Module2: Virus host interaction

Lecture 7: Consequences of virus infection to animals and humans (Part I)

Virus contains its genetic material in the form of nucleic acid (DNA/ RNA) surrounded by a protein coat called as capsid. Viruses are the obligatory intracellular parasites of cells. This means that the viruses can only replicate within a living host cell. The virus does this by subverting the biosynthetic pathways and protein synthesizing capacity of the cell. This helps the virus to replicate its viral nucleic acid, make viral proteins, and facilitate its escape from the parasitized cell.

In order to know the outcome of virus infection on the animal cells two factors play an important role -- **virulence** of the virus and the **susceptibility** of the host.

Virulence – It may be defined as the ability of the virus to cause disease or in other words it gives the relative degree of pathogenicity of the infecting virus. Viral virulence differs greatly among the strains depending on the pathogenic nature of the virus. Virus may be categorized as pathogenic or non- pathogenic. The pathogenicity of the virus range from mild to severe depending on the virulence of the viral strains. The term virulence is used as a quantitative measure of its pathogenicity. The degree of virulence is usually related with the ability of the pathogen to multiply within the host and depends on other factors such as host environment and its immune status.

7.1 Terms describing infections of an organism

Lytic infection- When virus enters the cell and hijacks its cellular machinery to rapidly multiply and in the process kills the cell is termed as lytic infection (many influenza viruses).

Lysogenic infection- It is the process characterized by the incorporation of viral DNA to the cellular DNA. Once incorporated, the viral DNA replicates along with the host DNA. The incorporated viral DNA permits the host cell to undergo normal cell cycle.

Acute infection- It is a rapid onset of disease symptoms resulting in severe illness or death of the infected animal (influenza, viral hemorrhagic fever).

Chronic Infection- It is a prolonged infection in which the organism is not immediately killed and may carry the virus for long period of time (hepatitis, HIV).

Terms describing virus transmission

Horizontal transmission is defined as the transmission of virus or other pathogen to host at any age after birth while **vertical** transmission is the passage of a virus from mother to the new born child.

Zoonosis is defined as the disease which is naturally transmitted between animals and man (Rabies, H1N1 influenza virus, Rift valley fever virus).

Sometimes the virus can be transmitted through an insect vector (arboviruses). Viruses present in the saliva of the infected insect are transmitted during feeding of blood meal to the susceptible host.

Persistent infection is a condition where the virus remains associated with the cell without actively multiplying or killing it. This often occurs when the viral genome gets integrated into the host genome (retroviruses) and sometime without integration (Herpesvirus).
Persistence can be categorized into three types
(1) Virus genome persists within the cell without actual release of the virus, eg. Some retroviruses.
(2) Virus released sporadically but remains in a state of "latent" for most of the time (herpes simplex).
(3) Virus released continuously without lysis of the host cell, eg. hepatitis B virus.

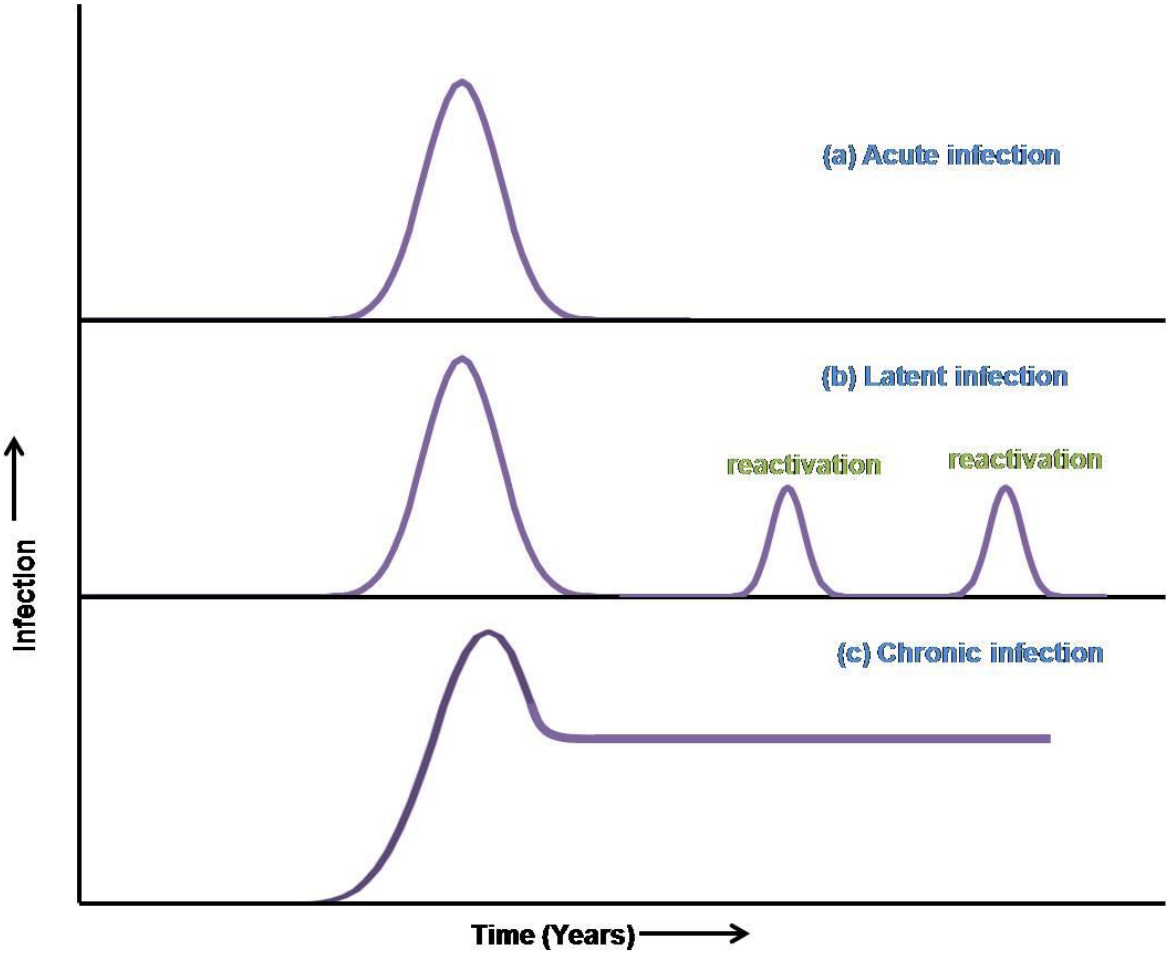
Multiplicity of Infection (m.o.i.)- This is the ratio of total virus infected to the number of target cells in an infection condition. This is usually used to describe the infection of a cell type grown *invitro* in a culture system.

Infectious dose50 (ID50)- The dose required to infect 50% of the inoculated animals.

Lethal dose50 (LD50)- The dose required to kill 50% of the inoculated animals.

Incubation period- The time between the initial infection to the actual onset of disease symptoms. This period can range from a few days (cold viruses) to years (HIV).

Figure 7.1 Schematic diagrams showing the patterns of viral infection.



