Ministry of Health of the Russian Federation
Volgograd State Medical University

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GENERAL PHARMACEUTICAL CHEMISTRY

VIRUSES. CLASSIFICATION. FEATURES OF CHEMOTHERAPY OF VIRAL INFECTIONS.

Lesson 8
IV term

Volgograd, 2022

VIRAL INFECTIONS

Viral infections are one of the most important factors that have formed and continue to form the history of humanity. Thus, if smallpox, measles and yellow fever had not reached the New World, it is possible that an completely different natural landscape and culture might have existed in the Americas. Biogenic factors that affect human civilisation include infectious diseases of a viral nature.

In recent decades, there has been a steady increase in the number of infectious diseases of viral etiology. This eventually led to a significant spread of both known and emerging diseases: HIV, hepatitis C and B, Dengue, Chikungunya, Zika, Ebola and Marburg fevers, SARS and MERS coronavirus infections, etc.

Viral infections currently account for about 90% of the total infectious disease incidence. The prevalence of viral diseases in the human population is illustrated by the following facts:

- ✓ Approximately 2/3 of the world's population are infected with herpes simplex virus-1 and HSV-2; more than 95% of people over 50 are seropositive for varicella zoster virus; antibodies to CMV (cytomegalovirus) have been detected in 60% of adults in developed countries and in 100% of developing countries; about 90% of people have seropositive for Epstein-Barr virus even in their teenage years.
- ✓ More than 280 million people are infected with hepatitis B virus (HBV) and have a chronic course of disease.
- ✓ More than 180 million people are infected with hepatitis C virus (HCV) and have a chronic course of the disease.
- ✓ Arbovirus infections (dengue virus, Chikungunya virus, Zika virus, etc.) are common in equatorial and subequatorial areas of the world, where over 3.9 billion people are at risk of infection.
- ✓ The influenza virus is the cause of annual epidemics that affect most countries around the world.

Some viruses cause malignant tumours. In particular, herpesviruses cause various localised cancers in humans: CMV causes brain tumours, Epstein-Barr virus causes gastric cancer, Berkitt lymphoma, non-Hodgkin and Hodgkin lymphomas, nasopharyngeal carcinoma, human herpesvirus type 8 causes Kaposi sarcoma. HBV and HCV cause hepatocellular carcinoma of the liver.

The mortality rate associated with diseases of viral etiology is also quite high.

CHARACTERISTICS OF VIRUSES

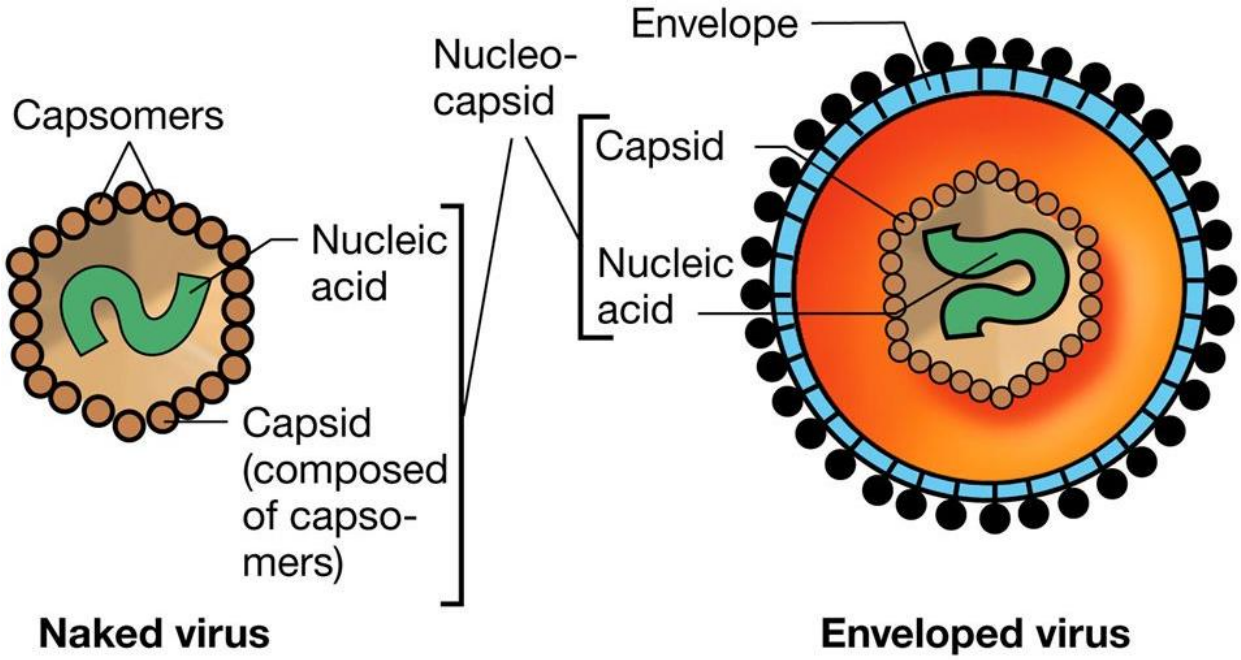
A virus (lat. virus - poison) is a non-cellular infectious agent that can only reproduce inside living cells. Viruses affect all types of organisms, from plants to animals. Viruses (satellite viruses) have also been found to reproduce only in the presence of other viruses.

