Oncolytic Viruses

It may seem unlikely that viruses could a key tool for fighting cancer. Viruses are known for causing human suffering and death – from the common cold to HIV and influenza. Because viruses are so good at invading and taking over cells they have great potential as cancer killers. The following section gives some background on cancer killing (oncolytic; onco=tumor lysis=breaking down) viruses and describes some of the most promising ones.

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History of Viruses as a Treatment for Cancer

The idea of using viruses to treat cancer has been around a**very long** time.1 After it was observed that infection with viruses could lead to improvement (but not cure) of patients with leukemia, attempts were made to infect cancer patients with viruses to cure their cancers. While some responses were seen, the viral infections also caused illnesses and the death of some patients. Later trials, using viruses to treat cervical cancer, showed the ability of viruses to target cancer, but still did not extend the lives of the patients.

The first successes in virus cancer therapy were achieved in the 1970s using the mumps virus. Because mumps itself causes serious disease, use of an unaltered version of this virus was not a good idea. Since that time, many animal and human viruses have been investigated for their ability to kill cancer cells.

The path to approval of viruses for cancer was a long one! The first oncolytic virus to be approved was an adenovirus, approved in China (more below). 2

Viruses as Cancer Killers

Despite the misery that viral infections cause to almost every kind of living thing, viruses themselves not considered to be alive. Unlike cells, viruses do not have biochemical processes like metabolism. Instead, viruses are parasites made of relatively simple protein and genetic parts. In order to survive and reproduce, viruses must take over control of living cells. In many cases, this process ends in the death of the infected cell.

To take over a cell, viruses first have to attach and enter cells through the cell surface. Cell membranes are dotted with many different proteins, which help the cell to stick to things, move, and complete other cellular activities. There are many types of proteins, each with a slightly different shape and function. Viruses also have proteins on their surfaces. The proteins on the virus bind to proteins on the surface of the target cell, like a key fitting into a lock. Once in place, the virus is able to enter the cell or inject its genetic material into the cell.

Once infected by a virus, a cell is forced to produce more viruses. Living cells have the ability to make copies of their genetic information and to reproduce. Viruses take advantage of this and force the cells to make copies of the virus' genetic material instead of their own. Viruses also take over the machinery inside cells that produces proteins and other biological structures. Often the process ends in the release of many more viruses and the death of the infected cells.

But what if, instead of killing healthy cells, these viruses could be programmed to specifically target, infect, and kill cancer cells? Viruses can be used to fight cancer cells in two main ways: by infecting cancer cells and causing them to self-destruct (a process called apoptosis) or by triggering an immune response against the cancer cells3 Cancers take root by evading the immune system, viral infections can alert the body that something is wrong.

The viruses used to treat cancer are changed so they can't cause illness. During the process, scientists can insert genes that cause the virus to only target cancer cells (leaving all healthy cells unharmed) and/or disable the virus' ability to take over healthy cells.4 Evidence shows that oncolytic viruses can destroy stubborn cancer-causing cells that are sometimes survive through current treatments.5 A handful of viruses are currently being investigated for use in cancer therapies; four of these - herpes simplex viruses, reovirus, measles virus and adenovirus - are described below:

Herpes viruses

Herpes is a common human infection generally spread to oral or genital areas through bodily fluids. Unaltered versions of herpes viruses can cause disease in humans (i.e. cold sores).

The herpes virus is easily genetically modified, making it a good tool for treating different types of cancer. Genes can be added to target cancer cells, improve delivery or increase the activity of chemotherapy.[6] The viruses can be also coated and protected to increase the efficiency of the treatment.[6] The presence of the herpes virus alters patient immune responses. Work is being done to see if this can cause immune cells to attack the cancer.[7] [8]

In 2015 a herpes-based oncolytic virus (talimogene laherparepvec (T-VEC); brand name Imlygic™) became the first oncolytic virus approved by the U.S. Food and Drug Administration (FDA). T-VEC is approved for the treatment of some cases of melanoma skin cancer.[9] [10] [11]

View clinical trials using T-VEC.

Reovirus

Reoviruses are typically harmless. It is found in the gastrointestinal and respiratory tracts. Reovirus has potent abilities to shrink tumors.Tumors with mutations in theRAS oncogene are particularly susceptible to treatment with reovirus.[12] A 2009 study showed that reoviruses can cause tumor regression in mice.[13]

Pelareorep (brand name Reolysin®) successfully completed a Phase II trial of patients withmetastatic breast cancer.[14] In the trial overall survival was significantly improved. A Phase III trial involving patients with head and neck cancers is currently ongoing.[15] Other clinical trials of pelareorep are onging.

View clinical trials using pelareorep (Reolysin®).

Learn more about the RAS oncogene.

Measles Virus

Measles virus causes an infectious disease of the same name. The virus frequently attacks the respiratory tract of young children. Researchers have used the measles virus to develop MV-NIS, a virus which targets a protein (called CD46) found on most myeloma cells.[16] CD46 provides a doorway into the cell for MV-NIS. A 2014 study showed that MV-NIS appeared to reduce tumor size in two patients.[17] Clinical trials with MV-NIS are underway.

View clinical trials using MV-NIS.

Adenovirus

Adenovirus is different from the others on this list because it can target resting (nondividing) cells in addition to dividing cells. It can cause mild upper-respiratory or digestive infections in healthy humans.[18] The adenoviruses used for cancer are genetically altered. The altered viruses are called recombinant **c**onditionally **r**eplicative **ad**enoviruses (CRAds).They have been changed so they can only reproduce in cancer cells, not in healthy cells.[19] Wild-type (not genetically modified) adenoviruses attach to normal cells by binding to a protein on the surface of the cells. the receptor protein is found on many healthy cells, but very few tumor cells.[20] First, scientists genetically modify the viruses so that the viruses are unable to attach to this receptor and therefore unable to infect healthy cells. The viruses can be also engineered to carry a variety of genes used to help the viruses accurately identify, infect, and destroy tumor cells.[21] Some studies have shown that when used in with chemotherapy, CRAds can improve patient outcomes.[22]

In November 2005, an oncolytic adenovirus (H101) became the first one to be approved for use in people. H101 was approved in China for the treatment of some patients with head and neck cancers.[2]

View clinical trials using oncolytic adenoviruses.

Poxvirus

For over 12,000 years poxviruses caused illness and death. Smallpox is thought to have killed hundreds of millions of people.[23]

Smallpox was also the driving force for the creation of the first vaccine. Based on work previously done by others, Edward Jenner, an English physician intentionally infected a young man with cowpox and then with smallpox. He was protected! The results paved the way for the development of an effective vaccines against several different viral infections. The horror of

smallpox was ended in 1979 after a massive global immunization program eliminated the disease.[24] [25]

In the last few years, modified poxviruses have gained attention for their ability to kill cancer cells and induce a strong immune response against tumors.[26]

A modified virus, called CF33, developed by Imugene[27] and City of Hope[28] is currently being tested against solid cancers in patients who have failed at least two previous treatments.[29] The CF33 virus is designed to enhance the immune response of patients against their cancers. Because of this, the treatment can cause the death of cancer cells that have not been infected with the virus - it can trigger immune responses to do that.[30] [31]

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