IMMUNE RESPONSE

Microbiology

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INTRODUCTION

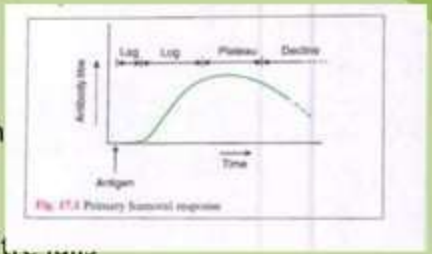
- The specific reactivity induced in a host by an antigenic stimulus is Known as *immune response*
- It may lead to consequence which may be either beneficial, indifferent or injurious
- The immune response can be of 2 types
  - Humoral Mediated Immunity (HMI)
  - Cell Mediated Immunity (CMI)
- Humoral mediated immunity is also known as Antibody mediated immunity (AMI)
- AMI generally provides primary defence against most extracellular bacteria and help defence against those viruses infect through respiratory or intestinal tracts
- CMI protects against fungi, viruses and intracellular bacteria like *M. tuberculosis*, *M. leprae* and parasites such as *Leishmania* and trypanosomes

Humoral Mediated Immunity (HMI)

- Antibody mediated
- Antibody-produced from plasma cell present in blood and other body fluid (Humoral – body fluid)
- Provides primary defence against most extracellular bacteria and viruses (respiratory or intestinal tracts)
- Also participates in pathogenesis of type 1, 2, 3 hypersensitivity reaction and auto-immune disorder

Antibody production pattern

- It involve 4 step
- **Lag phase**
  - ❖ The immediate stage following antigenic stimulation when no antibodies is detectable in circulation
- **Log phase**
  - ❖ There is steady rise in titre of antibodies
- **Plateau**
  - ❖ There is an equilibrium between antibody syn catabolism
- **Phase of decline**
  - ❖ Catabolism exceeds the production and the titre falls



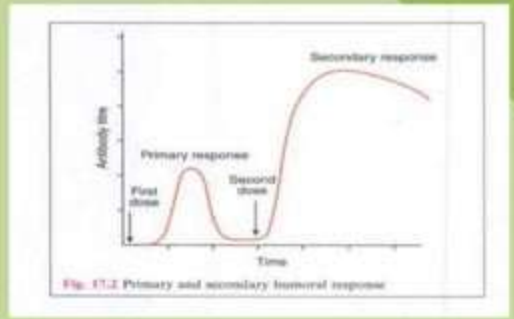
(A) Primary and Secondary response

- Antibody response to initial antigenic stimulus is called primary response
  - ✓ Long lag phase and low titre of antibody
  - ✓ Slow, sluggish and short lived
  - ✓ Predominantly IgM

- Subsequent to primary response is called secondary response
  - ✓ Short or negligible lag phase
  - ✓ Prompt, powerful and prolonged
  - ✓ Much higher level of antibodies for longer period
  - ✓ Predominantly IgG

Negative Phase

- When an antigen is injected in individual already carrying specific antibody, there is temporary fall in antibody level
- Combination of antigen with the antibody



(B) Production of Antibodies

1. Antigen are presented to immunocompetent cells by Antigen presenting cells (APC)
2. Antigen presenting cells(ACP) – activated
   - ✓ Macrophage
   - ✓ Dendritic cells
3. ACP binds with Major histocompatibility complex (MCH) II
4. Immature T-cell binds with earlier formed complex with the help of T-cell receptor(TCR)
5. Whole complex produces signal for activation of CD4 cells
6. Activation of CD4 cells – Maturation of T helper cell (TH-cells)
7. Forms IL-2, IL-4, IL-5, IL-6: B-cell maturation and subsequently release of plasma cells
   - ✓ Plasma cells – forms antibodies
   - ✓ Some of the plasma cells – memory cells

(C) Fate of antigen in tissues

- Antigen introduced intravenously are rapidly localised in spleen, liver, bone marrow, kidneys and lungs.
- About 70-80% of these antigens are broken down by reticuloendothelial cells and excreted in the urine.

(D) Theories of Antibody formation

Instructive Theories

The instructive theories postulate that an immunocompetent cell (ICC) is capable of synthesising antibodies of all specificity. The antigen instruct ICC produce the complementary antibody.