To date, more than 5,000 species of viruses have been described in detail; it is thought that there are many more. Viruses have been found in almost every ecosystem on Earth. They are the most numerous biological form.

Viruses are unique in nature. They are the smallest of all self-replicating organisms and are characterised by their ability to pass through filters that trap even the smallest bacteria. Viruses do not have their own metabolism, but are forced to infect cells and use the cell to produce their progeny, depleting the cell's resources in the process.

By their nature, viruses are obligate parasites, as they are unable to reproduce outside the cell. Outside the cell, viral particles show no living characteristics and behave like particles of biopolymers. Viruses differ from living organisms, which are intracellular parasites, in their complete absence of metabolism and energy exchange.

Viral particles - virions - consist of several components: genetic material in the form of DNA or RNA; a protein shell (capsid) that protects these molecules; and, in some cases, an additional lipid shell. Viruses can thus be divided into two types: naked viruses, consisting of nucleic acid and a capsid; and Enveloped viruses, consisting of an additional lipid bilayer. Such a shell is called a supercapsid.



Virus capsids are made up of protein subunits called capsomers assembled in a highly specific way. Some viruses have a number of enzymes in their capsid that carry out transcription and replication of the viral genome, called RNA and DNA polymerases. These enzymes are called structural proteins.

The size of the average virus is about one hundredth of the size of the average bacterium.

CLASSIFICATION OF VIRUSES

The Baltimore classification of viruses. It identifies seven main groups:

Class I: Double stranded DNA (dsDNA) viruses

A double stranded DNA virus enters the host nucleus before it begins to replicate. It makes use of the host polymerases to replicate its genome, and is therefore highly dependent on the host cell cycle. The cell must therefore be in replication for the virus to replicate.

Examples of Class I viruses include Herpesviridae, Adenoviridae, and Papoviridae.

Class II: Single stranded (+) sense DNA (ssDNA) viruses

Most ssDNA viruses have circular genomes and replicate mostly within the nucleus by a rolling circle mechanism.

Some examples of Class II viruses are Anelloviridae, Circoviridae, and Parvoviridae.

Class III: Double stranded RNA (dsRNA) viruses

Double stranded RNA viruses replicate in the core capsid in the host cell cytoplasm and do depend as heavily on host polymerases as DNA viruses. The genomes of Class III viruses may be segmented, and unlike viruses with more complex translation, each gene codes for only one protein.

Examples of Class III viruses include and Birnaviridae.

Class IV: Single stranded RNA (+) sense (ssRNA) viruses

Class IV ssRNA viruses have positive-sense RNA genomes, meaning they can be directly read by ribosomes to translate into proteins. They are further divided into viruses with polycistronic mRNA and those with complex transcription.

Polycistronic mRNA is translated into a polyprotein that is subsequently cleaved to form separate proteins. Viruses with complex transcription use ribosomal frameshifting and proteolytic processing to produce multiple proteins from the same gene sequences.

Examples of some Class IV viruses are Coronaviridae, Flaviviridae, Astroviridae, and Picornaviridae.

Class V: Single stranded RNA (-) sense (ssRNA) viruses

Class V viruses have a negative-sense RNA genome, meaning they must be transcribed by a viral polymerase to produce a readable strand of mRNA. The genomes of Class V viruses may be segmented or non-segmented.

Some viruses in Class V are Orthomyxoviridae, Paramyxoviridae, and Rhabodviridae.

