Immune Responses: when Ag enter the body two immune response is occur

A-Nonspecific Immune Responses

Inflammation: Function is to destroy invaders & prepare area for healing & repair includes:

1-Bacterial invasion or tissue damage

2-Release of histamine by mast cells (plus chemotaxins by damaged cells)

3-Arterial vasodilatation & increased capillary permeability

4-Increased blood flow to tissue & accumulation of fluid

5-Increased numbers of phagocytes & more clotting factors into surrounding tissues

6-Defense against foreign invader plus 'walling off' of inflamed area

Interferon: Interfere with replication of the same or unrelated viruses in other host cells. Mechanism of interferon:

1-Virus enters a cell

2-Cell releases interferon

3-Interferon binds with receptors on uninvaded cells

4-Uninvaded cells produce enzymes capable of breaking down viral mRNA

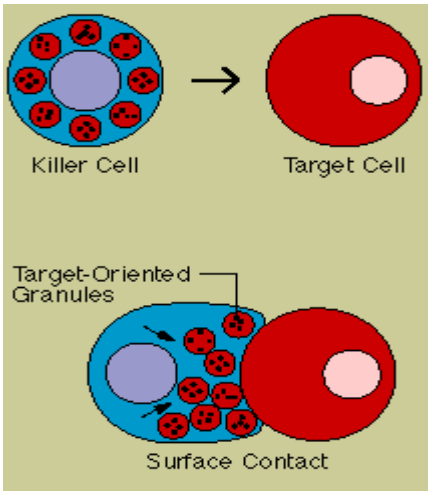
5-Virus enters previously-uninvaded cell (now with interferon)

6-Virus-blocking enzymes are activated

7-Virus unable to multiply in newly invaded cells

Natural killer cells

- NK cells are part of a group know as the "large granular lymphocytes
- destroy virus-infected cells & cancer cells by lysing their membranes upon first exposure
- mode of action similar to cytotoxic T cells (but latter can attack only cells to which they have been previously exposed)
- An important first line of defense against newly arising malignant cells and cells infected with viruses, bacteria, and protozoa. They form a distinct group of lymphocytes with no immunological memory. Natural Killer Cells constitute 5 to 16 percent of the total lymphocyte population. Their specific function is to kill infected and cancerous cells.



The Complement System :
Functions

1 - Membrane-attack complex proteins form a channel in membrane of invading cell. The resulting influx of water causes lysis (or bursting) of the invading cell.

2 - chemotaxis

3 - Opsonins (bind with microbes & thereby enhance their phagocytosis)

4 - Vasodilation & increase vascular permeability to increase blood flow to invaded area
5 - Stimulate release of histamine from mast cells (enhances vascular changes characteristic of inflammation)
6 - Activate kinins - reinforces vascular changes induced by histamine & act as powerful chemotaxins

B-Specific Immune Responses: Two classes of responses:

- Humoral immunity - antibodies produced by B lymphocytes
- Cell-mediated immunity - activated T lymphocytes

B-cells: Antibody-mediated immunity (Humoral immunity)

Induction of the humoral immune response begins with the recognition of antigen. Through a process of clonal selection, specific B-cells are stimulated to proliferate and differentiate. However, this process requires the intervention of specific T-cells that are themselves stimulated to produce lymphokines that are responsible for activation of the antigen-induced B-cells. In other words, B cells recognize antigen via immunoglobulin receptors on their surface but are unable to proliferate and differentiate unless prompted by the action of T-cell lymphokines. In order for the T-cells to become stimulated to release lymphokines, they must also recognize specific antigen. However, while T-cells recognize antigen via

their T-cell receptors, they can only do so in the context of the MHC molecules. This "antigen-presentation" is the responsibility of the antigen-presenting cells (APCs).

Several types of cells may serve the APC function. Perhaps the best APC is, in fact, the B-cell itself. When B-cells bind antigen, the antigen becomes internalized, processed and expressed on the surface of the B-cell. Expression occurs within the class II MHC molecule, which can then be recognized by T-helper cells ($CD4^+$).