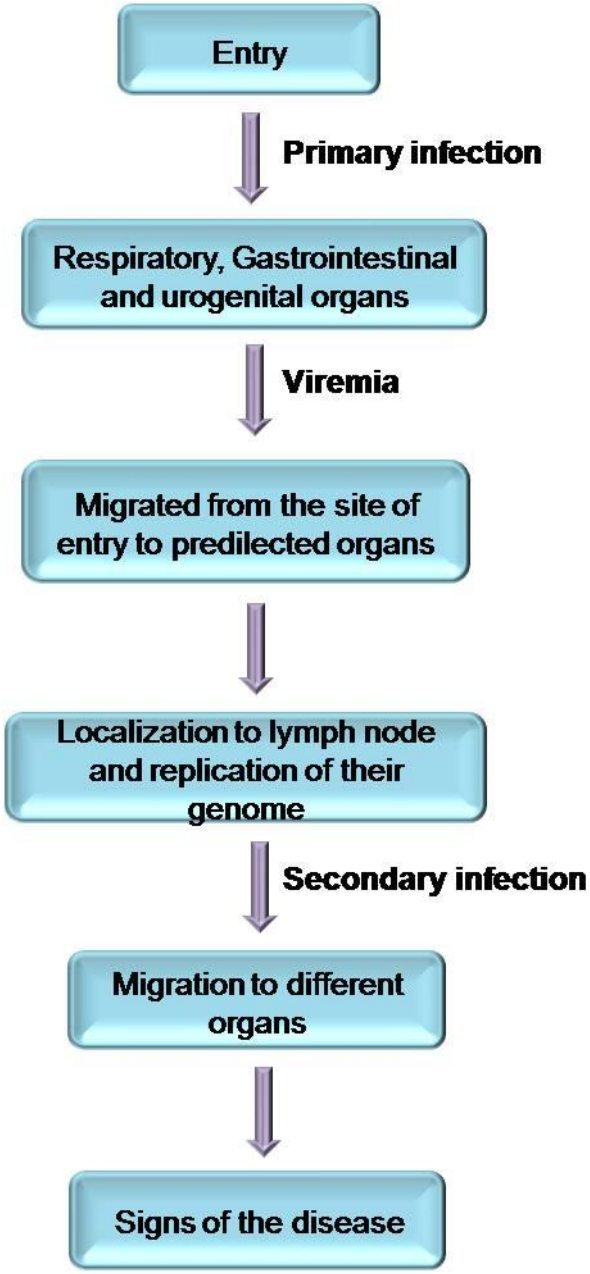
7.2 Virus entry to the host

The viruses generally enter the body through the epithelial surface of respiratory tract (influenza), alimentary tract (rotavirus), and reproductive tract (HIV). Sometimes they gain entry through small wounds in skin like insect bites (yellow fever virus) or through large wounds after animal bites (rabies). Herpesviruses (cold sores) and Epstein-Barr virus (EBV) are transmitted mostly by the oral secretions, while the HIV and herpes simplex virus are known to transmit vertically through mother to offspring. The disease caused by a virus is more generalized if it enters through the epithelial lining of the body (mumps, smallpox, measles etc).

7.3 Stages of viral infection

Primary infection occurs when virus enters the body through different portals. The viruses then enter into the blood streams and targeted to different organs, the stage is known as **viremia**. After entry into the predilected site they start their replication and transmitted to different organ and may shed outside through body secretions, the condition is referred as **secondary infection** (infection of brain tissue by encephalitis virus and liver by the hepatitis virus).

Figure 7.2 Schematic representation of viral infection from entry to the signs of the disease.



Lecture 8: Consequences of virus infection to animals and human (Part II)

8.1 Respiratory tract disease

Virus induced respiratory infections kill about millions of humans and children worldwide each year. Most viruses that infect only the upper and lower respiratory tract do not induce a strong immune response and therefore chances of reinfection with the similar or same strain is very common. On an average children get about 6 colds a year and adults 2-3.

Rhinitis (Common Cold) – Common signs and symptoms include nasal discharge and obstruction, sneezing, coughing, and mild sore throat.

Pharyngitis (mostly viral)- Common signs are sore throat, malaise, fever, and cough. RSV and adenovirus are the predominant causes in young children while Herpes viruses in young adults.

Laryngotracheobronchitis (Croup)- Common symptoms include fever, cough, respiratory distress, sometimes laryngeal obstruction. Most common causes are influenza and parainfluenza virus.

Bronchiolitis- Common signs and symptoms includes rapid and labored breathing, persistent cough, wheezing, cyanosis, atelectasis (Lung collapse), and emphysema. Major causes are Influenza, parainfluenza, and RSV.

Pneumonia- usually develops following upper respiratory tract infection. Symptoms include fever, cough, and difficulty in breathing. RSV, Influenza, parainfluenza, and adenoviruses are the major causes. It is a major cause of death to older people and young children. RSV is the major cause of death in young ones.

8.2 Gastrointestinal tract disease

It involves inflammation of the stomach and intestines leading to watery diarrhea. Fever and vomiting are common with some viral gastroenteritis. Diarrheal diseases kill 2 million children each year mostly in developing countries. Rotaviruses are the main cause of deaths. Astroviruses and Caliciviruses (Norwalk virus) can also cause diarrhea.

8.3 Central Nervous system diseases

Some viral infections can cause pathogenicity in the brain and spinal cord (central nervous system [CNS]). Viruses may be neuroinvasive (able to enter the CNS after crossing the blood brain barrier) and/or neurovirulent (can cause damage to the nerve cells). Mumps virus is highly neuroinvasive but not very neurovirulent while herpesviruses are more neurovirulent. Viruses can cause disease in a variety of ways including infection of a specific area of the brain or infect systemically to the CNS. Sometime their infection causes lysis of the neurons while other type of infections can cause demyelination of axons.

Meningitis- Virus infects the meningeal cells of the CNS. Symptoms include headache, fever, and neck stiffness with/or without vomiting. Mumps and Enteroviruses are most common agents.

Poliomyelitis- The disease involves demyelination of nerve cells and is most common in the countries where polio virus has not been eradicated.

Encephalitis- Symptoms include fever, headache, stiffness of the neck muscles, vomiting, and deviations from the normal state of consciousness. Patients are often lethargic and show signs of seizures. Sometimes paralysis may develop before coma and death. Recovered patience may show mental retardation, epilepsy, paralysis, deafness, and blindness. Many Arboviruses and Herpesviruses are associated with the severe form of encephalitis. **Guillain-Barre syndrome** is a condition caused by Epstein - Barr virus (EBV) infection. Similar kind of condition seen in the patients infected with influenza or chickenpox which are under aspirin treatment and are characterized by cerebral edema. The condition is often lethal and known as **Reye's syndrome**.

8.4 Urogenital system diseases

Herpes simplex virus and papillomaviruses are the major viruses infecting the genital area. Sexual transmission is the main way of acquiring these agents. Herpesvirus infection manifests as painful itching and ulcerated vesicular lesions occasionally accompanied by fever and malaise especially in woman. Recurrences are common although generally less severe than the initial infection. Certain types of HPV may progress over several years through stages of cervical neoplasia to invasive squamous cell carcinoma.

