Immune responses to bacteria

Immune responses to extracellular bacteria

Rapidly Streptococci in a surgical wound locally activate complement in the extracellular tissue. Proinflammatory complement fragments like C3a and C5a recruit neutrophils and activate local mast cells which increase blood flow and release a further cascade of proinflammatory mediators. Neutrophils cannot remove bacteria which are in the blood. The spleen plays a crucial role in the removal of pathogens which are not coated with antibody from the bloodstream.

Immunity to encapsulated bacteria

To evade the immune response, certain strains of bacteria have become encapsulated with a polysaccharide coat. Encapsulated bacteria grow less well than their nonencapsulated counterparts but can evade the immune system as they activate complement poorly, and immunity is dependent on generating antibody to the polysaccharide capsule. Three types of bacteria are clinically important in humans:

Neisseriae meningitidis
Pneumococci

All these strains of bacteria can cause sepsis and meningitis. The polysaccharide capsule of these bacteria is poorly degraded by human cells and cannot elicit conventional T cell help.

Although the mechanism of antibody formation is poorly understood, polysaccharides probably activate B cells directly.

Via complement-mediated lysis

When bacteria, such as ***Neisseria meningitidis,*** invade the body, they are attacked by immune proteins called **complement proteins**. Complement proteins assist in bacterial killing via three pathways, the classical complement pathway, the alternative complement pathway or the lectin pathway.

C3 convertase (by cleaving C2 and C4 complement components) that participates in forming MAC.

Via phagocytosis

Antibodies bind to the surface of bacteria by a process called **opsonisation**. Opsonised bacteria are, therefore, coated with molecules that phagocytic cells recognise and respond .Activated phagocytes engulf and destroy opsonised bacteria by a process called **phagocytosis**. Complement C3b is a particularly

important opsonisation protein for controlling bacterial infections by this mechanism. Opsonisation allows killing of Gram-positive bacteria (e.g. ***Staphylococcus spp***.) that are resistant to killing by MAC.

Humoral immunity by activating **B cells**. B cells make antibodies that stick to extracellular bacteria and prevent their growth and survival.

Via cell-mediated immunity

Some bacteria engulfed during phagocytosis avoid the killing mechanisms of the phagocyte to survive inside cells. **Macrophages** are a common targets for **intracellular bacteria** (e.g. ***Salmonella spp.)*** that live inside cell compartments. These bacteria cannot be detected by complement or antibody but, instead, are eliminated using a **cell-mediated response**. Infected macrophages present bacterial peptides on their cell surface using MHC class II molecules. This mechanism is called **antigen presentation**.

If a bacterial peptide is presented, the Th1 cell releases IFN-γ. This cytokine stimulates killing mechanisms, (such as production of **lysozyme**) inside the infected macrophage to digest and destroy the invading bacterium. IFN-γ also increases antigen presentation by cells, making the bacterium more visible to the immune system and more to attack .

Immune response to Viruses

Innate immunity plays a key role in resistance to viral infection:

• Viral replication rapidly stimulates innate immunity

• Interferons (IFN) are anitviral factors expressed by many cells

when virally infected Natural Killer (NK) cells recognize virally infected cells and kill them via cytotoxicity.

• Complement proteins MAC can disrupt the viral envelope Phospholipid bilayer stolen from the host cell.

• Complement can opsonize viral particles for phagocytosis by Macrophage.

Natural Killer (NK) cells can control viral infections:

