Virus Infection

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Glossary

attenuation The reduction in virulence or ability to cause disease or other consequences of infection by a microbe while it still remains viable.

burst The abrupt release of many progeny virus upon the disintegration of the infected cell in which the virus has been growing.

eclipse The period from the entry of a virus into a cell when it loses it infectivity as an independent particle to the appearance inside of the cell of fully infectious progeny virus particles.

envelope The biological lipid–protein membrane that surrounds the protein and nucleic acid core of some viruses.

interferon Specific cellular proteins that are synthesized in response to virus infection and are secreted outside the infected cell, rendering the neighboring uninfected cells resistant to virus infection.

latent A virus that has entered into a nonreplicative mode of existence in a cell but is propagated along with the cell by certain mechanisms that allow limited viral genome replication without full expression of viral functions and production of mature infectious virus particles.

lysogenic A mode of virus interaction with cells in which the virus enters the latent state and can be induced to enter the full replicative cycle with subsequent disruption (lysis) of the cell and production of a full burst of progeny virus.

lytic A mode of virus interaction with cells in which the virus undergoes a complete replicative cycle with the production of many progeny virus particles and the subsequent release of these virus upon disruption (lysis) of the cell.

persistence A mode of virus interaction with a population of cells in which a few cells are always in a lytic mode of infection but the majority of cells are uninfected but potentially susceptible to lytic virus infection.

tropism The specificity of a virus for infection of a specific cell type or specific species.

viremia The presence of virus in the bloodstream.

virulence The ability of a virus to cause more or less severe disease symptoms of a specific type.

Abbreviations

AZT azidothymidine
ddC dideoxycytidine

HIV human immunodeficiency virus
HPV human papillomavirus

Defining Statement

Viruses are obligate intracellular parasites that can exist as potentially active but inert entities outside of cells. While there are viruses that infect many animal, plant, and protist cells and result in effects on the host that range from inapparent infection to lethality, all virus infections have some features in common. These include an entry phase, an intracellular phase consisting of multiplication, integration, or latency formation, a virus release phase, and usually some sort of host responses to the presence of the virus infection. It is often these host responses that appear as the most prominent signs and symptoms of virus infection.

