

## Retrovirus

### I. Introduction

Retrovirus, any virus belonging to the family Retroviridae, whose members share a unique method of *replicating* (copying) themselves when they infect living cells. Retroviruses store their genetic information in molecules of ribonucleic acid (RNA). However, unlike other RNA viruses, retroviruses use RNA as a *template* (master pattern) for forming deoxyribonucleic acid (DNA), the genetic material that puts viral replication instructions into effect. This process, called reverse transcription, is the exact opposite of the normal flow of genetic information in living things in which DNA serves as the template for RNA formation (*see* Genetics).

Retroviruses affect a wide range of animals, although the best-known types are those that target vertebrates. Some retroviruses are harmless, but many can cause malignant transformation—a genetic change that makes healthy cells cancerous. Disease-forming retroviruses can cause diseases such as leukemia (cancer of the blood) in mammals and malignant tumors and other disorders in birds. From a human perspective, by far the most significant retroviruses are a small group called lentiviruses, which include human immunodeficiency virus (HIV), the virus that causes acquired immunodeficiency syndrome (AIDS).

### II. Retrovirus Structure

On average, retroviruses are about 90 nanometers (nm, about 0.000004 in) across, which means they are so small that they can only be seen with an electron microscope. Retroviruses consist of a flexible outer membrane called the envelope that surrounds a protein case known as the capsid. The envelope is studded with glycoproteins, chemical receptors that enable the virus to lock on to target cells.

The capsid's hollow interior contains two identical strands of RNA. These RNA strands make up the virus's genetic program and store all the instructions needed to replicate the virus once it has infected a host cell. Retroviruses also contain molecules of an enzyme called reverse transcriptase. When a virus infects a cell, reverse transcriptase copies the genetic instructions in the virus's RNA and uses it to build complementary strands of DNA.

In common with most viruses, retroviruses are highly selective about the hosts that they infect. For instance, HIV only causes disease in human cells, not the cells of other types of animals. Also like most viruses, retroviruses show no signs of life when they are isolated from living cells. Many retroviruses, including HIV, are relatively fragile. Their ability to infect cells lessens after prolonged exposure to the environment outside a host cell.

When retroviruses do infect a host cell, their mode of replication leads to frequent mutations—changes in the genetic makeup of viral offspring. These mutations enable viruses to evolve at a rapid rate. Genetic mutation is one of many reasons why retroviral infections are difficult to treat—medicines developed to combat one retrovirus with a specific genetic makeup are not effective against mutated offspring of that retrovirus.

### III. How Retroviruses Infect Organisms

A retroviral infection begins when a virus comes into contact with a suitable host cell. In the initial stages of an HIV infection, for example, the hosts are T cells—white blood cells that belong to the human immune system. Other common retrovirus targets include connective tissue cells, which form muscle, cartilage, or bone. On encountering a host cell, the retrovirus attaches itself to receptors on the surface of the host cell's membrane. In this two-way process, the retrovirus's glycoproteins and the host cell's receptors bind together, locking the virus in place. The outer envelope of the retrovirus then fuses with the host cell membrane, enabling the viral capsid to enter the cell itself.

Once inside the cell, the capsid opens, releasing RNA and reverse transcriptase into the cell's cytoplasm, a watery fluid that is rich in proteins and other chemicals. Using the cell's chemical resources, reverse transcriptase builds up a double-stranded DNA molecule that mirrors the information stored in the viral RNA. Initially, this DNA molecule is circular, but it is later spliced apart and inserted into the DNA of the host cell. From this moment onward, the viral DNA, known as a provirus, behaves like the host cell's own genes. The only difference is that the provirus contains instructions for assembling replicated viruses, rather than instructions for building or controlling a living cell.

As viral replication proceeds, the provirus directs the host cell to manufacture all the parts needed for more viruses, including capsids and viral RNA. These viral parts spontaneously self-assemble to form new viruses, and the new viruses migrate toward the exterior of the cell. The newly formed viruses bud away from the host cell, taking with them small areas of the cell membrane, which the viruses use to form outer envelopes. The host cell may survive this viral breakout, but in many infections it becomes so weakened that it dies. As viruses replicate and infect more cells, the number of cell deaths lead to tissue destruction and disease.

### IV. Retroviral Diseases

Retroviruses are not known to cause disease in plants, but they can produce a wide range of diseases in animals. In some retroviral infections, symptoms appear soon after an infection. In other infections the retrovirus genes become incorporated into a host cell's DNA and enter a *latent* (dormant) state until some unknown agent or event triggers them to churn out new viruses. In these cases, symptoms may not become apparent for months or even years after the initial infection. Once installed, a retrovirus can damage host cells directly, or it can trigger cancer by disabling the systems that normally prevent cells from multiplying out of control.

