A glimpse into the world of human viruses

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It is a matter of opinion, or of definition, whether viruses are considered living organisms or peculiar chemical substances.
THEODOSIUS DOBZHANSKY

Viruses are tiny biological agents that possess a genome but cannot replicate on their own. In order to replicate, they need to infect host cells and hijack the host's machinery. Therefore, one can argue that they are not really living organisms. Alive or not, viruses are very successful at tricking and hijacking cells. There are an estimated 10^{31} viruses on this planet, which infect all forms of life. They play an important role in many ecosystems and shape life on earth. In this issue, we will have a look at viruses that infect humans. But don't forget—no form of life is safe.

Viruses are classified as "DNA viruses" and "RNA viruses" depending on how their genetic material is stored (either as DNA or as RNA, respectively). About 70% of all viruses are RNA viruses. As you already know, RNA is less stable than DNA and RNA replication is more prone to errors. Thus, RNA viruses have a higher mutation rate than DNA viruses.

Outside of host cells, the genetic material of a virus is packed within the *capsid*, a shell of proteins. The entire unit (genetic material and capsid) is called a *virion*. When a virus infects a host cell, the viral DNA or RNA is released from the capsid into the cell, where it is replicated by the molecular tools of the host cell. Finally, viruses need to spread from cell to cell within an organism and from one organism to another, i.e. from the cells of one organism to the cells of another organism (see the box on viral transmission below).

We are all infected by viruses. However, luckily, many of them do not cause symptoms and remain unnoticed. They may have negative long-term effects, be entirely harmless, or even provide benefits — it's often hard to know. We only notice viruses when they cause diseases.

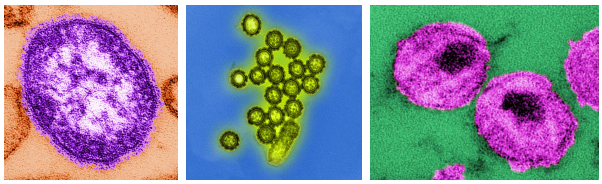


Fig. 1: Colorized transmission electron microscopic images of the virions of measles, influenza, and HIV (from left to right).[a]

[a] Images: (1) CDC/Cynthia S. Goldsmith; William Bellini, Ph.D. (2) National Institute of Allergy and Infectious Diseases (3) CDC/A. Harrison; Dr. P. Feorino.

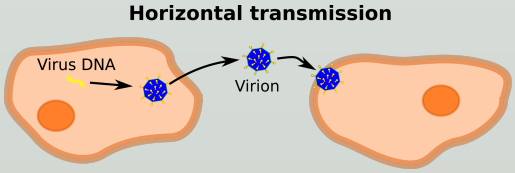
Viral diseases

Viruses are responsible for many human diseases, including the common cold, influenza, measles, chickenpox, rubella, hepatitis, AIDS, Ebola, Zika, and others. Some viruses can even cause cancer (Peyton Rous was awarded the 1966 Nobel prize in Medicine for this discovery).

Viral transmission: How do viruses spread?

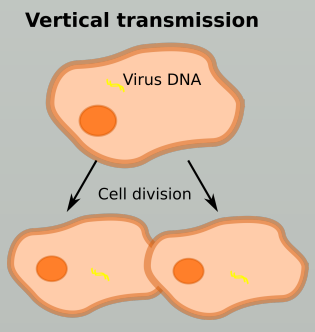
Viruses can pass to new cells in two ways, either *horizontally* or *vertically*.

Horizontal transmission denotes the spread of the virus from an infected to an uninfected cell of the same generation.



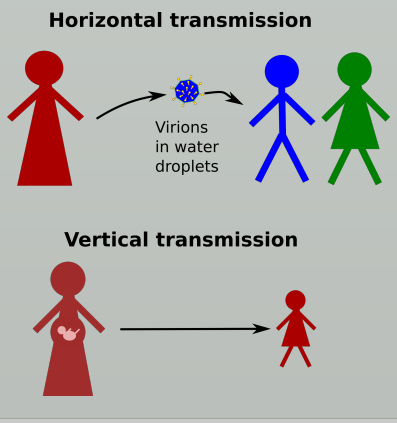
In order for horizontal transmission to take place, new virions must be produced. To do this, the virus makes use of the molecular machinery of the host cell to build a capsid and assemble the virion. Then, to reach uninfected cells, the new virions are usually released into the liquid surrounding the cell. This release can happen all at once, in a process that kills the host cell, or more gradually, in a way that leaves the host cell intact. Free virions cannot move by themselves. Rather, they rely on luck—on random encounters with new host cells. Virions can also reach uninfected cells through *cell-to-cell spread*—in this process, virions pass directly from an infected to an uninfected adjacent cell without passing through any liquid. This direct transmission is conducive to viral spread within an organism, because it is fast and helps the virus escape the individual's immune system.

