Mechanisms of Infection and pathogenesis

Master lecture
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Viral disease :proliferation of a harmful **virus** inside the body and cause disease.

Viral pathogenesis interaction of viral and host factors that leads to disease production

steps of a virus life cycle that shape pathogenesis

1-Entry of the virus into the body.

2- Local replication in susceptible cells

(tissue tropism, modulate the host innate immune response)

3-Dissemination and spread to secondary tissues and target organs

4-Secondary replication in susceptible cells

5-Shedding of the virus into the environment

6- transmission to new host

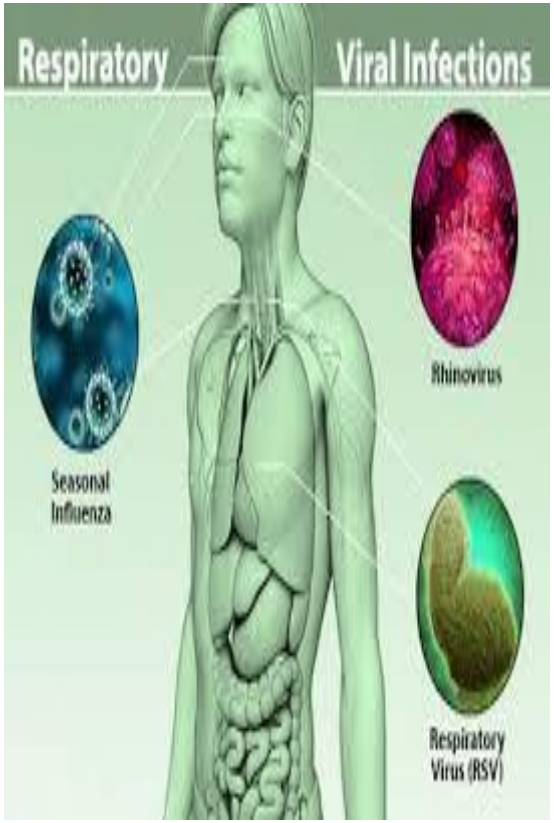
Entry of the virus

-Entry via the Respiratory Tract

-attaching to specific receptors on epithelial cells of mucosa

-remain localized (adenoviruses, influenza).

-become systemic by disseminated via lymphatics or bloodstream (rinderpest virus, Newcastle virus).



-Entry via the Oropharynx and Intestinal Tract

-acquired by ingestion

swallowed ,reach the stomach and intestine directly or may first infect oropharynx

- esophagus is rarely infected (its tough epithelium and the rapid passage of swallowed material over its surface)

-rotaviruses, caliciviruses, and enteroviruses

-acid and bile resistant

-Entry via the Skin

-Breaches in skin (e.g. cuts, punctures, abrasions, or wounds)

-bite of arthropods(mosquitoes,ticks,Insects)

-bite of an animal(**rabies**).

predispose for viral infection

either remain in skin (**Papillomaviruses)**

or Deeper trauma introduce viruses into the dermis with its rich supply of vessels, lymphatics, nerves ,underlying subcutaneous tissue and muscle.

- Entry via the Genitourinary Tract

-abrasions to the vaginal, rectal, and urethral epithelium during sexual activity can facilitate virus entry

(e.g., papillomaviruses,Herpes simplex virus 2)

