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The Immune response

THE ADAPTIVE IMMUNE RESPONSE

One big problem in defending against pathogens is that they reside in different compartments:

Extracellularly : within tissue: most bacteria, traveling viruses

on outer epithelial surfaces: Candida, enteric pathogens

Intracellularly: in the cytoplasm: replicating viruses, some bacteria

In vesicles: some bacteria, e. g., Mycobacteria

To be able to fight pathogens in all these various circumstances, a broad spectrum of tools had to be developed.

Especially useful tools to combat extracellular pathogens are antibodies.

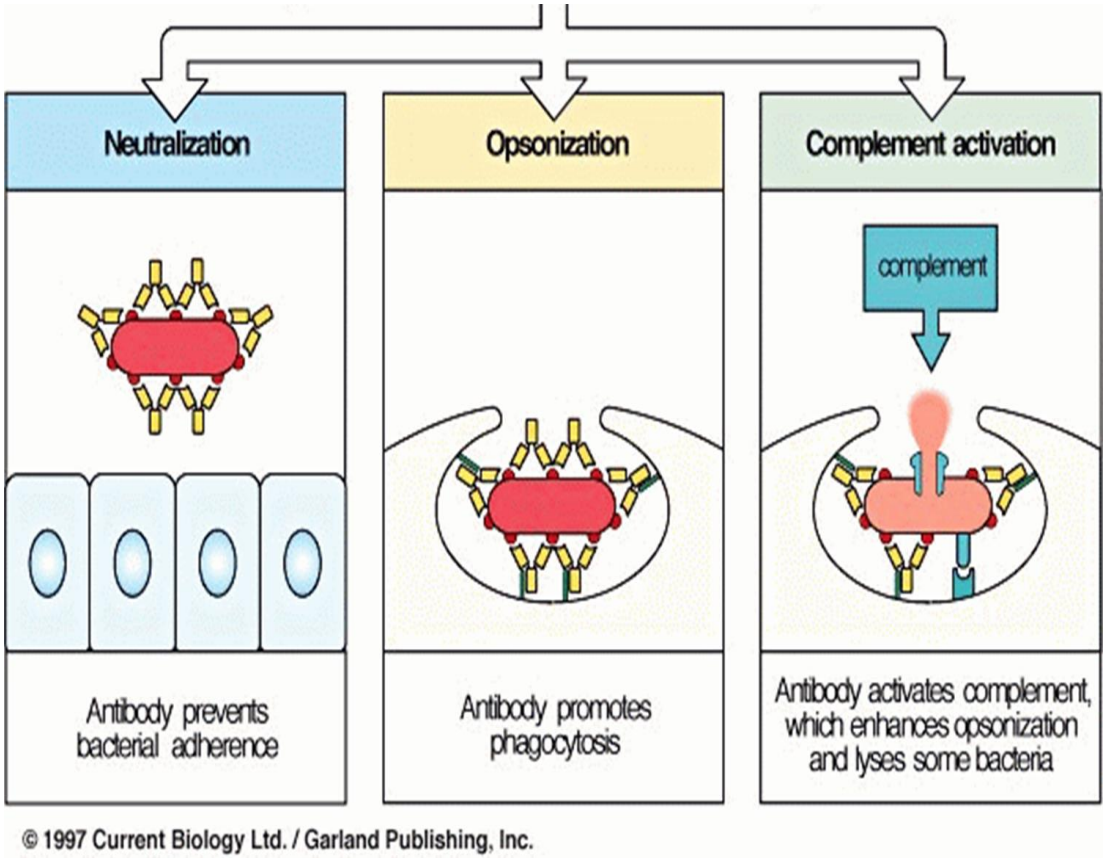
Antibodies

Antibodies ,or immunoglobulins (Igs) are the secreted products of B-Lymphocyte which have become activated following binding of antigen to their B-cell receptors (BCRs) .The specificity for antigen of the secreted antibody is the same as that of the BCR, so they will bind to the same antigen that induced their production .The formation of the antigen –antibody complex may result in :

*Neutralization of antigen (e.g. soluble toxins ,viruses).

*Removal of the complex by phagocytic cells ,which bind via Fc receptors (FcRs) to the Ig constant region .

*Killing of antigen –bearing cells by the membrane attack complex of complement or by natural killer (NK) cells monocyte /macrophages or granulocytes ,which bind antibody-coated cells via FcRs .



The basic Y-shaped ,four –chain structure of the antibody molecule fig(9.1). Antigen –binding specificity is provided by the combined variable (V) region of heavy (H) and light (L) chains .There are five distinct classes of Ig(IgG, IgA ,IgM, IgD and IgE) .