Other types of antigen-presenting cells include the macrophage and dendritic cells. These cells either actively phagocytose or pinocytose foreign antigens. The antigens are then processed in a manner similar to that observed for the B-cells. Next, specific antigen epitopes are expressed on the macrophage or dendritic cell surface. Again, this expression occurs within the class II MHC molecule, where T-cell recognition occurs. The stimulated T-cells then release lymphokines that act upon "primed" B-cells (B-cells that have already encountered antigen), inducing B-cell proliferation and differentiation.

The antigen-dependent stages of B-lymphocyte differentiation occur in the spleen, lymph nodes and other peripheral tissue. These stages are, of course, initiated upon encounter with antigen and activation by T-cell lymphokines. The activated B-cell first develops into a B-lymphoblast, becoming much larger and shedding all surface immunoglobulin. The B-lymphoblast then develops into a plasma cell, which is, an antibody factory. This terminal differentiation stage is responsible for production of primarily IgM antibody during the "primary response". Some B-cells, however, do not differentiate into plasma cells. Instead, these cells undergo secondary DNA rearrangements that place the constant region of the IgG, IgA or IgE genes in conjunction with the VDJ genes. This "class switch" establishes the phenotype of these newly differentiated B-cells; these cells remain as long-lived "memory cells". Upon subsequent encounter with antigen, these cells respond very quickly to produce large amounts of IgG, IgA or IgE antibody, generating the "secondary response".

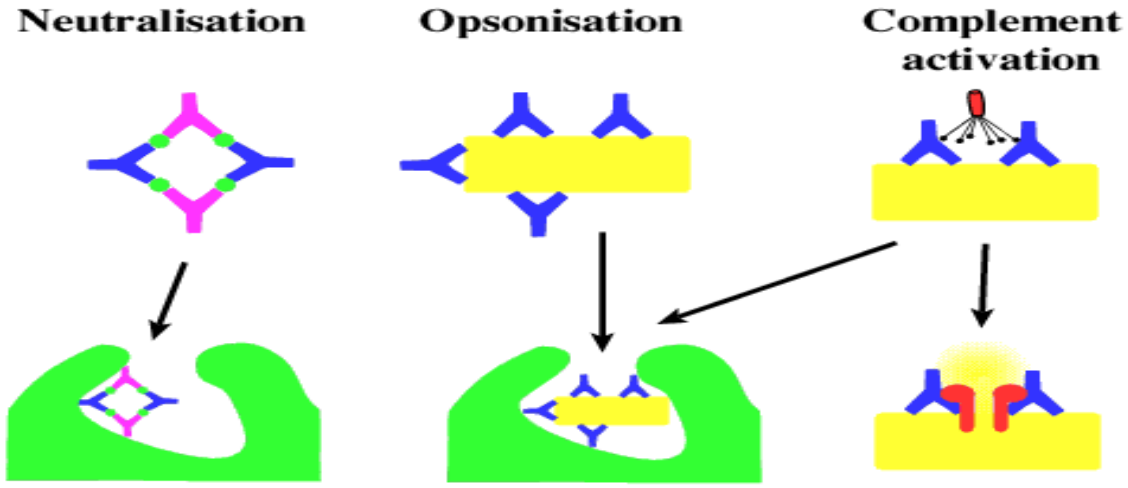
Functions of antibodies.

1. **Neutralization**: blocks a molecule on the pathogen surface that is essential for adherence of the pathogen or entry into host cells. Antibodies can block the active sites of toxins.
2. **Opsonization:** When specific antibody binds to the surface of a pathogen, the Fc region of the antibody can bind to Fc receptors on the surface of macrophages and neutrophils which facilitate trigger phagocytosis. Enhancement of phagocytosis is known as **opsonization.**

A substance which enhances phagocytosis is known as an **opsonin**. Antibodies can act as opsonin.