8.5 Viral disease affecting other organs and systems

Eye diseases- Many infants viral diseases can involve conjunctivitis (Inflammation of the conjunctiva which is the transparent membrane covering the sclera). It leads to redness, discomfort and discharges from the eye and is commonly termed as **pink eye** condition. Sometime it is also associated with cornea (kerato-conjunctivitis). Herpes simplex virus is the most common form of virus associated with this condition. Many other kind of eye disorder including cataract and glaucoma are associated with rubella virus and cytomegalovirus infection.

Viral Hepatitis- Inflammation of the liver accompanying damage of the hepatocytes (liver cells) is called as hepatitis. Besides Hepatitis viruses A, B, C, D, E, and G which infect the liver as the primary organ other viruses can also cause hepatitis such as herpes and hemorrhagic fever viruses. Symptoms include jaundice (yellowing of the skin caused by accumulation of bilirubin in the blood), and flu-like symptoms. The disease may become chronic depending on the infectious agent and terminally leads to cirrhosis (fibrosis of the liver tissue).

Viral arthritis- Characterized by stiffness in the joint accompanied by pain, fever, and myositis (inflammation of muscle tissue). The major causative agents are flaviviruses, togaviruses, and bunyaviruses.

Hemorrhagic fever- Symptoms include widespread hemorrhages from the epithelial tissue including eyes, ears, nose, and gastrointestinal tract. Ebola, yellow fever virus, Hantavirus, Lassa fever virus, and Marburg virus are the common cause of viral hemorrhagic fever. Severe damage of the internal organs is often associated with viral hemorrhagic fever. Ebola and Yellow fever virus can cause severe damage to the hepatocytes.

Chronic fatigue syndrome- There is no such evidence of any virus to be associated with this condition. The disease is characterized by extreme fatigue and is most common following the infection of CMV, EBV, enteroviruses, and HTLV.

Viral carditis-myocarditis- Characterized by inflammation of the heart muscles. The disease is often associated with certain enteroviruses (a family of picornaviruses) such as coxsackie B virus. The infections usually reoccurs leading to permanent myocardial damage, enlargement of the heart, or congestive heart failure.

Lecture 9: Viral infection: affect on host macromolecules (Part I)

A cell is said to be **permissive** when it supports the virus multiplication. Viruses infecting the permissive cells are usually **cytocidal** (kill the host cell) while infection to non- permissive cells do not produce any effect upon infection hence called **abortive.** When the virus replication gets completed, no more viral mRNA or protein are produced in the infected cells and is referred as **restricted**. In some cases viral DNA or RNA may sequester indefinitely inside a host cell and this condition is called as **persistent infection**.

9.1 Cytolytic infections

Cytolytic infections can be clearly visualized under a light microscope. The characteristic of CPE effect is an important parameter for a virologist to identify the virus species. In some viral infections inclusion bodies which are formed upon viral infection are identified after specific staining methods and are used as a tool for identifying the virus. Seller's stain is used to visualize the Negri bodies in the cells infected with Rabies virus. Inclusion bodies are the remnants of viral structural and non-structural proteins. Alternatively, inclusion bodies may be formed by a host cell macromolecule upon virus infection. For example, Cytomegalovirus infection to a cell changes the cytoskeleton of infected cell which are then visible as inclusion bodies. Viral infection to a permissive cell is often associated with changes in cellular biosynthetic pathways, its morphology, and cell physiology.

Table 9.1 Viral inclusion bodies in some human diseases

	Location in Cell	
Virus	**Nucleus**	**Cytoplasm**
Adenoviruses	Cowdry type A	
Herpesviruses	do	Present (cytomegalovirus)
Rabies virus		Negri bodies
Reovirus		Present
Vaccinia		Guarnieri bodies

9.1.1 Effects on biosynthetic pathways

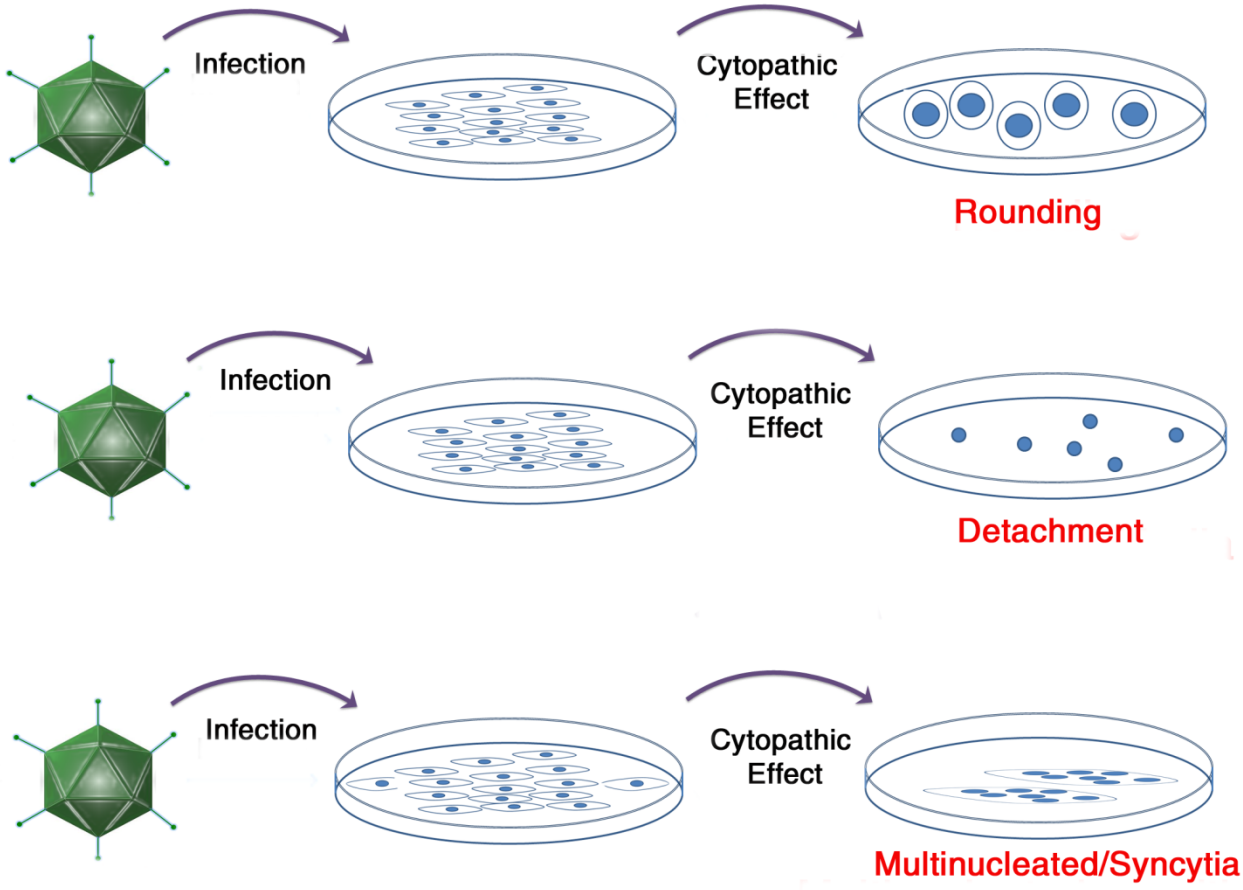
Virus infection to a host cell inhibits its DNA and/or RNA, and its protein synthesis. Sometimes it also causes breakage and fragmentation of host chromosome. Moreover it also changes the growth characteristics, shape, and surface protein expression of the infected host cell. Viruses often subvert the host biosynthetic pathway for their own benefits at the cost of cellular macromolecules.