Virus Life Cycles

Viruses are small and relatively simple microbes that cannot grow outside of living cells, that is, they are obligate intracellular parasites (**Figure 1**). At the structural level, all viruses have some general features in common: a
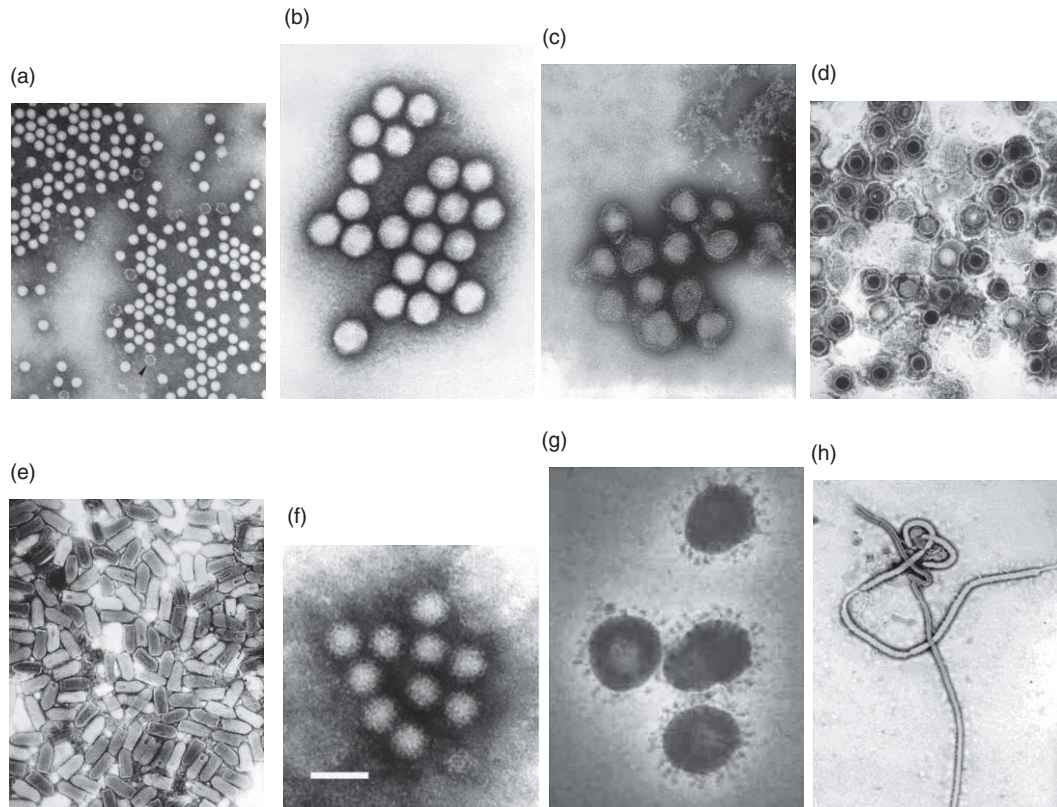
Figure 1 Electron microscope images of representative viruses. (a) poliovirus (30 nm diameter); (b) adenovirus (90–100 nm diameter); (c) influenza A virus (80–120 nm diameter); (d) herpes simplex type 1 (180 nm diameter); (e) rabies virus (180 × 75 nm); (f) Norwalk virus (27–38 nm diameter); (g) SARS coronavirus (120–160 nm diameter); (h) Ebola virus (80 × 1000 nm). Reproduced from the Public Health Image Library, Center for Disease Control and Prevention, in the public domain.

virus has a core of nucleic acid (either RNA or DNA) that acts as the genome of the virus and encodes some of the biological functions of the particular virus. Also, at the functional level, all viruses share some common processes of interactions with their host cells. While virus classification schemes are still debated among virologists, the nature of the genome and the mode of mRNA synthesis of a given virus are generally useful and widely employed bases for classification. David Baltimore has proposed a scheme based on mRNA metabolism (**Figure 2**). The chemical structure of the viral genome (DNA vs. RNA, single vs. double strandedness) is also a widely used basis for viral taxonomy (**Table 1**).

At the cellular level a virus must first have some way of entry into the cell, often by adsorption or attachment to some structure or specific molecule on the surface of the target host cell. Often, the virus attachment site can be a molecule or group of molecules that the cell uses for other purposes, for example, a protein in the maltose transport system is used by bacteriophage lambda for attachment to *Escherichia coli*, and one of the lymphocyte cell recognition molecules is used by the human immunodeficiency virus (HIV) as its cell surface attachment site. In all virus infections the genome of the virus enters the host cell;

in some cases only the viral nucleic acid enters the cell, leaving the protein coat of the virus outside of the cell; in other cases, the entire virus is taken into the cell and the genome is exposed after a process of intracellular 'uncoating'. In some instances, the viral nucleic acid enters the host cell with one or a very few genome-associated proteins while the bulk of the virus structural proteins remains on the outside of the host cell. Upon entering the cell, or soon thereafter, the infectious virus particles are disrupted, and even if the cell is artificially broken open, no infectious viruses are found. This period between the loss of infectivity and the appearance of fully infectious progeny virus is called the 'eclipse' phase of the virus life cycle.

In the cases where some viral proteins enter along with the genome, such proteins play a necessary role in helping to express the viral genes or in the replication of the viral genome. In some instances, some of the imported viral proteins function to suppress the host gene expression so as to help the virus in effectively shutting down host functions as the virus subverts the cellular processes to its own program.

