**Recognition of Microbes by Immune System**cells of innate immune response (macrophages, dendritic cells, mast cells) can recognize pathogens ( virus, bacteria, parasite, fungui) through specific structures that shared by many microbes and called a **pathogen-associated molecular pattern (PAMP).** **lipopolysaccharide (LPS), peptidoglycan (PGN), lipoteichoic acid, double-stranded RNA virus, and the cell wall component of yeast called manan are among PAMP.** These PAMPs do not show antigenic variability, and host cells do not share the same molecular patterns with these pathogens.

Cells of the innate immune response have receptors for these PAMPs called **pattern-recognition receptors (PRR) .** **There are two classes of receptors the first one in the cytoplasm of cells called NOD like receptors and Toll like receptors TLR 3,7,9 that recognize microbes within cells and the second one called C type lectin receptors that include Dectin receptors and TLR 1,2,4,5 , 6 that recognize microbes outside of cells.**

**Binding of PAMPs to PRRs lead to signal transduction inside the immune cells that enhances transcription, translation and release of inflammatory mediators which directly potentiate the adaptive immune response.**

**After recognition** of the pathogen by antigen presenting cells e.g. macrophage, it processed and fragment of it called **antigens** or **epitopes** presented t the native CD4 helper Tcells (TH) . TH then under the effect of cytokines that released from innate immne response differentiated to:

1. TH1 that release mediators important in activation of cell mediated immune response (IL2, IL12, IFN γ, TNF, …) that activate CD8CTL , macrophages and others.

CD8 CTL then recognize infected cells when present the microbial Ag in association with type I MHC.

1. TH2 that release mediators (IL4, IL5) responsible for differentiation of B lymphocytes to plasma cells then antibody production (humeral immune response HIR

**NOTE: usually both types of immune response (CMIR, HIR) are produced but according to the type of microbe (pathogen) the effective immune response will be dominated. For intracellular microbe (viruses, certain bacteria and parasites) and fungi , CMIR is the effective in eradication while HIR is the effective in extracellular pathogens.**

**Viral Infection**

**The innate immune response to viral infection:**

* Secretory IgA in mucous secretions plays an important role in host defense against viruses by blocking viral attachment to mucosal epithelial cells.
* Cells of innate immune response recognize PAMPs of virus by TLR with the aim of amplifying the inflammation and activating the adaptive cellular immune response.
* Double stranded RNA (dsRNA) induces production of type I interferons (IFN-α- and IFN-β) which resist viral replication. Once bound, IFN-α- and IFN-β - activate the JAK-STAT pathway, which in turn induces the transcription of several genes

a. Gene encodes enzyme known as 2-5-oligo-adenylate synthetase [2-5(A) synthetase], which activates ribonuclease L (RNAase L) that degrades viral mRNA

b. Gene encods a specific protein kinase called dsRNA-dependent protein kinase (PKR). PKR inactivates the translation initiation factoreIF-2 by phosphorylating it, thus blocking viral replication in infected cells

c. The binding of IFN-α- and IFN-β to NK cells induces lytic activity, making them very effective in killing virally infected cells.

* IL12 greatly enhances the activity of NK cells

**Antibodies (humeral immunity) to viral infection**

Antibodies are particularly effective in protecting against infection if they localized at the site of viral entry into the body (attachment receptor**) which can include the followings:**

1. Secretory IgA in mucous secretions a site of entry
2. Abs Bind to epitopes that are necessary to mediate fusion of the enveloped virus with the plasma membrane.
3. Abs Opsonize viral particles and function as an opsonizing agent to facilitate phagocytosis.
4. Abs Activate complement system which mediates opsonization by C3b that enhance phagocytosis and lysis of enveloped viral particles by membraneattack complex

All these antibodies may be of innate immune response , Previous infection or from Vaccine

**Cell-Mediated Immunity to viral infection**

It is Important for Viral Control and Clearance in established viral infection (virus inside the cells). Although antibodies have an important role in containing the spread of a virus in the acute phases of infection, they are not usually able to eliminate the virus once infection has occurred. Once an infection is established, cell-mediated immune mechanism **is the effective mechanism in host defense** and cytotoxic T lymphocytes CTL is the effector cell against viral infection . The activation of cell mediated immune response occur by :

I// **Antigen presenting cells (APC) presenting viral antigen with MHC II to native CD4 cells that trigger the followings**

1. Native CD4 cells differentiated to CD4 TH1 cells. Activated TH1 cells produce a number of cytokines, including IL-2, IFN-γ,and TNF.
2. IFN-γ acts by Increases expression of classes I and II MHC.
3. IL-2 acts indirectly by assisting in the recruitment of CD8 (cytotoic T lymphocytes CTL) and macrophages.
4. TNF can directly induce apoptosis.
5. IL-2 activate NK cells, which play an important role in host defense during the first days of many viral infections. The killing of viral infected cells occur by antibodydependent cell-mediated cytotoxicity (ADCC)

**II//viral infected cells can directly presenting viral antigens with MHC I to CD8 cells and indce apoptosis (cell death)**

Although NK cells and macrophages included in CMI response, CTL cells are the most effector cells.