3. **Antibody-dependent cell-mediated cytotoxicity (ADCC):** Antibody can enable cells of the innate immune system to kill pathogens by ADCC. Killing of target cells or pathogens can occur when the Fc portion of antibody bound to the target binds to the Fc receptors of a cell which has cytotoxic capability. Cells which can participate in ADCC include NK cells, macrophages, monocytes, neutrophils, and eosinophils. If the target is too large to be phagocytized, the cells degranulate and damage the target by releasing proteolytic enzymes at the immune cell/target cell interface.

4. **Complement Activation** classical pathway of complement, leading to lysis of the pathogen. Which isotype is produced often controls the effector functions of abs. Some isotypes are better at some functions than others.

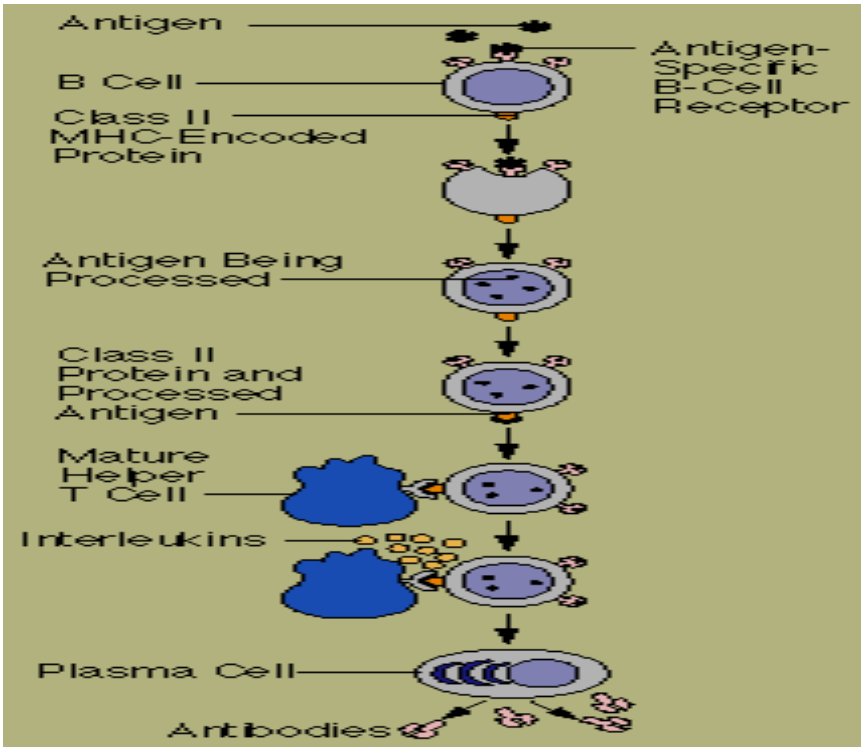


Plasma cells

- prolific producers of customized antibodies (IgG antibodies)
- have lots of ROUGH ENDOPLASMIC RETICULUM (RER) because antibodies are proteins & RER is needed to make proteins (because of the associated ribosomes) and then transport them out of the cell
- Formation and subsequent production of takes several days after exposure to an antigen & peak antibody production may occur a week or two after exposure. This is referred to as the PRIMARY RESPONSE.

Memory cells:

- Remain dormant but respond quickly if exposed to the antigen a second time
- Responsible for SECONDARY RESPONSE, a response so fast & effective that infection is typically prevented.
- form the basis for long-term immunity



HUMORAL IMMUNE RESPONSE(**T-dependent Ag)**

If immune response is humoral or C.M.I.there are two types of I.R. through these response Primary & Secondary response

1. Primary (1º) Ab response - The kinetics of a primary antibody response to and antigen.

a) Latent or lag phase - In this phase the Ag is recognized as foreign and the cells begin to proliferate and differentiate in response to the antigen. The duration of this phase will vary depending on the antigen but it is usually 5-7 days.

b) Log or Exponential Phase - In this phase the Abs concentration increases exponentially as the B cells that were stimulated by the antigen differentiate into plasma cells which secrete antibody.

c) steady-state phase - In this phase Ab synthesis is balanced by Ab decay so that there in no net increase in Ab concentration. . Furthermore, plasma cells begin to die. When the rate of antibody synthesis equals the rate of antibody decay the stationary phase is reached.

d) Decline or decay phase - Ab may reach base line levels, When no new antibody is produced because the antigen is no longer present to activate T and B cells and the residual antibody slowly is degraded, the decay phase is reached.