- Direct template theory
- Indirect template theory

Selective Theories

Selective theories postulate that ICCs have only a restricted immunological range. The antigen select the appropriate ICC to synthesis an antibody.

- Side chain theory
- Natural selection theory
- Clonal selection theory

INSTRUCTIVE THEORY:

❑**Direct template theory – According to this theory, the antigen enters antibody forming cells and acts as a template so that antibodies are formed with complimentary combining sites to antigen.**

❑**Indirect template theory – According to this theory, a genocopy of antigenic determinant was incorporated in antibody producing cell genome and transmitted to progeny cell.**

SELECTIVE THEORY:

❑**Side chain theory – According to this theory, cells have surface receptors which have capability to react with substances have complimentary side chains.**

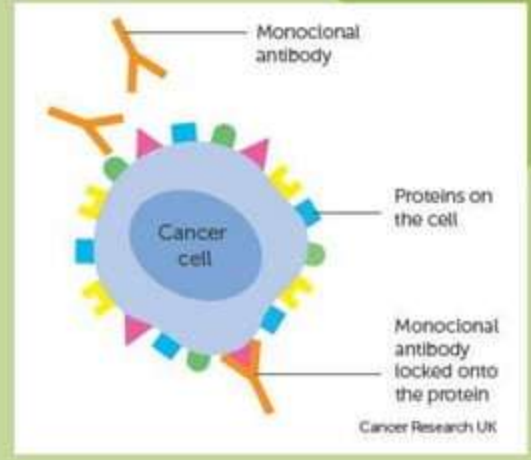
❑**Natural selection theory – In this, million globulin molecules are formed in embryonic life with full range of antigenic specificities (natural antibodies).**

❑**Clonal selection theory – This theory states that during foetal development a large number of clones of ICC bearing specific antibody patterns are produced by a process of somatic mutation of ICC against all possible antigen. This theory is most accepted nowadays.**

(E) Monoclonal Antibodies

Principle

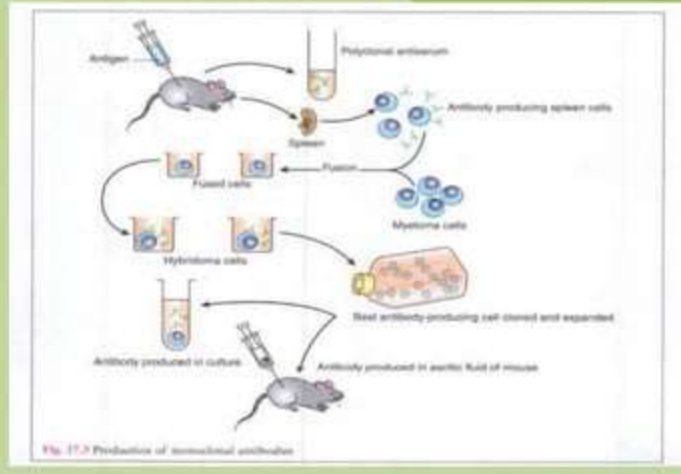
- Kohler and Milstein (Noble Prize 1984)
- A single antibody forming cell or clone produces Antibodies against a single antigen
- Antibodies are usually polyclonal



Technique

- Prepared by fusing immortal myeloma cells with the spleen cells B cells (derived from the mouse that has been immunized with the intended antigen) to produce monoclonal antibody-producing cells, hybridomas.

- Hybridomas have the characteristic of both cells i.e. produce antibodies and reproduce infinitely



Application

- Diagnostic tests
  - ✓ Detect small amounts of drug, toxins or hormones
  - ✓ e.g. monoclonal antibodies to human chorionic gonadotropin (HCG) – pregnancy test kits
- AIDS by the ELISA test
- Treat viral diseases
- Detection and immunotherapy of cancer
- Large amount of pure antibody of define class can be prepared

(F) Factors Influencing Antibody Production

- Age
- Genetic Factors
- Nutritional Status
- Route of Administration
- Dose of Antigen
- Multiple Antigens
- Adjuvants
  - ✓ *Type of adjuvants*
  - ✓ *Action of adjuvants*
- Immunosuppressive Agents
  - ✓ *X-irradiation*
  - ✓ *Radiomimetic drugs*
  - ✓ *Corticosteroids*
  - ✓ *Antimetabolites*
  - ✓ *Antilymphocytic serum(ALS)*
  - ✓ *Cyclosporine*

