Antiviral drug

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Antiviral drugs are a class of medication used specifically for treating viral infections rather than bacterial ones.[1] Most antivirals are used for specific viral infections, while a **broad-spectrum antiviral** is effective against a wide range of viruses.[2] Unlike most antibiotics, antiviral drugs do not destroy their target pathogen; instead they inhibit their development.

Antiviral drugs are one class of antimicrobials, a larger group which also includes antibiotic (also termed antibacterial), antifungal and antiparasitic drugs,[3] or antiviral drugs based on monoclonal antibodies.[4] Most antivirals are considered relatively harmless to the host, and therefore can be used to treat infections. They should be distinguished from viricides, which are not medication but deactivate or destroy virus particles, either inside or outside the body. Natural antivirals are produced by some plants such as eucalyptus.[5]

Contents

Medical uses

Most of the antiviral drugs now available are designed to help deal with HIV, herpes viruses, the hepatitis B and C viruses, and influenza A and B viruses. Researchers are working to extend the range of antivirals to other families of pathogens.

Designing safe and effective antiviral drugs is difficult, because viruses use the host's cells to replicate. This makes it difficult to find targets for the drug that would interfere with the virus without also harming the host organism's cells. Moreover, the major difficulty in developing vaccines and anti-viral drugs is due to viral variation.

The emergence of antivirals is the product of a greatly expanded knowledge of the genetic and molecular function of organisms, allowing biomedical researchers to understand the structure and function of viruses, major advances in the techniques for finding new drugs, and the intense pressure placed on the medical profession to deal with the human immunodeficiency virus (HIV), the cause of the deadly acquired immunodeficiency syndrome (AIDS) pandemic.

The first experimental antivirals were developed in the 1960s, mostly to deal with herpes viruses, and were found using traditional trial-and-error drug discovery methods. Researchers grew cultures of cells and infected them with the target virus. They then introduced into the cultures chemicals which they thought might inhibit viral activity, and observed whether the level of virus in the cultures rose or fell. Chemicals that seemed to have an effect were selected for closer study.

This was a very time-consuming, hit-or-miss procedure, and in the absence of a good knowledge of how the target virus worked, it was not efficient in discovering effective antivirals which had few side effects. Only in the 1980s, when the full genetic sequences of viruses began to be unraveled, did researchers begin to learn how viruses worked in detail, and exactly what chemicals were needed to thwart their reproductive cycle.

Virus life cycle

Viruses consist of a genome and sometimes a few enzymes stored in a capsule made of protein (called a capsid), and sometimes covered with a lipid layer (sometimes called an 'envelope'). Viruses cannot reproduce on their own, and instead propagate by subjugating a host cell to produce copies of themselves, thus producing the next generation.

Researchers working on such "rational drug design" strategies for developing antivirals have tried to attack viruses at every stage of their life cycles. Some species of mushrooms have been found to contain multiple antiviral chemicals with similar synergistic effects.[6] Viral life cycles vary in their precise details depending on the type of virus, but they all share a general pattern:

- Attachment to a host cell.
- Release of viral genes and possibly enzymes into the host cell.
- Replication of viral components using host-cell machinery.
- Assembly of viral components into complete viral particles.
- Release of viral particles to infect new host cells.

Limitations and Policy Implications

Several factors including cost, vaccination stigma, and acquired resistance limit the effectiveness of antiviral therapies. These issues are explored via a health policy perspective.

Research and prices

Rising Costs

Cost is an important factor that limits access to antivirals therapies in the United States and internationally.[7][8][9] The recommended treatment regimen for hepatitis C virus infection, for example, includes sofosbuvir-velpatasvir (Epclusa) and ledipasvir-sofosbuvir (Harrvoni).[10] A twelve week supply of these drugs amount to $113,400 and $89,712, respectively.[11][12] These drugs can be manufactured generically at a cost of $100 - $250 per 12 week treatment.[13] Pharmaceutical companies attribute the majority of these costs to research and development expenses. On average, the research and development costs required to bring a new drug to market amount to $17.2 billion.[14] However, critics point to monopolistic market conditions that allow manufacturers to increase prices without facing a reduction in sales, leading to higher profits at patient's expense.[15] Intellectual property laws, anti-importation policies,[16] and the slow pace of FDA review limit alternative options. Recently, private-public research partnerships have been established to promote expedited, cost-effective research.[17]

