Unit 4

Cell Communication and signaling

Unit Map

4.A Host parasite interaction

4.A.1 Recognition and entry processes of different pathogens

Several defense mechanisms have been developed by the host against the pathogens, which in turn are needed to respond with new strategies to gain entry into host cells. Diverse pathogens and toxins actively induce the initial steps of their uptake into a wide range of target cells. In most cases, the pathogen plays a key role in bringing down the cellular machinery to stimulate actin (the cytoskeletal protein) rearrangements, which facilitates the invasion process. Key to their ability to respond to pathogens, a closely related family of proteins called ***kinases*** either associate with these receptors or are present as part of the receptors themselves. These kinases face two challenges. First, the signals must be carefully modulated, as its mis-regulation can result in diseases. Second, these signaling systems must be resilient to attempts by pathogens to interfere with and block defense responses.The kinases are linked to pathogen receptors and initiate innate immune responses, which results in an alteration within a critical functional domain of the kinase that is not commonly found in similar kinases that control the nondefense pathways.

Plants and animals mediate early steps of the innate immune response through pathogen recognition receptors (PRRs). PRRs commonly associate with or contain members of a monophyletic group of kinases called the ***interleukin-1 receptor-associated kinase (IRAK) family*** that include *Drosophila* Pelle, human IRAKs, rice XA21 and *Arabidopsis* FLS2. Animal and plant innate immune systems use a set of similar receptors to recognize disease-causing microbes. These receptors function in pathogen surveillance and are located either at the cell surface or inside the cell. They provide a first line of defense against pathogen attack and rapidly activate defense-signaling pathways following the infection.The initial step in the cellular uptake process of diverse pathogens and toxins is characterized by the binding to carbohydrate moieties exposed by a lipid or a protein in the plasma membrane of the target cells. *Example* cholera toxin binds with its B-subunit to the ganglioside GM1 (monosialotetrahexosyl ganglioside) in intestinal cells, the opportunistic human pathogen *Pseudomonas aeruginosa* attaches to the respiratory cells by binding to asialo-GM1 and asialo-GM2 through pili and the influenza A virus initiates its uptake by binding to sialic acids in the host cell membrane. Conventionally considered as adhesion receptors for toxins, viruses and bacteria, glycosphingolipids are also crucial parameters for the self-induced endocytosis of toxins and viruses.

- **Pathogen recognition**

  Activation of inducible defense is triggered by a specific recognition of pathogen invasion by plants. Perception in host specific resistance involves receptors with high degrees of specificity for pathogen strains, which are encoded by constitutively expressed ***defense resistance (R) genes***, located either on the plasma membrane or in the cytosol. Large repertoires of distantly related individual R genes with diverse recognition specificities are found within a single plant species. Individual R genes have narrow recognition capabilities and they trigger resistance when the invading pathogen expresses a corresponding avirulence (Avr) gene. ***Avr genes*** from different pathogen classes are structurally very diverse and have different primary functions. Specific recognition of the attacking pathogen by the plant requires the presence of matching Avr and R genes in the two species, which is thought to be mediated by ligand receptor binding. Over 20 R genes with recognition-specificity for defined Avr genes have been isolated from seven plant species, including both monocots and dicots. These genes are effective against bacterial, viral and fungal pathogens.

  In spite of the great diversity in lifecycles and pathogenic mechanisms of the disease causing organisms, R genes were found to encode proteins with certain common motifs.

  The recognized five classes of R proteins are

  i. Intracellular protein kinases
  ii. Receptor-like protein kinases with extracellular leucine-rich repeat (LRR) domain
  iii. Intracellular LRR proteins with a nucleotide binding site (NBS) and a leucine zipper (LZ) motif
  iv. Intracellular NBS-LRR proteins with a region having similarity to the Toll and interleukin-1 receptor (TIR) proteins from Drosophila and mammals
  v. LRR proteins that encode membrane bound extracellular proteins

  Plant R genes encode proteins that serves two functions. *One* it determines recognition of specific Avr proteins and *two* it initiates signal transduction pathways leading to complex defense responses. In addition to the gene for gene recognition mediated by R and Avr genes, non-host resistance is achieved through the recognition of specific pathogen or plant cell wall derived signal molecules, termed as exogenous or endogenous elicitors, respectively.