Cell Mediated Immunity (CMI)

- Cell mediated immunity refer to specific acquired immune response mediated by sensitised T cells
- Specific immune response that do not involve antibody
- It participate on following immunological function:
  - ✓Delayed hypersensitivity (type IV hypersensitivity).
  - ✓immunity in infectious diseases caused by intracellular organisms.
  - ✓Transplantation immunity and graft-versus-host (GVH) reaction.
  - ✓Immunological surveillance and immunity against cancer.
  - ✓Pathogenesis of certain autoimmune diseases e.g. thyroiditis.

(A) Induction of CMI

- Foreign antigen is presented by antigen presenting cells (ACP) to T-lymphocytes
- T-lymphocytes posses antigen recognition receptor – T cells
- T-cell recognise antigen only when presented with MHC molecule
- CD8 cells can recognise combination of foreign antigen with MHC – I and differentiate into *Tc* & *Ts* lymphocytes
- CD4 cells can recognise combination of foreign antigen with MHC – II and differentiate into *Th* & *Td* cells
- *Tc* lymphocyte recognise foreign antigen and MHC-I antigen and get attached to the target cell.

(B) Cytokines

- Biological substances secreted from monocytes, lymphocytes and other cells
- Lymphokines – if derived from lymphocytes
- Monokines – if derived from monocytes and macrophages
- Interleukines are chemical substances that function primary as growth & differentiating factors
- All these biological substances (lymphokines, monokines & interleukines) are collectively known as Cytokines
- Some of the important cytokines are:
  - *Interleukin - 1*
  - *Interleukin - 2*
  - *Interleukin - 3*
  - *Interleukin - 4*
  - *Interleukin - 5*
  - *Interleukin - 6*
  - *Colony stimulation factors (CSF)*
  - *Tumour necrosis factors (TNF)*
  - *Interferons (IFN)*

Lymphokines

Migration inhibiting factor (MIF)
- Inhibit the migration of normal macrophage

Macrophage activating factor (MAF)
- Restrict macrophage movement and increase phagocytic activity

Macrophage chemotactic factor (MCF)
- Stimulate chemotaxis of macrophage

Macrophage stimulating factor (MSF)
- Stimulate macrophage migration to the site of action

(C) Detection of CMI

CMI can be detected by following methods:

- ✓ *Skin tests for delayed hypersensitivity*
- ✓ *Lymphocyte transformation test*
- ✓ *Migration inhibiting factor (MIF) test*
- ✓ *Rosette formation*
- ✓ *Detection of T-cells by immunofluorescence technique*

(D) Transfer Factor (TF)

- Lawrence (1954)
- Low molecular weight substances, resistance to trypsin but get reactivated in 56^0 C in 30 minutes & can remain stable for several years at -20^o C and in the lyophilised form at 4^o C
- Not antinenic
- Humoral immunity is not transferred by TF
- Mechanism of action is not known
- TF can be used in:
  - ➢ *T – cells deficiency*
  - ➢ *Treatment of disseminated infections associated with deficient CMI (Lepromatous leprosy and tuberculosis)*
  - ➢ *Treatment of malignant melanoma and other types of cancer*

IMMUNOLOGICAL TOLLERANCE

❖A state in which contact with an antigen specifically abolished the capacity to mount an immune response against that particular antigen when it is administered subsequently, the immune reactivity to other antigens being unaffected.

❖Immune response is of two types
✓Natural
✓Acquired

❖Natural tolerance- It is non-responsiveness to self antigens. Any antigen which comes in contact with immunological system during its embryonic life is recognised as self antigen and would not provoke an immune response in the mature animal.

❖Acquired tolerance- it arises when a potential antigen induces a state of unresponsiveness to itself.

Mechanisms of Tolerance

Tolerance can arise through following mechanisms:

1. *Clonal Deletion*
2. *Clonal Anergy*
3. *Suppression*
4. *Other Mechanisms*

THANK YOU