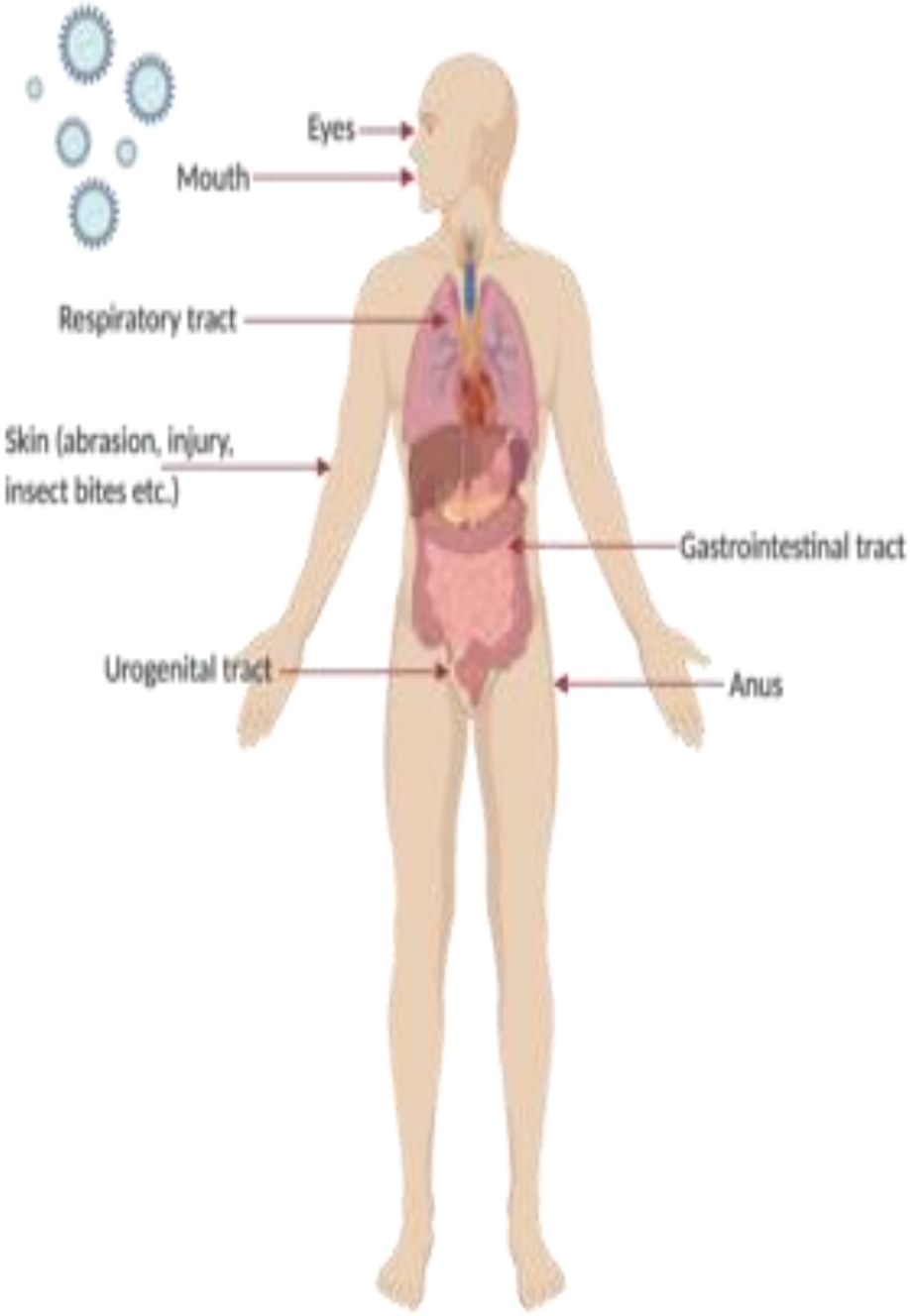
-HIV-1 and 2, human T-lymphotropic viruses 1 and 2 and hepatitis B and C viruses, do not produce local lesions but are sexually transmitted.

- Entry via the Eyes

Virus can reach the eye by aerosol, rubbing with contaminated fingers, ophthalmic procedures with improperly sterilized instruments, swimming pool water. (e.g., some adenoviruses, influenza viruses, South American arenaviruses, and enteroviruses)

Typical sites of virus entry into the body:

The first steps of viral infection is determined by the site at which the virus implants into the body. This would subsequently dictate the mechanisms of viral pathogenesis.



Local replication and spread

- Following initial entry to the host,. Here, the virus must modulate the host innate immune response to prevent its elimination by the body while facilitating its replication. Replicated virus from the initially infected cell then disperse to infect neighbouring susceptible cells, This results in a localised infection, like ,common cold (rhinovirus), flu (parainfluenza), gastrointestinal infections (rotavirus) or skin infections (papillomavirus).