After the viral genome enters the cell, some or all of its genetic information is expressed. In the case of
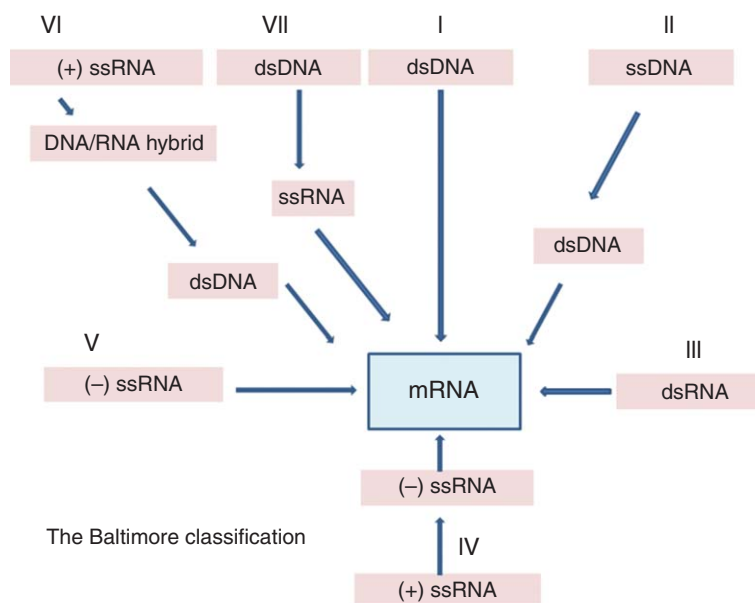
Figure 2   The Baltimore classification of viruses based on the method of viral mRNA synthesis. Reproduced from NIH, in the public domain.

Table 1   Virus classification based on genetic structure and replication strategy of virus

Group	Genome	Typical representative
I	DNA (double-stranded)	Herpesviruses (fever blisters)
II	DNA (single-stranded, + sense)	Parvoviruses (fifth disease)
III	RNA (double-stranded)	Reoviruses (rotavirus)
IV	RNA (single-stranded, + sense)	Picornaviruses (polio)
V	RNA (single-stranded, − sense)	Orthomyxoviruses (influenza)
VI	RNA (single-stranded, + sense, DNA intermediate)	Retroviruses (HIV)
VII	DNA (double-stranded, DNA intermediate)	Hepadnaviruses (hepatitis B)

viruses that have evolved to be 'virulent', that is, virus that will replicate and kill the host cell, some of the genes of the virus are expressed immediately and their translation into proteins results in the beginning of the intracellular replication phase of the virus. The usual genetic program of such viruses (e.g., bacteriophage T4, herpes simplex virus) is to direct the synthesis of viral DNA and when there are many copies of the viral genome, then to express the genes for the structural components of the virus, for example, the capsid (coat) proteins, and the envelope proteins, in the case of enveloped viruses. Once a large number of viral genomes have been produced and once a sufficiently large pool of virus structural proteins has accumulated, virus assembly is possible. When a large number of mature virus particles have accumulated, the cell often bursts because of disrupted metabolism or is lysed from within by specific lysis enzymes. This process releases the progeny virus in a 'burst' of hundreds to thousands of new infectious virus particles able to initiate another round of infection. Figure 3 shows in diagrammatic outline the various steps in the infectious cycle of a specific virus, the influenza A virus.