With **vertical transmission**, the virus is passed on from the mother cells to the daughter cells during cell division.



Some viruses incorporate their genetic material into the host genome, so it gets replicated together with the host DNA. RNA viruses that use this strategy are called retroviruses. Upon infection of a cell, they reverse-transcribe their RNA into DNA. This is very unusual—as you learned in a previous issue, the process normally goes in the other direction. The viral DNA is then integrated somewhere in the genome of the host cell. You will learn more about an important retrovirus—the HIV virus—below.

Transmission between individuals can occur either horizontally or vertically. Horizontal transmission between different individuals can, for example, happen through free virions in saliva droplets. Other viruses use *vectors*—some outside agent—to spread from one individual to another. For instance, most plant viruses use insects to get from one plant to another. Vertical transmission is, for instance, possible from the mother to the fetus. This happens with the rubella virus, the cause of German measles. Normally, German measles is not a serious disease. However, if a pregnant woman passes the virus to her child, this can cause serious harm to the child's health. Furthermore, viruses can be passed on to the next generation by infecting cells of the germ line (egg/sperm). Viruses that are transmitted via the germline are usually not very harmful to their host—otherwise, they would compromise their own survival. We will talk more about such transmission and its consequences later.



Most (if not all) human viruses derive from animal viruses. For example, the measles virus most likely evolved from (an ancestor of) rinderpest, a virus that infects cattle. Normally, viruses that are well-adapted to an animal host are not well-adapted to humans. This happens because viruses need to interact with many of their host's proteins to complete their life cycle. These proteins are not always identical in animals and humans, which means the viral tools cannot be used on the human version of a protein. However, if the virus is not entirely unfit in the new environment of the human body and also has some chance to spread from human to human, it might accumulate adaptive mutations and evolve into a well-adapted human pathogen. This transition is facilitated through close contact between animals and humans (providing the virus with many chances to infect humans) and large, dense communities (allowing the virus to spread between humans more easily). The emergence of new human viruses from animal viruses is hence often associated with changes in human lifestyle. For example, the evolution of the measles virus is hypothesised to have occurred 3000-2500 BC, when humans in the Middle East started to keep livestock and to live in large communities. (However, other researchers think measles originated much later, in the 11th or 12th century.)

Even after the successful transition from an animal to a human pathogen, viruses continue to be challenged by the human immune system. On one hand, the genes coding for the components of our immune system can evolve through mutation and recombination, bringing about variants that are better at fighting common pathogens. This is a process happening across human generations. On the other hand, the immune system of a single person itself is adaptive and can—once an infection occurs—respond and produce new tools tailored to fighting the specific virus that is attacking (however, some viruses manage to hide from our immune system).

One of these tools is antibodies. The production of antibodies is triggered by surface proteins of the virion (proteins belonging to the capsid or to an envelope that covers the capsid). Substances that trigger an immune response are called *antigens* (antigen = *anti*body *gen*erator). The antibodies produced by the immune cells inactivate the virus by binding to these antigens. Antibodies are antigen-specific, i.e. they can only bind to the antigens they are designed for (see extra-box at the end of the article). Another tool to fight viruses are killer T-cells that circulate through the body to find and kill infected cells. Killer T-cells recognise infected cells from the viral antigens present on their surfaces. However, just like antibodies, killer T-cells are antigen-specific, and infection by a particular virus triggers the production of specialised killer T-cells that can act against it. Following an infection, we keep producing the specific antibodies and killer T-cells for decades.[1]

If a virus gains mutations that alter its antigens, the old antibodies and killer T-cells will not work anymore, and our immune system must produce new, suitable ones to fight the evolved virus. There is great variation in the patterns of antigenic evolution across viruses. Some viruses evolve antigenic changes very slowly. Once we have manufactured the antibodies (and other tools) to fight them, we are immune for the rest of our lives, since the virus does not change a lot over the course of decades—for some, we do not observe any antigenic evolution at all. An example is the measles virus. Other viruses change more quickly. While they might not escape the immune system during the course of infection, a slightly changed variant might come back one or two years later and is able to infect us anew.