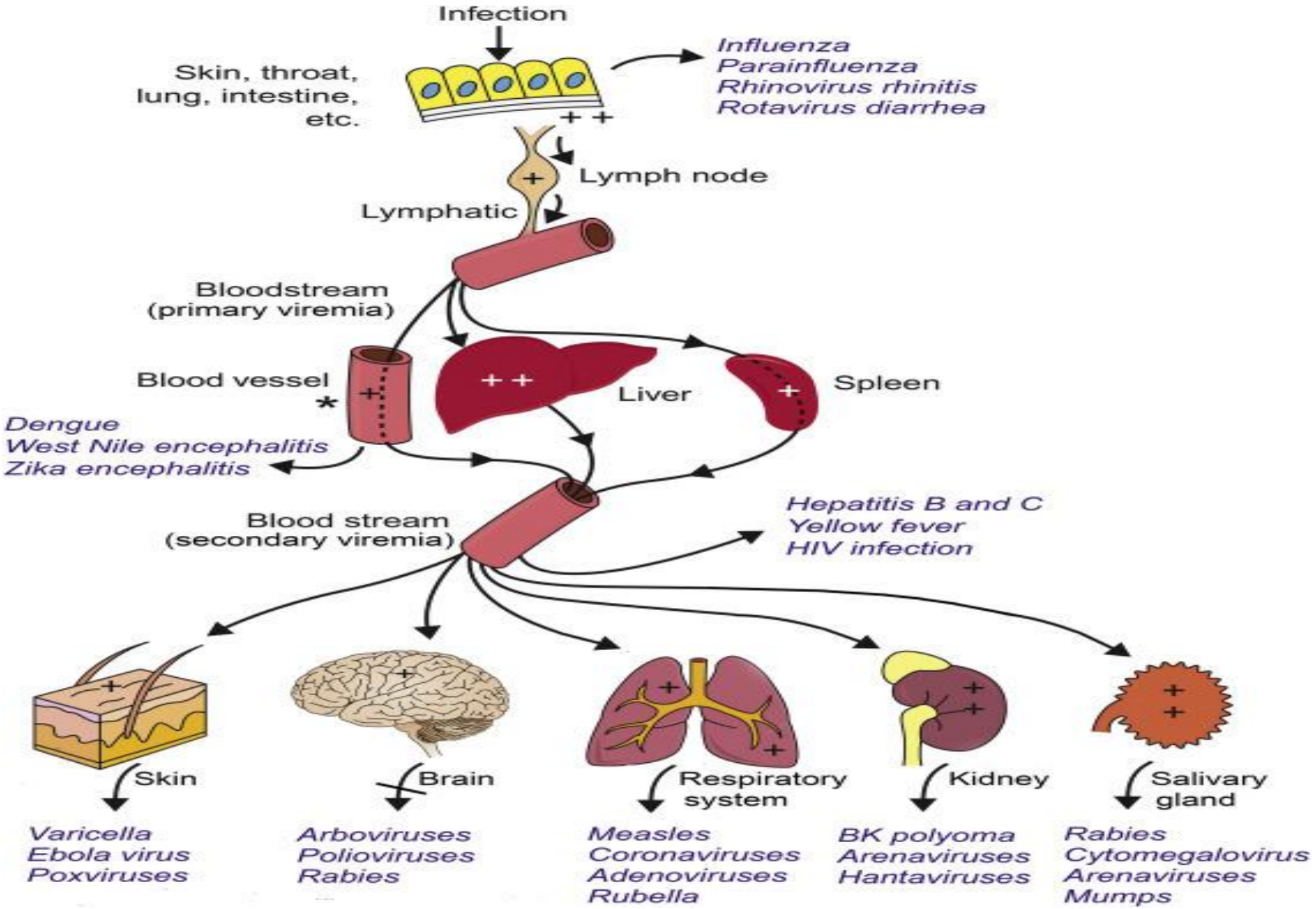
Dissemination and secondary replication

A- via blood stream (viremia)

virus can cause systemic disease through a disseminated infection spread throughout the body via blood or lymphatic system, e.g.,chickenpox (varicella zoster virus), smallpox (variola), HIV (human immunodeficiency virus). A minority of viruses can disseminate via the nervous system.

This early viremia is called ***primary viremia*** ***(****may* be clinically silent). Virus replication in major target organs leads to the sustained production of much higher concentrations of virus producing **a *secondary viremia*** *which can in turn lead* to the establishment of infection in yet other parts of the body.