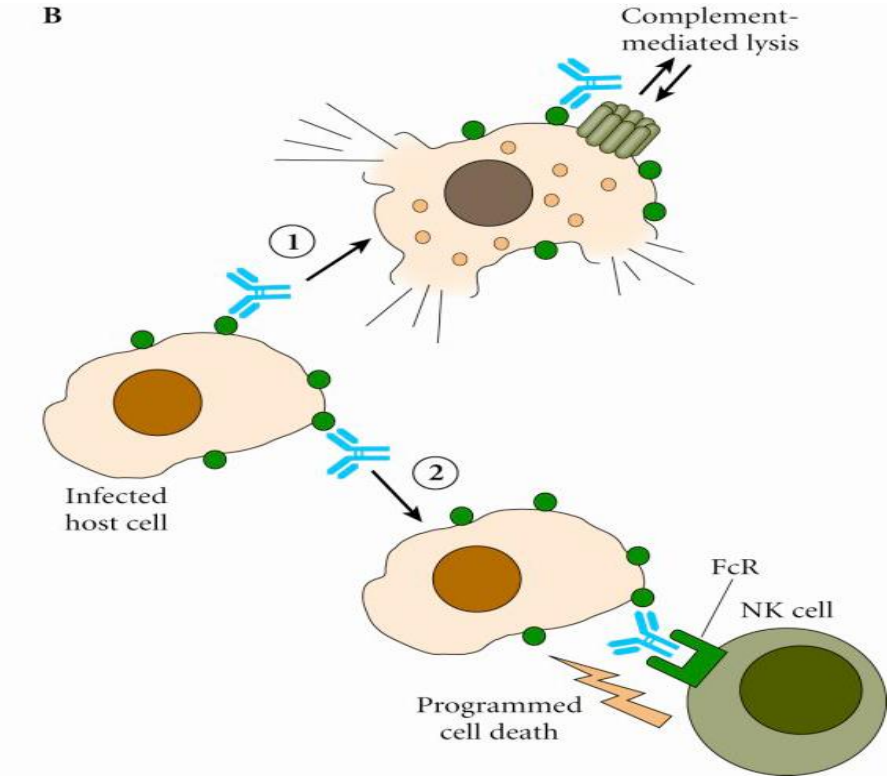
• The virally induced MHC class I downregulation triggers NK cells to kill the infected cells.

• Recognize infected cells coated with antiviral antibodies using Fc receptors (FcR) and kill them through antibody dependent cell mediated cytotoxicity (ADCC).

Viruses and Acquired Immunity:

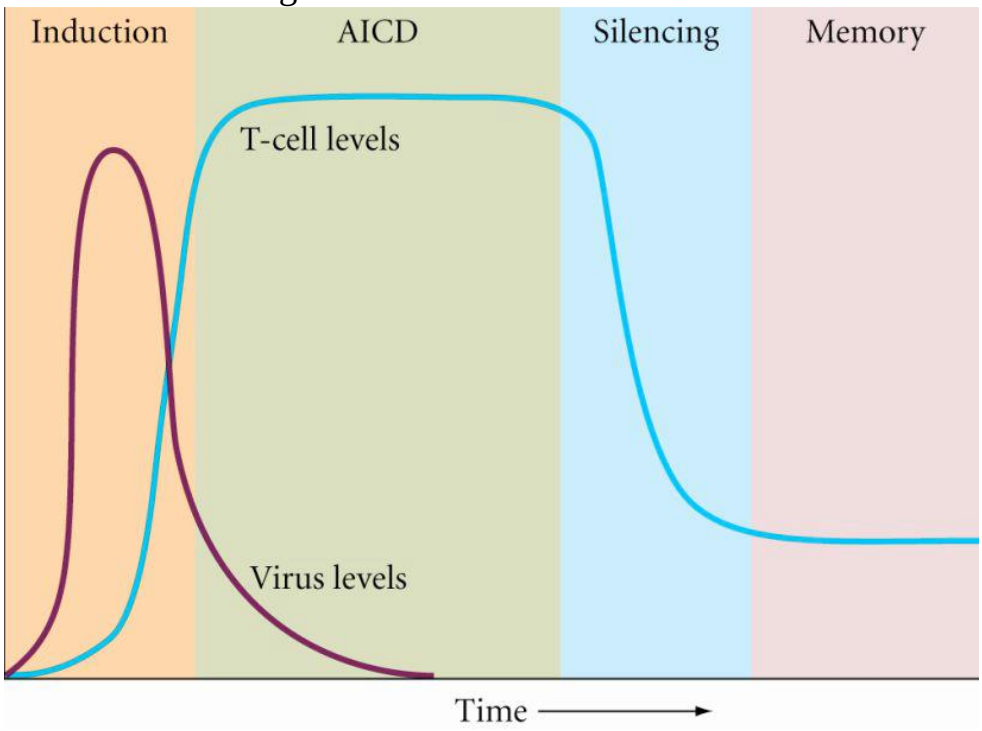
• Antibody mediated immunity or humoral immunity