[1] Our immune system has many further components. In particular, it also has non-adaptive parts that act rapidly and are not specific to a given pathogen. E.g. we also have natural killer cells that are not antigen-specific and constantly "patrol" in our body to kill infected cells as a quick first response to invading pathogens. Another important defence mechanism of our immune system is that certain cell types, when infected, secrete molecules that serve as warning signals to other cells. After receiving these signals, cells become more selective about which substances can enter the cell—making infection less likely—and more ready to degrade nucleic acids—destroying the virus if it is already present within the cell.

For instance, influenza viruses do not evolve much during the time spent in a person, but they evolve a great deal from one season to the next. Still other viruses perpetually escape our immune systems, leading to chronic infections. The reason can be that their antigens evolve very rapidly or that we cannot eliminate the virus quickly, giving it sufficient time to change. An example of a virus that evolves a lot within each single patient and repeatedly escapes our immune system is the human immunodeficiency virus (HIV).

Why viruses are so variable in their antigenic evolution is an important topic of ongoing research. Researchers have some insight into why the measles virus, the influenza virus, and the human immunodeficiency virus adapt to the pressure of our immune systems to such different extents, but it is not yet fully understood.

In the following paragraphs, we will take a closer look at these three viruses. All of them are RNA viruses, but, as you will see, they are very different from each other.

Measles

The measles virus infects a range of human cells including various cells of the immune system, which greatly weakens our immune systems and makes us susceptible to infections by other pathogens. The measles virus itself normally does not kill us, but these secondary infections can be life-threatening. In countries with good health care, mortality is low and only 0.1% of infected people die. In Africa, however, 5-10%, and in refugee camps up to 25%, of people die following a measles infection. Further, while measles is usually cleared fully by our immune system, in rare cases, it can infect our central nervous system, persist there, and ultimately lead to a fatal neurological disease.

Fortunately, once we recover from measles, we have acquired life-long immunity. The protein that serves as an antigen in measles is needed for entry into the host cell. Research suggests that the specific structure of this protein cannot easily change without compromising the virus' ability to attach and infect host cells. The vast majority of mutations that change the antigen hence make the virus unable to complete its life cycle.

The life-long immunity acquired through infection implies that the measles virus can only persist if the community size is large enough that sufficiently many new susceptible individuals are born every year. Otherwise, the virus fails to find new victims fast enough at some point and dies out. The measles virus requires a community size of around 250,000-500,000 inhabitants to persist. This also means that it can only have evolved once people settled in such large communities.

Influenza

The seasonal flu epidemics are caused by two related viruses, influenza A and B.

The primary hosts of influenza A are birds. It infects the gut of the bird without causing many symptoms. However, influenza A variants can infect a wide range of species—including humans. In humans, it infects the epithelial cells[2] of the respiratory system. Influenza B is an almost exclusively human pathogen.

Influenza viruses possess two proteins on their surface, hemagglutinin (H) and neuraminidase (N). These two proteins are crucial for the entry of the virus into the cell and for its release from the cell. They are also the main antigens of influenza. For Influenza A, there are 18 subtypes of hemagglutinin and 11 subtypes of neuraminidase, which exist in many combinations. Influenza A viruses are classified on the basis of their H and N subtypes, e.g. as H1N1 or H3N1. The subtypes differ considerably from each other, and not all of them work on human cells.