Primary and secondary viremia



Shedding and secondary transmission

the viruses spread to sites where shedding into the environment can occur. The respiratory, alimentary and urogenital tracts and the blood are the most frequent sites of shedding in the form of bodily fluids, aerosols, skin, excrement(**the same body opening is involved in entry and exit)**. The virus would then go on to be transmitted to another person, and establish the infection cycle again.

Factors affecting pathogenesis

- Virus tropism
- Virus factors
- Host factors

Virus tropism refers to the virus' preferential site of replication in discrete cell types within an organ. In most cases, tropism is determined by the ability of the viral surface proteins to fuse or bind to surface receptors of specific target cells to establish infection.

Virus factors

Viral genetics encoding viral factors will determine the degree of viral pathogenesis which measured as virulence. In other words, different virus strains possessing different virus factors can lead to different degrees of virulence. Virus factors encoded in the genome often control the tropism, routes of virus entry, shedding and transmission and variety of immunomodulation mechanisms to subvert the host immune response

Host factors

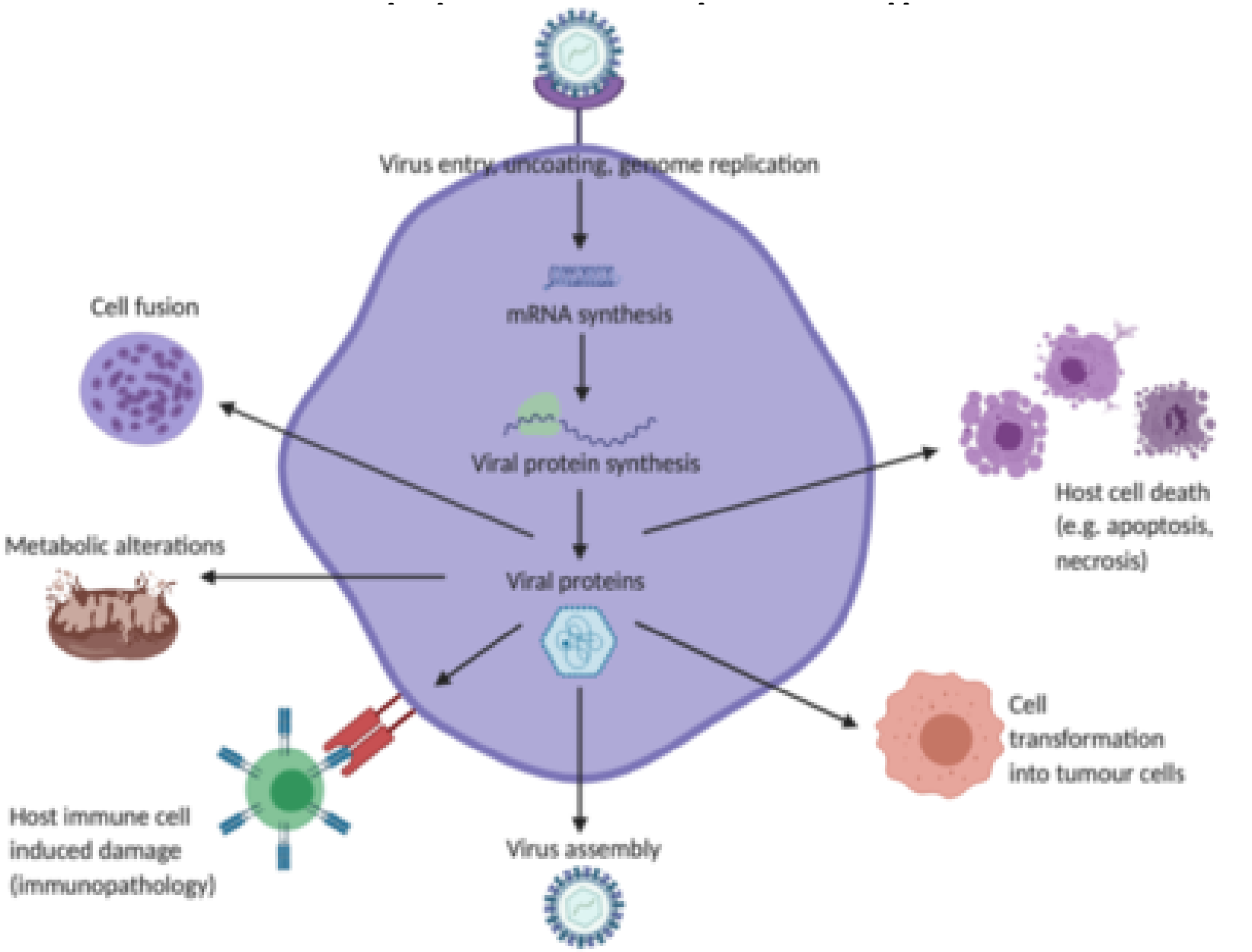
Several viral infections have displayed a variety of effects, ranging from asymptomatic to symptomatic or even critical infection, solely based of differing host factors alone.