• Antibody mediated antiviral responses. Antibodies directed at viral surface antigens are the most effective in controlling and clearing viral infections.
• Antigens are usually proteins
• Virus can escape antibody binding by mutating the viral antigen gene thereby changing the antigen .
Antibody dependent control of viruses
– Example HIV



If a virus succeeds in infecting a cell, the antibody can recognize viral antigens on the membrane of the infected cell. Cell is lysed through activation of complement or by ADCC by activating NK cells expressing FC. Antiviral Cellular immune responses are required to inhibit the further spread of virus in the infected cells and are essential for clearing the host of virus once infection has been established . Effector cells are Cytotoxic T lymphocytes (CTLs)
Antiviral CTL responses occur in 4 phases:
1. Induction phase CD8+ precursor T cells proliferate, differentiate into effector cells, and attack and kill virally infected cells
2. Activation-induced cell-death (AICD) phase .Activated CTLs responding to another encounter with viral antigen undergo apoptosis
3. Silencing phase . Loss of AICD but continuation of apoptosis in virus-specific CTLs
4. Memory phase . Some of the virus-specific activated CTLs remain viable and stable as memory cells . Mostly dormant or resting - but have ability to recognize

specific viral antigens, proliferate, and lyse infected cells upon reencounter with the same viral antigen.



Evasion of Host Antiviral Immune Defenses

Produce viral cytokines that decrease immune response .Poxviruses encode soluble IFN that bind the IFN and prevent binding to the real thing on NK and CTLs.

Tumor Immunology

Describes immune responses against tumor cells.

Tumor antigen

Many human tumors express antigens that can induce and be the target of cellular and humoral responses.

1.These antigens are found only in tumor cells and not present in normal cell and therefore represent ideal targets for an immunologic attack.

2. Tumor-associated determinants which are found in tumor cells and also in some normal cells.

Carcinoembryonic antigen (CEA)*:* It is a glycoprotein found on fetal gut and human colon cancer cells, but not on normal adult colon cells.

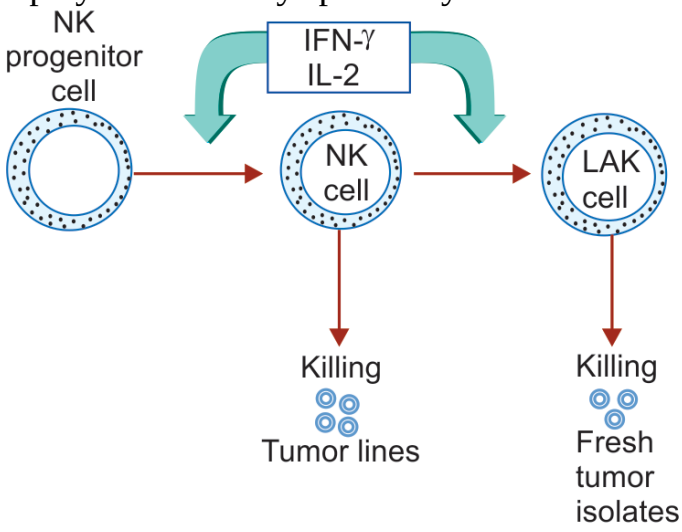
α-fetoprotein: This is an α-globulin, normally secreted by fetal liver and yolk sac cells and is found in the serum of patients with liver and germinal cell tumor.

Cancer testis antigens: They are tumor-associated proteins detected in malignant cells and germinal tissue.

Immune Response to Tumor

Natural Immunity

Natural immunity to tumors is mediated by activated macrophages, neutrophils and natural killer cells (NK cells). Their action may be cytolytic or cytostatic inhibiting tumor growth. This type of immunity does not require antibodies and displays no antibody specificity.



