Medical microbiology

Virology **Dr.Zeytoon Alkhafaji**

Control of viral infections:

- **Host defenses**
- **Antiviral chemotherapy**
- **vaccinations**

Host defenses

Non specific host defenses

1-Anatomic barriers: located either at body surface (skin and mucus membrane) or within body (endothelial cells).

2- **Interferons (IFNs):**

Are host-coded proteins that are members of the **large cytokine family** and which **inhibit viral replication**. They are produced very quickly (**within hours**) in **response to viral infection or other inducers and are one of the body's first responders in the defense against viral infection**. IFNs are central to **the innate** antiviral immune response. They also modulate humoral and cellular immunity and have broad cell growth regulatory activities.

Mode of action: It appears to involve the **induction of host cell enzymes** that **inhibit viral RNA translation**, ultimately leading to the degradation of viral mRNA and tRNA.

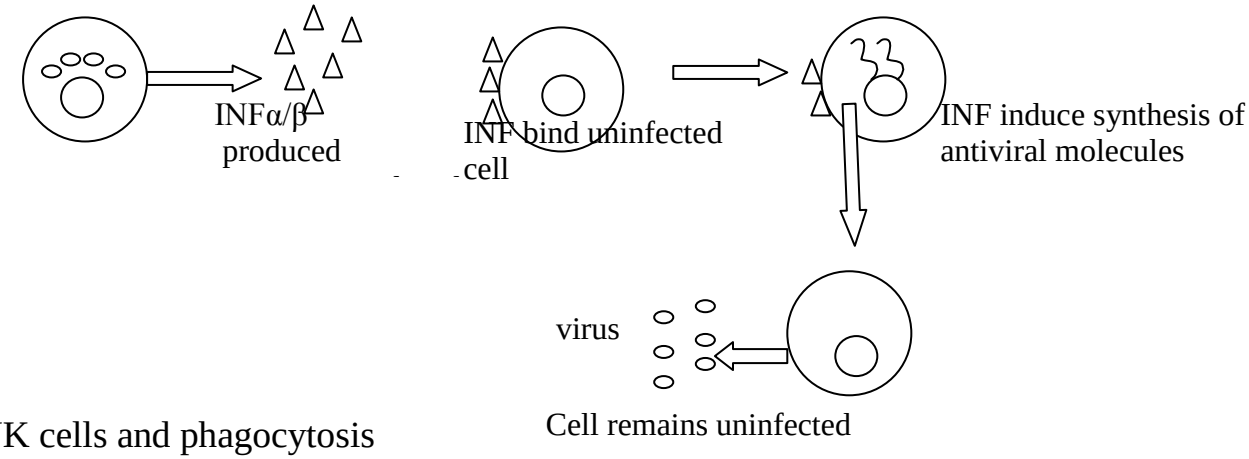
IFNs are divided into three types based on the cell of origin:

a- IFN-alpha is produced by leukocytes, it is induced by viruses.

b- IFN-beta is produced by fibroblasts, it is induced by viruses.

c- IFN-gamma is produced by lymphocytes, it is induced by mitogen stimulation.

virus infected cell uninfected cell



3-NK cells and phagocytosis

- **NK cells** are important parts of the innate defenses against virus infected cells .They kill virus –infected cells **by secreting some enzymes ,which causes death of infected cells .**
- Viruses may be phagocytosis by different PMN leucocytes and macrophages .The effect of phagocytosis may be virus inactivation,and result in clearance of virus

Specific host defenses

1-Produced antibodies and stimulate the cytotoxic T-cell in first exposure to virus .

2-IgM and IgG confer protection against viruses that enter or are spread through the blood

Tow main mechanism for kill the virus by antibodies:

1-nutralization (antigen antibody reaction).

2-lysis of infected cells.

Antiviral Chemotherapy

Unlike viruses, bacteria and protozoans do **not rely** on host cellular machinery for replication, so processes specific to these organisms provide ideal targets for the development of antibacterial and antiprotozoal drugs. **Because viruses are obligate intracellular parasites, antiviral agents must be capable of selectively inhibiting viral functions without damaging the host, making the development of such drugs very difficult**. So few drugs are selective enough to prevent viral replication without injury to the host. Antiviral chemotherapy drugs are available to treat a **few viral diseases when compared with many antibacterial drugs.**

Targets of antiviral drugs :

Antiviral drugs specifically **inhibit one or more steps of viral replication**, which act as target site for these drugs.

1. Inhibit early steps of infection; attachment, penetration and uncoating.
2. Interfere with synthesis of viral mRNA .
3. Prevent protein synthesis.
4. Inhibit replication of viral N.A
5. Inhibit assembly and releasing of mature viral particles from infected cell.

Types of antiviral drugs:

1-Nucleoside analogues: They target the viral enzymes (thymidine kinase, DNA polymerase, reverse transcriptase) that are involved in the synthesis of viral DNA (replication), they act as **chain terminators**. The **majority of available antiviral agents are nucleoside analogues**. Selective toxicity is based on the differences in the ability of the analogue to bind and be utilized by the enzymes used in viral DNA synthesis versus those used in host cell DNA synthesis.

2-Nucleotide Analogues: It differs from nucleoside analogues in having an **attached phosphate group**. Their ability to persist in cells for long periods of time increases their potency. Cidofovir is an example.