Virus infection to a cell forms many early proteins that mediate the changes in cellular biochemical pathways. Viral nucleic acid contains specific signal sequences that help in migration of nucleic acids to different cellular locations. In addition, it also contains some motifs that bind to regulators of cellular transcriptional machinery. Therefore many viral early proteins contain binding sites for a wide range of cellular transcriptional factor. These interactions and bindings are very important for the activation of virus protein synthesis and production of progeny viruses. The biochemical events sometimes include glycosylation and phosphorylation of viral proteins. These modifications are often associated with the increase or decrease of the pathogenicity and virulence of the viruses. Generally virus alters the cascades that are involved in the synthesis of protein kinases and secondary messengers (cyclic AMP,cyclic GMP, etc). Occasionally virus triggers the cells to overproduce regulatory proteins that changes the cellular biochemical pathways. These regulatory proteins may be transforming growth factors, interleukins, cytokines, NF-kβ or TNFα and TNFβ (HIVand Herpesviruses). In some viral infections cellular mRNA get degraded (Influenza virus). Alternatively herpesviruses and reoviruses inhibit the cellular DNA synthesis. Interestingly Pox virus degrades the host DNA with the help of virus associated DNase.

9.1.2 Effects on cell morphology

Changes evident in a cell following the virus infection are called cytopathic effects (CPE). There are various kinds of CPE depending on type of infection. For example, detachment of cells from monolayer, rounding of cells, formation of syncytia (multinucleated cells formed after fusion of nuclei) and nuclear or cytoplasmic inclusion bodies formation.

Figure 9.1 Cytopathic effects in the cells infected with viruses



9.1.3 Effects on cell Physiology

Virus infection to a cell changes many of the physiological events, including changes in cellular metabolism, alteration in the ATP synthetic pathways, and deviation in the ion channel system. Physiological condition of a viable cell has a great effect on the outcome of a virus infection because the host cell provides the cellular machinery, regulatory proteins, and source for the viral nucleic acid, and protein synthesis. Attachment of virion with the receptors present on cell membrane leads to a series of events that are associated with the changes in morphological, physiological and biochemical characteristics of the cell. The receptor present on the cell surface determines the host range as well as tissue tropism of a viral species. Influenza virus infects the cell after binding to the sialic acid

receptor present on the cell membrane. Similarly HIV infects the T-cells upon binding to the chemokine receptors of the cell. Usually virus infection alters the intracellular ion concentration that affects the cell membrane permeability (For example picornaviruses).

Table 9.2 Proposed cell membrane receptors for some viruses

Viruses	Representative cell type	Receptors
DNA viruses		
Adenovirus	Respiratory epithelium	Integrins
Epstein-Barr virus	B lymphocytes	CD21
Hepatitis B virus	Liver	IgA
Herpes simplex virus	Oral and genital epithelium	Heparin sulfate
Vaccinia virus	Oropharyngeal epithelium	Epidermal growth factor receptor
RNA viruses		
Echovirus	Alimentary epithelium	Integrins
Influenza	Respiratory epithelium	Sialic acid
HIV	T lymphocytes	CD4
Measles virus	Respiratory epithelium	CD46
Paramyxovirus	Respiratory epithelium	Sialic acid
Poliovirus	Oropharyngeal cells	Polio virus receptor
Rabies virus	Neurons	Acetylcholine receptor
Reovirus	Neurons, lymphocytes	Adrenergic receptor
Rhinoviruses	Nasal epithelium	Intercellular adhesion molecules

9.1.4 Effect on host chromosome

Virus infection to a cell directly or indirectly leads to the damage of the host cell chromosome that may be lethal to the cell. If the cell does not die, viral genome may persist within the cell causing instability of cellular genome and alteration in the expression of proteins.

Lecture 10: Viral infection: affect on host macromolecules (Part II)

10.1 Persistent infection

In persistent infection virus is not eliminated from the cell. Persistent infection may be chronic, latent, and transforming. In chronic infection the spread of virus is checked by host immune system while in latent infection only few cells express the viral protein and virus replication is largely restricted. In transforming persistent infection cell undergoes genetic changes that results in malignancy.

Persistent infection may sometime cause autoimmune disease condition in the host cell. Newly viruses bud out from the cell membrane following the virus infection, this leads to change in the antigenicity of the host cell. Immune system recognizes it as a nonself and produces an immune response which eventually causes death of the cell. The immune response also causes formation of viral antigen-antibody (Ag-Ab) complexes which may get deposited into vital organs like brain and kidney. Deposition of Ag-Ab complex elicits inflammatory condition in those organs (nephritis and encephalitis)