In particular, genetic factors, age and immunocompetence play an important role is dictating whether the viral infection can be modulated by the host

Viral Disease mechanisms

A viral infection does not always cause disease. A viral infection simply involves viral replication in the host, but disease is the damage caused by viral multiplication. An individual who has a viral infection but does not display disease symptoms is known as a carrier.

Mechanisms by which viruses cause damage



Damage caused by the virus

viruses can destroy cells through a variety of mechanisms.

Viruses often induce direct cytopathic effects to disrupt cellular functions through releasing enzymes to degrade host metabolic precursors, or releasing proteins that inhibit the synthesis of important host factors, proteins, DNA and/or RNA

Viral infections

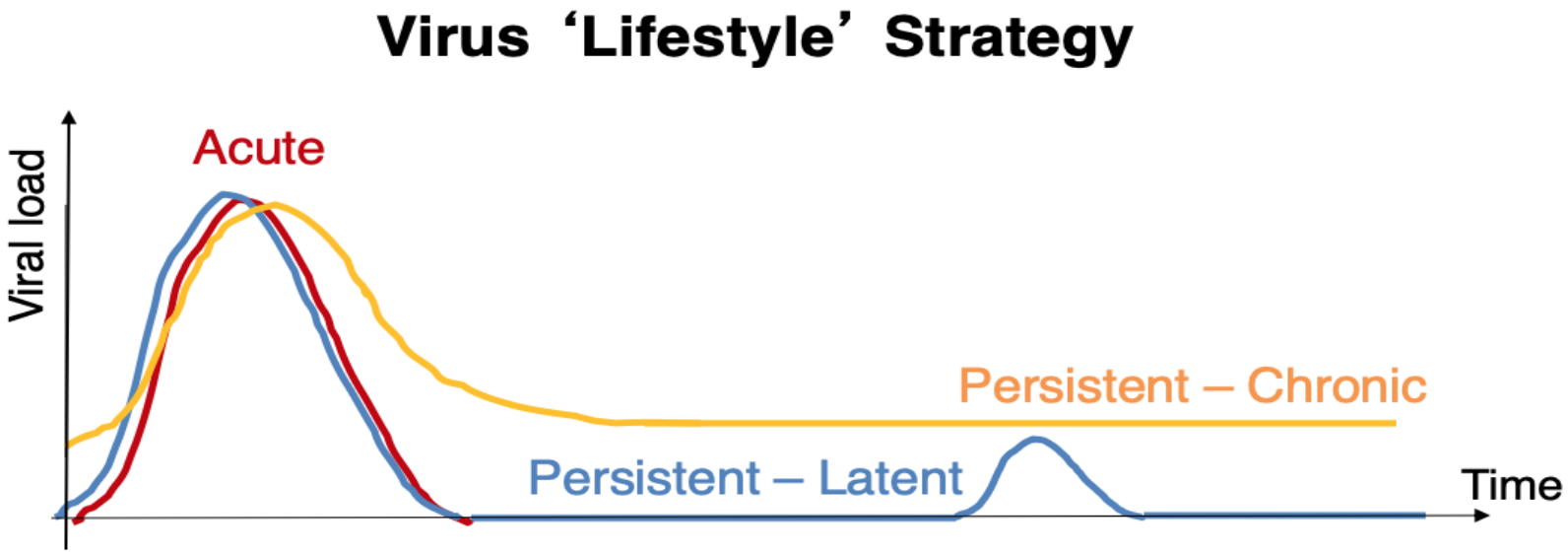
Importantly, viral infections can differ by the "lifestyle strategy". **Persistent infections** happen when cells continue to survive despite a viral infection and can be further classified into **latent** (only the viral genome is present, there is no replication occurring) and **chronic** (basal levels of viral replication without stimulating an immune response). In acute infections, lytic viruses are shed at high titers for rapid infection to a secondary tissue/host, whereas persistent viruses undergo shedding at lower titers for a longer duration of transmission (months to years)

lifestyle" strategies of viruses in host cells.