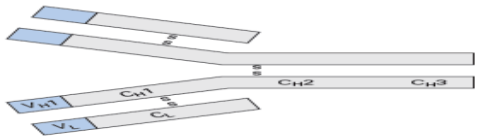


Fig. 9-1. Structure of the immunoglobulin molecule. C, constant region; H, heavy chain; L, light chain; C_H1, C_H2, C_H3 are globular domains with different biological properties; V, variable region.

Cytokines

cytokines are low –molecular –weight hormone-like glycoproteins secreted by leukocytes and various other cells in response to a number of stimuli .Lymphocyte –derived cytokines lymphokines ,those produce by monocyte / macrophage monokines many of the cytokines are referred to as interleukins (ILs).

Functions:-Initiation and regulation of all stages of the immune response from stem cell differentiation to effector cell activation.

Chemokines

are a family of low –molecular –weight ,structurally related cytokines that promote adhesion of cells to endothelium ,chemotaxis and activation of leukocytes .They are involved in leukocyte trafficking providing specific signals for lymphocyte entry into lymphoid and other tissue .

An antigen-presenting cell (APC) or accessory cell

is a cell that displays antigen complexed with major histocompatibility complexes (MHCs) on their surfaces; this process is known as antigen presentation. T cells may recognize these complexes using their T cell receptors (TCRs). APCs process antigens and present them to T-cells

Almost all cell types can present antigens in some way. They are found in a variety of tissue types**. Professional antigen-presenting cells, including macrophages, B cells and dendritic cells,** present foreign antigens to helper T cells, while other cell types can present antigens originating inside the cell to cytotoxic T cells. In addition to the MHC family of proteins, antigen presentation relies on other specialized signaling molecules on the surfaces of both APCs and T cells.

Antigen-presenting cells are vital for effective adaptive immune response, as the functioning of both cytotoxic and helper T cells is dependent on APCs. Antigen presentation allows for specificity of adaptive immunity and can contribute to immune responses against both intracellular and extracellular pathogens. It is also involved in defense against tumors. Some cancer therapies involve the creation of artificial APCs to prime the adaptive immune system to target malignant cells.

Dendritic cells

This complex family of cell types are the main "professional" antigen presenting cells of the immune system .

*They play a vital role in activating T helper cells and memory cells .

*They are formed in the bone marrow and circulate in the bloodstream until they reach their target tissues, where they are activated by pathogens and differentiate into their mature forms

*They phagocytose pathogens before migrating to lymph nodes, where they present antigens on their cell surfaces with the costimulatory molecules required to activate the adaptive immune response

*They have numerous characteristic “dendritic” processes branching from their cell membranes *There are several specialized dendritic cell types, including **Langerhans cells** in the skin.

B-cell activation

B cells represent about 25% of the total lymphocyte population – this varies depending on the activity of the immune response and can be up to 50%

important B cell surface markers include CD19, CD20 and CD21, as well as MHC II

they are essential for humoral immunity, also known as the antibody-mediated immune response

plasma cells are mature B cells which secrete antibodies, which recognise specific foreign antigens and bind to them or destroy them

memory B cells “remember” the offending foreign antigens to allow the immune system to mount a quicker antibody response to any subsequent infections

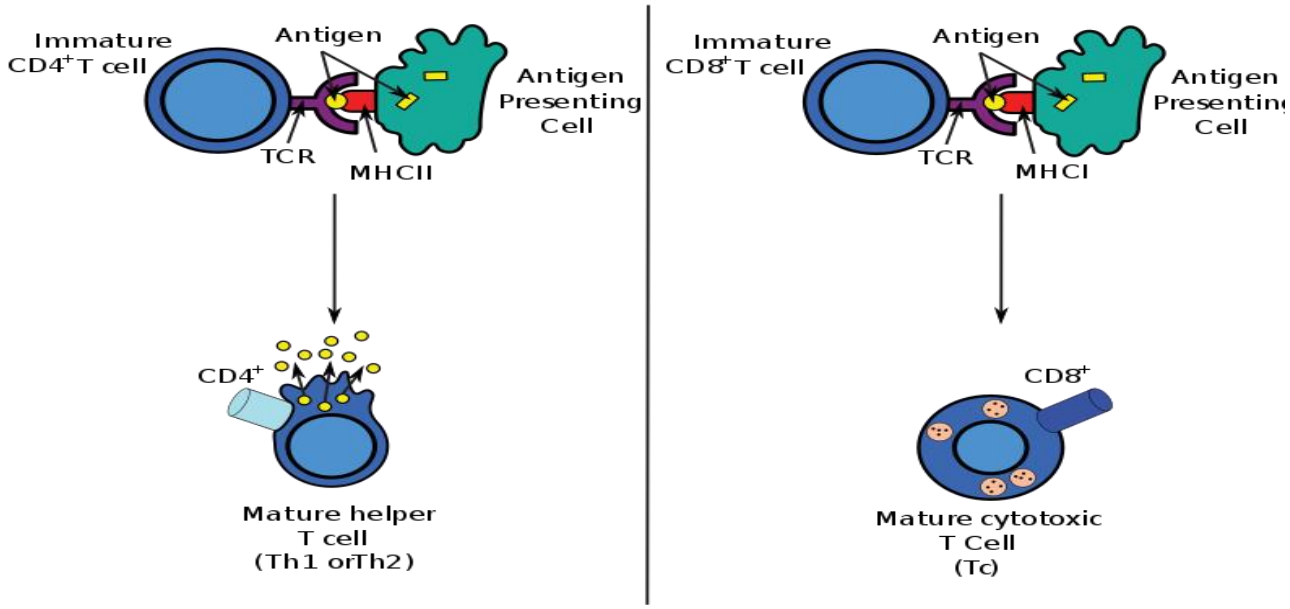
B-cells are highly efficient APCs (Antigen Presenting Cells) .