Vaccinations and stigma

Vaccines and population health

While most antivirals treat viral infection, vaccines are a preemptive first line of defense against pathogens. Vaccination involves the introduction (i.e. via injection) of a small amount of typically inactivated or attenuated antigenic material to stimulate an individual’s immune system. The immune system responds by developing white blood cells to specifically combat the introduced pathogen, resulting in adaptive immunity.[18] Vaccination in a population results in herd immunity and greatly improved population health, with significant reductions in viral infection and disease.[19]

Vaccination policy

Vaccination policy in the United States consists of public and private vaccination requirements. For instance, public schools require students to receive vaccinations (termed “vaccination schedule”) for viruses and bacteria such as diphtheria, pertussis, and tetanus (DTaP), measles, mumps, rubella (MMR), varicella (chickenpox), hepatitis B, rotavirus, polio, and more. Private institutions might require annual influenza vaccination. The Center for Disease Control and Prevention has estimated that routine immunization of newborns prevents about 42,000 deaths and 20 million cases of disease each year, saving about $13.6 billion.[20]

Vaccination controversy

Despite their successes, there is plenty of stigma surrounding vaccines that cause people to be incompletely vaccinated. These “gaps” in vaccination result in unnecessary infection, death, and costs.[21] There are two major reasons for incomplete vaccination:

1. Vaccines, like other medical treatments, have a risk of causing serious complications in some individuals (i.e. severe allergic reactions). While these complications are less common than the risks faced when not vaccinated, negative media coverage can instill fear in a population.[22] Other controversies involve the association of autism with vaccines, although the Center for Disease Control and Prevention,[23] Institute of Medicine,[24] and National Health Service[25] regard this link as unfounded.
2. Low vaccine-preventable disease rates as a result of herd immunity also make vaccines seem unnecessary and leave many unvaccinated.[26][27]

Although the American Academy of Pediatrics endorses universal immunization,[28] they note that physicians should respect parents’ refusal to vaccinate their children after sufficient advising and provided the child does not face a significant risk of infection. Parents can also cite religious reasons to avoid public school vaccination mandates, but this reduces herd immunity and increases risk of viral infection.[19]

Limitations of vaccines

Vaccines bolster the body's immune system to better attack viruses in the "complete particle" stage, outside of the organism's cells. They traditionally consist of an attenuated (a live weakened) or inactivated (killed) version of the virus. These vaccines can, in very rare cases, harm the host by inadvertently infecting the host with a full-blown viral occupancy. Recently "subunit" vaccines have been devised that consist strictly of protein targets from the pathogen. They stimulate the immune system without doing serious harm to the host. In either case, when the real pathogen attacks the subject, the immune system responds to it quickly and blocks it.

Vaccines are very effective on stable viruses, but are of limited use in treating a patient who has already been infected. They are also difficult to successfully deploy against rapidly mutating viruses, such as influenza (the vaccine for which is updated every year) and HIV. Antiviral drugs are particularly useful in these cases.

Public policy

Use and Distribution

Guidelines regarding viral diagnoses and treatments change frequently and limit quality care.[29] Even when physicians diagnose older patients with influenza, use of antiviral treatment can be low.[30] Provider knowledge of antiviral therapies can improve patient care, especially in geriatric medicine. Furthermore, in local health departments (LHDs) with access to antivirals, guidelines may be unclear, causing delays in treatment.[31] With time-sensitive therapies, delays could lead to lack of treatment. Overall, national guidelines regarding infection control and management standardize care and improve patient and health care worker safety. Guidelines such as those provided by the Centers for Disease Control and Prevention (CDC) during the 2009 flu pandemic caused by the H1N1 virus, recommend antiviral treatment regimens, clinical assessment algorithms for coordination of care, and antiviral chemoprophylaxis guidelines for exposed persons, among others.[32] Roles of pharmacists and pharmacies have also expanded to meet the needs of public during public health emergencies.[33]

Stockpiling

Public Health Emergency Preparedness initiatives are managed by the CDC via the Office of Public Health Preparedness and Response.[34] Funds aim to support communities in preparing for public health emergencies, including pandemic influenza. Also managed by the CDC, the Strategic National Stockpile (SNS) consists of bulk quantities of medicines and supplies for use during such emergencies.[35] Antiviral stockpiles prepare for shortages of antiviral medications in cases of public health emergencies. During the H1N1 pandemic in 2009-2010, guidelines for SNS use by local health departments was unclear, revealing gaps in antiviral planning.[31] For example, local health departments that received antivirals from the SNS did not have transparent guidance on the use of the treatments. The gap made it difficult to create plans and policies for their use and future availabilities, causing delays in treatment.

