***College of Vet. Medicine***

**Virology**

Viral Pathogenesis

Viral pathogenesis is the process by which a viral infection leads to disease.

Viral pathogenesis is an abnormal situation of no value to the virus.

The majority of viral infections are subclinical. It is not in the interest of the virus to severely harm or kill the host.

The consequences of viral infections depend on the interplay between a numbers of viral and host factors.

**Outcome of Viral Infection**

**Acute Infection**

Recovery with no residue effects

Recovery with residue effects e.g. acute viral encephalitis leading to neurological sequelae.

Death

Proceed to chronic infection

**Chronic Infection**

1- Silent subclinical infection for life e.g. CMV, ([Epstein–Barr virus](http://en.wikipedia.org/wiki/Epstein%E2%80%93Barr_virus))EBV.

2- A long silent period before disease e.g. HIV, SSPE, PML

3- Reactivation to cause acute disease e.g. herpes.

4- Chronic disease with relapses and exacerbations e.g. HBV, HCV.

5- Cancers e.g. (Human herpes-8)HHV-8

**Factors included in Viral Pathogenesis**

**For pathogenic virus, there are a number of critical stages in replication which determines the nature of disease they produce which included;**

1-Entry into the Host

2-Course of Infection (Primary Replication, Systemic Spread, Secondary Replication)

3-Cell/Tissue Tropism

4-Cell/Tissue Damage

5-Host Immune Response

6-Virus Clearance or Persistence



**1- Entry into the host**

The first stage in any virus infection. In the case of pathogenic infections, the site of entry can influence the disease symptoms produced. Infection can occur via:

**A- Skin,** dead cells therefore cannot support virus replication. Most viruses which infect via the skin require a breach in the physical integrity of this effective barrier, e.g. cuts or abrasions. Many viruses employ vectors, e.g. ticks, mosquitoes or vampire bats to breach the barrier.

**B- Respiratory tract-** In contrast to skin, the respiratory tract and all other mucosal surfaces possess sophisticated immune defense mechanisms, as well as non-specific inhibitory mechanisms(ciliated epithelium, mucus secretion, lower temperature) which virus must overcome.

**C- Gastrointestinal tract-** a hostile environment; gastric acid, bile salts, etc. Viruses that spread by GI tract must be adapted to this hostile environment.

**D- Genitourinary tract-** relatively less hostile than the others.

**E-Conjunctiva and other mucous membranes** - rather exposed site and relatively unprotected

**2-Course of Viral Infection**

**Primary Replication**

After entry to potential host, the virus must initiate an infection by entering a susceptible cell. This frequently determines whether the infection will remain localized at the site of entry or spread to become systemic infection.

**Localized infections**

Virus primary replication

Rhinoviruses upper respiratory tract

Rotaviruses Intestinal epithelium

Papillomaviruses Epidermis

**Systemic Infections**

Virus primary replication secondary replication

Enteroviruses Intestinal epithelium Lymphoid tissues, C.N.S

Herpesviruses Oropharynx or G.U. tract Lymphoid cells, C.N.S

**Secondary replication**

Occurs in systemic infections when a virus reaches other tissues in which it is capable of replication, e.g. poliovirus (gut epithelium- nervous in brain &spinal cord). If the virus can be prevented from reaching tissues where secondary replication can occur, generally no disease results.

**3- Spread throughout the host**

Apart from direct cell-cell contact, there are 2 main mechanisms for spread throughout the host:

**Via the bloodstream**

**Via nervous system**

Virus may get into the blood stream by direct inoculation- e.g. Arthropod vectors, blood transfusion or I.V drug abuse.

The virus may travel free in the plasma (Togaviruses, Enteroviruses) or in association with red cells (Orbiviruses) platelets (Herpes simplex virus). Primary viraemia usually proceeds and is necessary for spread to the blood stream, followed by more generalized higher titer secondary viaremia as the virus reaches other target tissues or replicates directly in blood cells.

As above, spread to nervous system is preceded by primary viaremia.