Unlike measles, the influenza antigens are flexible, allowing for mutations to occur without detrimental effects to the virus. The process of antigenic changes due to mutations is called *antigenic drift*. Influenza A has yet another way to evolve. The RNA of the influenza

[2]Epithelial cells are the cells at the surfaces of organs or cavities like the lung.

virus does not exist in a continuous stretch but is divided into segments (eight for influenza A). When two different strains (or *variants*) infect the same cell, these segments can be shuffled. This is called *antigenic shift*. Due to its broad host range, co-infection of cells by two different strains is relatively common for influenza A (unlike influenza B). This co-infection could, for example, happen in pigs that have contact with both birds and humans: the pig might be simultaneously infected by an avian and a human influenza A strain. Sometimes, these newly combined viruses are able to infect humans, and since they are different from previously encountered strains, we may not have immunity. They can therefore cause pandemics with many infected patients. One such pandemic is called the Spanish flu, which started in 1918 and lasted three years, causing 50-100 million deaths in this time.

HIV

The human immunodeficiency virus (HIV) is a retrovirus, i.e. it integrates its genetic code into the host genome. It targets various cells of the immune system that carry the protein $CD4^+$ on their cell surface, among them helper T-cells. HIV therefore harms the immune system. Without treatment, it causes so many helper T-cells to die over time that the immune system breaks down, resulting in AIDS (= acquired immunodeficiency syndrome). People then become easy targets for other pathogens, leading to very poor health and ultimately death. HIV thus kills indirectly. Unlike influenza and measles, HIV does not get transmitted through everyday contact. Infection occurs through unprotected sex, contaminated blood transfusions, needles shared between drug addicts, or from mother to infant at birth.

The evolution of HIV

It took scientists a great deal of effort to uncover the evolutionary history of HIV. By sampling blood from monkeys, collecting thousands of samples of faeces from apes, and comparing the DNA sequences of human and simian viruses, they eventually identified SIV (Simian immunodeficiency virus) as the ancestor of HIV. SIV is a virus that infects many non-human primates in Africa. While we do not know with certainty how it jumped over to humans, the accepted view is that hunters caught the virus from the blood of killed monkeys and apes. The infection of hunters with SIV has probably happened many times, but either the foreign virus could not proliferate well in the new host or could not be transmitted to other people. In a few cases, however, the transition was successful, and the virus accumulated mutations that made it better adapted to life within and transmission between humans. Transmission was, however, not only facilitated through viral adaptation but also through changes in human lifestyle in the early 20th century. Many people in Africa transitioned from small communities to large cities with a high population density, dramatically increasing the contact rate between infected and uninfected people. It is estimated that HIV became established in the human population in the 1930s. Since people also started to travel more and farther, the virus could spread widely. One transition of SIV to humans was particularly successful. It occurred from chimpanzees and lead to the HIV strain that is called HIV-1 Group M, where 'M' stands for 'major'. This group of HIV viruses reached the US by the 1970s and is responsible for the worldwide HIV epidemic. Other groups of HIV are less prevalent: group O, for instance, is found almost exclusively in west central Africa, where it has infected about 100,000 people.

It is estimated that one HIV-infected helper T-cell produces 40,000-50,000 new virions. It is possible that the cell bursts to release the virions, but it may also stay intact. How else do the helper T-cells die in the process? At various points of the viral life cycle, viral

proteins may trigger molecular pathways that ultimately lead to death of the infected cell. Or the cell may be identified as infected and be killed by killer T-cells. However, the vast majority of helper T-cells that die in an HIV infection are not infected. They receive signals from infected neighbouring cells when the latter die. These signals prompt them to destroy themselves.

Not all infected cells start producing new virions right away. Some of them just continue to divide, passing the virus in their genome on to the daughter cells. These cells are called latently infected cells. They are the reason it is impossible (at present) to completely remove HIV from the human body. The virus hides within these cells from all currently available treatments and from our immune system—no antigens are presented at the surface of these cells—until at some point, the production of new viruses starts again.

Herpes viruses: hidden but ready to come back

You have probably heard about herpes viruses: herpes simplex 1 (HSV 1) is the culprit behind the blisters on your lips, and its more serious cousin – HSV 2 – causes sexually transmitted diseases. Few people know that chickenpox, a very common childhood disease, is also caused by a herpes virus (the varicella zoster virus).

While different herpes viruses cause very different diseases, most of them have something in common: once you have them, it is almost impossible to get rid of them. This happens because during infection, small numbers of viruses hide within cells and escape the immune system. In this way, the virus can persist in the host for the host's entire life. Most of the time, it does not cause any symptoms. Only from time to time, these hiding viruses reactivate and cause another round of infection—another blister on your lip. Herpes viruses are extremely widespread among humans, and a latent form of some herpes virus can be found in almost everyone.