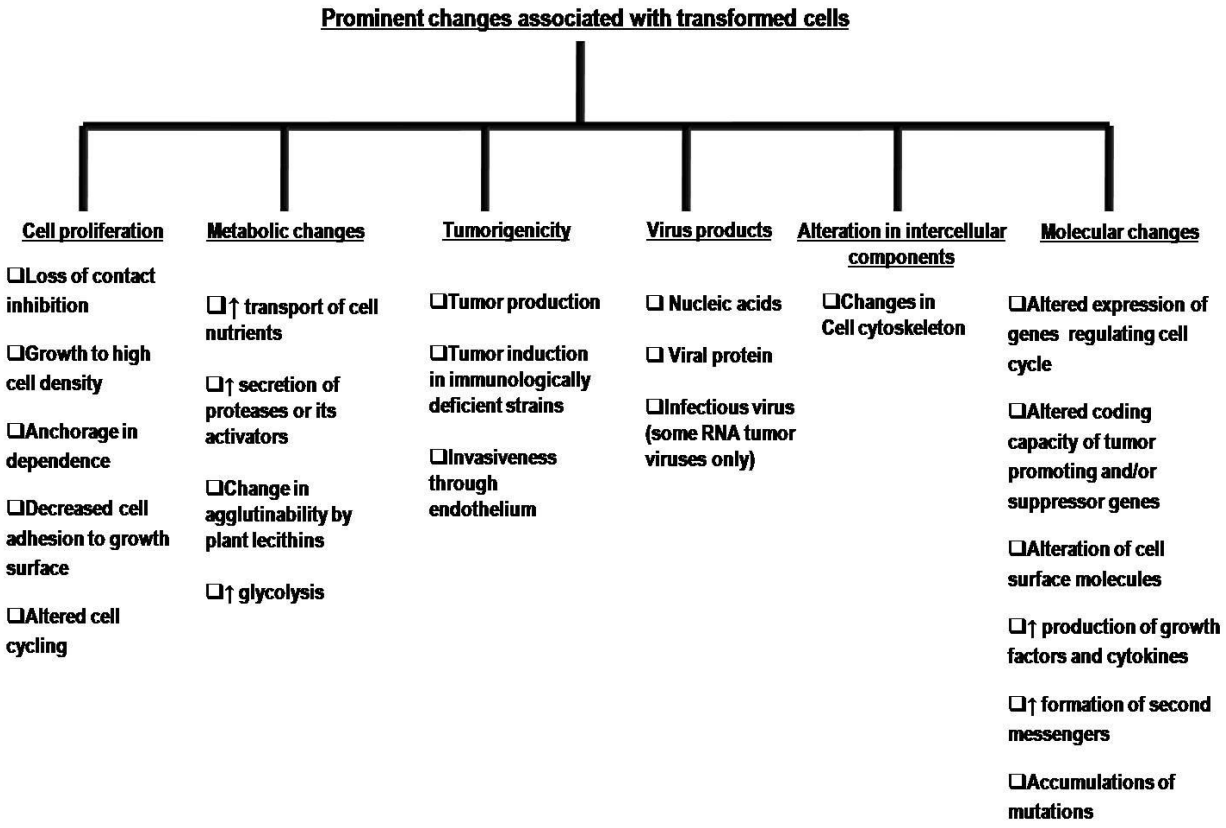
10.2 Transforming infection

Transformation refers to the ability of cells to multiply indefinitely that leads to cancerous condition. Mostly DNA viruses like Epstein Barr virus and polyoma virus can cause transformation in permissive cells. Transformation is essentially orchestrated by the viral proteins that may inactivate tumor suppressor proteins (Retinoblastoma proteins and p53) of the host cell.

Cellular transformation usually involves two stages namely

1) Immortalization and
2) Tumor production

Figure 10.1 List of changes associated with transformed cells:



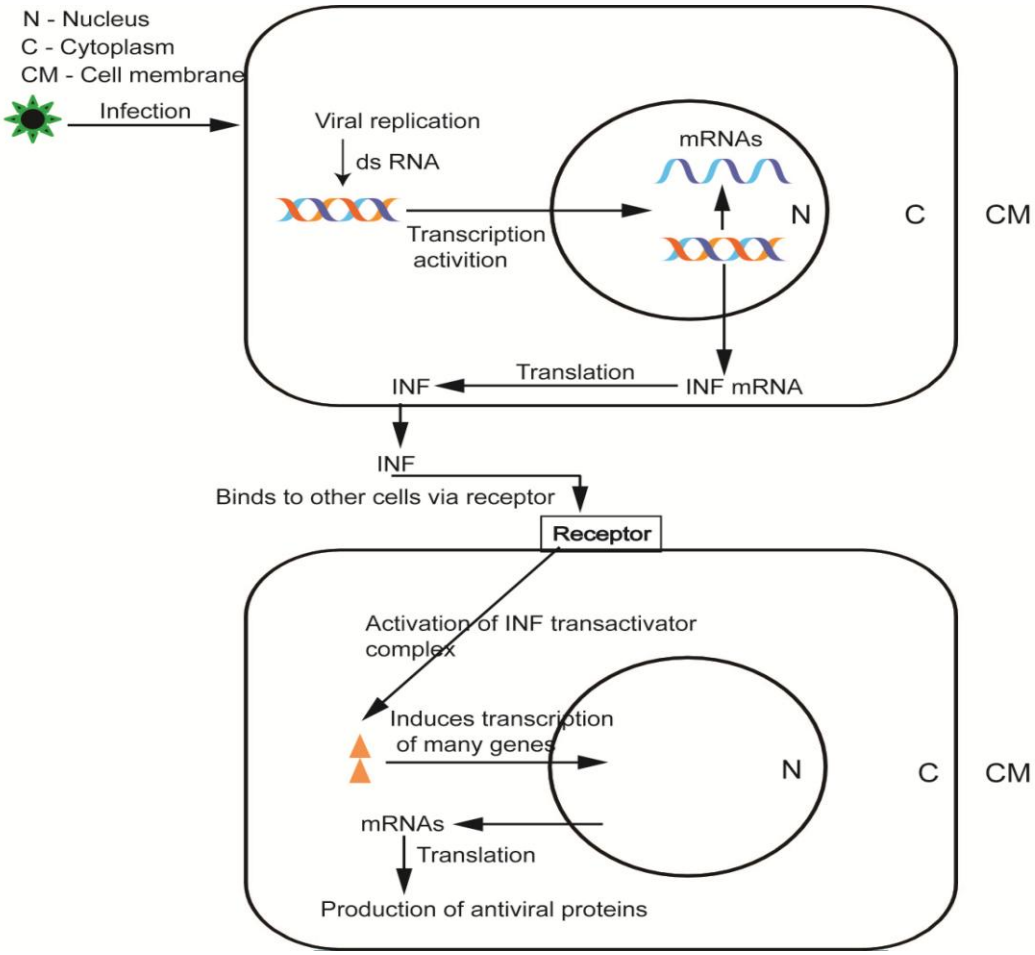
Lecture 11: Viral infection: establishment of the antiviral state (Part I)

Host immune response towards virus infection includes antibody mediated as well as cell mediated immune responses. Moreover macrophages, neutrophils and complement proteins also play an important role in clearing the virus infection from the body. Interestingly sometimes host cells sacrifice their life in order to protect other cells and restrict virus spread by a phenomenon called as **APOPTOSIS** (programmed cell death). Another very important player of host immune system that fights against viral invasion is **INTERFERON**.

INTERFERON:

Interferons are naturally occurring proteins secreted by cells in response to virus infections. When a cell is infected with a virus, it releases interferon which diffuses to the surrounding cells. After binding to the receptors present on the adjacent or surrounding cells; interferon stimulates the production of antiviral proteins in the cells.

