Antiviral Agents

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**. Another limitation is that many rounds of virus replication occur during the incubation period and the virus has spread before symptoms appear, making **a drug relatively ineffective**.

Molecular virology studies are succeeding in identifying virus-specific functions that can be serve as targets for antiviral therapy. The most amenable stages to target in viral infections include (1)attachment of virus to host cells ; (2)uncoating of the viral genome ; (3)viral nucleic acid synthesis ; (4)translation of viral proteins ; (5)and assembly (6)and release of progeny virus particles. In reality, it has been very difficult to develop antivirals that can distinguish viral from host replicative processes.

The mechanisms of action vary among antivirals. Oftentimes the drug must be activated by enzymes in cell before it can act as an inhibitor of viral replication ; the most selective drugs are activated by a virus-encoded enzyme in the infected cell. There are different classes of antiviral agents :

A- Nucleoside Analogs

The majority of available antiviral agents are nucleoside analogs. **They inhibit nucleic acid replication by inhibition of polymerases for nucleic acid replication**. In addition, **some analogs can be incorporated into the nucleic acid and block further synthesis or alter its function**.

Analogs can inhibit cellular enzymes as well as virus-encoded enzymes. The most effective analogs are those able to specifically inhibit virus-encoded enzymes, with minimal inhibition of analogous host cell enzymes. Virus variants resistant to the drug usually arise over time,

sometimes quite rapidly. The use of combinations of antiviral drugs can delay the emergence of resistant variants (e.g. "**triple drug**" therapy used to treat HIV infections).

Examples of nucleoside analogs include **acyclovir** (acycloguanosine), **lamivudine (3TC), ribavirin , vidarabine**(adenine arabinoside), and **zidovudine** (azidothymidine; AZT).

B- Nucleotide Analogs

Nucleotide analogs differ from nucleoside analogs **in having an attached phosphate group**. Their ability to persist in cells for long periods of time increases their potency. **Cidofovir** (HPMPC) is an example.

C- Non-nucleoside Reverse Transcriptase Inhibitors(NNRTI)

Nevirapine was the first member of the class of **NNRTI**. 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 enzymes catalytic site.** Resistant mutants emerge rapidly.

D- Protease Inhibitors (PI)

Saquinavir was the first protease inhibitor to be approved for treatment of HIV infection. It is a peptidomimetic agent designed by computer modeling as a molecule that fits into the active site of the HIV protease enzyme. Such drugs **inhibit the viral protease that is required at the late stage of the replicative cycle to cleave the viral *gag-pol* polypeptide precursors to form the mature virion core and activate the reverse transcriptase that will be used in the next round of infection**. Inhibition of the protease yields noninfectious virus particles. Protease inhibitors include **indinavir** and **ritonavir** and others.

E- Fusion Inhibitor

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

F- Other Types of Antiviral Agents

A number of other types of compounds have been shown to possess some antiviral activity under certain conditions.

1- **Amantadine & rimantadine:** These synthetic amines specifically inhibit influenza A viruses by **blocking viral uncoating**. They must be administered prophylactically to have a significant protective effect.

2- **Foscarnet (phosphonoformic acid):** Foscarnet, an organic analog of inorganic pyrophosphate, selectively **inhibits viral DNA polymerases and reverse transcriptases at the pyrophosphate-binding site.**

3- **Methisazone:** methisazone is of historical interest as an inhibitor of poxiviruses. It was the first antiviral agent to be described and contributed to the campaign to eradicate smallpox. **It blocked a late stage in viral replication**, resulting in the formation of immature, noninfectious virus particle.

Interferons (IFNs)

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. IFN was the first cytokine to be recognized. IFNs are central to the innate antiviral immune response. They also modulate humoral and cellular immunity and have broad cell growth regulatory activities, but the focus here will be on their antiviral effects.

A-Properties of IFNs

There are multiple species of IFNs that fall into three general groups, designated IFN-α , IFN-β, and IFN-γ. Both IFN-α and IFN-β are considered **type I** or **viral IFNs**, whereas IFN-γ is **type II** or **immune IFN**. The IFN-α family is large, being coded by at least 20 genes in the human genome; the IFN-β and IFN-γ families are coded by one gene each.

The different IFNs are similar in size, but the three classes are antigenically distinct. IFN-α and IFN-β are resistant to low pH. IFN-β and IFN-γ are glycosylated, but the sugars are not necessary for biologic activity, so cloned IFNs produced in bacteria are biologically active. Dendritic cells are potent IFN producers; under the same conditions, dendritic cells can secrete up to 1000 times more IFN than fibroblasts.

B-Synthesis of IFNs

IFNs are produced by all vertebrate species. Normal cells do not generally synthesize IFN until they are induced to do so. Infection with viruses is a potent insult leading to induction; RNA viruses are stronger inducers of IFN than DNA viruses. IFNs also can be induced by double-stranded RNA, bacterial endotoxin, and small molecules such as tilorone. **IFN-γ is not produced in response to most viruses but is induced by mitogen stimulation.**

The different classes of IFN are produced by different cell types. IFN-α and IFN-β are synthesized by **many cell types**, but IFN-γ is produced mainly by **lymphocytes, especially T cells and natural killer (NK) cells.** Dendritic cells potent IFN producers; under the same virus challenge conditions, dendritic cells can secrete up to 1000 times more IFN than fibroblasts.

C-Antiviral activity and other biologic effects

IFNs were recognized by their ability to interfere with viral infection in cultured cells. IFNs are detectable soon after viral infection in intact animals, and viral production then degreases.

Antibody does not appear in the blood of the animal until several days after viral production has abated. This temporal relationship suggests that IFN plays a primary role in the nonspecific defense of the host against viral infections. This inclusion is also supported by observations that agammaglobulinemic individuals usually recover from primary viral infections about as well as normal people.

IFN does not protect the virus-infected cell that produces it, and IFN itself is not the antiviral agent. Rather, IFN moves to other cells where it induces an antiviral state by prompting the synthesis of other proteins that actually inhibit viral replication. IFN molecules bind to specific cell surface receptor.

D- Virus Mechanisms to Counteract IFN

Viruses display different mechanisms that block the inhibitory activities of IFNs on virus replication, processes necessary to surmount this line of host defense. Examples: **(1) specific viral proteins may block induction of expression of IFN** (herpesvirus , papillomavirus , filovirus , hepatitis C virus , rotavirus); **(2) may block the activation of the key PKR protein kinase** (adenovirus , herpisviruses); **(3) may activate a cellular inhibitor of PKR** (influenza, poliovirus); **(4) may block IFN-induced signal transduction** (adenovirus, herpesviruses , hepatitis B virus) ; **(5) or may neutralize IFN-γ by acting as a soluble IFN receptor** (myxoma virus).