LAK*:* lymphokine-activated killer cell

Adaptive Immunity

When tumor antigens are introduced into experimental animals, it is seen that both, humoral immunity and cell-mediated immunity play important roles in causing destruction of the tumor cells.

B-Cell Responses to Tumors

Both IgM and IgG antibodies have been shown to destroy tumor cells *in vitro* in the presence of complement. Several studies conducted with mice indicate that antitumor antibodies are effective *in vivo* in destroying some leukemia and lymphoma cells and in reducing metastases in several other tumor systems. Other studies *in vivo* and *in vitro*, however, show that the same antibodies, in the presence of complement, are ineffective in destroying the cells of the same tumor in a solid form.

CELL-MEDIATED RESPONSES TO TUMOR CELLS

Destruction of Tumor Cells by T Lymphocytes

Destruction of tumor cells *in vitro* by tumor antigen-specific T cells has been demonstrated numerous times for a variety of tumors, both dispersed and solid. Moreover, from many studies with experimental animals , there is good evidence that tumor-specific, cytotoxic T cells are responsible for destruction of virally

induced tumors *in vivo*. Certain cytokines are essential players in antitumor responses mediated by CTLs including IFN-γ and TNF-a. CD4+ helper T cells also play a major role in the induction, regulation, and maintenance of such CTLs.

Antibody-Dependent Cell-MediatedCytotoxicity

Antibody-dependent cell-mediated cytotoxicity (ADCC) involves (1) the binding of tumor-specific antibodies to the surface of the tumor cells; (2) the interaction of various cells, such as granulocytes and macrophages, which possess surface receptors for the Fc portion of the antibody attached to the tumor cell; and (3) the destruction of the tumor cells by substances that are released from these cells that carry receptors for the Fc portion of the antibody. The importance of this mechanism in the destruction of tumor cells *in vivo* is still not clear.

Immunological Escape

The ability of a tumor to escape from immunological control may depend upon a balance between the effectiveness of the immune system and a variety of factors promoting escape.

Although the immune system clearly can respond to tumor cells, many of which express tumor antigens, the fact that so many individuals die each year from cancer suggests that the immune response to tumors is often ineffective. Some of these escape strategies involve loss of proteins by the tumor cells that helps them evade immune cell recognition and activation.

Reduced MHC Expression in Tumor Cells

Defects in antigen processing and presentation are common among the escape mutants arising in many tumors. These could include mutations that lead to reduced MHC expression . NK cells should recognize these cells lacking class I MHC. However, decreased expression of ligands that bind activating receptors on NK cells.

Sneaking through (tumor kinetics): Tumor cells administered sufficiently in low doses develop into cancer, while greater doses are rejected.

Antigen masking: Certain molecules , which are frequently bound to the surface of the tumor cells, mask tumor antigens and prevent adhesion of attacking lymphocytes.

Blocking factors: Soluble tumor antigens compromise the expression of T immunity by saturation of antigen-binding sites, particularly in the tumor environment.

Genetic factors: The immune response is under genetic control. The difference in immune response to tumor antigen. The difference in immune response to tumor antigen, shown by different individuals in a species is determined by genetic differences.