Some viruses, however, do not undergo this 'lytic cycle' but instead have evolved to enter into a symbiotic relationship with the host cell by promoting the integration of the viral genome into the host cell chromosome in a 'repressed' or latent state. Because these latent viral genomes can usually be reactivated by some conditions to full virus replication and gene expression with consequent virus production, cell lysis, and bursts of new virus particles, they are often called 'lysogenic' viruses (this terminology is most commonly used for bacterial viruses). The processes by which the infecting viral genome is integrated into the host chromosome is quite complex and differs for RNA- and DNA-containing viruses.
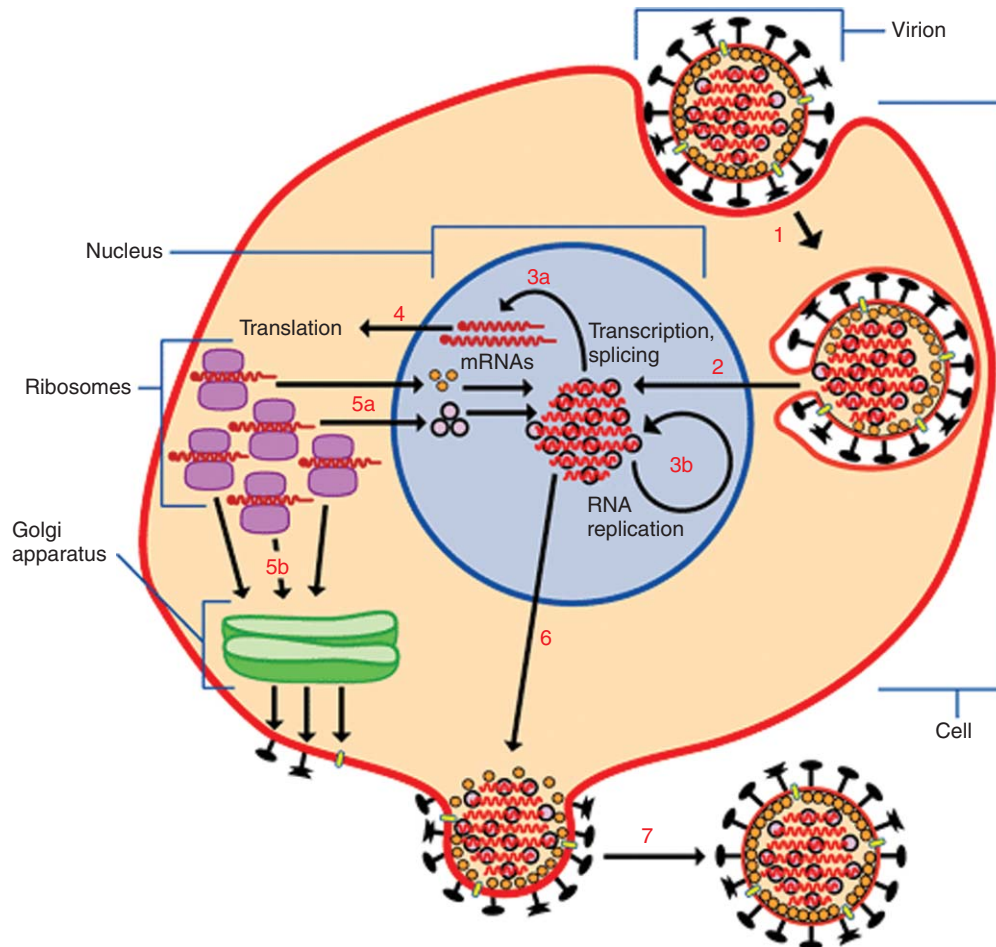
Figure 3 Diagrammatic representation of influenza virus replication cycle. Virus entry, uncoating, transcription, RNA replication, mRNA translation, protein processing in the Golgi apparatus, insertion of viral proteins into the infected cell membrane, and final virus assembly and budding are illustrated. Reproduced from NCBI, in the public domain.

Modes of Entry and Transmission of Viruses

At the organismal level, virus infection is related to the physiology of a particular organism. In plants, for example, virus entry and release is often promoted by cellular injury and the virus is carried through the vascular system of the plant. In animals, there are many routes of entry, each exploited by different viruses. Common routes of infection are through the respiratory tract, the gastrointestinal tract, directly into the bloodstream, and by venereal contact.