Class VI: Single-stranded (+) sense RNA viruses with DNA intermediate in life-cycle

Group VI viruses have a positive sense, single-stranded RNA genome, but replicate through a DNA intermediate. The RNA is converted to DNA by reverse transcriptase and then the DNA is spliced into the host genome for subsequent transcription and translation using the enzyme integrase.

Group VI includes retroviruses such as HIV, as well as Metaviridae and Pseudoviridae.

Class VII: Double-stranded DNA viruses with RNA intermediate

Class VII viruses have a double-stranded DNA genome, but unlike Class I viruses, they replicate via a ssRNA intermediate. The dsDNA genome is gapped, and subsequently filled in to form a closed circle serving as a template for production of viral mRNA. To reproduce the genome, RNA is reverse transcribed back to DNA.

Hepatitis B virus is a Class VII virus.

It should be understood that the sense of viral RNA is purely conventional and means:

- ✓ viral RNA of positive sense is used as both mRNA and genome;
- ✓ negative sense viral RNA serves only as the genome, while its complementary molecule, antigenomic RNA, is used as mRNA.

There are currently 27 known families of viruses that cause various human diseases. They can be divided into several groups ***according to their clinical features.***

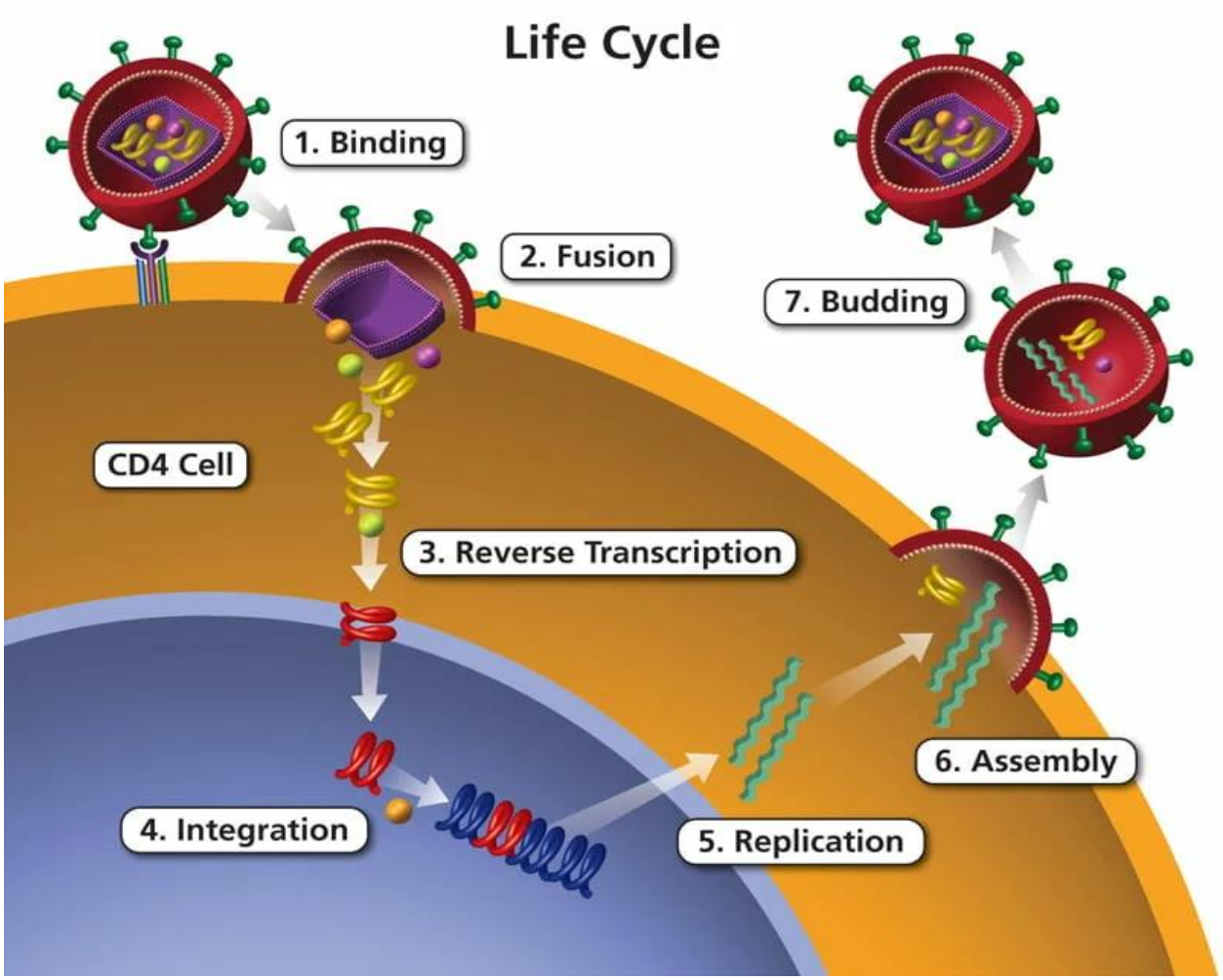
- ➢ The largest group is made up of viruses that ***affect the upper and lower respiratory tract and cause influenza and acute respiratory diseases***. This group includes the following viruses: influenza viruses type A and B, picornoviruses, human coronaviruses, adenoviruses, human respiratory syncytial virus and human parainfluenza virus.