In some cases, spread occurs directly by contact with neurons at the primary site of infection, in other cases via the bloodstream. Once in peripheral nerves, the virus can spread to the CNS by axonal transport along nervous (Herpes simplex virus). Viruses can across synaptic junctions since these frequently contain virus receptors, allowing the virus to jump from one cell to another.

**4- Cell/ Tissue tropism**

Tropism- the ability of a virus to replicate in particular cells or tissues- is controlled partly by the route of infection but largely by the interaction of a virus attachment protein(V.A.P) with a specific receptor molecule on the surface of a cell and has considerable effect on pathogenesis.

**5- Host immune response**

Has a major impact on the outcome of an infection. In the most cases the virus is cleared completely from the body and results in complete recovery. In other infections, the immune response is unable to clear the virus completely and the virus persists. In general, cellular immunity plays the major role in clearing virus infection whereas humoral immunity protects against reinfection.

**7- Cell /Tissue damage**

Virus may replicate widely throughout the body without any disease symptoms, if they do not cause significant cell damage or death. Retroviruses do not generally cause cell death, being released from the cell by budding rather than by cell lysis and cause persistent infections, even being passed vertically to offspring if they infect the germ line.

Conversely, Picornaviruses cause lysis and death of the cells in which they replicate, leading to fever and increased mucus secretion in the case of Rhinoviruses, paralysis or death (usually due to respiratory failure) for Poliovirus.

**8- Viral Clearance or Persistence**

The majority of viral infections are cleared but certain viruses may cause persistent infections. There are 2 types of chronic persistence infections.

1- True Latency -the virus remains completely latent following primary infection e.g. Herpes simplex virus.

2- Persistence e- the virus replicates continuously in the body at a very low level e.g. (HIV).

**Antiviral immunity**

Viruses are small, obligate intracellular parasites which cause infection by invading cells of the body and multiplying within them, within their life cycle they have relatively short extracellular period, prior to infecting the cells, and longer intracellular period during which they have undergo replication. The immune system has mechanism which can attack the virus in both these phase of its life cycle, and which involve both non-specific and specific effecter mechanism.

**Non-specific mechanisms**

**Interferon:**

Are proteins made and released by host cells in response to the presence of pathogens such as virus, bacteria etc. They allow for communication between cells to trigger the protective defenses of the immune system that eradicate pathogens or tumors.

IFNs belong to the large class of glycoproteins known as cytokines, they named after their ability to interfere with viral replication within host cells.

Viral infection of the cells directly stimulates the production of interferons. Type I interferons lead to the induction of an antiviral state in the cells, which is characterized by inhibition of both **viral replication and cell proliferation**, and also enhancement of the **ability of natural killer cells to lyses virally infected** cell.

**Mechanism of action of interferon**

As an infected cell dies from a cytolytic virus, viral particles are released that can infect nearby cells. However, the infected cell can warn neighboring cells of a viral presence by releasing interferon to reduce protein synthesis of both viral and host genes. Inhibied protein synthesis destroys both the virus and infected host cells. In addition, interferons induce production of hundreds of other proteins- known collectively as interferon-stimulated genes (ISGs) that have roles in combating viruses.

**Natural Killer cells: (NK):** Are a subset of lymphocytes found in the blood and tissue, which lack antigen specific surface receptors. NK cells possess the ability to recognize and lyses virally infected cell and certain tumor cells. Whilst not showing antigen specificity, they clearly exhibit some degree of selectivity in targeting abnormal cells for lysis. Thus NK cells may be effective early in the course of viral infection, and may limit the spread of infecting during this early stage, while antigen-specific lymphocytes are being recruited and clonally expanded.

**Specific Mechanism**

Both humoral and cell mediated immunity arms of the immune response play a role as specific effectors mechanism in antiviral immunity.

Antibody: Specific AB are important in protect against viral infection.

The most effective type of antiviral antibody is ‘neutralizing antibody’- this is antibody which binds to the virus, usually to the viral envelope or capsid proteins, and which blocks the virus from binding and fast entry to the host cell. Virus specific antibodies may also act as opsonins in enhancing phagocytosis of virus particles- this effect may be further enhanced by complement activation by antibody-coated virus particles.