The surface immunoglobulin that serves as the B-cell antigen receptor (BCR) has two roles in B-cell activation.

First, like the antigen receptor on T cells, it transmits signals directly to the cell's interior when it binds antigen fig 2.

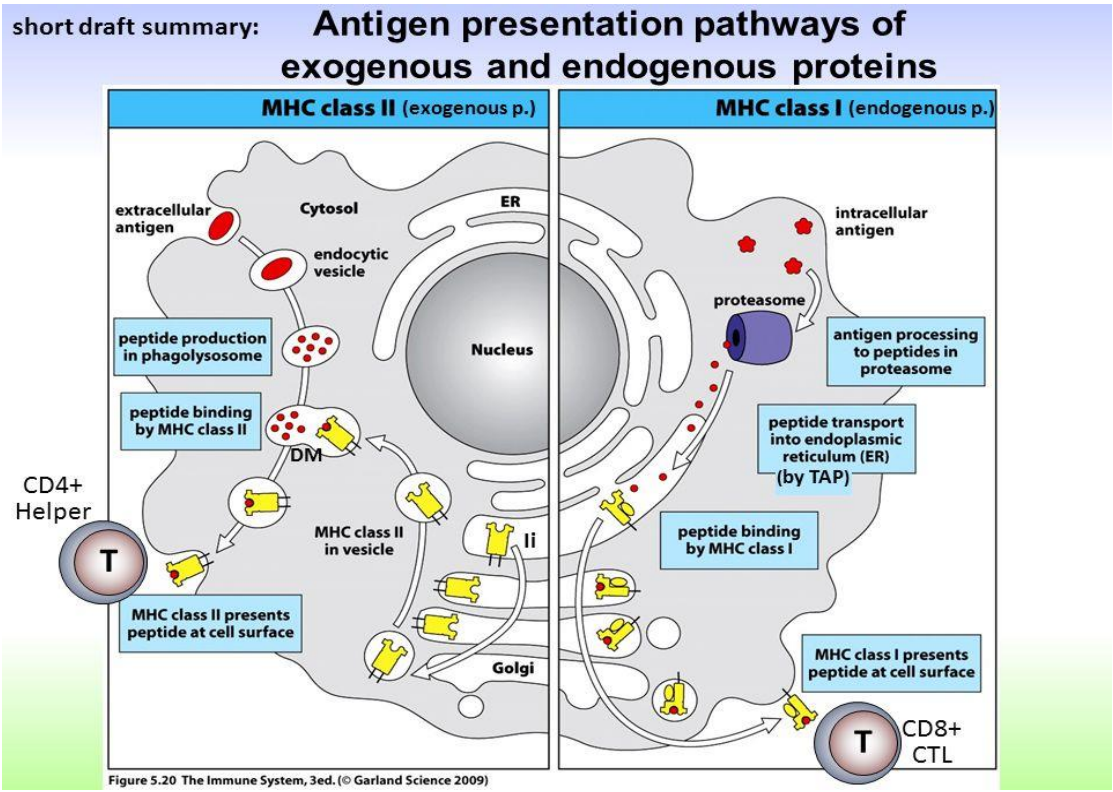
Second, the B-cell antigen receptor delivers the antigen to intracellular sites where it is degraded and returned to the B-cell surface as peptides bound to MHC class II molecules . When a T helper cell with a TCR specific for that peptide binds, the B cell marker CD40 binds to CD40L on the T cell surface. stimulating T-cells to make proteins IL-4,IL5 and IL10 that, in turn, cause the B cell (CD40) to proliferate and its progeny to differentiate into antibody-secreting cells(plasma cells). Some microbial antigens can activate B cells directly in the absence of T-cell help. The ability of B cells to respond directly to these antigens provides a rapid response to many important bacterial pathogens.

fig: 2 : Activation of B-cell .