Interestingly, the varizella zoster virus that causes chickenpox when we get infected with it for the first time causes a different disease with different symptoms when it is reactivated. Once you have overcome chickenpox, the virus persists in the nerve roots near the spinal cord. In principle, you have acquired immunity to the virus during the chickenpox infection. However, in times of weak immunity – for instance as the result of other diseases, stress, or simply old age –, the virus can reactivate and travel from the nerve root to the endings in the skin, producing painful blisters—a disease called shingles. Unlike the rash in chickenpox, the blisters usually only occur in a small area of the skin. One cannot contract shingles from another person. However, a person with shingles spreads the varicella zoster virus, which can cause chickenpox in someone who has not had it yet.

Our immune system produces antibodies and killer T-cells against HIV but it cannot keep up with the virus for several reasons. First, HIV destroys precisely those cells that are required for the immune response. Our body produces new helper T-cells, but at some point it gets tired and production slows down. Second, the virus evolves within our body during the infection, escaping our immune response—mutation and recombination within the viral population result in new variants that the antibodies already present and the killer T-cells cannot bind to. HIV has an extremely high mutation rate, which, combined with a very high replication rate, leads to the rapid appearance of mutants. These mutants can proliferate undisturbed until our body recognises them and can produce suitable new antibodies and build new killer T-cells. It is an arms race between the virus and our immune

system that our immune system finally loses.

A very small fraction of people—probably less than 1%—are resistant to HIV. One of the surface proteins on their helper T-cells has a different shape due to a genetic mutation, preventing the virus from entering the cell.

Vaccines

The potential for the antigenic evolution of a virus strongly influences how easily we can develop vaccines against the disease and how effective they are. Vaccines work by triggering an immune response equivalent to the one triggered by the pathogen, leading to the production of antibodies. Vaccines may contain dead viruses or modified live viruses that, for instance, are unable to replicate at the temperature of our body ("live vaccines").

Since the measles virus is so invariable, we only need to get vaccinated once to possess life-long immunity. This has a very important implication. Above, you have learned that the measles virus can only persist if the community size is large enough. Through vaccination, we can effectively reduce the community size. This, in turn, means that we could drive the measles virus to extinction if sufficiently many people are vaccinated. This strategy has been successful with its close relative, the rinderpest virus. In 2011, it was officially declared to be eradicated. This has been the second time in human history that a virus has been driven to extinction through vaccination. The first virus to be eliminated was the highly dangerous smallpox virus that was declared extinct in 1980.

Influenza, unlike measles, requires a shot with an updated vaccine every year. Normally, the vaccine contains antigens of three different influenza variants. In order to choose the variants to include, researchers predict which strains are most likely to spread in the next season. No vaccine has yet been found for HIV, but scientists are working on it. One difficulty is the huge genetic diversity of the HIV virus. Another is that we do not know what a successful immune response to HIV even looks like—nobody has it. Luckily, we have developed some very potent HIV drugs that control the virus extremely well.

Interestingly, vaccines can actually trigger viral evolution. First, viral strains with mutated antigens are favoured by natural selection. Unlike their ancestors, mutants may replicate not only in unvaccinated, but also in vaccinated hosts. Thus, they can spread more easily across the host population. However, the evolution of vaccine resistance is rare. Second, viruses might evolve to become more virulent in response to vaccine-acquired immunity, especially if the immunity is not perfect and allows the infecting virus to complete a few replication cycles. The new viral strain launches a much stronger attack than its ancestor (e.g. it replicates much faster) and the immune response acquired through vaccination is too weak to fight the evolved virus. For instance, the virus causing Marek's disease in poultry has evolved higher virulence in response to a series of vaccines. Third, attenuated viruses used in live vaccines can, in rare cases, acquire mutations that turn them pathogenic. This is, for example, a risk in the oral poliovirus vaccine. While vaccine-induced viral evolution is possible, the risk is very low, and the huge benefits of vaccines largely outweigh them.

Importantly, through vaccination, we not only protect ourselves, we protect others in our community. If we do not develop an infection, we cannot transmit the virus to the people around us, including those who cannot be vaccinated, e.g. because their immune system is compromised due to a disease or if they are too young to be vaccinated. If everyone around them is vaccinated, however, these people are protected as well. This is called *herd immunity*.