Anti-viral targeting

The general idea behind modern antiviral drug design is to identify viral proteins, or parts of proteins, that can be disabled. These "targets" should generally be as unlike any proteins or parts of proteins in humans as possible, to reduce the likelihood of side effects. The targets should also be common across many strains of a virus, or even among different species of virus in the same family, so a single drug will have broad effectiveness. For example, a researcher might target a critical enzyme synthesized by the virus, but not the patient, that is common across strains, and see what can be done to interfere with its operation.

Once targets are identified, candidate drugs can be selected, either from drugs already known to have appropriate effects, or by actually designing the candidate at the molecular level with a computer-aided design program.

The target proteins can be manufactured in the lab for testing with candidate treatments by inserting the gene that synthesizes the target protein into bacteria or other kinds of cells. The cells are then cultured for mass production of the protein, which can then be exposed to various treatment candidates and evaluated with "rapid screening" technologies.

Approaches by life cycle stage

Before cell entry

One anti-viral strategy is to interfere with the ability of a virus to infiltrate a target cell. The virus must go through a sequence of steps to do this, beginning with binding to a specific "receptor" molecule on the surface of the host cell and ending with the virus "uncoating" inside the cell and releasing its contents. Viruses that have a lipid envelope must also fuse their envelope with the target cell, or with a vesicle that transports them into the cell, before they can uncoat.

This stage of viral replication can be inhibited in two ways:

1. Using agents which mimic the virus-associated protein (VAP) and bind to the cellular receptors. This may include VAP anti-idiotypic antibodies, natural ligands of the receptor and anti-receptor antibodies.
2. Using agents which mimic the cellular receptor and bind to the VAP. This includes anti-VAP antibodies, receptor anti-idiotypic antibodies, extraneous receptor and synthetic receptor mimics.

This strategy of designing drugs can be very expensive, and since the process of generating anti-idiotypic antibodies is partly trial and error, it can be a relatively slow process until an adequate molecule is produced.

Entry inhibitor

A very early stage of viral infection is viral entry, when the virus attaches to and enters the host cell. A number of "entry-inhibiting" or "entry-blocking" drugs are being developed to fight HIV. HIV most heavily targets the immune system's white blood cells known as "helper T cells", and identifies these target cells through T-cell surface receptors designated "CD4" and "CCR5". Attempts to interfere with the binding of HIV with the CD4 receptor have failed to stop HIV from infecting helper T cells, but research continues on trying to interfere with the binding of HIV to the CCR5 receptor in hopes that it will be more effective.

HIV infects a cell through fusion with the cell membrane, which requires two different cellular molecular participants, CD4 and a chemokine receptor (differing depending on the cell type). Approaches to blocking this virus/cell fusion have shown some promise in preventing entry of the virus into a cell. At least one of theses entry inhibitors—a biomimetic peptide marketed under the brand name Fuzeon—has received FDA approval and has been in use for some time. Potentially, one of the benefits from the use of an effective entry-blocking or entry-inhibiting agent is that it potentially may not only prevent the spread of the virus within an infected individual but also the spread from an infected to an uninfected individual.

One possible advantage of the therapeutic approach of blocking viral entry (as opposed to the currently dominant approach of viral enzyme inhibition) is that it may prove more difficult for the virus to develop resistance to this therapy than for the virus to mutate or evolve its enzymatic protocols.

Uncoating inhibitor

Inhibitors of uncoating have also been investigated.[36][37]

Amantadine and rimantadine have been introduced to combat influenza. These agents act on penetration and uncoating.[38]

Pleconaril works against rhinoviruses, which cause the common cold, by blocking a pocket on the surface of the virus that controls the uncoating process. This pocket is similar in most strains of rhinoviruses and enteroviruses, which can cause diarrhea, meningitis, conjunctivitis, and encephalitis.