-Acute infections occur for short duration

-persistent infections (virus is not completely cleared from the body).

-latent infections, reactivation of disease occur a long time after the initial infection

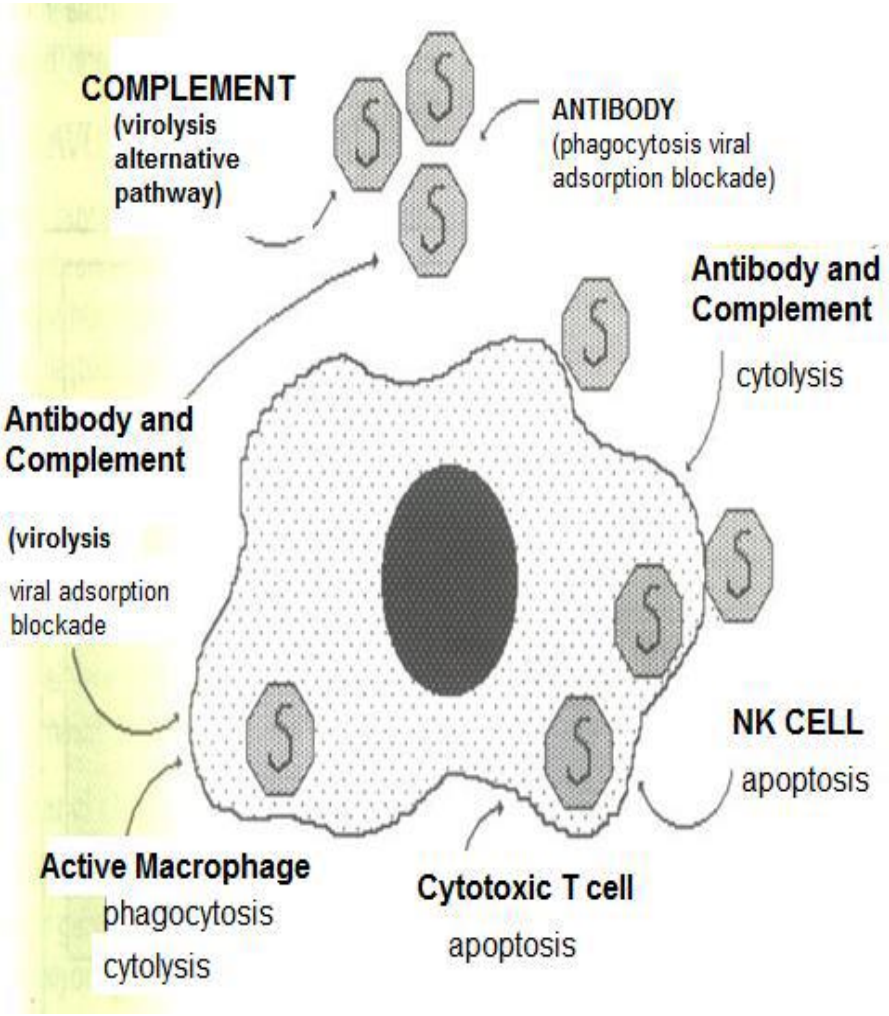


Damage caused by host immune system

- Sometimes, instead of cell death or cellular dysfunction caused by the virus, the host immune response can mediate disease and excessive inflammation. The stimulation of the innate and adaptive immune system in response to viral infections destroys infected cells, which may lead to severe pathological consequences to the host. This damage caused by the immune system is known as virus induced immunopathology.
- Specifically, immunopathology is caused by the excessive release of antibodies, interferons and pro inflammatory cytokines, Secretion of interferons and other cytokines can trigger cell damage, fever and flu-like symptoms. In severe cases of certain viral infections, as in avian H5N1 influenza in 2005, aberrant induction of the host immune response can elicit a flaring release of cytokines known as a cytokine storm

Immunological Defense Mechanisms

- Cellular Immune Response
- Against viruses in the cell
- Endosomally processed, presented to T-cytotoxic cells with MHC class I molecule, apoptosis occurs,
- T-cytotoxic cells express macrophage activation by synthesizing IFN gamma,
- Virus-infected cells stimulate NK cells by expressing IFN-alpha and IFN-beta (antibody-dependent and direct stimulation)
- The duration of the immunological memory is variable



Immune response to Viral Infections

A number of specific immune effector mechanisms, together with nonspecific defense mechanisms, are called into play to eliminate an infecting virus.