Airborne viruses, such as the common cold virus (rhinoviruses), measles virus, and influenza virus, enter the body through small droplets (aerosols) and the virus attaches to and penetrates the cells lining the surface of the respiratory tract. These viruses often replicate in the cells of the respiratory tract and cause these cells to initiate a local inflammatory response that results in many of the symptoms of these viral diseases. Viruses present in the respiratory secretions can be subsequently transmitted by coughing, sneezing, and other similar modes of spread to other susceptible individuals. Some viruses spread from these localized infections to the bloodstream (viremia – virus in the blood), which allows for dissemination throughout the body.

Other viruses, such as polioviruses, enter the body through ingested material (contaminated food and water), and because of their structural features they are able to survive the digestive actions of the stomach and intestines and then to infect cells of the intestinal tract. These viruses may cause local inflammation, such as various enteric fevers (various diarrheas, e.g.), or they may replicate and then be shed into the bloodstream for dissemination to other parts of the body. Poliovirus, for example, initially replicates in the gut with few symptoms but is borne by the blood to the central nervous system, where it infects specific cells to cause devastating effects. The viruses that replicate in the intestinal cells are often shed into the feces and passed on to others by the fecal–oral route of transmission.

Some viruses are efficiently transmitted by direct inoculation into the bloodstream. In nature these viruses often require insect vectors to effect this transmission. Well-known examples include the yellow fever virus, dengue fever virus, and the encephalitis viruses, all transmitted by blood-feeding arthropods such as mosquitoes and ticks. Many viruses, for example, hepatitis B virus and HIV, although not transmitted by direct inoculation into the bloodstream in nature, can be transmitted by blood inoculation through medical procedures (transfusions, injections) or trauma. The venereal route of transmission is also utilized by some viruses. Well-known examples include the herpes simplex virus type 2, certain human papillomavirus (HPV) strains, and HIV.

After the local infection of susceptible cells with an initial round of viral multiplication, the initial viremia (primary viremia) serves to transport the virus to specific target cells or tissues in the body where the virus may replicate further, giving rise to additional virus in the blood (secondary viremia). Often, the immunological responses of the individual are provoked only by massive secondary viremia because the primary viremia may be inadequate in duration or intensity to do so.

Certain unusual modes of virus transmission have been observed, for example, in rabies, where the virus enters the tissues by trauma, often an animal bite, whereupon it enters the peripheral nerve cells and the virus migrates along the nerves to the central nervous system where it then replicates and causes damage. The virus can find its way, perhaps by the bloodstream or by the nerves, to the salivary glands where it can be excreted through the saliva and thereby transmitted to another susceptible host. Table 2 summarizes the modes of transmission and average incubation periods of some common human pathogenic viruses.

Responses to Virus Infections

Most virus infections are asymptomatic or, at most, cause such common and inconsequential symptoms that the infection passes unnoticed. Analysis of the antiviral antibodies in normal human serum shows that we have many antibodies, which indicates a history of prior encounters with viruses of which we have been unaware. For example, approximately 85% of adults in the United States harbor latent Epstein–Barr virus (a herpesvirus) in their lymphocytes. Likewise, many individuals who cannot recall having fever blisters carry herpes simplex virus type 1 in a latent form in their bodies. Infection with poliovirus in infancy often provokes only a mild, self-limited febrile illness in contrast to the devastating infections of the central nervous system seen upon primary infection in older children and adults.

The first cellular response to infection by many viruses seems to be the induction of interferon-specific proteins that are secreted by the infected cells and function to render neighboring cells more resistant to virus replication. The interferon response aims at producing local resistance to virus infection so as to limit the spread of the virus. This response is immediate and occurs within hours to days of the initial infection. Some side effects of the production of interferon include fever as well as the general malaise associated with many virus infections.