These elicitors are often low-molecular-weight compounds that are either synthesized as such or are liberated from the polymeric precursors during infection. The chemical structure of different elicitors is of great variety; such as glycoproteins, peptides and oligosaccharides. Some proteinaceous elicitors are directly produced by hydrolases of bacterial or fungal pathogens, whereas biologically active oligosaccharides are released from pathogen and plant cell walls. Complex and largely unresolved sensing systems exist for these elicitors on the plant cell surface that activate multiple intracellular defense signaling pathways.The multi-component response of plants to pathogens in host and non-host resistance is activated by ligand/receptor interactions, in which Avr gene and pathogen or plant surface-derived elicitors serve as ligands for plasma membrane or cytosolic receptors.

- **Bacterial toxins**

A toxin is a specific substance, often a metabolic product of an organism that damages the host. Toxins can even induce disease in the absence of the organism that produced them. Diseases that result from the entrance of a specific toxin into the body of a host are called ***intoxication.*** The term toxemia refers to the condition caused by toxins that have entered the blood of the host. Toxins produced by the organisms can be divided into two main categories: exotoxins and endotoxins.

Properties of toxins

Property	Exotoxins	Endotoxins
Source	Gram (+) and gram (-) bacteria	Lipopolysaccharide of gram (-)
Secretion from the cell	+	-
Chemical nature	Polypeptide	Lipopolysaccharide
Location of genes	Plasmid/prophage /chromosome	Bacterial chromosome
Toxicity	High	Low
Antigenicity	High	Poor
Vaccines	Toxoids used as vaccines	No toxoids formed
Heat stability	Heat labile, inactivated rapidly at 60-80°C	Heat stable

Based on the structure and physiological activities exotoxins are categorized into neurotoxins (nerve tissue), enterotoxins (intestinal mucosa) and cytotoxins (tissues). Based on the mode of action they are categorized as

- **Toxins that act from cell surface** Toxins bind to the cell surface receptors and stimulate intracellular signaling pathways. *Example*, superantigens
- **Membrane damaging toxins** They disrupt the integrity of plasma membrane.

  Two subtypes of this type of toxins are

  i. **Channel forming toxins** alpha toxin of *Staphylococcus aureus* inserts itself into the host cell membrane via open channels called pores.

  ii. **Toxins that enzymatically damage the membrane** alpha toxin of *Clostridium perfringe*, which causes gas gangrene. The toxin has phospholipase activity which enzymatically damages the membrane by removing the charged polar head groups from the phospholipids.

Bacterial toxins and their mode of action

Bacterium	Disease	Mode of action
Cornebacterium diphtheria	Diphtheria	Inactivates EF-2 by ADP ribosylation
Clostridium tetane	Tetanus	Blocks release of theinhibitory neurotransmitterglycine
Clostridium botulinum	Botulism	*α-toxin* is a lecithinase
Clostridium perfringes	Gas gangrene	*α-toxin* is a lecithinase
Bacillus anthracis	Anthrax	One of the toxin is adenylate cyclase
Staphylococcus aureus	Toxic shock	Binds to class II MHC protein; includes IL 1and IL-2
Vibrio cholera	Cholera	Stimulates adenylate cyclase by ADP-ribosylation of Gs*α*
Bordetella pertussis	Whooping cough	Stimulates adenylate cyclase by ADP-ribosylation of Gs*α*

iii. **AB toxins** These are intracellular toxins. The toxic B-subunit attaches itself to the target regions on cell membranes and the A-subunit enters through the membrane and possesses the enzymatic activity that affects internal cellular bio-mechanisms. A-subunit lack binding and cell-entry capability whereas B-subunits bind to target cells but are non-toxic and biologically inactive. Toxins by *cholera, pertussis, shigella, tetanus, botulinum, anthrax* and heat labile enterotoxin from *E.coli* produce this type of toxins.