1. Innate immune response to viral infection

Interferon

A group of proteins produced in response to virus infection which stimulates cells to make proteins that block viral transcription, and thus protects them from infection.

Immune response to Viral Infections

dsRNA produced during viral replication induce the expression of interferons by the infected cells.

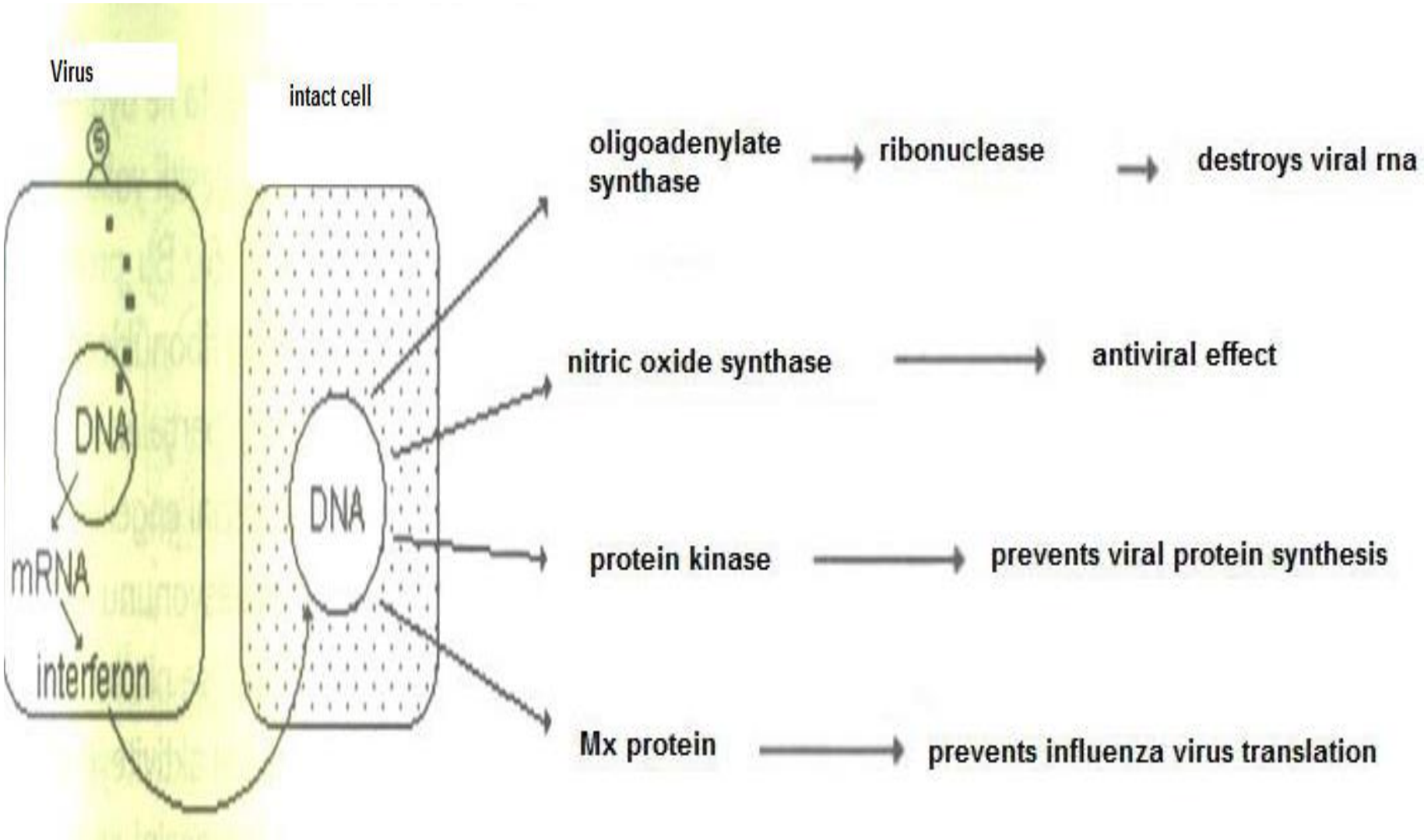
Monocytes , macrophages & fibroblasts also synthesize interferons .