The viremic phase of virus infection allows the cells of the immune system to detect and respond to the presence of virus. If the virus is sufficiently immunogenic (recognized as foreign to the body), the immune system produces a primary antibody response in about a week. This primary immune response results in the production of long-lasting memory-B-lymphocytes, which can be

Table 2 Routes of infection and incubation periods of some common human viral infections

Virus	Routes of infection	Average incubation period
Epstein–Barr Virus	Saliva, respiratory	30–50 days
Hepatitis A virus	Orofecal, some body fluids	15–45 days
Hepatitis C virus	Some body fluids	Years
Hepatitis B virus	Some body fluids	1–6 months
Herpes simplex virus	Skin contact	1–2 weeks
Human papilloma virus	Skin contact	Months to years
Human immunodeficiency virus	Blood, some other body fluids	0–10 years
Influenza virus	Respiratory	2–3 days
Measles virus	Respiratory	8–12 days
Mumps virus	Respiratory, direct contact	12–24 days
Norwalk virus	Orofecal	4–48 h
Parvovirus B19 (fifth disease)	Respiratory	4–20 days
Poliovirus	Orofecal	5–35 days
Rabies virus	Animal bite	3–7 weeks
Rhinovirus (common cold)	Respiratory	3–7 days
SARS coronavirus	Respiratory, direct contact	2–10 days
West Nile virus	Mosquito bite, blood	Variable
Yellow fever virus	Mosquito bite	3–6 days

activated later by subsequent exposure to the same virus to provide a more rapid and more intense secondary immune response. This immunological memory is the primary reason that we usually are more or less immune for life once we have survived a particular virus infection.

The specific antibodies produced by the primary immune response can combine with the virus in the blood and result in circulating immune complexes that facilitate the destruction and clearance of the virus from the body. Such circulating immune complexes, however, also result in activation of some other processes such as the production of fever. Some viruses, such as the herpes simplex virus, cause local immunological reactions of such intensity that much of the inflammation and pain at the site of the infection is the result of the action of the immune cells rather than the destruction of the infected cells by the virus alone. Another unusual immune reaction is observed in the case of infection by Epstein–Barr virus. This virus enters certain cells of the B-lymphocyte lineage and results in a growth transformation of these cells, providing them with the potential for unlimited cell division ('immortalization', the first step in the formation of a B-cell malignancy). The normal immune surveillance mechanism that involves the T-lymphocyte system is activated to respond to these transformed B-cells and kill them. The process of T-cell activation gives rise to a large population of unusual T-cells, and it was this population of activated T-cells (large cells with a large nucleus, initially thought to be unusual monocytes) that gave Epstein–Barr virus infection its name: infectious mononucleosis, or 'Mono'. That is, it was named for the cells that reacted to the virus infection rather than for the virus-infected cells themselves.

Some viruses that enter into a latent or symbiotic state within the host cell can provoke the cell to behave in abnormal ways. Many such viruses carry extra genes that regulate cell division and can result in the malignant transformation of the cell to produce a cancer. These cancer-causing viruses (oncogenic viruses) are a special group of viruses that are of great current interest for both their special biology and their practical importance.

Outcomes of Virus Infections

The usual outcome of a virus infection is recovery of the organism with long-lasting immunity. After the initial local multiplication, viremic phase, and immunological responses, the virus is eliminated from the body and the memory cells of the immune system stand ready to guard against another infection. It is this sort of immunity that is produced by successful iatrogenic virus infection called vaccination. If, however, the immune system is compromised, the virus replication overwhelms the immune system, or the virus manages to get into cells or tissues that are hidden from the immune system, the virus may destroy critical tissues or organs and result in serious illness or death.

Some viruses, after the primary infection, may enter into a latent form and be asymptomatic until periodic reactivation at later times. The herpes group of viruses are especially prone to such latent infections. Initial infection, such as with the chicken pox virus, gives rise to the viremia and generalized skin rash. The virus then enters into a latent infection of the dorsal root ganglia of the spinal cord and later, at times of lowered immunity, the virus may replicate and cause lesions in the skin along the local distribution of a particular spinal nerve, giving rise to the condition called 'shingles'. Both chicken pox and shingles are disease manifestations of the same virus, the varicella zoster virus.