In addition, in the case of some viral infections, viral proteins are expressed on the surface of the infected cell.

These may act as targets for virus specific antibodies, and may lead to complement-mediated lysis of the infected cell, or may direct subset of natural killer cells to lyse the infected cell through a process known as antibody –direct cellular cytoxicity(ADCC). At mucosal surfaces (such as respiratory and gastrointestinal tracts), virus infection may induce the production of specific antibodies of the IGA isotype, which may be protective against infection at these surfaces. (This is the basis of immunization with current oral polio vaccine).

Not all antibodies to the virus are protective, however, and in certain case antibody to the virus may facilitate its entry into a cell through FC receptor-mediated uptake of the antibody coated particle. Such antibodies are called enhancing antibodies.

During the course of a viral infection, antibody is the most effective at any early stage, before the virus has gained entry to its target cell. In this respect, antibody is relatively ineffective in primary viral infections, due mainly to the lag phase in antibody protection. Preformed antibody, particularly neutralizing antibody, however, is an effective form of the protective immunity against viral infection, as witnessed by the success of many viral vaccines, which work by stimulating virus-neutralizing antibody responses.

**Cytotoxic T cells: (**[CD8 cell](http://www.audioenglish.org/dictionary/cd8_cell.htm); CD8 T cell; [cytotoxic T cell](http://www.audioenglish.org/dictionary/cytotoxic_t_cell.htm); [killer cell](http://www.audioenglish.org/dictionary/killer_cell.htm); [killer T cell](http://www.audioenglish.org/dictionary/killer_t_cell.htm)**)**

Is a [T lymphocyte](https://en.wikipedia.org/wiki/T_cell) (a type of [white blood cell](https://en.wikipedia.org/wiki/White_blood_cell)) that kills [cancer](https://en.wikipedia.org/wiki/Cancer) cells, cells that are infected (particularly with [viruses](https://en.wikipedia.org/wiki/Virus)), or cells that are damaged in other ways.

Most cytotoxic T cells express [T-cell receptors](https://en.wikipedia.org/wiki/T-cell_receptor) (TCRs) that can recognize a specific [antigen](https://en.wikipedia.org/wiki/Antigen). An antigen is a molecule capable of stimulating an immune response, and is often produced by cancer cells or viruses. Antigens inside a cell are bound to [class I MHC](https://en.wikipedia.org/wiki/Major_histocompatibility_complex#Class_I) molecules, and brought to the surface of the cell by the class I MHC molecule, where they can be recognized by the T cell. If the TCR is specific for that antigen, it binds to the complex of the class I MHC molecule and the antigen, and the T cell destroys the cell.

In order for the TCR to bind to the class I MHC molecule, the former must be accompanied by a [glycoprotein](https://en.wikipedia.org/wiki/Glycoprotein) called [CD8](https://en.wikipedia.org/wiki/CD8), which binds to the constant portion of the class I MHC molecule. Therefore, these T cells are called CD8+ T cells.

The [affinity](https://en.wikipedia.org/wiki/Affinity_(pharmacology)) between CD8 and the MHC molecule keeps the TC cell and the target cell bound closely together during antigen-specific activation. CD8+ T cells are recognized as TC cells once they become activated and are generally classified as having a pre-defined cytotoxic role within the immune system. However, CD8+ T cells also have the ability to make some [cytokines](https://en.wikipedia.org/wiki/Cytokines).

The importance of CTL in the clearance of virus infection has been demonstrated in a wide variety of viral infections. As with virus-specific antibody responses, however, not all CTL responses to virus are beneficial to the host, and in some cases the tissue distraction caused by the virus-specific CTL is greater than the damaged down by the virus itself; and example of this would be the fuminant hepatitis associated in small proportion of cases with infection with hepatitis B virus, in which the liver damage is caused by virus-specific CTL rather than directly by the virus.