- Viruses ***causing diarrhoea and gastroenteritis*** are the second most common. This group consists of rotaviruses, noroviruses, calciviruses, adenoviruses (types 40 and 41), coronaviruses and enteroviruses.
- Another group includes viruses that ***cause hepatitis***. Hepatitis viruses belong to different families and differ in biochemical and molecular characteristics, but all of these viruses have in common that they cause hepatitis in humans. A large number of viruses are known to cause viral hepatitis: hepatitis A virus, hepatitis B virus, hepatitis C virus, hepatitis D virus (satellite virus), hepatitis E virus, hepatitis F virus, hepatitis G virus, rubella virus, cytomegalovirus and Epstein-Barr virus.
- There is also a group of viruses that can ***cause cancer in humans***. These include hepatitis B and C viruses, human cytomegalovirus, Epstein-Barr virus, Kaposi sarcoma virus, human papilloma virus, polyoma virus and human T-lymphotropic virus.
- A group of ***neurotropic*** viruses can also be distinguished. It includes viruses such as Japanese encephalitis virus, Venezuelan equine encephalitis virus, California encephalitis virus, polio virus, coxsackievirus, mumps virus, measles virus, rabies virus, and diseases caused by members of the family Herpesviridae.
- There is a group of viruses that can ***cause haemorrhagic fevers*** in humans. These viruses include primarily filoviruses (Ebola and Marburg viruses) but also flaviviruses (yellow fever and dengue viruses), arenaviruses (Lassa, Machupo, Junin and Guanarito viruses) and Bunyaviruses (Rift Valley fever and Crimean-Congo fever viruses).

THE LIFE CYCLE OF VIRUSES

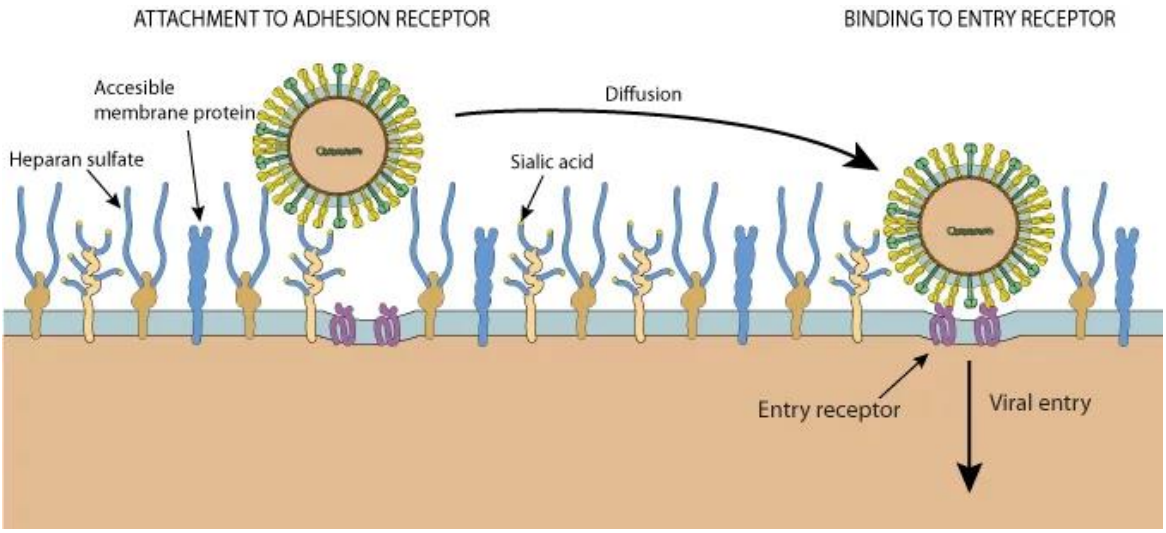
The development of highly effective and selective antiviral medicines requires knowledge of the life cycle of viruses. This is necessary to identify specific targets for chemotherapeutic action. Viral enzymes and proteins, as well as processes and events specific to viruses, can serve as such targets.