Antigen processing pathway of exogenous and endogenous protein

Exogenous, bacteria. Endogenous bacterial infected cell, virus- infected cell



APCs in cancer therapy

APCs naturally have a role in fighting tumors, via stimulation of B and cytotoxic T cells to respectively produce antibodies against tumor-related antigen and kill malignant cells. Dendritic cells, presenting tumor-specific antigen to T cells, are key to this process. Cancer therapies have included treating the patient with increased numbers of dendritic cells or cancer-specific T cells

Target cell killing

Cytotoxic T cells carrying CD8 activated via the endogenous antigen presentation pathway ,recognize and kill virus infected cells expressing MHCI foreign peptide .Cytotoxic cell contact with its specific target release cytoplasmic granules contain perforin and granzymes which activate the target cell's suicide programmed(apoptosis) which efficiently remove by phagocytosis .

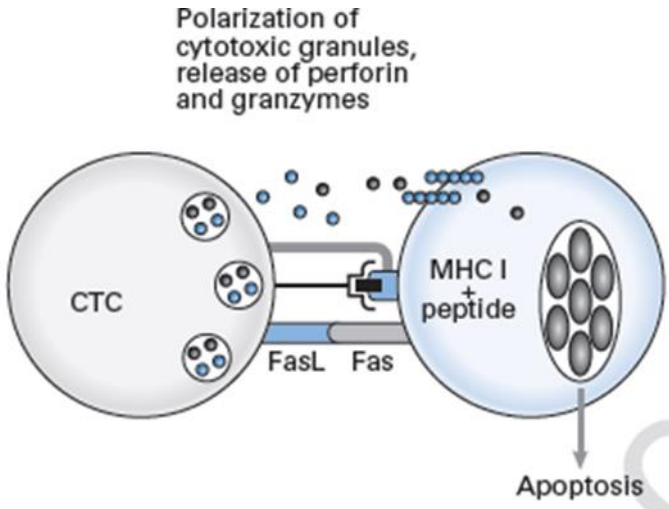


Fig. 9.6 Target cell killing. CTC, cytotoxic T cell; L, ligand; MHC, major histocompatibility complex.

Immunological memory

is the ability of the immune system to quickly and specifically recognize an antigen that the body has previously encountered and initiate a corresponding immune response. Generally these are secondary, tertiary and other subsequent immune responses to the same antigen. Immunological memory is responsible for the adaptive component of the immune system, special T and B cells — the so-called memory T and B cells. Immunological memory is the basis of vaccination.

Memory B cells :-are plasma cells that are able to produce antibodies for a long time. Unlike the **naive B cells** involved in the **primary immune** response the memory B cell response is slightly different. The memory B cell undergone clonal expansion and differentiation and affinity maturation, so it is able to divide multiple times faster and

produce antibodies with much higher affinity (especially IgG,IgA and IgE). In contrast, the naive plasma cell is fully differentiated and can not be further stimulated by antigen to divide or increase antibody production. Memory B cell activity in secondary lymphatic organs is highest during the first 2 weeks after infection. Subsequently, after 2 to 4 weeks its response declines. After the germinal center reaction the memory plasma cells are located in the bone marrow which is the main site of antibody production within the immunological memory

Memory T cells

Memory T cells respond more rapidly and more aggressively than naïve T cells the physiological basis for the faster response of memory T cells are due to present in higher numbers than naïve T cells. Gene-expression profile which is reprogrammed by changes in chromatin structure. For example, mRNA for interferon (IFN-g) and cytotoxic molecules such as perforin and granzyme B are not found in naïve T cells whereas these transcripts are elevated in memory CD8+ T cells. Therefore, memory CD8+ T cells have the capacity to produce larger quantities of these effector proteins more rapidly than naïve T cells

Immunity and infection

Immunity to Bacteria

Summary of defense mechanisms

*The bacterial cell wall peptidoglycan can be attacked by lysozyme .

*Bacteria release peptides that are chemotactic for polymorphs .

* polymorphs and macrophage use receptors for bacterial sugar to bind and slowly phagocytose them .

*Bacteria induce macrophage to release inflammatory cytokines such as interleukin-1 and 6 and tumor necrosis factorα(TNFα) .