Some scientists are making the case that a vaccine against rhinoviruses, the predominant cause of the common cold, is achievable. Vaccines that combine dozens of varieties of rhinovirus at once are effective in stimulating antiviral antibodies in mice and monkeys, researchers have reported in Nature Communications in 2016.

The quest for a vaccine against rhinoviruses may have seemed quixotic, because there are more than 100 varieties circulating around the world. But the immune system can handle the challenge.

Rhinoviruses are the most common cause of the common cold; other viruses such as respiratory syncytial virus, parainfluenza virus and adenoviruses can cause them too. Rhinoviruses also exacerbate asthma attacks. Although rhinoviruses come in many varieties, they do not drift to the same degree that influenza viruses do. A mixture of 50 inactivated rhinovirus types should be able to stimulate neutralizing antibodies against all of them to some degree.

During viral synthesis

A second approach is to target the processes that synthesize virus components after a virus invades a cell.

Reverse transcription

One way of doing this is to develop nucleotide or nucleoside analogues that look like the building blocks of RNA or DNA, but deactivate the enzymes that synthesize the RNA or DNA once the analogue is incorporated. This approach is more commonly associated with the inhibition of reverse transcriptase (RNA to DNA) than with "normal" transcriptase (DNA to RNA).

The first successful antiviral, acyclovir, is a nucleoside analogue, and is effective against herpesvirus infections. The first antiviral drug to be approved for treating HIV, zidovudine (AZT), is also a nucleoside analogue.

An improved knowledge of the action of reverse transcriptase has led to better nucleoside analogues to treat HIV infections. One of these drugs, lamivudine, has been approved to treat hepatitis B, which uses reverse transcriptase as part of its replication process. Researchers have gone further and developed inhibitors that do not look like nucleosides, but can still block reverse transcriptase.

Another target being considered for HIV antivirals include RNase H – which is a component of reverse transcriptase that splits the synthesized DNA from the original viral RNA.

On 10 August 2011 researchers at MIT announced the publication[39] of a new method of inhibiting RNA, the process selectively affected infected cells. The team named the process "Double-stranded RNA Activated Caspase Oligomerizer" (DRACO). According to the lead researcher "In theory, [DRACO] should work against all viruses."[40]

Integrase

Another target is integrase, which integrate the synthesized DNA into the host cell genome.

Transcription

Once a virus genome becomes operational in a host cell, it then generates messenger RNA (mRNA) molecules that direct the synthesis of viral proteins. Production of mRNA is initiated by proteins known as transcription factors. Several antivirals are now being designed to block attachment of transcription factors to viral DNA.

Translation/antisense

Genomics has not only helped find targets for many antivirals, it has provided the basis for an entirely new type of drug, based on "antisense" molecules. These are segments of DNA or RNA that are designed as complementary molecule to critical sections of viral genomes, and the binding of these antisense segments to these target sections blocks the operation of those genomes. A phosphorothioate antisense drug named fomivirsen has been introduced, used to treat opportunistic eye infections in AIDS patients caused by cytomegalovirus, and other antisense antivirals are in development. An antisense structural type that has proven especially valuable in research is morpholino antisense.

Morpholino oligos have been used to experimentally suppress many viral types:

- caliciviruses[41]
- flaviviruses (including WNV)[42]
- dengue[43]
- HCV[44]
- coronaviruses[45]

Translation/ribozymes

Yet another antiviral technique inspired by genomics is a set of drugs based on ribozymes, which are enzymes that will cut apart viral RNA or DNA at selected sites. In their natural course, ribozymes are used as part of the viral manufacturing sequence, but these synthetic ribozymes are designed to cut RNA and DNA at sites that will disable them.

A ribozyme antiviral to deal with hepatitis C has been suggested,[46] and ribozyme antivirals are being developed to deal with HIV.[47] An interesting variation of this idea is the use of genetically modified cells that can produce custom-tailored ribozymes. This is part of a broader effort to create genetically modified cells that can be injected into a host to attack pathogens by generating specialized proteins that block viral replication at various phases of the viral life cycle.

Protein processing and targeting

Interference with post translational modifications or with targeting of viral proteins in the cell is also possible.[48]

Protease inhibitors

Some viruses include an enzyme known as a protease that cuts viral protein chains apart so they can be assembled into their final configuration. HIV includes a protease, and so considerable research has been performed to find "protease inhibitors" to attack HIV at that phase of its life cycle.[49] Protease inhibitors became available in the 1990s and have proven effective, though they can have unusual side effects, for example causing fat to build up in unusual places.[50] Improved protease inhibitors are now in development.