A viral particle (virion) has one mission: to transport the viral genome from an infected cell to an uninfected host cell and deliver it to the cytoplasm or nucleus of the cell for replication. The target cell can be a neighbouring cell, a cell elsewhere in the host organism or a cell in another organism.



The initial step can be considered to be **the contact of the virion with the surface of the target cell**. This generates a complex series of events that are tightly coordinated with each other in time and space. Typically, these events include:

- ✓ recognition and binding to cell receptors,
- ✓ adsorption of the virus on the cell surface.

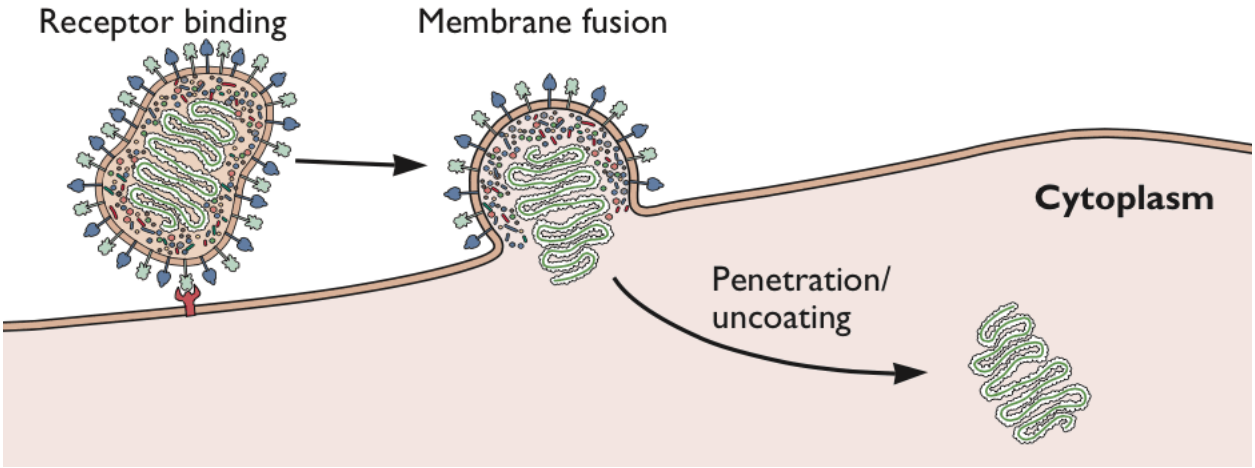


The adsorption of the virus onto the cell membrane is the starting point for the realization of its pathogenic properties. Without this, the virus cannot enter the cell and multiply in it, it is simply doomed to die. For each virus there are specific receptors on the cell membrane to which the viruses bind with their receptors. The so-called viral tropism is based on the presence of receptors in both cells and viruses. Due to the diversity of cellular and viral receptors, different viruses can be adsorbed on the same cells. *For example*, the receptors for influenza virus are mucopeptides containing free N-acetylneuraminic acid and the receptor for viruses that recognise it is a protein, haemagglutinin.