Anti-viral activity of interferons (IFNs)

Virus infected cells produce INF-α;

INF-α inhibit intracellular replication of viruses

Antiviral mechanisms of interferons



Immune response to Viral Infections

IFN-α activate NK-cells to kill virus infected cells

IFNs have no direct effect on extracellular virus

IFNs act early in viral diseases before antibody

INFs activity is not specific

NK cells

Destroy some virus-infected cells, and are not MHC restricted.

Natural killer cells lyse virally infected cells

Immune response to Viral Infections

2. Specific immune response

Humoral immunity

Anti-viral antibodies :

prevent spread during acute infection.

protect against reinfection .

Virus neutralization:- In viraemic infections, antibodies neutralize virus, preventing its attachment to receptor sites on susceptible. cells e.g. Poliovirus, mumps, measles, rubella

Immune response to Viral Infections

In superficial non-viraemic infections (infleunza) Secretory IgA neutralizes virus infectivity at the mucous surfaces.

Antibodies destroy free virus particles directly by:

i- Aggregation of virus and opsonization

ii- Complement mediated lysis

Both mechanisms also act on virus infected cells

Immune response to Viral Infections

Cell mediated immunity(CMI)

Cell – mediated immunity is important for control & clearance of viral infections.

CMI acts on virus infected cells through:

- Cytotoxic T-cells (CTLs)
- NK cells
- Activated macrophages

CTLs kill virus infected cells directly after recognition of viral antigens on cell surface in association with MHC I

Immune response to Viral Infections

- TH-cells stimulated by viral antigens release cytokines. Cytokines attract and activate macrophages to kill virus infected cells
- Nk-cells destroy virus infected cells early in infection before appearance of antibodies
- Antibody-dependent cell mediated cytotoxicity (ADCC):
  - Antibody binds to virus infected cells such cells are lysed by NK cells, macrophages and polymorphs

Immune response to Viral Infections

Immune evasion by viruses

Viruses can evade host defenses •

1. Overcome anti - viral effect of INFs blocking the action of protein kinase example Hepatitis C virus .
2. Reduce surface expression of MHC-I example Adenoviruses & CMV.
3. Reduce MHC -II levels example Measles ,CMV & HIV
4. A large no. of viruses cause generalized immnoduppression. example mumps , measles, EBV., CMV.,& HIV.
5. Antigenic variation example influenza virus

Ways of Viruses to Eliminate Immune Response

●Antigenic changes;

- antigenic variation
- antigenic transition (point mutation every 2-3 years)
- antigenic change (genetic recombination)

●Immunosuppression

- herpes viruses. Necrosis of the mouse thymus
- IBD virus. Necrosis in Bursa Fabricius
- HIV virus. CD_4 cell infection
- Bovine pox virus IL ..IL-1 inhibitor synthesis (virokine)

Summery on Mechanisms of humoral and cell-mediated immune responses to viruses

Response type	Effector molecule or cell	Activity
Humoral	Antibody (especially, secretory IgA)	Blocks binding of virus to host cells, thus preventing infection or reinfection
	IgG, IgM, and IgA antibody	Blocks fusion of viral envelope with host-cells plasma membrane
	IgG and IgM antibody	Enhances phagocytosis of viral particles (opsonization)
	IgM antibody	Agglutinates viral particles
	Complement activated by IgG or IgM antibody	Mediates opsonization by C3b and lysis of enveloped viral particles by membrane-attack complex
Cell-mediated	IFN-γ secreted by T_H or T_C cells	Has direct antiviral activity
	Cytotoxic T lymphocytes (CTLs)	Kill virus-infected self-cells
	NK cells and macrophages	Kill virus-infected cells by antibody-dependent cell-mediated cytotoxicity (ADCC)

Source: Kuby Immunology 2007 5th ed