Figure 11.1 Activation of interferon following virus infection:



Interferons are of two types

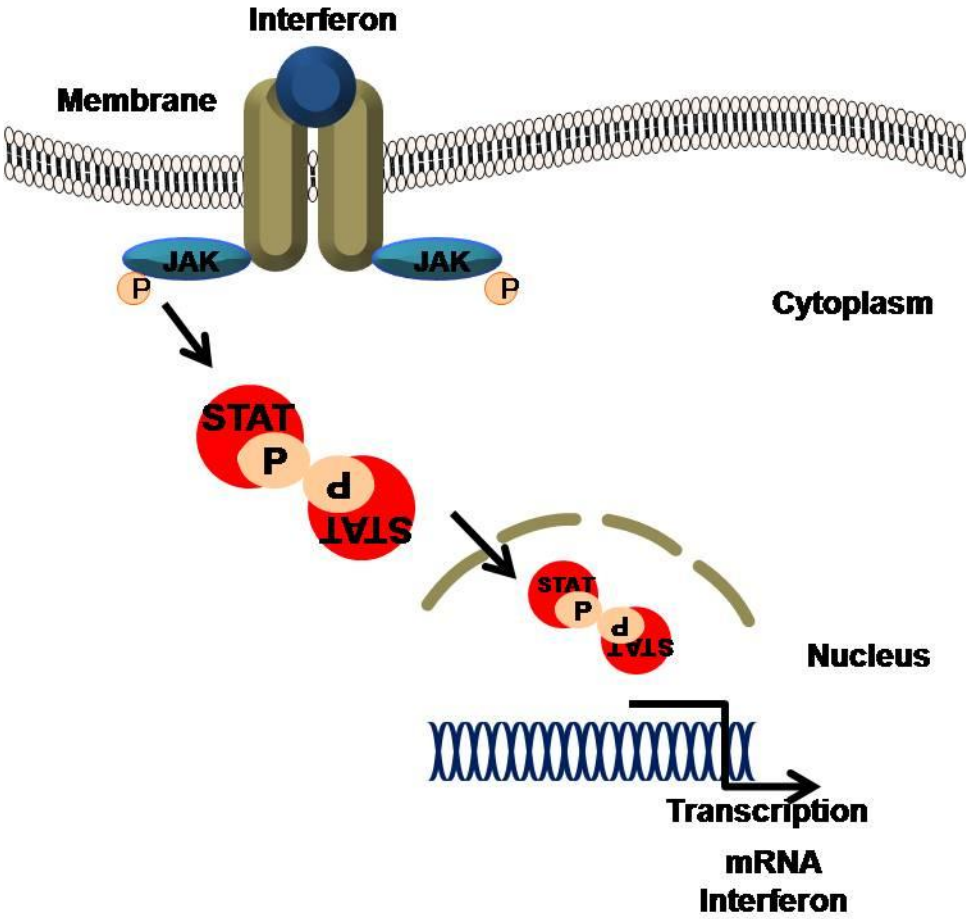
Type I (interferon α and β) and **type II** (interferon γ). Interferon α is produced by lymphocyte, β by fibroblast, and γ by T lymphocytes upon viral infection. The type of interferon are less or more potent against the class of virus species, for example, interferon α and β inhibits the vesicular stomatitis and encephalomyocarditis viruses better than interferon γ while interferon γ works better in case of vaccinia and reovirus infection.

How are interferons produced?

Generally all viruses can induce type-1 interferon production. Production of type-1 interferon is more pronounced in case of RNA viruses as compared to DNA viruses. In addition bacterial lipopolysaccharide and synthetic dsRNA analogs are known inducers of interferons. As a matter of fact dsRNA is a potent activator of interferon. dsRNA induce intereferon production by JAK/STAT signaling pathway. **Toll-like-receptor** 3 (TLR3) in presence of dsRNA can induce interferons by an alternate pathway. TLR7, TLR8, and TLR9 also induce interferon production through **interferon regulatory factor** 5 and 7 (IRF-5 and -7). Retinoic acid inducible gene 1 (RIG-1) activates interferon production by activating IRF- 3 and -7.

Interferons trigger **signal transducer and activator of transcription** (STAT) complexes by coordinating with their specific receptors. STATs belong to the family of transcription factors that control the expression of many immune system genes. Certain STATs are triggered by both type I and type II Interferons despite this each Interferon type can also activate unique STATs.
The classical **Janus kinase** – STAT (JAK-STAT) signaling pathway is the most explicit cell signaling pathway for all interferons which is also triggered by STAT activation.
The pathway involves coordination between JAKs and interferon receptors and phosphorylation of STAT1 and STAT2. Consequently this leads to the formation of a complex called as an **Interferon-stimulated gene factor** 3 (ISGF3). This complex comprises of STAT1, STAT2 and a third transcription factor called IRF9. After its formation the complex moves inside the cell nucleus where it binds to specific nucleotide sequences known as **interferon stimulated response elements** (ISREs) in the promoters of some specific genes called as **interferon stimulated genes** ISGs. Finally, coming together of ISGF3 and other transcriptional complexes triggered by interferon signaling initiates the transcription of genes responsible for secretion of interferons.

Figure 11.2 Interferon signaling pathway:



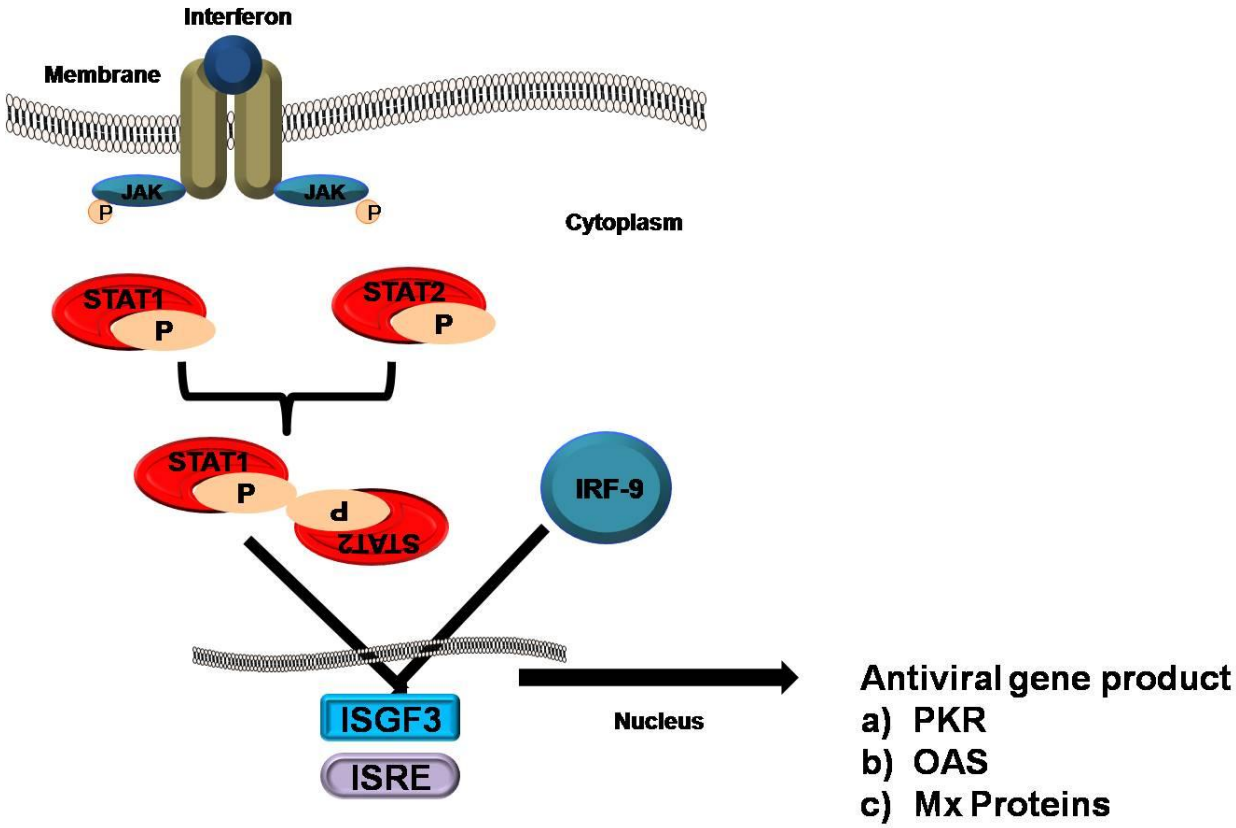
Lecture 12: Viral infection: establishment of the antiviral state (Part II)

12.1 Double stranded RNA activated antiviral state

Many genes are transcriptionally regulated by interferons following virus infection. Among all, three members have been studied extensively for their antiviral activities.