3-Nonnucleoside Reverse Transcriptase Inhibitors (NNRTI: Nevirapine was the first member of the class of non nucleoside reverse transcriptase inhibitors. It does not require phosphorylation for activity and does not compete with nucleoside triphosphates. **It acts by binding directly to reverse transcriptase and disrupting the enzyme's catalytic site**.

4-**Nucleoside and nucleotide Reverse Transcriptase Inhibitors (NRTIs)**: Zalcitabine, Didanosine, Stavudine and Zidovudine, These drugs have similar modes of action and are mostly used in conjunction with other main classes of antiretroviral drugs: NNRTI and Protease Inhibitors to treat HIV-1 infected individuals.

5-Protease Inhibitors: Saquinavir was the first protease inhibitor to be approved for **treatment of HIV infection**. Such drugs **inhibit the viral protease** that is required at the late stage of the replicative cycle to cleave the viral polypeptide precursors to form the mature virion core and activate the reverse transcriptase that will be used in the next round of infection. Protease inhibitors include indinavir, nelfinavir and ritonavir .

6-Fusion Inhibitor: Fuzeon is a large peptide that blocks the virus and cellular membrane fusion step involved in entry of HIV-1 into cells.

Other Types of Antiviral Agents

A- Antivirals targeting influenza viruses

1-Amantadine and Rimantadine: These synthetic amines specifically inhibit influenza A viruses by blocking viral uncoating.

2-Neuraminidase inhibitors: Neuraminidase is one of the two surface glycoproteins on the surface of influenza virus . Neuraminidase inhibitors act as competitive inhibitors of the neuraminidase enzyme active site, e.g zanamivir and oseltamivir

B- Pyrophosphate analogue that blocks the pyrophosphate-binding site on the viral DNA polymerase

Foscarnet (Phosphonoformic acid): An organic analogue of inorganic pyrophosphate, selectively inhibits viral DNA polymerases and reverse transcriptases at the pyrophosphate-binding site.

Acyclovir is a guanosine analog DNA polymerase inhibitor used for the treatment of HSV and varicella-zoster virus infections.

Ganciclovir is a nucleoside DNA polymerase inhibitor active against CMV whose specificity comes from phosphorylation by virus-specific kinases only in virally infected cells. Valganciclovir is the orally available **prodrug** for ganciclovir.

Table 1. Examples of Antiviral Compounds Used for Treatment of Viral Infections.

Drug	Nucleoside Analogues	Mechanism of Action	Viral Spectrum
Acyclovir	Yes	Viral polymerase inhibitor	Herpes simplex, varicella-zoster
Amantadine	No	Blocks viral uncoating	Influenza A
Cidofovir	No	Viral polymerase inhibitor	Cytomegalovirus, herpes simplex, polyomavirus
Didanosine (ddI)	Yes	Reverse transcriptase inhibitor	HIV-1, HIV-2
Foscarnet	No	Viral polymerase inhibitor	Herpes viruses, HIV-1, HBV
Fuzeon	No	HIV fusion inhibitor (blocks viral entry)	HIV-1
Ganciclovir	Yes	Viral polymerase inhibitor	Cytomegalovirus
Indinavir	No	HIV protease inhibitor	HIV-1, HIV-2
Lamivudine (3TC)	Yes	Reverse transcriptase inhibitor	HIV-1, HIV-2, HBV
Nevirapine	No	Reverse transcriptase inhibitor	HIV-1
Ribavirin	Yes	Perhaps blocks capping of viral mRNA	Respiratory syncytial virus, influenza A and B, Lassa fever, hepatitis C, others
Ritonavir	No	HIV protease	HIV-1, HIV-2

		inhibitor	
Saquinavir	No	HIV protease inhibitor	HIV-1, HIV-2
Stavudine (d4T)	Yes	Reverse transcriptase inhibitor	HIV-1, HIV-2
Trifluridine	Yes	Viral polymerase inhibitor	Herpes simplex, cytomegalovirus, vaccinia
Valacyclovir	Yes	Viral polymerase inhibitor	Herpesviruses
Vidarabine	Yes	Viral polymerase inhibitor	Herpesviruses, vaccinia, HBV
Zalcitabine (ddC)	Yes	Reverse transcriptase inhibitor	HIV-1, HIV-2, HBV
Zidovudine (AZT)	Yes	Reverse transcriptase inhibitor	HIV-1, HIV-2, HTLV-1

Vaccines

- Vaccination – **generation of antibody mediated and cellular immunity** against specific viruses by administration of whole virions or their components → only known means of preventing viral diseases.
- 2 types:

A-Whole virus vaccine - pathogenicity must be eliminated while ability to elicit antibody response retained

***** Killed (inactivated) virus vaccine** – ability to express viral genes and to reproduce is eliminated by chemical treatment

1- Generally administered by injection

2- Elicit antibodies against surface components of virion

3- Immunity of relatively **short duration – require boosters**

*****Attenuated live virus vaccine** – **genetic changes** abolish pathogenicity but not the ability to reproduce. Generally isolated from different host or adapted to growth in different cell type

1- Can be administered orally

2- Harder to make

3- Produce immune responses against external and internal virion components and virally-encoded proteins expressed in infected cells
4- Generally cheaper
5- Immunity relatively long-lasting → elicit good IgA response
6- Disadvantage – possibility of genetic reversion to a pathogenic form and persistent infection with the vaccine strain

B-Subunit (component) vaccines – consist of whole viral proteins, generally expressed **from molecularly cloned genes.**

Efficacy requires that structure resembles that found in the intact virion