Our genome marked by viruses

Interactions with viruses have shaped our genome in two fundamental ways. The first is based on the fact that viruses are pathogens

from which we must defend ourselves. Most obviously, viruses and other pathogens impose selection on the genes associated with our immune system. Less obviously, they also put selection pressure on many other genes. This is because viruses interact with many different kinds of proteins—e.g. those on the surfaces of cells—not just with the ones related to immune responses.

A second way in which viruses have shaped our genome is more direct. As explained above, some viruses can integrate into the genome of their host. Normally, they are in somatic cells, and in order to proliferate, they must infect other cells of the same and eventually of another host. Sometimes, however, they end up in cells of the germline (eggs, sperm). Then, they are passed on to the children of that individual who then carry the virus in every one of their cells. A virus that made it into the germline and is passed on vertically to the following generations is called an endogeneous virus. Initially, endogeneous viruses can still escape from host cells to infect other hosts. Over time, however, mutations accumulate in the viral genes until the virus can no longer produce viable virions and leave the host cell. They remain in our DNA as viral fossils. About 8% of our DNA consist of these viral relics. And now, it gets exciting: some of these viral genes give rise to new human genes that perform fundamentally important tasks in our body (see Box).

Syncytin-1 – an important ex-virus gene

The gene *Syncytin-1*, a viral fossil, is expressed exclusively in the placenta, where it is crucial to fusing the placenta to the uterus and therefore securing transport of nutrients from the mother to the fetus. The same gene that is found in humans is found in other primates as well. Similar genes are found in many mammal species such as mice, cats, and dogs. However, these genes do not derive from the same virus as our *Syncytin-1* gene. What does this mean? This means that there have been several infection events in different mammal lineages with different viruses whose genes have been co-opted by different hosts to fulfil the same function! Not all mammals have *Syncatin*-like genes. Actually, there is great diversity in how exactly the placenta functions across species, and one of the reasons is thought to be infection (or non-infection) by a range of retroviruses across species since the placenta (and hence live birth) evolved ca. 130 million years ago.

Making use of viruses

We have talked a lot about how viruses make us ill. In this section, you will learn how we can purposefully use them to *treat and cure* diseases. With scientific knowledge, we are turning our enemy into our friend.

As you learned in the previous series, some mutations in our genes can cause diseases. For instance, sickle cell anemia, a very severe and painful disease, is caused by a single nucleotide mutation in the haemoglobin gene. This mutation distorts the shape of the red blood cells, impairing oxygen transport in the blood. Patients often need blood transfusions.

What if we could replace or complement this gene by a functional, unmutated copy? We do not need to change it in all cells in the body, only in the source of red blood cells—the bone marrow, where the hematopoietic stem cells are found. These cells constantly divide and produce all kinds of blood cells. If we could replace at least part of the stem cells of a patient who has sickle cell anemia with stem cells that have a healthy gene, that would permanently cure the person. One way to achieve this is to transplant bone marrow from healthy individuals. However, suitable donors are only found for about 20% of all patients, because the immune system often rejects the foreign transplant. It would be much better if we could take the patients' own stem

cells and modify them. And this is where viruses enter the scene.

As we mentioned above, retroviruses integrate into the genome of the host cell. This property can be exploited for *gene therapy*. In order to develop a therapy for sickle cell anemia, researchers engineered an artificial virus that carries a healthy β-globin gene in its genome. This artificial virus is based on the human immunodeficiency virus but the researchers made so many changes to it that it cannot harm us (it can't even be replicated within cells). To treat patients with sickle cell anemia, doctors extract bone marrow from the patient, and let the artificial virus infect the extracted stem cells. This does not harm the cells, but they now carry a healthy copy of the gene. The doctors then implant the infected cells back. A 13-year old boy was treated this way in 2014. Fifteen months after this treatment—when the researchers and doctors wrote a report about the case—the boy still had enough healthy red blood cells that he no longer needed blood transfusions!

Conclusion

Viruses have been omnipresent in all of human history and evolution, and they are omnipresent in all of our lives. They have adapted to proliferate within our bodies and to spread from human to human and they keep evolving. In this article, we only glimpsed a small portion of their world. There is so much more yet to discover about this ubiquitous form of life—or not-life.