CTLs kill their target by inducing apoptosis. This process occurs in 3 pathways:

1. Exocytosis of granules contents :perforin creates pores in the membrane of the target cell through which granzymes (serine proteases) enter the target, inducing the activation of caspases which activate the "death domain''.

2. Cytokines such as IFN-y with TNF-a or TNF-B can directly induce apoptosis.

3. Activated CTLs express a membrane protein called Fas ligand (FasL), which may bind to its complementary( Fas )structure on the target. When this occurs, caspases are induced and death results.

In most viral infections, specific CTL activity arises within 3–4 days after infection, peaks by 7–10 days, and then declines. Within 7–10 days of primary infection, most virions have been eliminated, paralleling the development of CTLs

Viruses Can Evade Host Defense Mechanisms  
  
I- overcome the antiviral effect of the interferons by blocking or inhibiting the action of PKR eg HCV  
II- inhibition of antigen presentation to CTL by:

a. inhibiting antigen processing and formation of empty class I MHC molecules eg HSV

b. down-regulate class I MHC expression shortly after infection eg adenoviruses and cytomegalovirus (CMV)

III- inhibition of antigen presentation to CD4 TH cells by reducing levels of class II MHC molecules on the cell surface eg CMV, measles virus, and HIV

IV- Inhibiting complement pathways by secreting a protein that binds to theC3b ( HSV )or C4b ( Vaccinia virus) complement component   
V- some viruses constantly changing their antigens eg influenza viruses

VI- Causing generalized immune suppression either by infecting immune cells causing their destruction (HIV) or or by producing protein similar to human inhibitory cytokine eg EBV produce IL10 like protein

**Bacterial Infections**  
Immunity to bacterial infections is achieved by means of antibody unless the bacterium is capable of intracellular growth, in which cell mediated immune response has an important role.

Innate immune response to bacteria may include secretory IgA at site of entry and cells of innate immune response recognize the pathogen-associated molecular patterns (PAMPs) of bacteria by Toll-like receptors with the aim of amplifying the inflammation and activating the adaptive immune response.

Immune Responses to Extracellular Bacteria

* Humeral immune response HIR is the main protective response against extracellular bacteria.
* APC and after processing bacteria Ag presenting it to native CD4 cells
* CD4 cells differentiated to CD4 TH2

TH2 cells produce IL4, IL5 that enhances Bcells differentiation to plasma cells that producing specific Abs against bacterial infection

HIR against extracellular bacteria will lead to removal of bacteria and or its toxin

I// Removal of the bacteria

1- **phagocytosis** : Antibodies that bind to bacterial surface Ags and together with the C3b component of complement, act as an opsonin that increases phagocytosis

**2- Lysis** : Antibody-mediated activation of the complement system induce

1. Production of immune effector molecules eg C3a, C4a, and C5a that act as anaphylatoxins and chemo-attractants for neutrophils, mast cells, lymphocytes),
2. Lysis of bacteria by membrane attack complex

II// Inactivation of bacterial toxin

1. Exotoxins neutralized by specific **neutralizing** Abs

2. Endotoxin (LPS of gram-negative organisms) activate complement and and lysis of the bacteria by membrane attack complex

**Summary:** HIR against extracellular bacteria include phagocytosis, lysis and neutralization

Immune Responses to Intracellular Bacteria

Intracellular bacterial infections tend to induce a CMIR, specifically, delayedtype hypersensitivity. In this response,

* APC presents the processed Ag to native CD4 cells with ecess IL12
* CD4 cells differentiated to CD4 TH1 cells
* TH1 secreted IL2, IFNγ, which activates macrophages to kill ingested pathogens more effectively by delayed type IV HSR.

**Immune Responses Can Contribute to Bacterial Pathogenesis**

I// A variety of microorganisms produce exotoxins that act as superantigens e.g. enterotoxins, exfoliating toxins, and toxic-shock syndrome toxin (TSST) from *Staphylococcus aureus;* pyrogenic exotoxins from *Streptococcus pyrogenes;* and  
*Mycoplasma arthritidis* supernatant (MAS).

superantigens can activate large numbers of T cells irrespective of their antigenic specificity results in excessiveproduction of cytokines which is the causative agent of several diseases such as bacterial toxic shock and food poisoning.