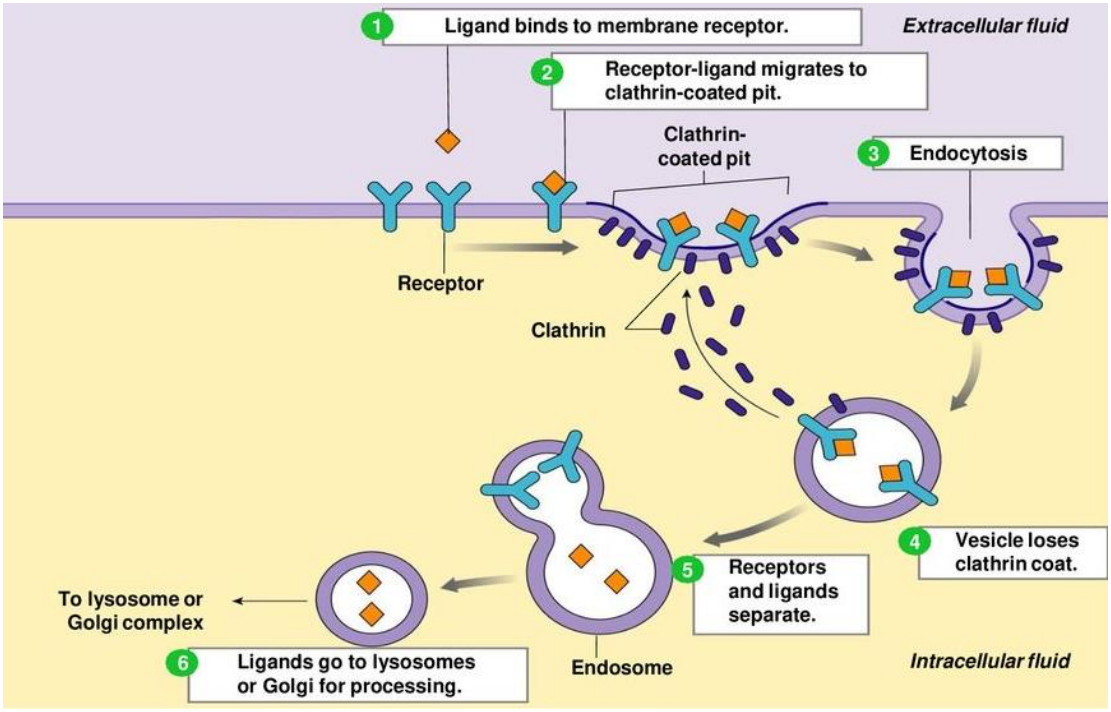
Virus entry into the cell

Two mechanisms for virus entry into the cell are known:

1. ***Through the fusion of the supercapsid of the virus with the cell membrane***. This results in the release of the nucleocapsid into the cytoplasm and the subsequent realization of the properties of the viral genome.



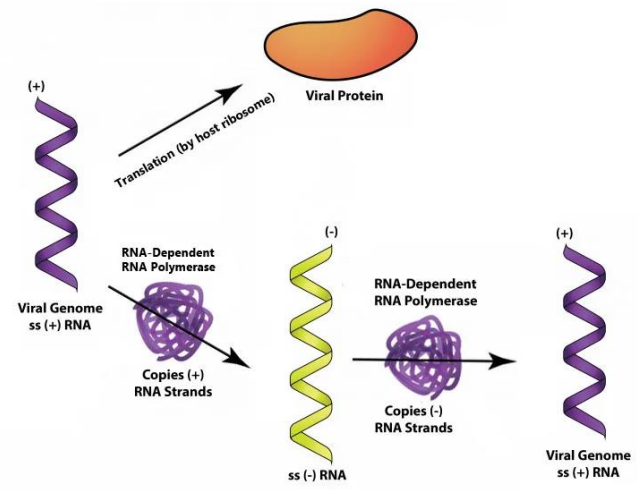
2. Another mechanism is called ***receptor-mediated endocytosis***. In this case, the virus binds to specific receptors in the coated pit (the area of the membrane bordered by peculiar bristles). It curves inwards into the cell and becomes a coated vesicle. The vesicle containing the absorbed virion rapidly fuses with an intermediate vesicle called the endosome, which fuses with the lysosome. Due to the special properties of the viral supercapsid proteins, the lipid layers of the supercapsid and the lysosome membrane fuse together. As a result, the nucleocapsid ends up in the cell cytosol, where further nucleocapsid stripping and release of genomic nucleic acid occurs.