1) dsRNA activated protein kinase (PKR)
2) 2',5'- oligoadenylate synthetase (OAS)
3) Mx proteins

Figure 12.1 Schematic representation of interferon signaling for the activation of antiviral gene

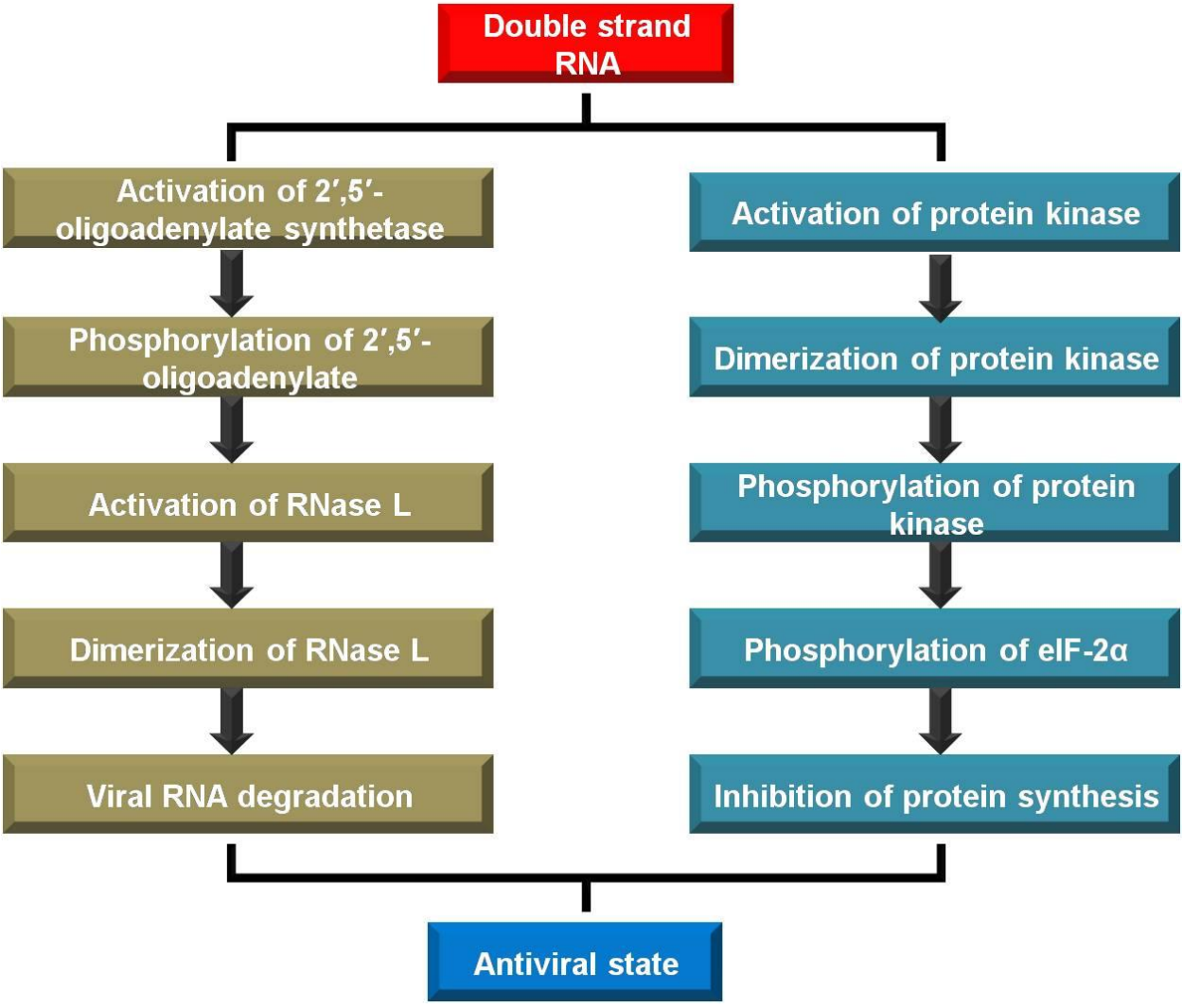


1) dsRNA activated protein kinase (PKR) – During dsRNA virus infection PKR forms the dimer, and is activated following phosphorylation. Eukaryotic translation initiation factor (EIF-2α) is the most important substrate phosphorylated by PKR. EIF-2α gets inactivated following its

phosphorylation leading to inhibition of viral protein synthesis. This way PKR exhibits antiviral activity.

2) 2', 5'- oligoadenylate synthetase (OAS) - Interferon inducible OAS is also activated by dsRNA formed during viral infection. It binds to RNase L triggering its dimerization and activation. Activated RNase L degrades the mRNA leading to inhibition of protein synthesis
3) Mx proteins - Interferon induced Mx protein have antiviral activity against several RNA viruses. Mice expressing Mx proteins are more resistant to many virus infections e.g. influenza.
   Mice deficient in PKR, RNase L and Mx proteins have been proved to be more sensitive to viral infection.

Figure 12.2 Schematic representation of dsRNA activated antiviral state



12.2 Apoptosis

Apoptosis (programmed cell death) is an interesting way explored by the host cell in order to prevent virus infection. In apoptosis cell must die before virus starts its replication. During apoptosis, cellular DNA undergo fragmentation and apoptotic bodies are formed which are then engulfed by macrophages and other cells of the immune system. Activation of apoptotic cycle involves release of "**cytochrome C**" from mitochondria and downstream activation of caspases (**c**ysteine-**as**partic **p**rote**ases**) cascade.

12.3 Role of the immune system against virus attack

Natural killer cells and cytotoxic T cells are the major type of immune cells involved against virus infection in the host. Natural killer cells are activated immediately upon virus infection and produce the cytokines such as **tumor necrosis factor** (TNF) and interferon γ. They also cause the direct cytotoxicity of the virus infected cells. In later stages of virus infection, the virus surface antigens are presented over the major histocompatibility antigens class I (MHC-I) molecules and activates the **cytotoxic T lymphocytes** (CTLs). CTLs exert antiviral state by secreting cytokines and apoptosis. Sometime the level of MHC-I gets downregulated in the virus infected cells, in that condition natural killer cells comes at the site of rescue to take over the task and kills the virus infected cells.