II//Sometime bacterial cell-wall **endotoxins** stimulate macrophages to overproduce IL-1 and TNF- to levels that cause **septic shock**. The symptoms of bacterial septic shock, which is often fatal, include a drop in blood pressure, fever, diarrhea, and disseminated intravascular coagulopathy DIC and shock which may lead to death.

III// Some intracellular bacteria eg M tuberculosis bacteria can induce chronic stimulation for CD4 cells. Cytokines secreted by these activated CD4+ T cells can lead to extensive accumulation and activation of macrophages with subsequent differentiation to epitheloid cells and multinucleated giant cell formation. This will lead to granuloma formation.

**Bacteria Can Evade Host Defense Mechanisms by:**

1. **For IgA that prevent attachment:**

Secretion of proteases that cleave secretory IgA dimers

1. **For Phagocytosis that prevent proliferation of the bacteria** :

Production of surface structures (polysaccharide capsule, M protein, fibrin coat) to retard phagocytosis

1. **For surviving within phagocytic cells**

inhibit phagolysosome attachment

1. **For antibodies that activate complement and neutralize toxins:**

Secretion of elastase that inactivates C3a and C5a and hyaluronidase which enhances bacterial invasiveness.

Immunity to fungal infection

Fungi cause first superficial infection (for skin and mucous membraine ) which are rarely life threatening and second invasive (systemic) fungal infection, IFIs, occur when fungal pathogens invade the bloodstream, resulting in a systemic life-threatening infection that affects multiple organs. IFIs are estimated to cause 1.5 million deaths annually, with four genera accounting for most of the infections:  
*Cryptococcus, Candida, Aspergillus,* and *Pneumocystis.*

Growth of commensal fungi in skin and mucous membrane is limited by release of antimicrobial peptides of skin and colonization by other microbial flora that compete for nutrients. Disruptions to this delicate balance for example by taking broad spectrum antibiotics can have serious pathological consequences.

Innate immune response

Fungi express highly conserved PAMPs that are recognized by PRRs expressed on host phagocytes.  
• Dectin-1 is a C-type lectin receptor (CLR) that acts as a PRR to recognize  
β-1,3 glucan expressed on the cell walls of *Candida, Aspergillus,* and other fungal pathogens.  
• TLRs recognize fungal cell wall components and nucleic acids. TLR2,4,6 extracellular receptors that recognize GXM Mannan of fungal cell wall while TLR 3, 7, 9 intracellular receptors that recognize fungal DNA and RNA  
• Engagement of PRRs and PAMPs initiates signaling that coordinates  
secretion of cytokines IFNγ, IL-12 , IL4, TNFα, IL6, TGF-β , IL-10, IL-2, reactive oxygen species (ROS) production, and presentation of fungal antigens to the adaptive immune system to facilitate elimination of the pathogen.

Addaptive immune response:

T-cell immunity is critical for fungal host defenses. Cytokines that released by innate immune response lead the followings:

1. IL6, TGF-β lead to differentiation of CD4 helper cells toward TH17 that release IL-17A, IL-17F, and IL-22 that have antifungal activity.
2. IL-12 lead to differentiation of CD4 helper cells toward TH1 that release IFNγ and other cytokines that potentiate macrophage and CD8 to limit or clear fungal infection.
3. IL4 lead to differentiation of CD4 helper cells toward TH2 to produce antibodies.

**Notes:**

• TH1 and TH17 T cell subsets are the most important T cells for control of fungal infection  
• Th2 cells mediate fungal asthma and hyperreactivity otherwise Humeral immunity may play a supportive role only.

Immunity to parasitic infection:

I// Helminthes infection: immune response characterized by the followings:

* Immunoglobulin E (IgE) antibody production, tissue and peripheral blood eosinophilia, mast cell involvement, innate lymphoid cell type 2 and Th2 cell expansion, and production of type 2 cytokines.
* In mucosal immunity to helminths, T-helper 2 (Th2) cell responses are initiated and sustained by innate populations (including tuft cells and innate lymphoid cells) through interleukin (IL)-25, IL-33, and thymic stromal lymphopoietin (TSLP).
* In tissues, helminths are acted upon by the host innate effectors, including macrophages, neutrophils, eosinophils, and basophils. Regulated by T cells and other cells producing IL-4, IL-5, IL-9, IL-10, and/ or IL-13.

Both mucosal and tissue immune response characterized by TH2 cell predominance (humeral immune response) and the induction of regulatory T cells (Tregs) that mediate downmodulation of immune responses to helminth infections and impact bystander phenomena, such as allergy and autoimmunity.

II// Protozoal infection:

Immunity against protozoal infection depends on type of the protozoa and stage of the parasite

Both humeral immu resp HIR &cellular immu resp CMIR can be involved

Immune response may be down regulated in certain time and up regulated in other circumstances.

The following is an example for immune response against intracellular parasites