2. Secondary (2º), memory response

a) Lag phase - In a secondary response there is a lag phase by it is normally shorter than that observed in a primary response.

b) Log phase - The log phase in a secondary response is more rapid and higher Ab levels are achieved.

c) Steady state phase

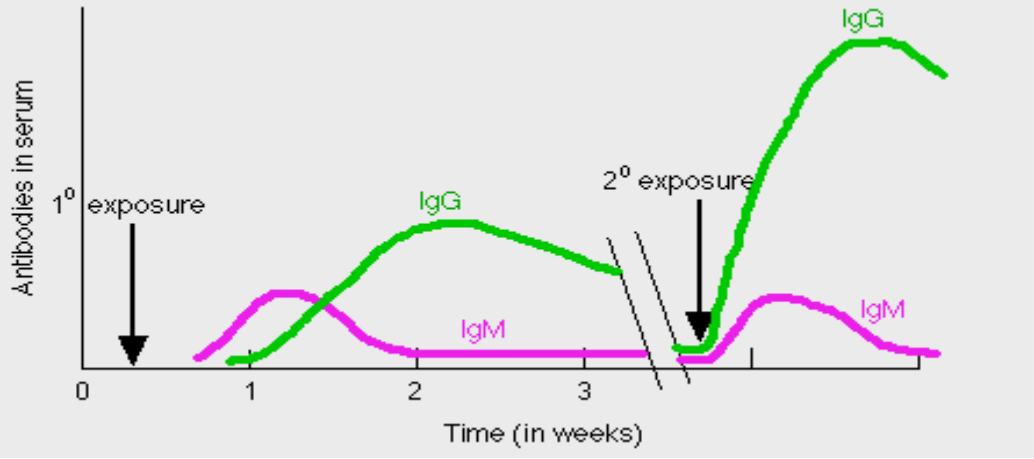
d) Decline phase - The decline phase is not as rapid and Ab may persist for months, years or even a lifetime.

Notes: Specificity of 1º and 2º responses

Ab elicited in response to an antigen is specific for that antigen although it may also cross react with other antigens which are structurally similar to the eliciting antigen. In general secondary responses are only elicited by the same antigen used in the primary response. However, in some instances a closely related antigen may produce a secondary response, but this is a rare exception

Ig class variation - In the primary response the major class of Ab produced is IgM whereas in the secondary response it is IgG (or IgA or IgE). The antibodies that persist in the secondary response are the IgG antibodies.
High IgM / Low IgG = recent exposure… High lgG /Low IgM = past exposure

Primary response vs. Secondary response



Ab response to T-independent Ag: Responses to T-independent Ag are characterized by the production of almost exclusively IgM Ab and no secondary response. Secondary exposure to the Ag results in another primary response to the Ag