- **Entry process**

Before pathogens can grow and cause a disease, they must first gain access to the tissues. There are several sites that act as the portals of entry of pathogens into the host. Some pathogens have specific portals of entry *for example* Cold viruses enter the host through the mucous membrane of the eye and upper respiratory tract, whereas pathogens responsible for causing sexually transmitted diseases enter through the mucous membrane of respiratory and reproductive tract along with mucous membrane of the eye and the upper respiratory tract.

i. Damaged skin
- Skin acts as a barrier to infections.
- Tetanus occurs when the bacterium *Clostridium tetani* enters the wound of respiratory tract

ii. Mucus membrane
- Air containing droplet of infectious material are breathed in
- *Mycobacterium tuberculosis* causes tuberculosis

iii. Digestive track
- *Vibrio cholerae* causes cholera when drinking water is infected with faeces
- *Salmonella enteritis* causes food poisoning when eating undercooked food
- These organisms are resistant to acidic conditions in the stomach
- Acid protects against microorganisms by providing a hostile environment

iv. Others
- Transmission by vectors (*example* malaria via Plasmodium parasite when mosquito vector takes blood)
- Direct entry through the intact skin (*example* Schistosomiasis where the larval stage schistosome burrows through the skin of the feet)

Process

Viral nucleic acids re-programme the cell operations to serve the goals of a viral replication. The specific symptoms of a viral disease are due to the type of cell infected and damaged. There are four sequential phases of entry process; attachment, penetration, biosynthesis and assembly. Their release however depends upon their type.

i. ***Attachment*** the protein coat of the virus envelope binds to the protein receptors present on the host cell membrane.

ii. ***Penetration*** the virus envelope fuses with plasma membrane and the virus capsid and then the nucleic acid enters host cell. Capsid disintegrates and the nucleic acid is released.

iii. ***Biosynthesis*** the copies of viral nucleic acids are replicated. Viral nucleic acids are used to synthesize new capsid proteins by employing organelles of host cell.

iv. ***Assembly*** the newly synthesized capsid proteins and viral nucleic acid molecules are assembled into new viruses.

v. ***Release*** the viruses with envelop acquire their envelopes as they are released from their host cell.

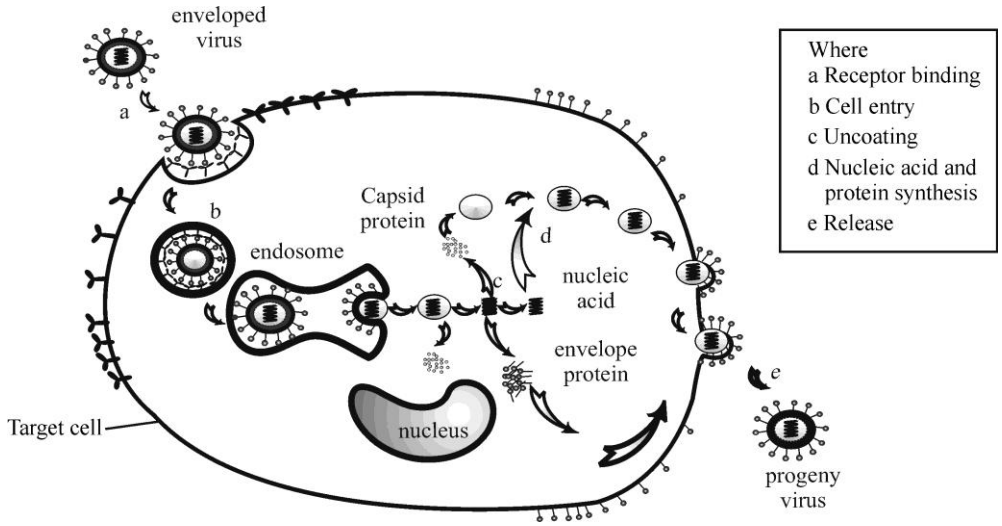

Figure 4.A.1-1

The attachment phase determines the specificity of virus for a particular type of cell. Having attached to the surface of the cell, the virus must affect entry to be able to replicate in a process called penetration. The un-coating takes place. The virus genome available is now used in biosynthesis phase.The new genomes come together with newly synthesized virus proteins to form progeny virus particles, this is called assembly. Finally particle leaves the cell in release phase.