Scientists first linked retroviruses to cancer in 1911, when American researcher Francis Peyton Rous investigated a form of tumor that occurs in chickens. Rous passed a solution containing cells from these chicken tumors through a fine filter. The filter was intended to capture infectious agents, such as bacteria and protozoans. Rous discovered that the filtered fluid from these tumors was still infectious, indicating the presence of an unknown infectious agent. He correctly concluded that a virus, which is so small that it passes through filters, was responsible for the chicken tumor. Called Rous sarcoma virus, it was discovered many years later to be a member of

the retrovirus family. Retroviruses also cause cancer in a range of mammals: Cats and rodents are two well-studied examples.

In 1965, while studying the Rous sarcoma virus, American virologist Howard Temin made the surprising discovery that the virus's RNA inserted its own genes into the DNA of the host cell. In 1970 Temin and American molecular biologist David Baltimore, working independently, identified an RNA viral enzyme that copies genetic information to the host cell's DNA. The enzyme later became known as reverse transcriptase. The discovery of reverse transcriptase shed new light on how a retrovirus changes a normal cell to a cancer cell.

The first human retrovirus was discovered in 1980. Known as human T-cell leukemia virus (HTLV), it exists in two forms, HTLV-I and HTLV-II, and appears to cause certain types of lymphoma (cancer of the lymphatic system) and leukemia. In 1983 a third and quite different human retrovirus was discovered in patients suffering from a new immune deficiency disease (an illness that damages the immune system). Initially labeled HTLV-III, it was renamed HIV in 1986 and has since gained worldwide notoriety as the cause of AIDS.

HIV attacks the immune system of its host, undermining the very defenses that keep most viruses in check. One group of immune system T cells, called CD4 cells, are particularly vulnerable to HIV and become primary targets soon after an infection begins. Initially, the amount of virus in the blood, known as the viral load, quickly climbs as newly replicated viruses are produced and released from host cells. Following this stage, known as acute retroviral syndrome, the viral load drops, and it looks as though the immune system has brought the infection under control.

Despite these promising signs, the virus is never completely eliminated. From its hiding place inside T cells themselves, HIV continues its attack, destroying T cells. As T cells die, the immune system loses its ability to fight back. Once the T-cell count drops below a critical level, microorganisms that are normally kept in check by a healthy immune system can reproduce at a rapid rate. Without effective treatment, these opportunistic infections, rather than HIV itself, often have fatal results.

Retroviruses that cause immune deficiency diseases affect animals other than humans. This group of retroviruses includes feline immunodeficiency virus (FIV), which infects cats, and simian immunodeficiency virus (SIV), which attacks monkeys and apes. SIV is of particular interest in medicine as the origin of HIV. Scientists believe that SIV from a chimpanzee likely infected humans and underwent mutations to form HIV.

## V. How Scientists Use Retroviruses

Given its huge impact on human health worldwide, HIV is at the forefront of retroviral research. In the last decade, the development of effective new drug therapies has helped thousands of people survive an HIV infection, although often at the expense of unpleasant side effects. Preventing the spread of the virus has proved a more difficult challenge. Despite intensive research, a vaccine against HIV still does not exist, largely because the virus mutates at such a rapid rate.

As a group, however, retroviruses may one day play a more positive role in human health. In gene therapy scientists use genetically altered viruses to insert beneficial genes into human cells. Once in place, these genes can potentially correct inherited disorders, such as cystic fibrosis. Retroviruses make suitable delivery vehicles because they have the chemical apparatus that is needed to splice genes into particular target cells. Once the genes are inserted, they are copied and handed on each time the recipient cells divide.

Gene therapy is still in its experimental stages, and where retroviruses are concerned, there are a number of practical problems to overcome. One of these involves the space where the genetic information of a retrovirus is stored. This space is small, which means that there is a limited amount of storage space for the beneficial genes that are to be transferred. Another problem is safety, a prime consideration with agents associated with disease. Retroviruses used in gene therapy are genetically engineered to prevent them from replicating. However, there is still a slight possibility that these genetically engineered retroviruses may insert genes in an inappropriate region of DNA, triggering cancer or other problems. In early 2003, the United States Food and Drug Administration (FDA) halted 27 gene therapy clinical trials that used a retrovirus to ferry genes into blood-producing cells. Two children involved in the trials became ill with a condition resembling leukemia, and the FDA decided it was unsafe to continue using this procedure. Once safety problems can be overcome, however, the use of retroviruses in gene therapy may become a matter of routine.

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