A few viruses are known that may be present in the body and replicate at such a low level and be relatively benign yet escape the immune system and thereby establish a true persistent infection. The early phase of HIV infection seems to be an example of this mode of virus–host interaction.

Varying degrees of cell proliferation may result from latent virus infections. These outcomes can result in local, limited growths such as viral warts and the small skin lesions caused by the virus of molluscum contagiosum, or can lead, in steps not yet fully understood, to malignant diseases such as Burkitt's lymphoma, nasopharyngeal carcinoma, Kaposi's sarcoma, and some types of cervical cancer.

Viral Virulence

Viruses vary in their ability to infect and cause changes in their host cells. Even the specific cell type (tropism) may vary. These variations may be because of heritable properties (genetic mutations) or because of properties acquired from the most recent host, for example, viral envelope structures of cellular origin (pseudotype variations). Viruses are said to be virulent if they have a high propensity to cause disease or other evidence of infection in the specific test organism. Thus, a virus stock may be virulent for one species and avirulent for another. Repeated selection for virulence in one species may select for mutations that render the virus less virulent (attenuated) in another. This principle has been widely exploited to produce vaccine strains of virus.

Some virulence may be related to the interaction of essential viral functions with related cellular functions. Other aspects of virulence may be simply a matter of virus interactions with the specific cell receptors for the virus. In certain cases, the genes of the virus that are known to be required for certain functions can be deleted or modified to make avirulent variants. Thus, nononcogenic

forms of some retroviruses can be constructed by deletion of their specific viral oncogene.

Virulence is a concept reserved for the capacity of a virus to produce an effect, not for the ability of the virus to survive inactivation. Some viruses are especially sensitive to drying, for example, and others are sensitive to organic solvents. These viruses may be virulent, even though they are, in some sense, very fragile and easily killed.

Antiviral Therapy and Prophylaxis

Because virus infections rely on many pathways and processes of the host cell, there are very few unique virus-specific steps in the infectious process that provide vulnerable points of attack for antiviral drugs or treatments. Viruses with RNA genomes, however, differ significantly from the host cell with regard to genome replication and, thus, antiviral agents have been designed to target this unique step in virus infection. Chemical analogues of specific RNA precursors can inhibit the RNA replication process. These nucleoside analogues, such as azidothymidine (AZT) and dideoxycytidine (ddC), have been effective in treating HIV infections. Other drugs such as nevirapine also target the RNA replication step by direct inhibition of the replication enzyme, reverse transcriptase, of HIV.

The prototype antiviral drugs have been analogues of DNA precursors such as the halogenated pyrimidines (iodo-deoxyuridine and bromo-deoxyuridine) and the sugar ring-opened purines (acycloguanosine and ganci-clovir) used against viruses in the herpes group (herpes simplex, cytomegalovirus). These viruses encode a specific enzyme, thymidine kinase, which can activate these drugs to their toxic form. Uninfected cells lack this virus-specific kinase and hence are not harmed by the inactive prodrug form of these compounds.

The best approach to controlling virus infection, however, is by active immunization. The first such success with this method was the well-known discovery of inoculation, and later, vaccination for small pox. Many vaccines have been developed that are highly effective in preventing or mitigating viral diseases, for example, rabies, measles, yellow fever, chicken pox, rubella, and influenza to name a few. This immunological approach has recently been extended to prevention of infection by human papilloma viruses with the consequent prevention of one of the long-term effects of such virus infection, cervical cancer. For malignancies that are caused or initiated by virus infection, this approach is highly promising.

See also: Antiviral Agents; Bacteriophage (overview); Evolution, Viral; Plant Pathogens: DNA viruses; Plant Pathogens: RNA viruses; Vaccines, Viral; Viroids/Virusoids; Viruses, Environmental

Further Reading

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