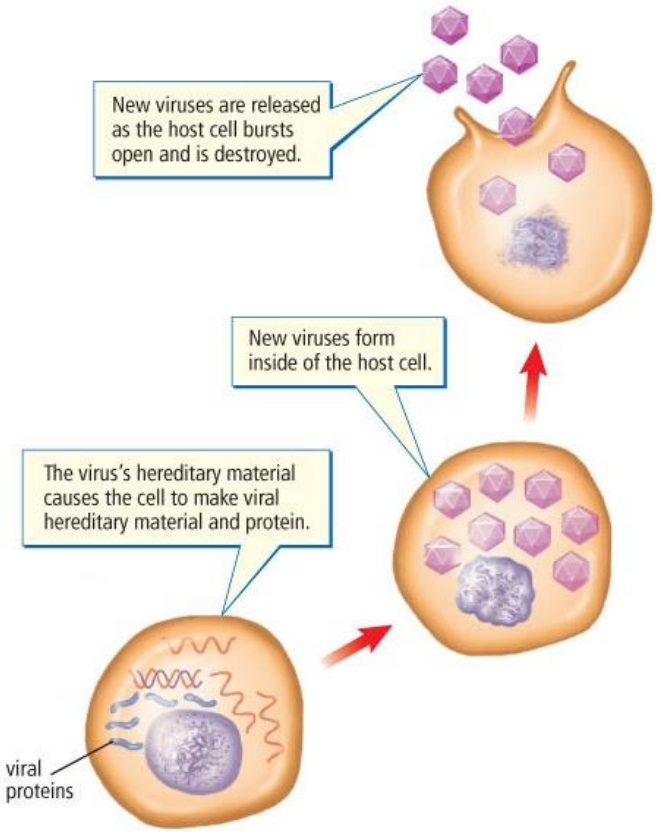
Deproteinisation of the capsid is an integral part of the process. The virion is modified and the monomer proteins (capsomes) that make up the capsid are destabilised and dissociated. The genome present in the capsid is released to participate in replication and/or transcription.

Genome replication is the most distinctive characteristic of living nature and nowhere in the biosphere is replication more economically and easily achieved than among viruses. To achieve replication of their genes, the different virus families have developed a variety of strategies and replicative cycles using cell biology.

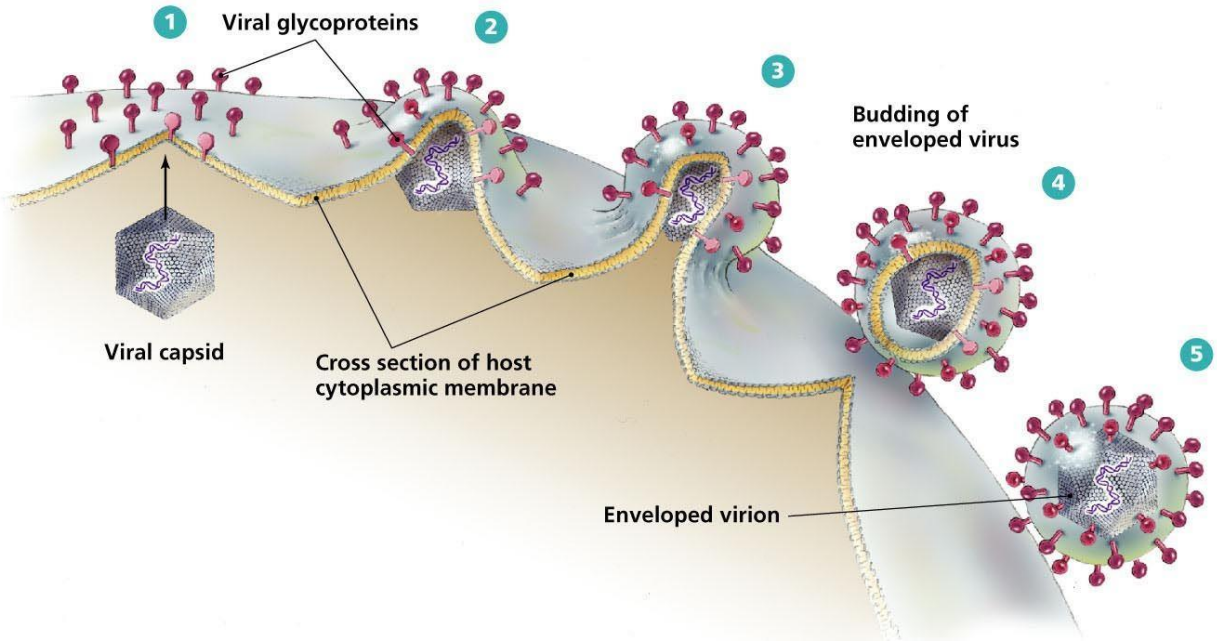
As viruses are obligate intracellular parasites, their life cycle is entirely dependent on the functions provided by the host cell. However, almost all viruses encode and express unique proteins and enzymes and many viruses use information transmission pathways that are unknown in other living systems.



