target cell by extracellular products (toxins and enzymes).

This type of CMI occurs when the foreign Ag persist for long time (e.g *Mycobacterium tuberculosis* infection is long standing intracellular infection), also, against some kinds of cancer cells.



Primary immune response

It is the first exposure to the Ag resulting of forming specific Abs and memory B-cells for HMI or T-cells and memory T-cells for CMI**,** the phases are:

1. **Latent Phase**: start after first time exposure to an Immunogen or after induction, include the followings:
   - No Ab level increase (titer).
   - Recognizing Ag as foreign after processing the Ag inside APC.
   - Cellular proliferation and differentiation.
   - Duration of this phase (period) is variable depending on many factors (Ag immunogenicity, Ag dose, Ag solubility, Ag route of immunization or exposure).
2. **Logarithmic phase:** starts when Ab titer begin to increase (active biosynthesis of Ab), last for 10-14 days till reach peak.
3. **Steady phase:** starts when the rates of both formation (synthesis) and catabolism of are equal, then serum concentration of Ab is constant.
4. **Decline phase:** starts when the Ab titer starts to fall down due to increase Ab catabolism rate than synthesis.

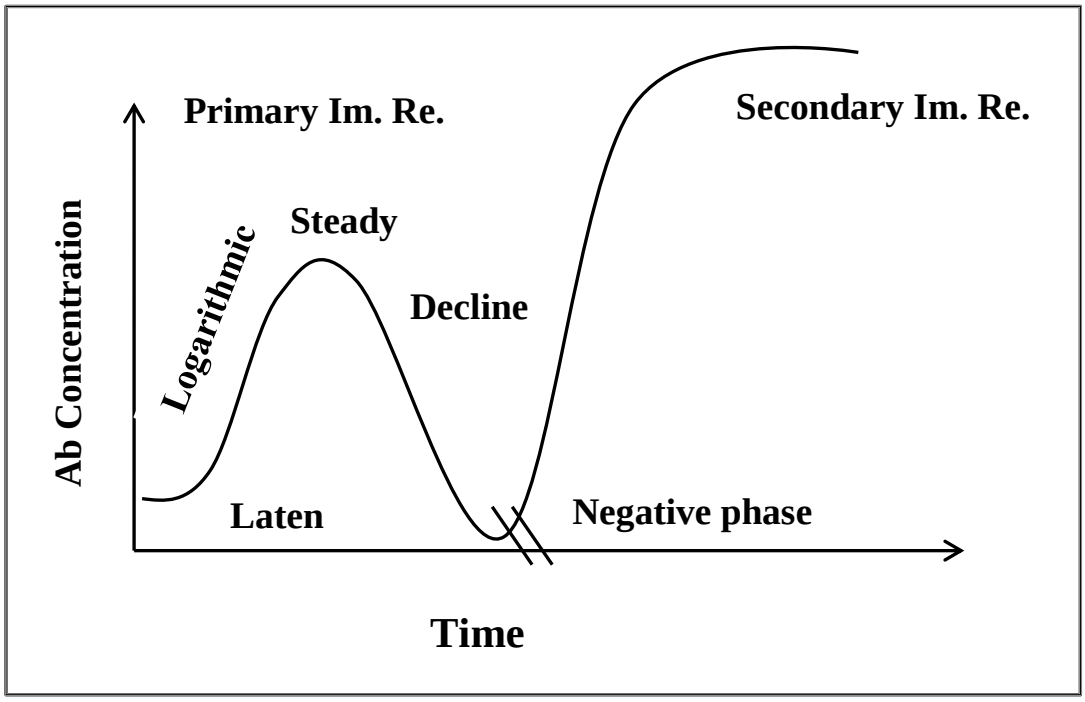
   Note: during early primary response, IgM class antibodies is predominant and first rise than IgG appears later.

Secondary immune response

It is the second exposure to the same immunogen that induced the first immune response (after booster dose of vaccination) may be after weeks, months, or even years later, includes:

1. Accelerated or fast appearance of Abs.
2. Shorter latent period.
3. Rapid rate of Ab synthesis.
4. Higher peak titer of Ab.
5. More presence of memory cells.
6. Dose of immunogen needed is lower than primary.
7. Predominant Ab Class is IgG.
8. Long standing steady phase, whereas Ab titer will stay high longer time.

Negative phase: occur between primary and secondary Immune response when immunogen second dose is small and/or there is pre-existing antibodies from the first immune response (primary), then immunogen will be all consumed in Ag-Ab complex formation and phagocytozed then removed with no induction to secondary immune response.



(Primary and Secondary immune response)