*Bacterial lipopolysaccharide and endotoxins activate the alternative complement pathway ,generating opsonizing C3b and iC3b on bacterial surface MAC can lysis gram negative but not positive bacteria .

*Bacterial polysaccharide (e.g. Pneumococcal) with multiple repeated epitopes may activate B cells independently of T-helper cells because of their ability to cross link BCRs. The resultant mainly IgM antibodies efficiently agglutinate bacteria and activate the classical complement pathway .

*Exogenous processing of phagocytosed bacteria by macrophages results in presentation of peptide to epitopes in the context of MHCII to T_H1. These induce macrophages activation for efficient bacterial killing .

*Processing of bacterial antigen by B cells induce T_H2 responses and high affinity antibodies production:

_IgG neutralize soluble bacterial production such as toxins

_IgA protect mucosal surfaces from bacterial attachment.

_Immune complexes activate classical complement .

Phagocytic uptake of bacterial coated with C3b/ iC3b and antibody rapid and efficient .

Bacterial evasion strategies

-Capsule resist phagocytosis. Encapsulated bacteria do not display sugar molecules for recognition by receptors on phagocyte .They are only phagocytosed when coated with antibodies ,so can proliferate in non-immune individuals in the first few days after infection .

-Some bacteria resist digestion even when they phagocytosed (*Haemophilus influenza, Streptococcus pneumonia Klebsiella pneumonia,Pseudomonas aeuginosa)*

- Bacteria can kill phagocytes Streptococci,Staphylococci, *Bacillus anthracis* .

-Mycobacterium ,Listeria and Brucella spp. are able to survive within the cytoplasm of non-activated macrophages and can only be killed by a cell-mediated immune response –derived by T_H1 macrophage-activating lymphokines .

Damage caused by immune response to bacteria

-rheumatic heart disease

-Glomerulonephritis .

-Persistent infection of macrophage e.g. with *mycobacterium tuberculosis* .

Immunity to virus

Summary of defense mechanisms

*Viral proliferation induces infected cells to produce interferons (INF)-α and β which protect neighboring cells from productive infection.

*Some viruses notably Epstein- Barr virus bind C1 and activate classical complement pathway resulting in MAC –induced lysis.

*Macrophage readily take up viruses non specifically and kill them.

*Processing of viral antigen by B cells and presentation to T_H2 cells induced high affinity antibody production .Antibody are effective against free rather than cell associated viruses .Antibody coated viruses may be destroyed by classical complement activation pathway or may be taken by phagocytes.

*Intracellular viral antigen are processed by the endogenous pathway and viral peptide present on MHCI molecule recognize by CD8(cytotoxic cell) and destroyed viruses infected cells and provide long-term protection against subsequent infection with the same virus .

*Free virions taken by macrophage and processed by the exogenous pathway stimulate specific T_H1 cells to release IFNγ protect neighboring cells from productive infection.

*Virally infected cell may be down regulate MHC and become susceptible to killing by NK natural killer .

Viral evasion strategies

_Certain v**iruses** can modify the structure of component that are targets for immune response (antigenic variation).

Antigenic drift: point mutation in genes coding viral antigens cause miner structural changes .

Antigenic shift: change of large segments of genetic material lead to changes the whole structure of the antigen .

_Viruses that can integrate their gene within the host cell genome , human herpes viruses provoke only low level immunity which fails to clear the latently infected cells.

_Viruses that infect cells of the immune system may inhibit their function

e.g. Epstein-Barr virus infected B-cell.

Measles – Human T lymphotropic virus type 1 .

HIV virus – T cells.

Dengue, Lassa, Marburg-Ebola ,HIV- Macrophage.

_Some herpes viruses and poxviruses can secret proteins that mimic and interfere with key immune regulators such as cytokines and cytokine receptors .

Damage cause by immune responses to viruses

Epstein –Barr virus is a potent T cell-independent polyclonal activator of B cells .It induce B cells including those with anti-self BCRs which are normally inactive due to purging of the corresponding anti-self T–helper cells ,to secret antibodies .Several viruses notably hepatitis B virus ,can cause chronic autoimmune disease due to release of previously sequestered (non-tolerogenic) self antigen following tissue damage . Complexes of antivirus antibodies with antigen can activate complement in the blood ,vessels ,joints and glomeruli causing vasculitis arthritis and glomerulonephritis .

Cytotoxic T cells may destroy essential host cells displaying viral antigens e.g.coxsackie virus (myocarditis),

Mumps virus (meningoencephalitis)

Viruses causing damage to the myelin nerve sheath .

References:

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