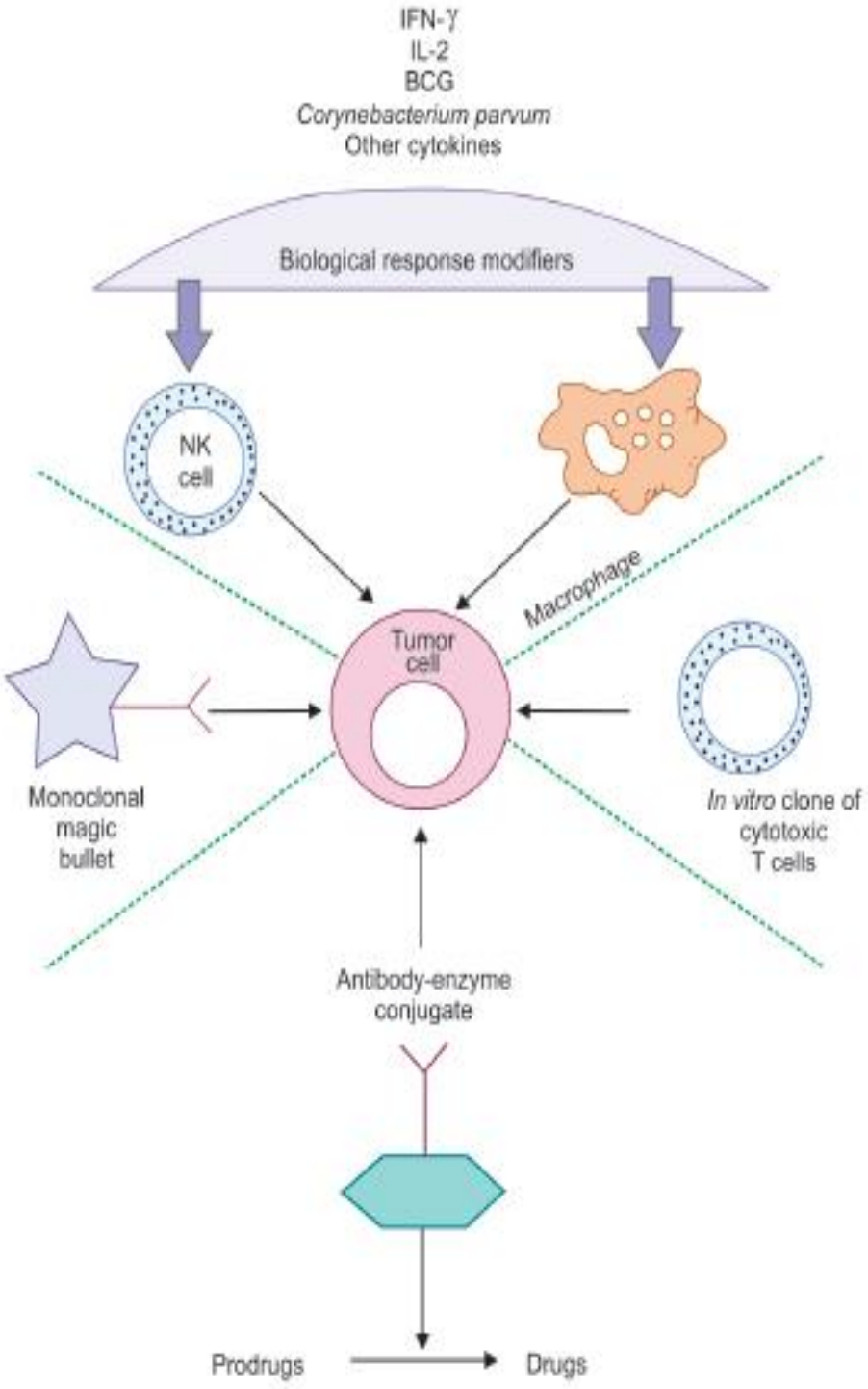
Tumor products: The destruction of immune response by products of tumors other than antigen .

Growth factors: Amplification of T cell responses is critically dependent on the availability in the production of IL-1 by macrophages or in the degree or cooperation between the T cell subsets or in the availability of IL-2 could conceivably limit the overall responses to a tumor.

Cancer Immunotherapy

Interferons cause antitumor activity in three ways:

1. All three types of interferon increase class I MHC expression in tumor cells.
2. IFN-γ also causes increased expression of MHC II molecules on macrophages.
3. Finally, IFN-γ directly or indirectly increases the activity of CTLs, NK cells and macrophages.


IFN-γ
IL-2
BCG
Corynebacterium parvum
Other cytokines
Biological response modifiers
NK cell
Macrophage
Tumor cell
Monoclonal magic bullet
In vitro clone of cytotoxic T cells
Antibody-enzyme conjugate
Prodrugs
Drugs