Acknowledgements

The authors thank Edward C. Schrom for providing invaluable answers to all our questions on the human immune system, Roland Regös for helpful discussions, and Lindi Wahl for many constructive comments on the text.

Other useful resources

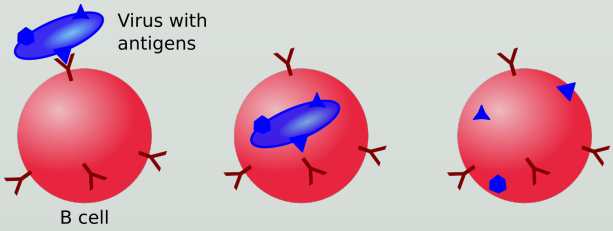
- A nice video about the origin of viruses: `www.youtube.com/watch?v=X31g5TB-MRo`
- Something about the flu virus: `www.youtube.com/watch?v=Rpj0emEGShQ&t=7s`
- A video about HIV lifecycle: `www.hhmi.org/biointeractive/hiv-life-cycle`
- CDC information about flu vaccination: `www.cdc.gov/flu/about/season/vaccine-selection.htm`
- A very nice book about viruses, if you are super interested: Carl Zimmer (2015). A Planet of Viruses (2nd edition). Chicago and London: The University of Chicago Press.

Extra-Box: How our immune system fights and remembers pathogens

The human immune system is very complex, involving many cell types, molecules, steps, and pathways. Here, we explain the basic principles of a very important component of our adaptive immune system, the production and maintenance of antibodies. Antibodies inactivate the virus by binding to its antigens. They are antigen-specific, i.e. a given antibody can only bind to specific antigens. When we are infected by a new virus that we have not previously encountered, we do not have the right antibodies readily available. However, our immune system is able to manufacture them, and this is why we call this part of it "adaptive". How does this work?

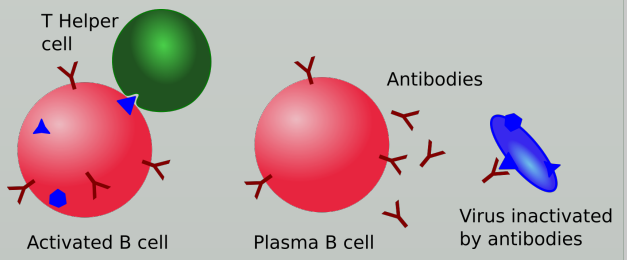
In the production of antibodies, two important cell types of our immune system are involved—*B-cells* and *helper T-cells*. The "factory" for the production of B-cells is in the bone marrow, whereas helper T-cells are produced in the thymus. We constantly produce new B- and helper T-cells for several decades (later in life, the production wanes). High rates of somatic recombination during their production lead to an enormous diversity in their cell pools. You will see in a moment why this diversity is crucial.

B-cells circulate in our body to "search" for pathogens. They possess receptors at their surface that can bind to viral antigens. A given B-cell can only bind specific antigens. Yet, thanks to the immense diversity in the pool of B-cells, it is nevertheless very likely that we possess B-cells that can bind the present antigens, at least weakly. Once the antigen has been bound to the B-cell, the cell engulfs it, chops it into little pieces, and presents some of the pieces on its cell surface.



Then, a helper T-cell (circulating in the body as well) attaches to the antigens presented by the B-cell. This "activates" the B-cell. Again, a given helper T-cell can only bind to specific antigens, and the diversity in the helper T-cell pool is important.

Once activated, the B-cell starts producing antibodies. However, these first antibodies often only bind weakly to the viral antigens (they very much resemble the B-cell receptors). The B-cell therefore undergoes several rounds of replication with very high mutation rates and selection for variants that bind the antigens more strongly. It then creates a lineage of two different kinds of B-cells, Plasma B-cells and Memory B-cells. The Plasma B-cells are the cells that produce the perfect antibodies.



Plasma B-cells and Memory B-cells can live for long periods of time. The Plasma B-cells continue to produce antibodies, and when the pathogen attacks us again, we are prepared and can fight it off quickly—before it can cause an infection. If the existing antibody concentration is insufficient to clear the pathogen, the Memory B-cells can be reactivated to produce new Plasma B-cells.