T Lymphocytes: Cell Mediated Immunity

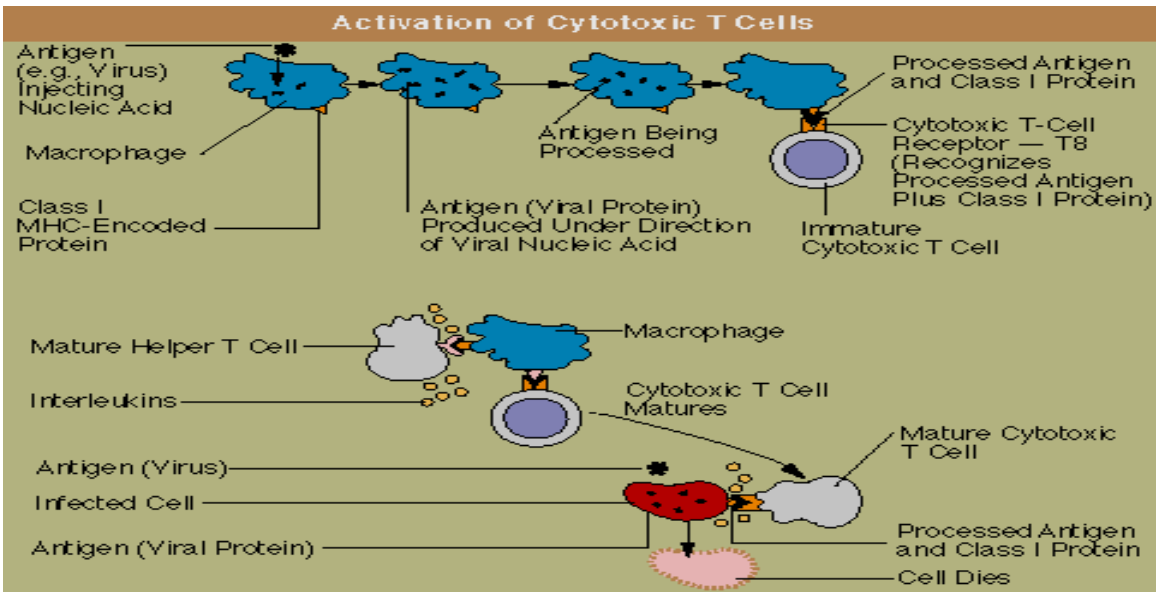
The second arm of the immune response is refered to as Cell Mediated Immunity (CMIR). As the name implies, the functional "effectors" of this response are various immune cells. These functions include:

- Phagocytosis and killing of intracellular pathogens
- Direct cell killing by cytotoxic T cells
- Direct cell killing by NK and K cells

These responses are especially important for destroying intracellular bacteria, eliminating viral infections and destroying tumor cells. This page will discuss the cell-mediated immune response, focusing on the mechanisms involved.

CELL MEDIATED CYTOTOXICITY

The second half of the cell-mediated immune response is involved in rejection of foreign grafts and the elimination of tumors and virus-infected cells. The effector cells involved in these processes are cytotoxic T-lymphocytes (CTLs), NK-cells and K-cells. Each of these effector's cells recognizes their target by different means, CTLs, like other T-cells are both antigen and MHC-restricted. That is, CTLs require 1) recognition of a specific antigenic determinant **and** 2) recognition of "self" MHC. Briefly, CTLs recognize antigen via their T-cell receptor. This receptor makes specific contacts with the antigenic determinant and the target cell's class I MHC molecule. CTLs also express CD8, which may assist the antigen recognition process. Once recognition is successful, the CTL "programs" the target cell for self-destruction. This process is thought to occur in one of several possible ways. First, CTLs may release a substance known as perforin in the space between the CTL and its target. In the presence of calcium ions, the perforin polymerizes, forming channels in the target cell's membrane. These channels may cause the target cell to lyse. Second, the CTL may also release various enzymes that pass through the polyperforin channels, causing target cell damage. Third, the CTL may release lymphokines and/or cytokines that interact with specific receptors on the target cell surface, causing internal responses that lead to destruction of the target cell. CTLs principally act to eliminate endogenous antigens.



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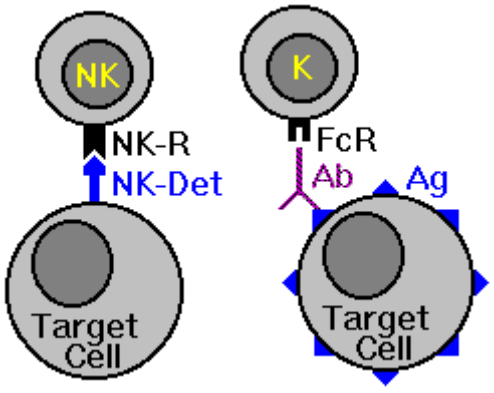
K-cells

K-cells are probably not a separate cell type but rather a separate function of the NK group. K-cells contain immunoglobulin Fc receptors on their surface and are involved in a process known as Antibody-dependent Cell-mediated Cytotoxicity (ADCC). ADCC occurs as a consequence of antibody being bound to a target cell surface via specific antigenic determinants expressed by the target cell. Once bound, the Fc portion of the immunoglobulin can be recognized by the K-cell. Killing then ensues by a mechanism similar to that employed by CTLs. This type of CMIR can also result in Type II hypersensitivities.