Lecture 13: Viruses counter attack mechanisms (Part I)

13.1 Viral strategies to escape host immune response

Adenoviruses upon entering into a permissive cell produces large amount of small RNA molecules called as **VA-1**. This VA-1 mimics the dsRNA and competitively binds to protein kinases to inhibit interferon production. Reoviruses and vaccinia virus produces dsRNA binding protein that inhibits the activity of dsRNA induced cascade of interferon production. Herpes virus produces 2'-5' oligoadenylate analogs that binds to RNase L and inhibits downstream activation pathway of interferon production. Some paramyxoviruses produce V protein which is known to inhibit interferon production by interfering STAT signaling pathway. Poxviruses produce soluble receptors known as decoy cytokine receptors which blocks the cell surface receptor and further inhibits the activation of cell antiviral response. Moreover many viruses inhibit the apoptotic pathways for their prolonged survival (herpesvirus, adenovirus, and poxvirus).

Table13.1 Mechanism developed by virus to inhibit effects of interferon:

Virus	Mechanism
Adenovirus	Block interferon signaling
Vaccinia	Binds to dsRNA
Hepatitis B virus	Block interferon signaling
HIV	Degrades PKR
Reovirus	Binds to dsRNA
Epstein-Barr virus	Block PKR activation
Herpesvirus	Block RNaseL activation

APOBEC is an apolipoprotein B mRNA-editing enzyme that can change C to U in a DNA strand. This mutation inhibits RNA polymerase to synthesize viral RNA because it cannot read U in the DNA strand. APOBEC is a very important enzyme encoded by host

cell against HIV infection. HIV encodes a protein called viral infectivity factor (**Vif**) that degrades the APOBEC for its better survival inside host cell.

Major Histocompatability class I antigen (MHC-I) present on the macrophages are required to present the viral antigens to the immune cells. Viral antigen presentation by MHC-I activates the cells of immune system, which eventually helps to clear the virus from the infected cells (HIV, and paramyxoviruses).

Viral RNA polymerase encoded by many RNA viruses is highly error prone. Viruses often escape immune system by gradual incorporation of mutation into their genome. The variation in the antigenicity because of mutation is called as **ANTIGENIC DRIFT** (HIV). Viruses which contain segmented genome often exchange their genome segments between different viruses of same species to evolve as a new virus; the phenomenon is called as **ANTIGENIC SHIFT** (Influenza). Both antigenic drift and shift is a major way adopted by many viruses to escape the host immune system.

13.2 Evasion of interferon system by viruses

Interferons are well studied and established defense system against virus infection. Nevertheless, cohabitation between the host and viruses resulted in the procurement of mechanism to inhibit interferon system by most of the viruses. Viruses inhibit the interferon activation by blocking the different steps involved in the interferon signaling cascade. Some of the unique strategies used by the viruses to decoy the interferon system are enlisted below

13.2.1 Inhibition of protein synthesis

Many viruses hijack the host protein synthesis machinery for their own benefits. This leads to inhibition of cellular protein synthesis and upregulation of viral protein synthesis. As the interferons are also proteins, viral mediated inhibition of host protein synthesis can assist to the inhibition of interferons. Translation inhibition by phosphorylation of eIF2α is a host mediated antiviral mechanism, many viruses evolved in a way to carryout eIF2α independent translation in order to escape the immune surveillance.

13.2.2 Inhibition of interferon production

Type-I interferon production is activated by dsRNA formed during virus infections. Many viruses encode dsRNA-binding proteins that inhibit the enzymes protein kinases and 2’-5’ oligoadenylate synthetase. The sigma protein of reoviruses, and the non

structural protein of rotavirus and influenza viruses are some examples of dsRNA-binding proteins.

13.2.3 Inhibition of interferon signaling

Herpes virus and papillomavirus blocks the interferon production by inhibiting the downstream signaling pathway. Adenoviruses, measles virus, and hepatitis viruses were also shown to inhibit the interferon production. All the essential components of interferon signaling pathways, i.e. interferon receptors, JAK/STAT and IRFs have been shown to be involved in virus mediated inhibition.

Despite the identification of the various strategies by which virus interfere with interferon action, little is known on the precise mechanism that exists between viruses and the interferon pathways, and its possible implications on viral pathogenicity, clearance, and viral immunity.

Lecture 14: Viruses counter attack mechanisms (Part II)

14.1 Virus response against apoptosis

Virus inhibits the apoptosis by interrupting the various stages of transcription and translation. Herpes and poxviruses are evolved in a way to modulate the apoptosis by blocking the activation of caspases. SV40 T antigen and E1 protein of adenovirus are known to bind with p53 and target it for proteasomal degradation. Although many viruses prevent apoptosis, herpes virus can selectively cause apoptosis in the lymphocytes in order to delay their removal from the host cell.

14.2 Virus response against host immune system

Many viruses come up with a system to reduce the expression of MHC-I molecules over the virus infected host cell surface. This explains the important role of MHC-I towards viral invasion into the susceptible host cells.

HIV, adenovirus, and herpesvirus inhibits the translocation of peptide within the endoplasmic reticulum, which is a necessary step for the loading and trafficking of the peptide over the MHC-I molecules. Cytomegalovirus produces a homologues of MHC-I molecule to decoy the host immune system.

Herpes simplex virus express a "glycoprotein E" that binds to the immunoglobulin molecules and prevents the activation of antibody mediated immune response.

Table 14.1 Inhibition of viral antigen presentation by MHC-I:

Virus	Function
Epstein-Barr virus	**Inhibition of transporter associated with antigen processing during MHC maturation**
HIV	**Enhance the endocytosis of MHC-I**
Adenovirus	**Modulate the trafficking of MHC-I**
Cytomegalovirus	**Degrades the MHC-I**
Herpes simplex virus	**Inhibition of transporter associated with antigen processing during MHC maturation**

14.3 Virus response against different host factors

RNA interference is an antiviral mechanism in animals and many other living species. Many viruses encode "**suppressors of RNA interference"** that function against the host RNA interference machinery. Influenza virus and adenoviruses were demonstrated to have this activity.

Some viruses encode specific proteins called as **VIROCEPTORS,** which mimic the cellular receptors and acts as a trap for chemokines and interferon. Poxvirus and cytomegalovirus are known to encode viroceptors.

Table 14.2 Inhibition of chemokines by viruses:

Virus	Function
Epstein-Barr virus	**Homologues of interleukin -10**
Vaccinia virus	**Homologues of interferon γ**
Cytomegalovirus	**Homologues of chemokine receptor**
Poxvirus	**Inhibition of interleukin -2**
Myxoma virus	**Inhibition of interleukin -1β**

Some Paramyxoviruses like Newcastle disease virus encodes V protein which is formed following infection in the cells. These V proteins bind to helicase protein **Melanoma Differentiation-Associated protein 5** (MDA5) in the cells, which is a sensor for dsRNA molecules. Thus MDA5 acts as an interferon antagonist.