Some viruses do not immediately follow the sequence of events described. Instead, there is a viral integration that takes place. Before producing viruses, the viral nucleic acid becomes a part of the host cell's DNA. This integration remains for lifetime of the cell and gets replicated before the host cell's mitotic division. After the mitotic division, the viral nucleic acid is passed to the two progeny cells.

4.A.2 Alteration of host cell behavior by pathogens

Certain viruses have the ability to enter a cell and follow one of two alternative courses. They both multiply in a normal manner and are eventually released from the cell, or they may be dormant in the cell and eventually transform the cell into a malignant cell. It is believed that the transformation process involves the integration of viral nucleic acid into the host chromosome. When this happens, the cell achieves certain characteristics of malignant cells.

- **Immune system**

Plants, like animals, have a ***basal immune system*** that includes a small number of pattern recognition receptors specific for the broadly conserved microbe-associated molecular patterns (MAMPs, also called ***pathogen-associated molecular patterns or PAMPs)***. Examples of these microbial compounds that elicit plant basal defense include bacterial flagellin or lipopolysaccharides, or fungal chitin. The defenses induced by MAMP perception are sufficient to repel the most potential pathogenic microorganisms. However, pathogens express effector proteins that are adapted to allow them to infect certain plant species; these effectors often enhance pathogen virulence by suppressing the basal host defenses.

- **Damage or destroy host cells** example HIV, Salmonella
  - **i.** Epithelial cells in the intestine take up the organism.
  - **ii.** Host specific ligand on the pathogen must fit onto receptor proteins on host. Some hosts are more susceptible than others because proteins depend on the gene coding.
  - **iii.** Destroy brush border of microvilli.
  - **iv.** Host creates a ruffled surface causing the invaded cells detach from intestinal wall, creating inflamed lesions followed by secretion of large amounts of watery fluid into the lumen of the gut; causing diarrhea.
- **Produce toxic waste** example *Vibrio cholera*
  - **i.** It is harmless but produce harmful "exotoxins" - toxins released from the cell
  - **ii.** Causes loss of chloride and hydrogen carbonate ions from the intestinal cells
  - **iii.** Osmotic loss of up to 10 liters of water per day.
  - **iv.** Impaired absorption of water and salt from the gut.
  - **v.** This explains severe watery diarrhoea and death from dehydration.
- **Body's own immune response** to the presence of microorganisms which produce the symptom example *Mycobacterium tuberculosis*
  - **i.** Body tries to destroy the invading bacteria
  - **ii.** This causes inflammation and damage to the surrounding cells occur
  - **iii.** Lesions may become hard or spongy, leaving "holes" in the lungs, sometimes damaging the blood vessels.

Some bacteria will cause all the above three; some require a large number of bacteria for a disease; some will onlycause a disease with a few numbers of bacteria. Microorganisms may enter the lymphatic system via tissue fluid and are carried around the body. The ability of bacteria to cause disease relies on

Location what tissue is colonized

Infectivity how easily a bacterium can enter the host cell

Invasiveness how easily a bacterium or its toxin spreads within the body

Pathogenicity how a bacterium cause disease.

- **Suppression of the immune mechanisms** Viruses are known to replicate in the cells of the lymphoreticular system, these viruses therefore can affect the immune system. Viruses or virus-like particles have been found in the thymus, lymph nodes, spleen, bone marrow, stem cells, plasma cells, lymphocytes, macrophages, monocytes, polymorphonuclear leukocytes and Kupffer cells. The nature and extent of the immunologic alteration depends on the organ or cell type infected and the species of virus causing the infection. These effects have been demonstrated in each of the following systems.