Note: Both memory T cells and memory B cells are produced and memory T cells survive longer than memory B cells. Upon secondary challenge with antigen not only are virgin T and B cells activated, the memory cells are also activated and thus there is a shorter lag time in the secondary response. Since there is an expanded clone of cells being stimulated the rate of antibody production is also increased during the log phase of antibody production and higher levels are achieved.

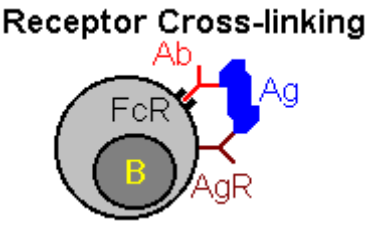
1° Immune Response	2° Immune Response
• Following the first exposure to a foreign antigen, a lag phase occurs in which no antibody is produced, but activated B cells are differentiating into plasma cells. The lag phase can be as short as 2-3 days, but often is longer, sometimes as long as weeks or months.	• If a second dose of the same antigen is given days or even years later, an accelerated 2° or anamnestic immune response (IR) occurs. This lag phase is usually very short (e.g. 3 or 4 days) due to the presence of memory cells.
• The amount of antibody produced is usually relatively low.	• The amount of antibody produced rises to a high level.
• Over time, antibody level declines to the point where it may be undetectable.	• Antibody level tends to remain high for longer.
• The first antibody produced is mainly IgM (although small amounts of IgG are usually also produced).	• The main type of antibody produced is IgG (although small amounts of IgM are sometimes produced).

Suppressor T cells:

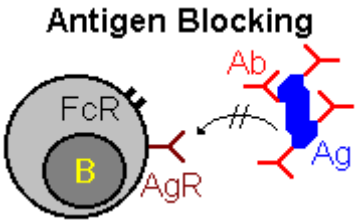
- limit responses of other cells (B & T cells)
- make immune response self-limiting
- prevents excessive immune response which might be detrimental to body
- may also prevent immune system from attacking a person's own cells & tissues (= TOLERANCE)

REGULATION OF THE HUMORAL RESPONSE

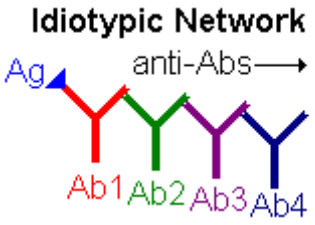
Regulation of the immune response is possibly mediated in several ways. First, a specific group of T-cells, suppressor T-cells, are thought to be involved in turning down the immune response. Like helper T-cells, suppressor T-cells are stimulated by antigen but instead of releasing lymphokines that activate B-cells (and other cells), suppressor T-cells release factors that suppress the B-cell response. While immunosuppression is not completely understood, it appears to be more complicated than the activation pathway, possibly involving additional cells in the overall pathway.



Other means of regulation involve interactions between antibody and B-cells. One mechanism, "antigen blocking", occurs when high doses of antibody interact with all of the antigen's epitopes, thereby inhibiting interactions with B-cell receptors. A second mechanism, "receptor cross linking", results when antibody, bound to a B-cell via its Fc receptor, *and* the B-cell receptor both combine with antigen. This "cross-linking" inhibits the B-cell from producing further antibody.



Another means of regulation that has been proposed is the idiotypic network hypothesis. This theory suggests that the idiotypic determinants of antibody molecules are so unique that they appear foreign to the immune system and are, therefore, antigenic. Thus, production of antibody in response to antigen leads to the production of anti-antibody in response, and anti-anti-antibody and so on. Eventually, however, the level of $[anti]_n$-antibody is not sufficient to induce another round and the cascade ends.



OVERVIEW OF THE ORIGINS AND ORGANIZATION OF THE CELLS PERTINENT TO NON-SPECIFIC AND SPECIFIC (Immunological) DEFENSE SYSTEMS