Virion assembly is a key step in the life cycle of any virus. It involves a process in which chemically different macromolecules are transported to a point inside the cell, where they assemble into a viral particle. *For example.* Virions that do not have a lipid shell, such as adenovirus, accumulate in the cell. The cell depleted of resources producing viral progeny lyses and the virions are released into the intercellular space.



The situation for *enveloped viruses*, such as HIV or influenza virus, is more complex. For a virus that assembles and buds from the cell surface, various virion components need to be transported to the assembly site: glycoproteins, monomer proteins (capsomers), viral enzymes and viral RNA in the form of a nucleoprotein complex. All of these macromolecules are matured in different parts of the cell and are transported by different pathways. Thus, there is a close interaction between viral and cellular proteins, between viral proteins, nucleic acids and lipids, and between viral proteins themselves, and this interaction underlies the assembly process of viral particles.

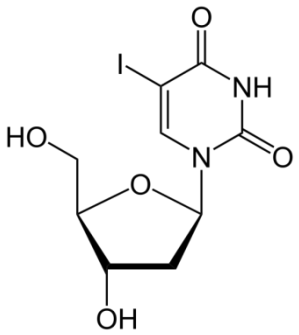


THE CHEMOTHERAPY OF VIRAL INFECTIONS

The chemotherapy of viral infections is a specific problem. Progress in finding effective antiviral therapeutic agents has not yet been as significant as in the area of antimicrobials.

The difficult part is creating drugs that selectively inhibit the reproduction of the virus and do not affect the vital processes of cells and the body as a whole. This is because the life cycle of viruses is closely linked to cellular processes, metabolism, energy metabolism and enzymatic reactions in the cell and almost always have a toxic effect on the cell as well. Antivirals have a narrow range of action (at best within the same family) and viruses quickly develop resistance to them. However, the field is developing intensively and new antiviral drugs are produced every year.

More than 60 years ago, the synthesis of **iodoxuridine**, an analogue of thymidine, was described. Later, in 1959, it became the first antiviral drug approved for topical use in ophthalmology for the treatment of herpetic conjunctivitis.



iodoxuridine

The advent of iodoxuridine marked the birth of the era of antiviral drugs. To date, more than 50 drugs have been approved for the treatment of the following human infections:

- ✓ ***HIV infection*** (anti-HIV drugs include the following classes - protease inhibitors, integrase inhibitors, entry inhibitors, nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors and phosphonate analogues of acyclic nucleosides);
- ✓ ***Hepatitis B virus (HBV) infection*** (anti-HBV drugs include lamivudine and other nucleoside analogues, also phosphonate analogues of acyclic nucleosides);
- ✓ ***Hepatitis C virus (HCV) infection*** (anti-HCV drugs include - ribavirin, NS3/4A protease inhibitors, NS5A inhibitors and NS5B polymerase inhibitors);
- ✓ ***Herpes simplex virus (HSV) type 1 and type 2 infections*** (anti-HSV drugs include - 5-substituted 2'-deoxyuridine analogues, entry inhibitors, nucleoside analogues, pyrophosphate analogues and acyclovir - an acyclic guanosine analog);
- ✓ ***Influenza virus infection*** (anti-influenza drugs include - ribavirin, M2 inhibitors, neuraminidase inhibitors, RNA polymerase inhibitors);
- ✓ ***human cytomegalovirus infections*** (acyclic guanosine analogues, phosphonate analogues of acyclic nucleosides, pyrophosphate analogues);
- ✓ ***varicella virus infection*** (acyclic guanosine analogues, nucleoside analogues, 5-substituted 2'-deoxyuridine analogues);
- ✓ ***respiratory syncytial virus infection*** (ribavirin and antibodies);
- ✓ ***papillomavirus infection*** (imiquimod, sinecatechin and podophilox).

According to a ***classification based on the chemical nature*** of antiviral drugs, the following groups are distinguished:

1. abnormal nucleosides;
2. adamantane derivatives;
3. thiosemicarbozone derivatives;
4. synthetic amino acids;
5. pyrophosphate analogues;
6. virulicide drugs;
7. others;
8. interferons and interferon inducers.