Protease inhibitors have also been seen in nature. A protease inhibitor was isolated from the Shiitake mushroom (*Lentinus edodes*).[51] The presence of this may explain the Shiitake mushrooms noted antiviral activity *in vitro*.[52]

Assembly

Rifampicin acts at the assembly phase.[53]

Release phase

The final stage in the life cycle of a virus is the release of completed viruses from the host cell, and this step has also been targeted by antiviral drug developers. Two drugs named zanamivir (Relenza) and oseltamivir (Tamiflu) that have been recently introduced to treat influenza prevent the release of viral particles by blocking a molecule named neuraminidase that is found on the surface of flu viruses, and also seems to be constant across a wide range of flu strains.

Immune system stimulation

A second category of tactics for fighting viruses involves encouraging the body's immune system to attack them, rather than attacking them directly. Some antivirals of this sort do not focus on a specific pathogen, instead stimulating the immune system to attack a range of pathogens.

One of the best-known of this class of drugs are interferons, which inhibit viral synthesis in infected cells.[54] One form of human interferon named "interferon alpha" is well-established as part of the standard treatment for hepatitis B and C,[55] and other interferons are also being investigated as treatments for various diseases.

A more specific approach is to synthesize antibodies, protein molecules that can bind to a pathogen and mark it for attack by other elements of the immune system. Once researchers identify a particular target on the pathogen, they can synthesize quantities of identical "monoclonal" antibodies to link up that target. A monoclonal drug is now being sold to help fight respiratory syncytial virus in babies,[56] and antibodies purified from infected individuals are also used as a treatment for hepatitis B.[57]

Acquired resistance

Antiviral resistance can be defined by a decreased susceptibility to a drug through either a minimally effective, or completely ineffective, treatment response to prevent associated illnesses from a particular virus.[58] The issue inevitably remains a major obstacle to antiviral therapy as it has developed to almost all specific and effective antimicrobials, including antiviral agents.[59]

The Centers for Disease Control and Prevention (CDC) inclusively recommends those six months and older to get a yearly vaccination to protect from influenza A viruses (H1N1) and (H3N2) and up to two influenza B viruses (depending on the vaccination).[58] Comprehensive protection starts by ensuring vaccinations are current and complete. The three FDA-approved neuraminidase antiviral flu drugs available in the United States, recommended by the CDC, include: oseltamivir (Tamiflu®), zanamivir (Relenza®), and peramivir (Rapivab®).[58]

A study published in 2009 in Nature Biotechnology emphasized the urgent need for augmentation of oseltamivir (Tamiflu®) stockpiles with additional antiviral drugs including zanamivir (Relenza®). This finding was based on a performance evaluation of these drugs supposing the 2009 H1N1 'Swine Flu' neuraminidase (NA) were to acquire the Tamiflu-resistance (His274Tyr) mutation which is currently widespread in seasonal H1N1 strains.[60]

Origin of antiviral resistance

The genetic makeup of viruses is constantly changing and therefore may alter the virus resistant to the treatments currently available.[61] Viruses can become resistant through spontaneous or intermittent mechanisms throughout the course of an antiviral treatment.[58] Immunocompromised patients, more often than immunocompetent patients, hospitalized with pneumonia are at the highest risk of developing oseltamivir resistance during treatment.[58] Subsequent to exposure to someone else with the flu, those who received oseltamivir for “post-exposure prophylaxis” are also at higher risk of resistance.[62]

Detection of antiviral resistance

National and international surveillance is performed by the CDC to determine effectiveness of the current FDA-approved antiviral flu drugs.[58] Public health officials use this information to make current recommendations about the use of flu antiviral medications. WHO further recommends in-depth epidemiological investigations to control potential transmission of the resistant virus and prevent future progression.[63] As novel treatments and detection techniques to antiviral resistance are enhanced so can the establishment of strategies to combat the inevitable emergence of antiviral resistance.[64]

See also

- Antiretroviral drug (especially HAART for HIV)
- Discovery and development of CCR5 receptor antagonists (for HIV)
- Monoclonal antibody
- List of antiviral drugs
- Virucide
- Antiprion drugs and Astemizole
- Discovery and development of NS5A inhibitors

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